Local and Iterative Visual Processing Deficits in Schizophrenia

A DISSERTATION

SUBMITTED TO THE FACULTY OF THE

UNIVERSITY OF MINNESOTA

BY

Tori Espensen-Sturges

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

Advisor: Cheryl Olman, Co-Advisor: Shmuel Lissek

May 2017

Abstract

Evidence of dysfunctional visual processing in schizophrenia patients has been noted in all stages of the visual processing pathway. The iterative nature of vision- with hierarchical feedforward signals, modulating feedback signals, and horizontal intracortical connections- makes it difficult to pinpoint exact loci that are driving these deficits. This dissertation uses several contextual modulation paradigms in an effort to isolate and explain the nature of disruptions in iterative visual processing in schizophrenia.

Chapter 1 provides an overview of visual processing dysfunctions in schizophrenia, and examines a variety of mechanisms that may play a role. These include neurotransmitters, magnocellular versus parvocellular processing streams, abnormal local connections, and abnormal long-range feedback connections. These are presented in the context of several theoretical perspectives of visual neuroscience. Chapter 2 provides functional magnetic resonance imaging data from a fractured ambiguous object task that probes the role of high-level qualities in primary visual cortex activation and interregional connectivity, and how these may be disrupted in psychosis. Chapter 3 introduces a computational model that attempts to fit parameters to psychophysical data to isolate disrupted mechanisms in schizophrenia. This model focuses on the role of gain control and segmentation of center and surround stimuli in a tilt illusion paradigm.

Chapter 4 presents previous work, examining the modulatory effect of the NMDA receptor agonist d-cycoserine on conditioned fear generalization. This work was done in healthy controls as a step in expanding our knowledge of the function of d-cycloserine in increasing specificity and efficacy in the fear learning process.

Table of Contents

List of Tables

List of Figures

List of Equations

Chapter 1: Iterative Visual Processing in Schizophrenia

Relationships between schizophrenia and vision have been noted in the scientific literature since at least the 1950s. Two phenomena were observed during this decade: the first was that schizophrenia did not occur in people suffering from congenital blindness (Chevigny & Braverman, 1950). The second was that qualitative descriptions of living with schizophrenia often included some sort visual perception problem, such as this explanation of fragmented percepts: "I have to put things together in my head. If I look at my watch, I see the watch, watchstrap, face, hands, and so on, then I have got to put them together to get it into one piece". (Chapman, 1966, as cited in Silverstein and Keane, 2011).

Early research on vision in schizophrenia patients was primarily focused on comparing the visual abilities of these "functional" brain disorders versus those with "organic" brain disorders, essentially, schizophrenia versus dementia. The earliest studies were done using paradigms that targeted the ability to distinguish rapidly presented flashes of light, and observed a difference between functional and organic groups, but not between the functional group and healthy controls (Irvine, 1954; King, 1962). Studies on perception of apparent motion, on the other hand, found schizophrenia patients and "organics" more similar in their deficits, and was at the time proposed as a diagnostic tool for research purposes (Deabler & Saucer, 1956; Saucer, 1958). Color discrimination was also a topic of interest, with some studies finding higher rates of color vision disorders in the schizophrenia population (Meduri, 1969; Pevzner, 1969). In the 1960s, the study of visual deficits in schizophrenia patients expanded exponentially, driven primarily by studies of visual evoked potentials (VEP), the measurement of electrical responses over the occipital cortex in response to visual stimuli. The VEP literature consistently found a decrease in

VEP amplitude in response to paired flashes in schizophrenia patients as compared to non-psychiatric controls, and that VEP responses were often correlated with symptomatology and drug treatment (Heninger & Speck, 1966; Ishikawa, 1968; Shagass & Schwartz, 1965; Speck, Dim, & Mercer, 1966) These findings taken together confirmed the qualitative reports of visual disturbances in the disorder, and drove an extensive body of research into the exact nature and mechanisms of these perceptual dysfunctions(Uhlhaas & Silverstein, 2005).

Deficits in High-Level Visual Processing

The end goal of vision is to be able to recognize and interact with the world around us. To this end, high-level facial and object recognition can be important measures of overall functioning of the visual system. Facial processing theories suggest that subjects must be able to identify individual facial features, such as the eyes, lips, hairline, and nose, and then integrate these features with correct spatial information to get an accurate holistic representation of a face(Diamond & Carey, 1986). This process requires the ability to group individual elements correctly, which may be impaired in schizophrenia (Joshua & Rossell, 2009; Shin et al., 2008; Steven M. Silverstein & Keane, 2011) Deficits are also observed in the ability to detect a face in a line drawing or other crowded stimuli, which may also reflect this difficulty in perceptually grouping features(Chen, Norton, McBain, Ongur, & Heckers, 2009; Chen, Norton, & Ongur, 2008; McBain, Norton, & Chen, 2010) though it may also partially reflect more cognitive processes like visual search. This behavioral finding is supported by ERP studies examining the N170 component, which has been associated with early structural encoding of faces. Data have consistently shown that N170 amplitudes are smaller and latencies are longer in patient groups, which is suggestive

of less response and slower processing times (Feuerriegel, Churches, Hofmann, & Keage, 2015; Herrmann, Ellgring, & Fallgatter, 2004; Lynn & Salisbury, 2008; McCleery et al., 2015; Onitsuka et al., 2009; Zheng et al., 2016). Magnetic resonance imaging studies of face processing in schizophrenia have primarily focused on the fusiform gyrus, where reports are conflicted. Studies report no difference in fusiform gyrus activation when viewing emotionally neutral face stimuli(Quintana et al., 2011; Yoon, D'Esposito, & Carter, 2006), but do demonstrate differences when faces are degraded. Schizophrenia patients have higher activations to degraded face in the fusiform gyrus that may be due to the region having to work harder to overcome integration deficits or poorer signaling from earlier visual areas(S. M. Silverstein et al., 2010).

Facial processing is a subcategory of object processing, which is also dysfunctional in schizophrenia patients. Studies have indicated that patients are not necessarily less accurate at recognizing ojects, but require more information to make an accurate determination. This finding is associated with a reduced N_{Cl} component (an EEG component observed over the lateral occipital complex associated with perceptual closure) as well as reduced P1 over both the dorsal and ventral visual streams, suggestive of both early and late stage deficits (Doniger, Foxe, Murray, Higgins, & Javitt, 2002). Relatives of schizophrenia patients seem to demonstrate similar P1 deficits over the midline dorsal region and bilaterally over LOC during biological object recognition tasks (Yeap et al., 2006). Correlates of these deficits have been noted in fMRI studies, where patients have demonstrated smaller activations in the dorsal visual stream that seem to result in reduced activations in the prefrontal cortex, as well as smaller activations in the ventral stream that are correlated with scores on behavioral measures of perceptual grouping (Sehatpour et al.,

2010). In an attempt to further tease apart deficits, Calderone et al. used high and low spatial frequency objects in an fMRI experiment. This study found preferential responding to high spatial frequency objects in the precuneus and right superior temporal gyrus in patients, opposite the pattern observed in controls, and the disappearance of a difference between stimuli types for patients in the dorsolateral prefrontal cortex and left caudate (2012). These results taken together are indicative of deficient object processing that begins earlier than object oriented regions of the brain, and that simply studying high-level vision is not enough to understand what is driving visual deficits in schizophrenia.

Deficits in the Magnocellular Visual Processing Stream

As both object and face processing are high-level visual processing skills, it is likely that deficits in these abilities are driven by dysfunctional processing upstream. One important distinction is whether these deficits are precipitated by dysfunctions in basic feature coding, poor responding in a single visual area, or in more complex signaling within and between parts of the visual system.

Dysfunctions in feature coding seem to be related both to the specific stimulus feature being encoded, as well as the visual pathway processing it. There are two main visual processing streams, though the two do experience overlap. Both start in the retina, synapse in the lateral geniculate nucleus (LGN), project to different layers of early visual cortex, and then through higher visual areas. The magnocellular pathway derives its name from the large cell bodies characteristic of the LGN neurons that signal low spatial frequency, color-blind, low-contrast information relatively quickly. This pathway tends to capture movement, onset/offset stimulus information, and big picture stimulus organization. It primarily projects to the dorsal visual stream, supporting eye movements,

attentional modulation, motion perception, and motor guidance and integration for the purposes of locating visual information in space (Steinman, Steinman, & Lehmkuhle, 1997). The parvocellular pathway, on the other hand, has small LGN cell bodies and processes high spatial frequency information and color information much more slowly than the magnocellular pathway. It projects mainly to the ventral stream, which is specialized for object recognition and processes information about orientation, size, contours, form, objects, and faces (Jeffries, Killian, & Pezaris, 2014).

Several studies have suggested that perception of magnocellularly biased stimuli is more disrupted in schizophrenia than parvocellularly biased stimuli. Behaviorally, schizophrenia patients perform more poorly on spatial frequency tasks biased to the magnocellular pathway(Kéri, Kelemen, Benedek, & Janka, 2004). These results are supported by deficient ERP generation when the spatial frequency of stimuli is designed to activate the magnocellular pathway, but intact processing of high spatial frequency stimuli that activate the parvocellular pathway (Butler et al., 2007; Dias, Butler, Hoptman, & Javitt, 2011). MRI results suggest that while there may not be any differences in BOLD activation magnitude between patients and controls in the visual cortex, the spatial area responding to low spatial frequency stimuli is reduced in schizophrenia, while the number of voxels responding to high spatial frequency stimuli are comparable between the two groups (Martínez et al., 2008). In the case of luminance tasks, again schizophrenia patients do not exhibit any ERP differences from controls if the stimuli are designed to preferentially activate the parvocellular visual processing pathway, but do show disrupted processing in the case of magnocellularly biased stimuli (Butler et al., 2001)

Contrast determination, on the other hand, appears to be disrupted regardless of the design of the stimuli. Psychophysical experiments reveal that patients need a larger difference between contrast levels for the difference to be noticeable (Calderone et al., 2013; Cimmer et al., 2006; Dakin, Carlin, & Hemsley, 2005; M.-P. Schallmo, Sponheim, & Olman, 2015). These reports are supported by MRI findings that during a contrast discrimination task, a smaller area of the occipital cortex was recruited in patients than in controls, regardless of whether the contrast stimuli were biased toward magnocellular or parvocellular processing (Calderone et al., 2013).

These results suggest that visual deficits are not inherent to basic feature processing. There is a compelling body of evidence indicating that the magnocellular system may be selectively dysfunctional in schizophrenia, but this does not seem to hold true for contrast discrimination tasks. These contrast discrimination deficits are observable across a range of contrasts, which is inconsistent with the magnocellular deficit theory. One caveat to this body of research is that it can be difficult to observe neurological correlates of magnocellular processing, particularly early in the stream, because of the distribution of magnocellularly and parvocellularly biased neurons. Most MRI studies do not have the resolution to discern magno- vs parvocellular layers in the early visual system, and EEG is limited to simply observing slow versus fast responses with very coarse spatial resolution.

Deficits in Iterative Processing

Visual processing in general relies on the ability to integrate feedforward signals from early visual areas to higher visual areas, feedback signals from higher to lower areas, and horizontal signals from within the same visual area. This results in recurrent processing loops, in which information from one area of the visual system can modulate

neural responding in both higher and lower visual regions; the modulated responses are then communicated back to other areas in an iterative process (Lamme & Roelfsema, 2000). This process allows for increased efficiency and the ability to combine information from across multiple receptive fields (Rao & Ballard, 1999). The feed forward signals would typically be driven by stimulation of the classical receptive field, while feedback and horizontal connections may be driven by a variety of potential factors.

A general deficit in prediction in schizophrenia may be related to dysfunctions in the recurrent processing stream. Predictive coding theories suggest that the visual system is able to learn statistical regularities of the natural world. Higher visual areas communicate predictions about stimuli to lower visual areas, allowing the lower areas to essentially disregard any information that confirms those predictions, and focus processing power on information that is in conflict with them (Rao and Ballard, 1999). In this case, early visual neurons would not be responding to the image intensity, but rather to the difference between the expected value and the actual value. Models of predictive coding account for a hierarchical model where each stage predicts the response of the one before it, not after. The prediction error is then sent forward to higher visual areas to improve the prediction. These stages are occurring concurrently, which results in an iterative loop of feedforward and feedback responses. It has been argued that this type of coding scheme increases efficiency of visual processing, particularly in early areas, and can explain a variety of visual phenomena. Contextual modulation could be the result of feedback signaling expecting the surround to be similar to the central stimulus, which would provide an explanation for facilitation when the center and surround are very different, and suppression when the center and the surround are very similar (Spratling, 2011). Reduced

activity in early visual cortex for coherent shapes and contours as compared to random patterns could be the result of higher visual areas indicating that that is the expected grouping of stimuli (Rao & Ballard, 1999).

Predictive coding is not necessarily confined to the visual system Several studies have noted alterations in the mismatch negativity (MMN) ERP component, a component related to an unexpected stimulus in a sequence (Lee et al., 2017; Rentzsch, Shen, Jockers-Scherübl, Gallinat, & Neuhaus, 2015; Wacongne, 2016). MMN aberrations are indicative of impaired predictions about what comes next, or weak signaling of the prediction error. Either of these could result in disrupting the iterative prediction loop, either by affecting the feedback connections signaling the prediction, or just the feedforward projections coding for the error. Some researchers have noted attenuation of neural response in the ventral striatum to reward prediction error and exaggerated responses to predictable events, and have suggested that these aberrations may be related to the anhedonia observed in schizophrenia (Choi, Lee, Ku, Yoon, & Kim, 2014; Deserno, Heinz, & Schlagenhauf, 2016; Dowd, Frank, Collins, Gold, & Barch, 2016; Morris et al., 2012; Shergill et al., 2014). Patients with schizophrenia also tend to exhibit disturbances in sense of agency, or the awareness of generating and executing one's own movements. Sense of agency tasks have revealed that inadequate or delayed predictions may be correlated with task performance (Hughes, Desantis, & Waszak, 2013; Koreki et al., 2015; Maeda et al., 2013). It has also been hypothesized that impaired prediction ability may play a role in positive symptoms. For example, in the case of auditory hallucinations, there is a reduction in prediction error signaling response in the auditory cortex, particularly during silence, that was associated with severity of auditory verbal hallucinations (Fletcher & Frith, 2009;

Griffiths, Langdon, Le Pelley, & Coltheart, 2014; Horga, Schatz, Abi-Dargham, & Peterson, 2014). Models have proposed that this might be due to recursive feedback from the prefrontal cortex to the auditory cortex that develops vague probability into an explicit percept (Nazimek, Hunter, & Woodruff, 2012). This body of research suggests that deficits in prediction and prediction error coding are likely a global dysfunction in schizophrenia.

Other proposals for the function of feedback connections include providing information about attentional allocation (Reynolds & Heeger, 2009), homogeneity of stimuli (Coen-Cagli, Kohn, & Schwartz, 2015), and the probability that stimuli will be grouped together (Schwartz, Sejnowski, & Dayan, 2009). Computational models can be used to explain the behavior of both single neurons and populations of neurons and allow for the prediction of responses given certain properties of the stimulus and the neurons of interest. By quantifying and reducing neural responding to the output of a series of equations, it becomes easier to understand the effects of a number of different inputs on neural activity, due to the ability to manipulate multiple inputs systematically. Theoretical models, then, allow for an intermediary step between data ascertained from overly simplified experimental paradigms and neural responses to the natural environment. A neurophysiobiologically plausible model can test the hypothesis that perturbation of a single neural mechanism can result in the range of contextual modulation deficits demonstrated behaviorally.

Most models that account for contextual effects in early visual cortex incorporate some form of divisive normalization, dividing the response of a neuron by the summation of the responses of neighboring or similar neurons (Heeger, 1992). Schwartz et al. (2009) proposed one such model to attempt to explain orientation surround effects, specifically in

the tilt illusion, using high-level center-surround segmentation as a regulating factor for gain control. In this model, a center neural unit has a linear tuning represented by an idealized Gaussian tuning curve and a nonlinear divisive gain control that is determined by similarly oriented filters in both the center and the surround. Overall strength of the gain control pool is set by an additive constant; the degree to which surround filters are included in the divisive gain control pool is modulated by the probability that the center and the surround are grouped (a prior developed from natural scene statistics). Perceived orientation is predicted from the population of neurons representing the center stimulus, using a population vector decoding scheme.

Reynolds and Heeger propose a model that accounts for three different neuronal receptive fields: a) a "stimulation field" that accounts only for the specificity of neuron's orientation and spatial preferences, b) a "suppressive field" that accounts for the features and positions that contribute to suppression when presented simultaneously with a preferred stimulus, and c) an "attention field" that accounts for the effects of attention (2009). The model suggests that the stimulus drive is multiplied by the attention field, essentially retuning the population response. This combined stimulus drive and attentional field is then divided by the suppressive drive plus a constant representing the neuron's contrast gain, effectively normalizing the response, to account for the output firing rate. Attention, then, modulates both stimulation and suppression of neurons. Parameters that effect the output in the model include stimulus size relative to the sizes of both the stimulation and suppression fields, features of the stimulus, and features and size of the attentional field. This function is mediated by a parameter representing the response gain, which dictates the maximum potential response. This model predicts that by altering

attention field and stimulus size, the effect of attention will shift from response gain to contrast gain. It also predicts that attention modulates surround suppression, attention effects will be strongest for high contrasts, and that attention may play a role in determining response latency (Reynolds and Heeger, 2009).

An alternative model by Coen-Cagli et al. takes a standard normalization model and adds a factor accounting for whether a neuron interprets an image to be homogenous or heterogenous (2015). In the basic model they adapted, response to an image is determined by drive to the receptive field divided by a denominator that includes the strength of the receptive field normalization pool multiplied by the drive to the normalization pool, as well as the strength of the surround normalization pool multiplied by the drive to the surround normalization pool. Other parameters include relationships between the drive and the spiking rate. The additional factor added by Coen-Cagli amounts to a binary gating parameter on the surround that is determined by the probability that a neuron infers the center and surround to be homogenous or heterogenous, as determined by training on natural image statistics.

It seems likely that the most accurate model is some combination of all of these, probably with an even more complex set of modulating parameters. In these models, feedforward connections are represented by the output response, intracortical, lateral connections are captured in the strength of the gain pool, and feedback connections are determined by probability of grouping in the Schwartz model, the attention field in the Reynolds and Heeger model, and the inference of homogenous and heterogenous in the Coen-Cagli model. Probability of grouping and inference of homogeneity can both be viewed as the high-level predictions that are incorporated into predictive coding, thus,

while these models are not directly represented in terms of iterative processing, they in fact are consistent with this hypothesis. Below is an exploration of visual task performance in schizophrenia, with a focus on how these data are explainable by dysfunctions in recurrent processing.

Surround suppression. The discovery of extra-classical receptive fields (ecRF) by Hubel and Wiesel (1968) brought with it the revelation that the context a stimulus exists in can modulate neuronal response to that stimulus in early visual processing. An ecRF is a region immediately proximal to a classical receptive field that elicits no response when stimulated on its own, but can modulate the response of a cRF when stimulated together. More recent size tuning experiments have offered more support for the ecRF by demonstrating that the maximal response is elicited when a stimulus fills the cRF, but when the stimulus is expanded to fill the cRF and extend into the the ecRF, response diminishes (Angelucci et al., 2002; DeAngelis, Anzai, Ohzawa, & Freeman, 1995).

The amount of this response suppression is dependent on qualities of the stimulus and the surround. Surround suppression is typically stronger when the orientation of patterns the surround is similar to the orientation of the center (Cannon & Fullenkamp, 1991; Cavanaugh, Bair, & Movshon, 2002; DeAngelis et al., 1995; McDonald, Mannion, Goddard, & Clifford, 2010; Williams, Singh, & Smith, 2003; Xing & Heeger, 2000). However, the rules for predicting the interaction between center and surround are complex, depending on the relative contrasts of center and surround (Cavanaugh et al., 2002; Yu, Ponomarev, & Davis, 2004), the location of the stimuli in the visual field (Polat & Sagi, 2007), the particular tuning of the neuron (Alitto & Usrey, 2004), and proximity of the surround to the center (Shushruth et al., 2012; Williams et al., 2003; Yu et al., 2004).

A modern view of surround suppression effects in V1 is that the result from the concerted effort of 1) feed-forward influences from the lateral geniculate nucleus, (Angelucci & Bullier, 2003; DeAngelis et al., 1995; Nassi, Lomber, & Born, 2013; Ozeki, Finn, Schaffer, Miller, & Ferster, 2009; Shushruth et al., 2012), 2) divisive gain control, an inhibitory mechanism in which the response of orientation-selective units in V1 is normalized by the pooled activity of similar units (Schwartz et al., 2009), and 3) tuned inhibitory mechanisms that are regulated by 4) cortico-cortical projections from both higher visual areas and horizontal projections from other areas of V1 potentially tied to γ-amino butyric acid (GABA) (Atallah, Bruns, Carandini, & Scanziani, 2012; Ma et al., 2010; Nienborg et al., 2013; Yoon et al., 2010).

In general, patients tend to display less contextual modulation across a variety of different stimuli (Chen et al., 2008; Michael-Paul Schallmo, Sponheim, & Olman, 2013; Seymour et al., 2013; Tibber et al., 2013). Weaker surround suppression during contrast discrimination tasks in patients with schizophrenia has been observed in several different paradigms (Dakin et al., 2005; Dias et al., 2011; Seymour et al., 2013; Tibber et al., 2013; Yang et al., 2013; Yoon et al., 2009). Current literature on whether patients also experience weaker suppression in other visual domains such a luminance and motion is mixed, with some evidence for increased surround suppression (Chen et al., 2008), and others finding no effect (Tibber et al., 2013; Yang et al., 2013).

Most evidence seems to implicate cortical processing as the origin of these dysfunctions (Dakin et al., 2005; Dias et al., 2011; Seymour et al., 2013; Tibber et al., 2013; Yoon et al., 2009), although the exact timing of cortical dysfunctions is unclear. Early hypotheses suggested that V1 was the likely locus of abnormality given that this is

the first cortical area that is selective for orientation (DeAngelis et al., 1994). In patients with schizophrenia, fMRI studies have shown suppression of BOLD signal to parallel surrounds in V1 but not higher visual areas (Seymour et al., 2013). Psychophysical evidence of deficits in orientation dependent surround suppression but not luminance dependent suppression supports this hypothesis, given that orientation is initially encoded in and fed forward from V1, while luminance, while a modulator of V1 activity, is not generative of V1 signals (Yoon et al., 2009; Yang et al., 2013).   It may be that these dysfunctions are related to more general deficits in inhibitory mechanisms, particularly local inhibition (Yoon et al., 2009). Imaging results suggest that inhibitory neural signals in V1 are disrupted in schizophrenia, which could affect either local inhibition or feedback from higher visual areas (Seymour et al., 2013).

Surround suppression deficits could also be explained by feedback projections carrying information related to whether the center and surround are part of the same stimulus. This could be related to homogeneity as modeled by Coen-Cagli (2015), probability of grouping as modeled by Schwartz (2009), or prediction based on natural image statistics (Spratling, 2012). In the first two cases, weakening the feedback signal in patients with schizophrenia would result in an increased likelihood of viewing the center and the surround as separate entities, which would result in less interaction, particularly in the form of lateral inhibition, between neurons. In the case of a lack of prediction information, none of the response to the center would be subtracted based on redundancies with the surround.

Tilt illusion.   Surround suppression falls under a much broader category of contextual modulation.   One psychophysical task that can be used to probe surround

suppression is the tilt illusion, where an oriented grating target stimulus is presented surrounded by an offset grating (Blakemore, Carpenter, & Georgeson, 1970; Gibson, 1937). Generally, when the difference in orientation between a center grating and a surrounding grating is small, the orientation of the center is perceived as tilting away from the surround (repulsion) in what is known as the direct tilt illusion. When the difference between the center orientation and surrounding orientation is large, the center is perceived at tilting toward the orientation of the surround (attraction), in the indirect tilt illusion. Similarly to surround suppression tasks, contrast and proximity of the central and surrounding gratings can mediate the magnitude of the illusion (Durant & Clifford, 2006; Georgeson, 1973; Qiu, Burton, Kersten, & Olman, 2016; Tolhurst & Thompson, 1975).

Given the findings of reduced surround suppression, it seems likely that similar deficits would be observed in patients with schizophrenia during the tilt illusion, since the two phenomena have a significant overlap in explanation. However, that does not currently seem to be the case. Two studies have found no significant differences in the magnitude of tilt repulsion between patients and healthy controls (Yang et al., 2013; Tibber et al., 2013). One of these studies did report a positive correlation between magnitude of tilt repulsion and duration of illness and symptom severity, which seems counterintuitive given that patient populations tend to experience less contextual modulation (Yang et al., 2013); however, Tibber et al. found no correlation with symptom severity.

The results of studies of the tilt illusion in schizophrenia patients make it difficult to postulate a mechanism for why these results may conflict with surround suppression data. More data is needed in order to deepen our understanding of the nature of the tilt illusion in schizophrenia before many compelling conclusions can be drawn.

Backward masking. Backward masking involves the rapid presentation of two visual stimuli so that the subject is only aware of the second presentation. Schizophrenia patients have been found to require a longer interstimulus interval (ISI) between the two stimuli presentations than healthy controls do to detect the target (Skottun & Skoyles, 2010; Sponheim, Sass, Noukki, & Hegeman, 2013). Because backward masking ISIs are typically on the order of milliseconds, it is thought to rely on mechanisms of the very earliest stages of visual processing (Fahrenfort, Scholte, & Lamme, 2007). Longer ISIs observed in patients with schizophrenia, then, are suggestive of disrupted or slower early visual processing. While there may be some correlation between longer ISI times and the presence of negative, but not positive, symptoms, these deficits are also observed in remitted patients, suggesting that they are likely more trait markers of schizophrenia than state (M. F. Green & Nuechterlein, 1999; M. F. Green, Wynn, Breitmeyer, Mathis, & Nuechterlein, 2011; McClure, 2001).

EEG recordings have suggested that masking impairs an intermediate stage of processing during which signals are being sent back towards early visual cortex, after features have already been detected by V1, suggesting that reentrant processing is necessary for visual awareness (Fahrenfort et al., 2007). Backward masking's reliance on feedback connections may be critical to understanding visual processing deficits in schizophrenia, given the substantial body of evidence suggesting that masking is disrupted in the disorder. Studies using fMRI have suggested that these deficits may be mediated in part by deficient activity and connections involving the lateral occipital complex (LOC) (Green et al., 2009). Green et al. (2005) interpret LOC's role in backward masking as being the first location in the processing chain where there are neurons that prefer the target

stimulus over the mask stimulus and that neurons are integrating information over a relatively extended temporal window. This results in two stimuli with a slightly asynchronous offset being treated as being presented simultaneously. This does not, however, rule out potential upstream dysfunctions before signals arrive in LOC.

Others have suggested that rather than a deficit in LOC, backward masking performance may be driven by generally weak enhancement of target processing that occurs across brain systems in schizophrenia patients, hinging on impaired attentional performance (Herzog, Roinishvili, Chkonia, & Brand, 2013). Still others have associated backward masking deficits with a failure to establish cortical oscillations between 30 Hz and 70 Hz in the visual cortex (Green & Nuechterlein, 1999). Although backward masking was one of the earlier visual dysfunctions studied in schizophrenia, there is more research to be done to both narrow down the potential locus of these dysfunctions as well as relate them to other visual processing impairments.

By altering features of the target stimuli and mask, researchers have probed the different roles of magno- and parvocellular processing in backward masking. A substantial body of literature exists that, once again, suggests magnocellularly driven deficits in backward masking (Butler et al., 2001; Cadenhead, 2002; Michael F. Green et al., 2009), though there may be some parvocellular dysfunction as well (Butler et al., 2001). However, given the crosstalk between the two pathways, parvocellular disruption may also be related magnocellular disruptions, particularly slower signaling of feedback from higher visual areas. These results may also not be related to specific visual pathway at all; as poorer detection occurs across a variety of time points in patient groups, it may actually be

reflective of slower visual signaling in general, both feedforward and feedback (Skottun & Skoyles, 2010).

Contour integration. Contour integration also relies on the iterative nature of visual processing, as it necessitates spatially integrating stimuli that activate neighboring receptive fields to detect edges and coherent lines. This process relies on recurrent processing both for local feature integration and global scene perception (Kovács, 1996; Pettet, 1999). Depending on the arrangement of elements in a scene, early visual cortical responses may be either facilitated or suppressed in the presence of coherent contours (Altmann, Bülthoff, & Kourtzi, 2003; Dumoulin & Hess, 2006; Hansen & Neumann, 2008; Kapadia, Ito, Gilbert, & Westheimer, 1995; Qiu et al., 2016; Roelfsema, Lamme, & Spekreijse, 2004). In a strictly hierarchical, feedforward model, feature processing in V1 should react identically to the local features of the stimulus regardless of global arrangement, and so one explanation is that feedback from areas that are interpreting the image as a whole is modulating responses in V1. Another possible explanation is that horizontal connections within V1 link neurons with a similar orientation preference, resulting in the ability to incorporate information from a much larger area than a single neuron's receptive field (Angelucci et al., 2002; Gilbert, 1992; Malach et al., 1995).

Patients with schizophrenia require elements to be spaced closer to each other in order to detect a contour than do healthy controls (Uhlhaas, Phillips, & Silverstein, 2005), however, patients are not proportionally worse at detecting contours made up of either closely spaced or distantly spaced elements (Keane et al., 2012). Patients are also less adept at detecting contours on a background of random noise (Robol et al., 2013). When a background is made up of elements nearly parallel to those in the contour, however, there

25

is less of a reduction in performance than is seen in controls, as would be consistent with impaired contextual modulation. There is some evidence that these deficits may be specifically related to the presence of disorganized (Silverstein, Kovács, Corry, & Valone, 2000; Uhlhaas et al., 2005), though other work suggests that performance on contour integration tasks does not improve over time, and therefore may not be related to symptomatology (Feigenson, Keane, Roché, & Silverstein, 2014).

The behavioral results suggest that the neural dysfunction underlying contour integration deficits are primarily in local inhibitory connections. Observed deficits with small gaps between elements that do not proportionally increase with distance suggest that dysfunctions are primarily due to these short-range connections as opposed to longer-range faciliatory interactions (Keane et al., 2012). Robol et al.'s results also suggest inhibitory deficits, as the near-parallel background does not suppress the ability to identify a contour as much in patient groups as it does in healthy controls, suggesting a reduction in the suppression of central stimuli that is normally seen when surrounded by parallel flankers (2013). This, however, is in conflict with imaging results, which do not find a difference between patient groups and controls in early visual cortex during these tasks, but do see increased activity in the lateral occipital complex and superior parietal lobule in patients (Steven M. Silverstein et al., 2015). This is indicative of reduced efficiency in processing global form in schizophrenia, which would suggest that contour integration deficits may hinge on feedback signaling. Another potential option is a feedforward deficit not related to activity in early visual areas but to the integrity of connections, resulting in the LOC having to work harder to make sense of the communication, but little work has been done in connectivity analyses of the visual system with schizophrenia patients.

Amodal perception. Amodal perception describes the ability to discern a whole object with only partial sensory information. These tasks include shape discrimination tasks, illusory contour tasks, Mooney face tasks, and figure-ground separation tasks, which all depend on interpreting fragmented parts of a perceptual object as an integrated unit distinct from a surround. While these tasks have some things in common with contour integration, amodal perception may require the use of prior knowledge about stimuli or the environment in order to assign meaning or coherent shape to a stimulus.

Like contour integration, amodal perception also involves both the integration of information from neighboring receptive fields in early visual cortex as well as feedback about global information from higher visual areas (Kourtzi, Tolias, Altmann, Augath, & Logothetis, 2003; Murray, Schrater, & Kersten, 2004; Scholte, Jolij, Fahrenfort, & Lamme, 2008; Supèr, Spekreijse, & Lamme, 2001; Wokke, Vandenbroucke, Scholte, & Lamme, 2013; Yoshino et al., 2006). Early visual areas tend to have less of a response to completed shapes than to simple Gabor patches, suggesting that there is some coding of global form in V1 in addition to local features (Murray, Kersten, Olshausen, Schrater, & Woods, 2002). LOC activity, on the other hand, is increased during the processing of completed shapes as compared to randomly oriented stimuli. One interpretation to link these data is that increased LOC activity is fed back to V1 to modulate early visual activity. Support for the importance of recurrent processing in amodal perception is furthered by the results of MEG studies, in which it has been observed that when a TMS pulse is applied in an early time epoch over LOC, but not V1/V2, overall task performance decreases. A pulse during a later, intermediate time period over V1/V2, but not LOC, also disrupts performance

(Wokke et al., 2013). Electrophysiological studies in monkeys and EEG studies in humans both indicate that in figure-ground separation tasks, V1 activity is identical for both the figure and the ground until about 90ms after stimulus onset. At this point, neural responding in V1 is lower for the background than the figure (Super et al., 2001; Scholte et al., 2008). These data taken together suggest that there is essential processing happening in higher visual areas that is modulating V1 response.

These amodal perception tasks are disrupted in schizophrenia patients. In a Kanizsa Square illusory contour task, where "pac men" shapes are oriented in such a way that the removed wedges are suggestive of a square, patients have a higher threshold for an illusory contour as opposed to a fragmented condition. When combined with performance impairments in response to distractor lines that are indistinguishable from healthy controls, these data are suggestive of a difficulty incorporating illusory contours into shape perception (Keane, Erlikhman, Kastner, Paterno, & Silverstein, 2014). During these illusory shape tasks, patients tend to exhibit a smaller difference of early gamma oscillations in occipital regions to shapes versus fragmented stimuli than do healthy controls, suggesting that they treat the two conditions more similarly (Spencer, 2008). In studies examining visually evoked potentials, patients have delayed and decreased N150 amplitude over the occipital cortex, representing a slower and less accurate response to global stimuli (Johnson, Lowery, Kohler, & Turetsky, 2005). On a Mooney face task, which involves perceptual grouping of fragments based on Gestalt principles, schizophrenia patients perform more poorly, have slower reaction times, and display disrupted synchrony of beta, but not gamma, oscillations (Uhlhaas & Singer, 2006). Amodal perception deficits have also been noted to correlate with the presence of

disorganized symptoms (Keane et al., 2014) and positive symptoms (Uhlhaas & Singer, 2006) and may increase with longer illness duration (Keane, Paterno, Kastner, & Silverstein, 2016)

These dysfunctions in amodal perception are consistent with impaired long-range connectivity between higher visual areas and early visual areas. Results showing a decrease in ability to detect illusory shapes but not an illusory contour suggest that earlier processing responsible for forming contours may be primarily intact, but the ability to integrate those contours into a global form is disrupted, a skill that would conceivably be driven by feedback information about the global distribution of stimuli, suggest that later processing is disrupted in schizophrenia (Keane et al., 2014). There have not been many imaging studies performed specifically with these higher level perceptual grouping tasks in schizophrenia patients, so this is an area that would be a valuable area to dedicate future research studies.

The general deficit of predictive coding in schizophrenia may be related to these recurrent processing dysfunctions. Predictive coding theories suggest that the visual system is able to learn statistical regularities of the natural world. Higher visual areas communicate predictions about stimuli to lower visual areas, allowing the lower areas to essentially disregard any information that confirms those predictions, and focus processing power on information that is in conflict with them (Rao and Ballard, 1999). In this case, early visual neurons would not be responding to the image intensity, but rather to the difference between the expected value and the actual value. Models of predictive coding account for a hierarchical model where each stage predicts the response of the one before it, not after. The prediction error is then sent forward to higher visual areas to improve the

prediction. These stages are occurring concurrently, which results in an iterative loop of feedforward and feedback responses. It has been argued that this type of coding scheme increases efficiency of visual processing, particularly in early areas, and can explain a variety of visual phenomena. Contextual modulation could be the result of feedback signaling expecting the surround to be similar to the central stimulus, which would provide an explanation for facilitation when the center and surround are very different, and suppression when the center and the surround are very similar (Spratling, 2012). Reduced activity in early visual cortex for coherent shapes and contours as compared to random patterns could be the result of higher visual areas indicating that that is the expected grouping of stimuli (Rao and Ballard, 1999).

In the case of iterative processing, this probability of grouping, based either on prediction or stimulus features, corresponds to the strength of inhibitory connections which set the effective gain, while feedback projections correspond to top-down signals (Fogelson, Litvak, Peled, Fernandez-del-Olmo, & Friston, 2014). Dynamic causal modeling studies show that schizophrenia patients have stronger backward connectivity, particularly between the infertemporal region and V5, as well as from V5 to V1, that accounts for abnormal gain control by not modulating synaptic efficacy (Dima, Dietrich, Dillo, & Emrich, 2010; Fogelson et al., 2014). The attenuation of context effects that are reliant on recurrent processing may be accounted for by this lack of modulation.

An inability to modulate recurrent inhibitory connections could potentially be related to concentration of the inhibitory neurotransmitter γ-amino butyric acid (GABA). Reduced GABA has been noted in the visual cortex of patients (Yoon et al., 2010). consistent with the reduction of cortical GABA across the brain (Goto et al., 2009). GABA

is critical for both short-range, horizontal projections and long-range, feedback projections in the case of center-surround interactions. Reductions in GABA, therefore, can contribute to explaining impaired surround suppression, and indeed, GABA levels correlate with the amount of suppression experienced (Yoon et al., 2010). GABA has also been implicated in neuronal selectivity to orientation, which would suggest that reduced GABA may lead to the broadened tuning curves that may be associated with schizophrenia (Edden, Muthukumaraswamy, Freeman, & Singh, 2009; Katzner, Busse, & Carandini, 2011)

Upstream of GABA, glutamate, specifically modulated by the N-methyl-D-aspartate (NMDA) receptor, has also been proposed to play a role in schizophrenia. It is claimed to more fully account for both positive and negative symptoms (Daniel C. Javitt, 2010). When an NMDA antagonist is introduced to the LGN, reductions in neuronal gain occur that are similar to reductions observed in schizophrenia patients, suggesting that there may be an NMDA driven glutamatergic deficit in schizophrenia (Butler et al., 2003; Kwon, Nelson, Toth, & Sur, 1992). In the visual cortex, Cavus et al. reported impaired cortical plasticity that may be driven by a reduction in NMDA receptors (2012). Javitt has proposed that glutamate disruptions in schizophrenia are responsible for GABA-ergic effects (2010).

Implications

Despite perceptual deficits not necessarily being outwardly observable or diagnostic symptoms of schizophrenia, studying them offers the potential findings that may be critical to furthering our understanding the disorder. For example, several studies have found that these deficits may be related to symptomatology of the disease. Contour integration has been found not only to be impaired in schizophrenia patients as compared to controls, but the magnitude of impairments, measured both behaviorally and with event

31

related potentials (ERPs) as a proxy for neural activity, is correlated with disorganized symptoms (Butler et al., 2013; Silverstein et al., 2000; SSilverstein & Keane, 2011). Disorganized symptoms include inappropriate affect, non-constructive behavior, and disorganized thought and speech. ERP deficits in the detection of the Mooney Face illusion have been correlated with negative symptoms of schizophrenia (Uhlhaas & Singer, 2006), as have deficits in contour detection (Walter L. Slaghuis, 2004). This category of symptoms includes flat affect, anhedonia, alogia, and social withdrawal. Spencer et al. has correlated deficits in the Kanizsa Square illusion with positive symptoms, such as hallucinations and delusions (2004). Although there are inconsistencies in the groups of symptoms that segregate with visual deficits, it seems likely that there are some tenable relationships between measured impairments and symptomatology. These inconsistencies may be due to task differences; for example, perhaps early stage visual processing deficits are more related to negative symptoms, while more intermediate stages are related to disorganized symptoms. Given these potential relationships, research into visual perceptual anomalies may provide more insight into the biological action responsible for clinical symptoms. This is of particular interest as psychopathology research moves more toward the Research Domain Criteria (RDoC) approach of describing mental disorders as a continuum of both symptoms and biological markers. The RDoC approach is well-tailored to schizophrenia, given the variety of phenotypic expressions of the disorder, as well as the spectrum of related disorders, and has the potential to greatly improve diagnosis and treatment.

Visual deficits have, in fact, been proposed not just as a correlate of positive symptoms, but as an underlying mechanism of visual hallucinations. It has been suggested

that dysfunctions in connectivity between sensory areas may result in the inability to make high level predictions about the nature of the visual environment. This information might then be incorrectly filled in by areas higher in the sensory processing stream, resulting in misperceptions or hallucinations (Fletcher & Frith, 2009; Sterzer, Mishara, Voss, & Heinz, 2016). As hallucinations are not limited to the visual domain, this hypothesis becomes more compelling when other sensory modalities are considered; it would make sense that all hallucinations would have a similar underpinning. There are correlates of these deficits in the auditory system, including acoustic separation (Coffman, Haigh, Murphy, & Salisbury, 2016), auditory pattern perception (Coffman et al., 2016), auditory subcortical suppression (Lavigne, Menon, & Woodward, 2016), and mismatch negativity (Bodatsch et al., 2011), so this interpretation may be worth further exploration.

Perhaps one of the most compelling reasons for studying visual processing in schizophrenia patients is that dysfunctions in this system may be exemplars of more general dysfunctions in schizophrenia. Patients experience major global cognitive deficits, many of which occur in high level processing in frontal regions of the brain (Schaefer, Giangrande, Weinberger, & Dickinson, 2013), but these deficits may be difficult to characterize neurally given the relative complexity of higher cortical areas. The visual system, on the other hand, currently contains the most thoroughly described neuronal networks in the brain (Felleman & Van Essen, 1991). Overall, its organization is relatively straightforward compared to many other areas of the cortex. Understanding neural function in the canonical architecture of the visual system may elucidate mechanisms that can be generalized to more frontal brain processes (Butler et al., 2008; Phillips and Silverstein, 2013; Yoon et al., 2013).

For example, many have theorized that patients with schizophrenia have general deficits when it comes to the ability to make predictions, on both a neuronal and behavioral level. An inability to integrate and update predictions have been postulated as a mechanism for hallucinations, by allowing for inappropriate inferences about what is occurring in the gap between actual stimuli and expected stimuli (Adams, Stephan, Brown, Frith, & Friston, 2013; Fletcher & Frith, 2009; Horga et al., 2014; Sterzer et al., 2016). Predictive coding errors could also account for the observed mismatch negativity deficits, because if a patient fails to anticipate the next item in a sequence of stimuli, they will not have as dramatic of a response to an unexpected stimulus (Bodatsch et al., 2011; Rentzsch et al., 2015; Wacongne, 2016). Prediction errors may also play a role in observed general attentional deficits by making it more difficult to disregard stimuli that are in keeping with expected patterns, resulting in the need for divided attention focusing on more things (Feldman & Friston, 2010). Problems with reward prediction may lead to generalized learning deficits, as diminishing feedback about whether an outcome is what was expected can slow the process of determining whether a learned stimulus-outcome pairing is correct (Reinen et al., 2014). Reduced "sense of agency" observed in schizophrenia may be due to longer latencies between prediction of an outcome of an intentional act and the observable effect (Koreki et al., 2015). Studying prediction error in the visual system may provide information about a deficit that is consistent across modalities and provide a better understanding of the underlying nature of the disorder.

Contextual modulation deficits occur in schizophrenia patients across a wide range of visual tasks. Weaker surround suppression during contrast discrimination tasks in patients with schizophrenia, meaning that patients perceive the center stimulus more

accurately, has been observed in several different paradigms (Dakin, et al., 2005; Yoon, et al., 2009; Dias et al., 2011; TIbber et al., 2013; Seymour et al., 2013, Yang et al., 2013). Like prediction errors, contextual modulation deficits are not limited to the visual domain, but appear in more cognitively driven tasks as well. These deficits are observed in working memory tasks (MacDonald et al., 2005), inhibition-related tasks (Cohen, Barch, Carter, & Servan-Schreiber, 1999), social cognition (Baez et al., 2013), and reward learning (Reinen et al., 2014). Recent computational modeling efforts are able to explain working memory deficits in terms of local inhibition between tuned neural populations(Murray et al., 2014); the similarity between the working memory model and the perceptual contextual modulation model supports the hypothesis that alteration of a single neural mechanism can produce a number of different behavioral effects associated with schizophrenia.

Finally, visual processing deficits may be of particular importance, because a large number of studies have suggested that similar deficits occur in unaffected first-degree relatives of schizophrenia patients (Avsar et al., 2011; Bedwell, Brown, & Miller, 2003; Chkonia et al., 2010; Davenport, Sponheim, & Stanwyck, 2006; Force, Venables, & Sponheim, 2008; Kéri et al., 2004; Niendam et al., 2014; Michael-Paul Schallmo et al., 2013; Sponheim et al., 2013). This opens visual deficits up as a potential biomarker for schizophrenia, or potentially an endophenotype (Gottesman & Gould, 2003). Further research must be done in order to determine which visual skills may have both sensitivity and specificity for identifying remitted patients, active patients, and first-degree relatives so that they may be targets for future studies into genetic vulnerabilities for schizophrenia.

Chapter 2: Visual Connectivity During Meaningful Object Presentation in Psychosis and Healthy Controls

The range of observed visual deficits in schizophrenia (SZ) span the entirety of the processing stream, from the retina to high-level vision (Silverstein & Rosen, 2015; Silverstein & Thompson, 2015)These deficits have been associated with negative symptoms (Ulhaas et al., 2006; Slaghuis et al., 2004), disorganized symptoms (Silverstein et al, 2000; Silverstein and Keane, 2011; Butler et al., 2013), and have been proposed as a potential underlying mechanism of hallucinations and positive symptoms (Spencer et al, 2004; Fletcher and Frith, 2009; Sterzer et al., 2016). There is substantial evidence that perceptual grouping tasks, which invoke the ability to extract coherent shapes from a meaningless background, are disrupted in SZ (Uhlhaas and Silverstein, 2005; Silverstein and Keane, 2011). In patient groups, performance on these tasks correlates with the presence of disorganized symptoms (Keane et al., 2014), and appear to increase with illness duration (Keane et al., 2016), which suggests that these may be an interesting target for seeking to understand more about the nature of symptoms in the disorder.

Perceptual grouping tasks rely on the ability to integrate information from neighboring receptive fields in early visual areas as well as information about global organization from higher-level areas (Kourtzi et al., 2003; Murray et al; 2004; Scholte et al, 2008; Super et al, 2001; Wokke et al, 203; Yoshino et al, 2006). These tasks include figure-ground segmentation, illusory shapes and contours, and shape discrimination tasks. A system that only relied on a traditional feedforward hierarchical model of visual processing would result in identical V1 responses to similar features, regardless of whether they were presented individually or as part of a coherent global arrangement. Imaging data

suggest that this is not the case; in fact, blood oxygen level dependent (BOLD) response in V1 to stimuli that belong to a completed object is smaller than the response to ungrouped stimuli with the same receptive field properties (Murray et al., 2002). On the other hand, the high level lateral occipital complex (LOC) shows increased activity to completed objects as opposed to simple stimuli (Malach et al., 1995). Data in both humans and monkeys suggest that early neural activity in the occipital cortex is identical for both figure and ground stimuli, but starts to deviate around 90ms after stimulus onset, and are subsequently lower for the ground than the figure, which would be consistent with feedback from a higher area modulating V1 response (Super et al., 2001; Scholte et al., 2008). This idea of feedback modulating early visual response is further supported evidence that deactivating higher visual areas such as V5 or LO early in the visual processing timeline reduces the response to the stimuli in V1 (Hupé et al., 1998; Pascual-Leone & Walsh, 2001; Wokke et al., 2013).

These results suggest the presence of three different types of connections: 1) horizontal connections within V1 linking neurons with proximal receptive fields and similar orientation preferences, resulting in the ability to incorporate information from a much larger area than a single neuron's receptive field; 2) feedforward connections from early visual areas to higher visual areas, consistent with a hierarchical model of visual process, and 3) feedback from higher visual areas to early visual areas interpreting the organization of the image as a whole (Gilbert, 1992; Malach et al., 1993; Angelucci et al., 2002).

This type of perceptual grouping has primarily been probed in SZ patients with illusory contour and shape tasks. While performing these tasks, patients tend to display

both a delayed and decreased N150 amplitude over the occipital cortex (Johnson et al., 2005), a visually evoked potential component generated in the deep layers of the parietal cortex (Di Russo, Martínez, Sereno, Pitzalis, & Hillyard, 2002) This represents a slower and less accurate response to globally biased stimuli that could conceivably be driven by disruptions in any of the three previously mentioned types of connections. Patients also display a smaller difference in gamma oscillations in the occipital region to shapes versus fragmented stimuli than do healthy controls (Spencer, 2008). This is suggestive of SZ patients not incorporating global form information as efficiently as do healthy controls. This hypothesis is further supported by behavioral results that indicate that patients have impairments similar to those of controls when distractor lines are presented near the illusory figure, indicating that their ability to form illusory contours is relatively intact. They did, however, have higher thresholds on the illusory condition as compared to a fragmented condition, revealing a difficulty with using illusory contours to understand global form (Keane et al., 2014).

The pattern of these deficits is consistent with the presence of recurrent processing deficits. A delayed and decreased N150 VEP component could be reflective of weaker or slower feedback signals being incorporated into early visual representations (Johnson et al., 2005). Smaller differences in neural oscillations between contours and fragmented conditions are indicative of a failure to properly modulate early responses to coherent stimuli by not taking global properties into account and treating them more like fragmented stimuli (Spencer, 2008). Keane and colleague's results suggest that local feature processing may be relatively intact, while feedback about global form is disrupted (2014). In a Mooney Face task, which relies on grouping fragmented parts into a coherent whole

based on Gestalt principles, schizophrenia patients have poorer performance, slower reaction times, and disrupted neural synchrony of beta oscillations. These results further support the idea of impaired long-range connectivity (Uhlhaas and Singer, 2006).

Given the observed relationship between deficits in perceptual grouping tasks and symptomatology in SZ, we included both bipolar (BP) and SZ patients to determine whether the observed deficits were related to diagnosis or psychotic symptoms. In order explore the nature of feedforward, feedback, and local connections during perceptual grouping tasks and attempt to localize dysfunctions, we presented these patients with fragmented ambiguous objects during a functional magnetic resonance scanning session. We performed both a general linear model analysis as well as a generalized psychophysiological interaction connectivity analysis to explore disruptions in the relationships between brain areas during visual processing tasks in patients with psychosis.

Methods

Participants

Thirty-four stable outpatients with a diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder and fifteen age- and sex-matched healthy controls were recruited through the Minneapolis VA, Craigslist, and the community. Experimental protocols were approved by the University of Minnesota and Minneapolis VA Institutional Review Boards, and all participants signed a statement of informed consent and were monetarily compensated for their time. Exclusion criteria included English as a second language, mental retardation, current alcohol or drug dependence, current or past central nervous system condition, history of electroconvulsive therapy, history of head injury with

skull fracture or substantial loss of consciousness, age under 18 or over 60, and all standard MRI contraindications. All participants had normal or corrected to normal vision.

Participants were administered the Weschler Adult Intelligence Scale III Vocabulary, Digit Symbol, Block Design, and Digit Span subtests to estimate IQ. The Brief Psychotic Rating Scale (BPRS) was administered as a measure of psychiatric symptomatology, as well as the Sensory Gating Inventory (SGI) as a measure of perceptual experiences. Controls were also administered the Schizotypal Personality Questionnaire. Diagnostic category was determined by a doctoral level clinical psychologist. There was no significant difference between schizophrenia patients and controls on age or IQ. Demographic and clinical data are presented in Table 1.

Group	Age	IQ	Education (Years)	BPRS Total	BPRS Negative Symptoms	BPRS Positive Symptoms	SGI Perceptual Modulation
Schizophrenia	m=46.16	m=99.75	m=13.67	m=40.42	m=3.92	m=8.08	m=1.66
	SD= 9.96	SD=14.5	SD=2.18	SD=9.27	SD=1.08	SD=3.65	SD=0.98
Bipolar	m=48.92	m=98.72	m=14.92	m=37.75	m=3.75	m= 5.17	m=1.81
	SD=10.40	SD=13.65	SD=2.61	SD=9.81	SD=1.71	SD= 1.47	SD=1.43
Control	m=48.1	m=111	m=15.33	m=25.71	m=3	m=4	m=.70
	SD=9.09	SD =6	SD=1	SD=1.4	SD=0	SD=0	SD=.86

Table 1- Demographic and clinical information for schizophrenia, bipolar, and control groups. IQ was estimated by score on the vocabulary, digit symbol, block design, and digit span subtests on the WAIS-III. Only scores of the Perceptual Modulation subscale of the Sensory Gating Inventory were used for this analysis.

Stimuli

Stimuli were presented using PsychoPy software on an iMac running Mac 10.9. Images were 324x324 pixels in size. Images of objects were converted into abstract outlines of seven pixel long, discontinuous line segments using a computational model that emulated neural responses in V1. Orientation of the line segment at a given point in the outline was determined by a winner take all approach of orientation driven neural responding at that point. These outlines were set against a background of parallel seven pixel line segments. The 126 images that were most frequently identified as being recognizable objects by a separate group of healthy college students were labeled as the "meaningful" condition, while 126 images that were frequently reported to be unrecognizable objects were labeled "meaningless" (Figure 1). Meaningful and meaningless stimuli were matched in terms of number of line segments as well as mean orientation across the group of stimuli.
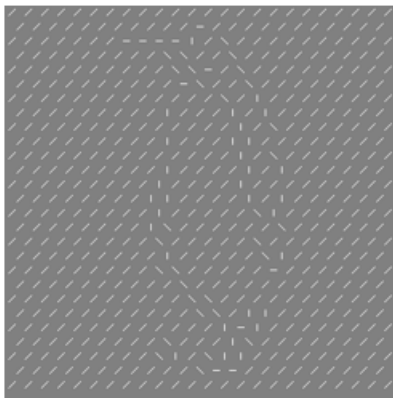
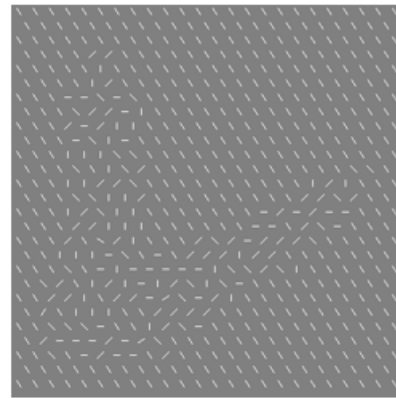A.   B.

Figure 1. A- Example of meaningful stimulus. B- Example of meaningless stimulus. All stimuli were created by transforming pictures obtained from image databases into 7 pixel long oriented line segments based on a model of neuronal responding in V1. Orientation of a line segment at any given point was determined by a winner-take-all approach of orientation driven responding.

fMRI

Stimuli were presented with a NEC NP4100 projector with a resolution of 1024 x 768 pixels and a refresh rate of 60 Hz back-projected onto a translucent screen placed inside the scanner bore. Stimuli were viewed through a mirror placed over the observer's eyes, mounted on the head coil. Viewing distance was 112 cm, with the region images were presented in subtending 8° of visual angle. The mean luminance of the projector was 110 cd/m^2.

Functional MRI data were collected using a 3T Siemens PRISMA system (Siemens, Erlangen, Germany) equipped with a 32-channel head coil. Whole brain EPI data were acquired with a field of view of 208 mm and a matrix size of 88 x 88, resulting in an in-plane resolution of 2.4 mm isotropic. Sixty slices were collected with a 2.4 mm slice thickness. Echo time (TE) was 30 ms, repetition time (TR) was 1.5 s, and flip angle was 75°. Datasets were collected in the transverse direction. One T_1-weighted anatomical image (MP-RAGE) with 1 mm isotropic resolution was also collected sagitally for anatomical reference.

A scanning session consisted of a total of seven functional runs; however, six of these scans were performed to collect data for other studies, and so only one run will be analyzed here. Other scans will be analyzed elsewhere. Each twelve second block contained 8, 1.5 s presentations of either meaningful stimuli, meaningless stimuli, or rest periods presented in random order. Subjects were asked to press one button if the shape on the screen was "tall and skinny" and another button if the shape on the screen was "short and fat" in order to divest them from trying to actively determine image meaning.

Behavioral responses were reported using a fiber-optic button box (Current Designs, Philadelphia, PA)

Preprocessing

Functional data with was preprocessed using Analysis of Functional NeuroImages software (AFNI; Cox, 1996), with the first EPI collected in the anterior-posterior direction used as a reference volume. The motion corrected data were unwarped using AFNI's 3dQwarp function with an EPI collected in the posterior-anterior direction used as reference. EPIs were aligned to the anatomical scan using AFNI's 3dAllineate and spatially smoothed (FWHM = 2 mm).

Analysis of Functional Data

Functional data analysis was conducted using a general linear model via AFNI's 3dDeconvolve function. The BOLD response was modeled using the BLOCK function in 3dDeconvolve. The *a* priori LOC ROIs were defined by the group level contrast across all participants between meaningful stimuli and meaningless stimuli with a voxelwise probability of $p=.001$ and a clusterwise probability of $p=.01$. The individual *a priori* V1 ROIs were defined in two steps. First, an all-visual-activity mask was created by thresholding the contrast of stimulus presentation (regardless of meaning) with baseline by a voxelwise probability of $p=.01$ and clusterwise probability of $p=.05$. This was then limited by a calcarine mask. Average beta weights were calculated in these ROIs for statistical purposes.

Connectivity analysis

Generalized psychophysiological Interactions (gPPI) was used to estimate interregional connectivity based on the correlation between *a priori* seed regions and the variance in other cortical areas with a GLM analysis (Cisler, Bush, & Steele, 2014; McLaren, Ries, Xu, & Johnson, 2012). The effects identified by the original GLM performed above were subtracted out of the functional data, leaving a residual dataset. A PPI term was generated to serve as a regressor in a GLM. This term was created by estimating the physiological response in a seed region by deconvolving the time series from that seed region with its estimated hemodynamic response function (HRF). This estimation of physiological response was multiplied by the event code, resulting in the PPI term. This term was convolved with the estimated HRF response resulting in a regressor at the level of hemodynamic response that could be compared to the residual data from the original GLM analysis. See Figure 2 for an explanation of this analysis. Seed regions included the left LOC, right LOC, and the voxels in an anatomically and functionally defined V1 region active during the task as described above. Correlated cortical activations were thresholded at a voxelwise probability of *p*=.01 and a clusterwise probability of *p*<.05.
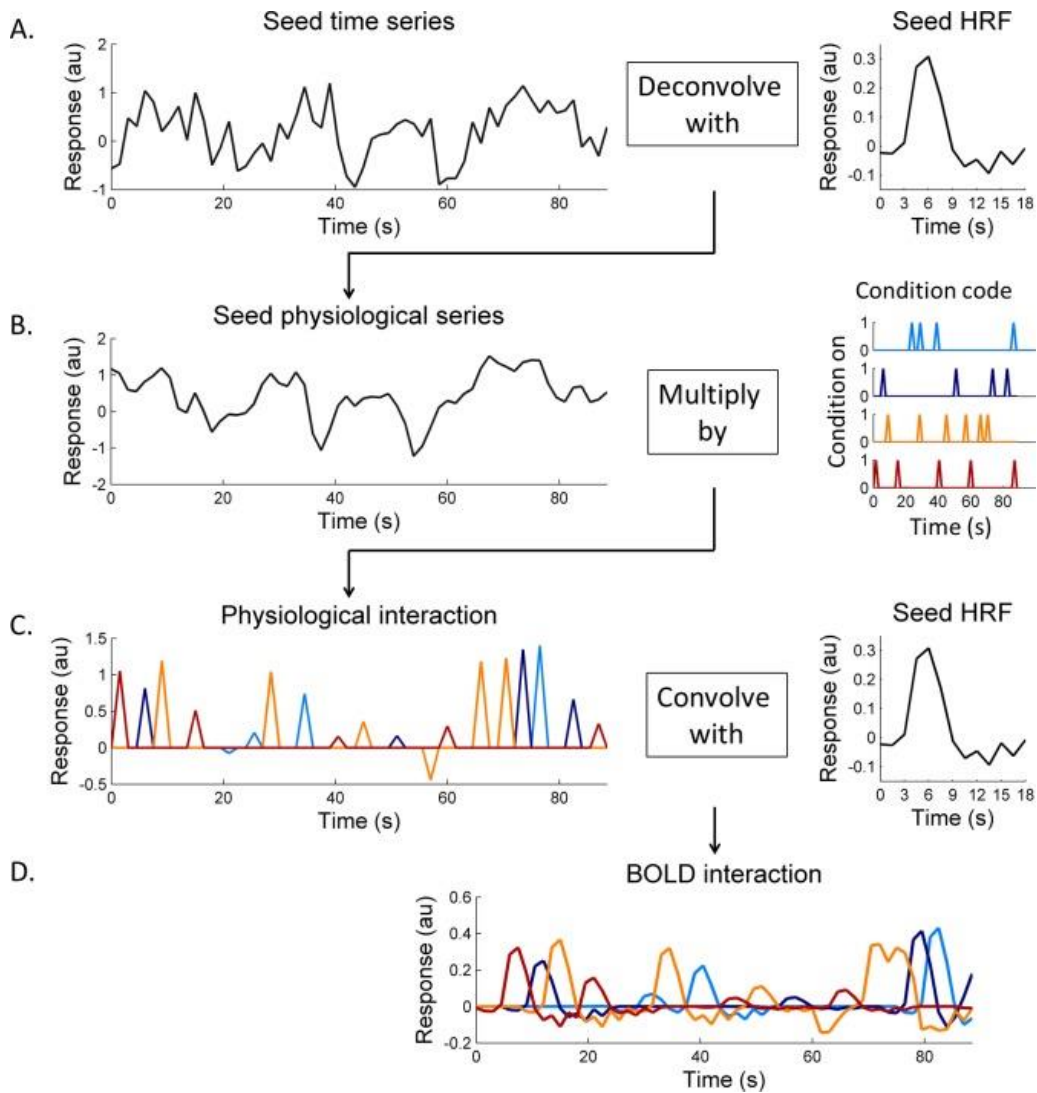
Figure 2. A- The time seed series was deconvolved with an estimated hemodynamic response function. B-The physiological response from A was multiplied by the seed physiological series by the condition code for each condition. C- This interaction was reconvolved with the estimated HRF. D- The BOLD interaction of this terms was compared with the residual time series from other ROIs. (Qiu et al., 2016)

Results

After subjects were excluded due to not performing the task, not foveating on the stimuli, or having no visual response, analyses were performed with twenty five schizophrenia, schizoaffective, and bipolar patients and ten healthy controls. As expected,

patients demonstrated elevations in measures of clinical symptoms. There was a significant difference between diagnostic group on the total score of the Brief Psychotic Rating Scale (F(2)=13.654, *p*=.003), driven by differences between both patient groups and the controls (SZ and CTRL-*p*=.003; BP and CTRL- *p*=.016). There was also a significant difference on the Positive symptom subscale of the BPRS (F(2)=7.254, *p*=.003) due to differences between the schizophrenia group and the other two (SZ and BP- *p*=.019; SZ and CTRL-*p*=.005). No other clinical measures revealed a significant difference between groups. Clinical results are summarized in Table 1.

A contrast between meaningful and meaningless stimuli across all groups revealed two statistically significant clusters representing the right and left lateral occipital complexes along with their corresponding fusiform gyri, hereafter referred to as LO+ (voxelwise probability- *p*= .001, F= 3.921; clusterwise probability- *p*< .01). These clusters were used as ROIs for the group analysis as well as seeds for the psychophysiological (PPI) analysis. In a repeated measures ANOVA, there was no main effect of diagnosis (rLO+- F(2)=.424, *p*=.658, lLO+- F(2)=1.662, *p*=.206) or significant interaction between average BOLD signal change across meaning condition and diagnosis for either the right LO+ (F(2)=.559, *p*=.577) or left LO+ (F(2)=.640, *p*=.534).

Across all participants, there was a significantly larger BOLD response in the V1 ROI to meaningful stimuli than meaningless stimuli, consistent with previous research (F(1)=4.413, *p*=.044) (Qiu et al., 2016; Altmann et al, 2003; Kapadia et al, 1995; Roelfsema et al., 2004; Ban et al., 2006). However, the repeated measures ANOVA did not reveal a main effect of group (F(2) = .239, *p*=.789) or a significant interaction effect

between stimulus condition and diagnostic group (F(2)=.224, *p*=.80). See Figure 3 for
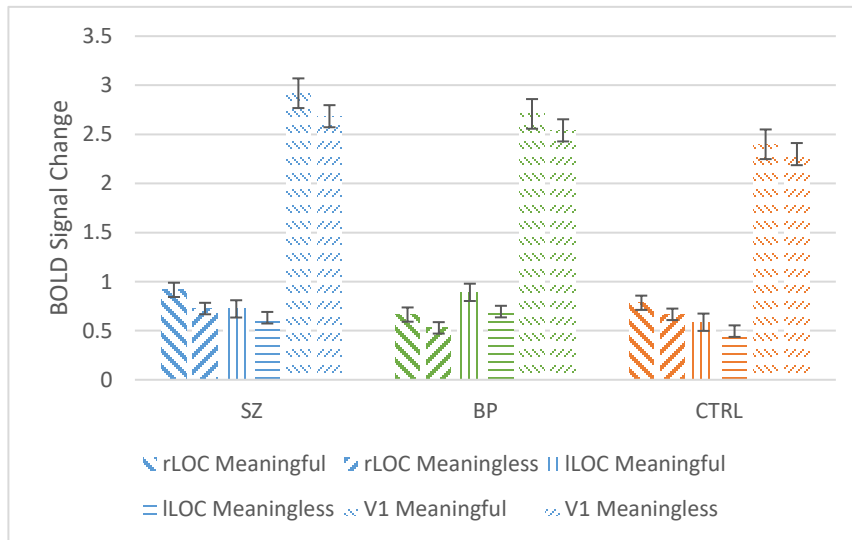
ROIs used in this analysis.

A.
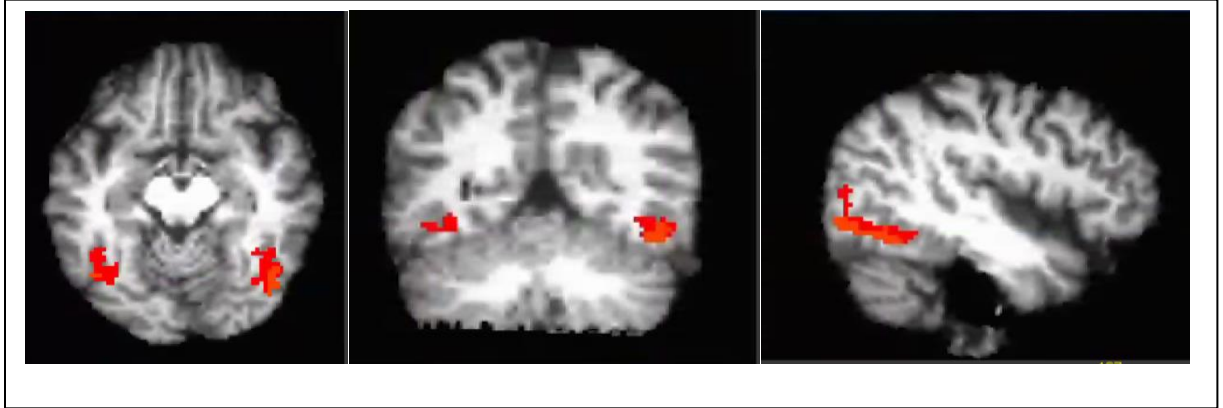
B.
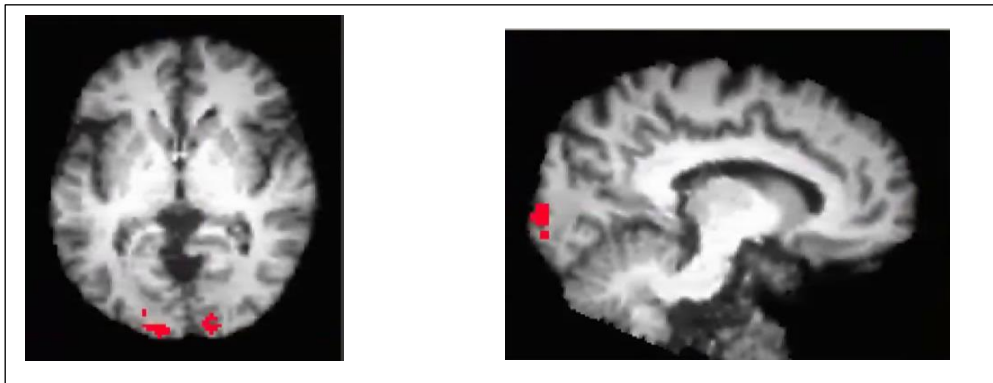
C.

Figure 3. A- Right and left LOC ROIs as determined by a contrast of meaningful and meaningless stimuli. B- A sample V1 ROI created by intersecting areas that were active in an individual subject during presentation of visual stimuli regardless of meaning category with an anatomically defined Brodmann area 17 mask. C- BOLD signal change across groups for each ROI and stimulus condition. All ROIs are statistically significant across meaning category, but there are no group differences or meaning x group interactions. Error bars represent standard error.

We also correlated the magnitude of the difference between BOLD response in V1 and the bilateral LO+ to meaningful and meaningful stimuli with clinical measures. There were no significant correlations between difference magnitudes and clinical symptomatology.

In the psychophysiological interaction (PPI) analysis, the V1 ROI was used as seed regions in the determination of interregional connectivity. Two clusters showed significant differences in correlation with the V1 seed region during presentation of different stimulus categories, one in the right LO+ (voxelwise probability p=.01, clusterwise probability p=.04) and one in the medial frontal gyrus (voxelwise probability p=.01, clusterwise probability p=.08). In a repeated measures ANOVA, the right LO+ region demonstrated a negative correlation with V1 activity for meaningful stimuli and a positive correlation with V1 for meaningless stimuli ($F(1)$=25.977; $p<.001$), but there were no differences between diagnostic groups ($F(2)$=.130, p=.878,). The medial frontal region demonstrated the opposite pattern, with a positive correlation with activity in V1 for meaningful stimuli and a negative correlation with meaningless stimuli ($F(1)$=20.402, $p<0.001$), but no main effect of group ($F(2)$=.483, p=.641,) or meaning by group interaction ($F(2)$=.377, p= .689). See Figure 4 for PPI ROIs used.
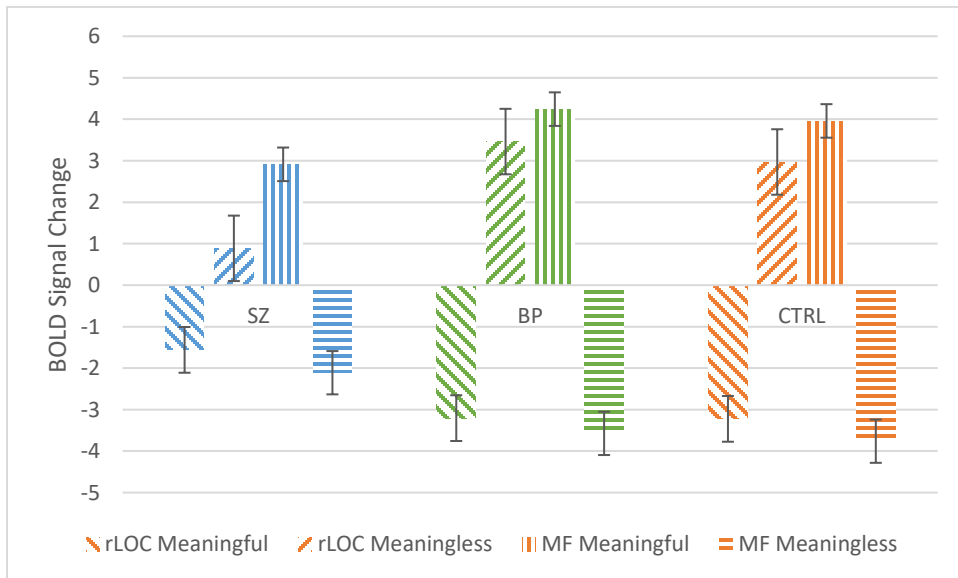
A.
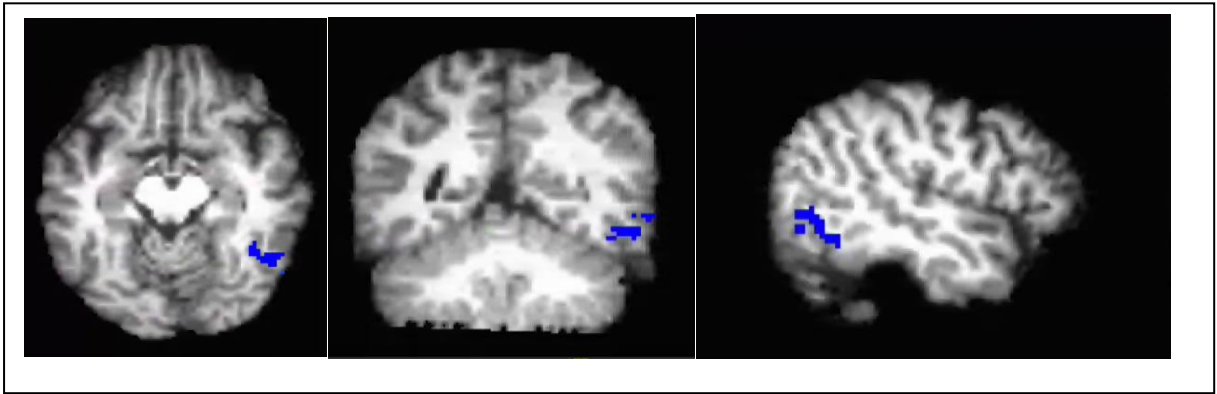
B.
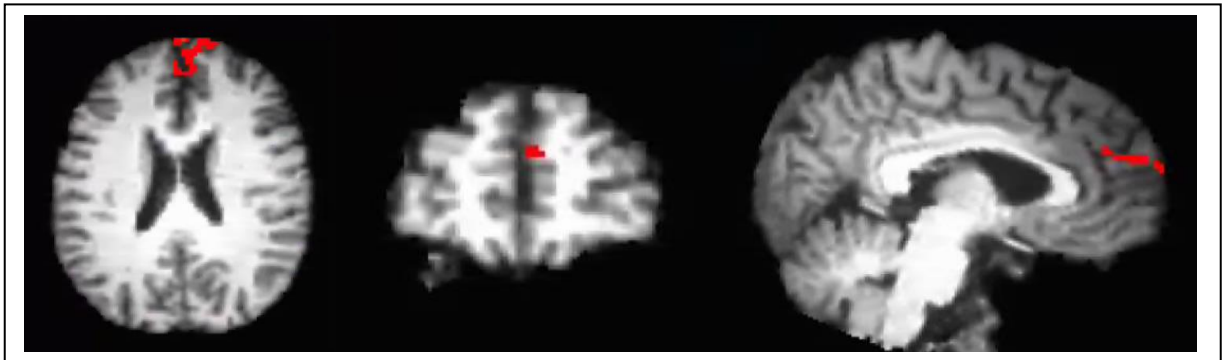
C.

Figure 4. A- Right LOC ROI generated by gPPI analysis using V1 as a seed region. B-Medial frontal ROI

generated by gPPI analysis using V1 as a seed region. C- BOLD signal change across groups in the

identified ROIs. Both ROIs are statistically significant across meaning category, but there are no group differences or meaning x group interactions. Error bars represent standard error.

Discussion

The results of this study did not reveal a significant effect of diagnostic category on BOLD responses in the right LO+, left LO+, or V1 in response to meaningful and meaningless stimuli presentations. It did, however, identify two regions that had variable correlations with V1 activity depending on stimulus meaning.

Increased BOLD signal in V1 to meaningful stimuli as compared to meaningless stimuli, as noted in this study, is consistent with previous studies (Qiu et al., 2016; Altmann et al, 2003; Kapadia et al, 1995; Roelfsema et al., 2004; Ban et al., 2006). This pattern of facilitation seems to be specific to objects that are embedded in background clutter, as our stimuli were (Qiu et al., 2016). This is potentially inconsistent with a predictive coding model in which higher visual areas specialized for object recognition use prior knowledge to infer characteristics of a stimulus, and then use those predictions in early visual areas to disregard expected inputs (Mumford, 1992; Murray et al., 2004; Rao & Ballard, 1999). If those predictions are being used to enhance the figure and suppress the background, however, it could result in an increase in V1 activation to meaningful stimuli if meaning helps determine the extent of figure-ground segregation. Most previous research in early response differences contrasts stimuli that either can or cannot be segmented from the background, as opposed to this study, in which both meaningful and meaningless conditions had strong segmentation cues, so it is difficult to compare our results with previous studies. Our results may reflect a mechanism by which V1 extracts more specific or detailed feature information in order to identify an object in background clutter than

when presented with a coherent shape that is non-recognizable. No significant difference in V1 activation between patient and control groups is also consistent with previous research (Silverstein et al., 2015).

Previous studies that have suggested differences in the lateral occipital complex in schizophrenia patients have primarily relied on measures of perceptual closure (Doniger et al., 2002; Harvey et al., 2011), contour integration (Silverstein et al., 2015), or backward masking and visual awareness (Green et al., 2009), all of which rely more on the processing of shape as opposed to the processing of meaning. One study by Wynn et al. did use objects and scrambled objects as their stimuli, a task far more reliant on object recognition or identification, and found no differences in magnitude of LO+ activation between schizophrenia patients and controls (2008). These results suggest that dysfunctions in LO+ in schizophrenia may be more related to processing coherent global form than extracting meaning from those forms.

A lack of statistically significant group differences in any of our analyses has a few possible explanations. The first is simply insufficient sample size. Several analyses were suggestive of developing trends in the correlations between symptom clusters, so it is possible that with a larger group of subjects or recruiting specifically for variability in symptoms, we may be able to capture differences that segregate not with diagnostic category, but with symptom severity. For example, a trend toward negative correlations existed in the relationship between BOLD activations to both meaningful and meaningless stimuli in the right LO+ ROI and score on the perceptual modulation index of the Sensory Gating Inventory. There was also a trend toward a negative correlation between the gPPI BOLD activations in the medial frontal cluster for meaningless stimuli and severity of

perceptual modulation symptoms, as well as a small positive correlation between magnitude of difference in the gPPI BOLD activation in this area and these symptoms. These results indicate that it may be of more value to study symptomatology as opposed to diagnosis. There is currently a conflicting body of evidence regarding which symptom clusters are most highly related to visual deficits, with some evidence pointing toward negative symptoms (Ulhaas and Singer, 2006; Slaghuis et al., 2004) some pointing toward disorganized symptoms (Silverstein et al, 2000; Silverstein and Keane, 2011; Butler et al., 2013) and somewhat fewer studies suggesting a relationship with positive symptoms (Spencer et al, 2004; Fletcher and Frith, 2009; Sterzer et al., 2016). These inconsistent results indicate that the relationship between visual processing and cross-diagnostic symptomatology may be an interesting one for further exploration.

The results from the generalized PPI analysis can be interpreted as indicating what brain areas are differentially correlated with the seed region during presentation of one stimulus type as compared to the other. It is not reflective of which areas are generally correlated with the seed regions across all conditions. When V1 was used as the seed region, two areas displayed differential coupling: the right LO+ and a cluster in the medial frontal cortex. The right LO+ was negatively correlated with V1 activity for meaningful stimuli, but positively correlated with V1 when the participant was viewing meaningless stimuli. This analysis does not allow for determinations of directionality, so it is possible that this is due to either weaker feedforward signals or feedback signals, or potentially both. This may be reflective of less need for frequent revision of a prediction formed by the right LO+ when the stimulus is clearly recognizable.

The identified medial frontal cluster is roughly consistent with Brodmann area 9, which has a large range of proposed functions. In this case, the correlation between activity was positive between this cluster and V1 for meaningful stimuli and negative for meaningless stimuli. Previous research has suggested that this area may play a role in overriding automatic responses (Kübler, Dixon, & Garavan, 2006). It may be that subjects are experiencing more need to suppress an automatic response of identifying the object when it is clearly recognizable in order to respond correctly to the shape features they are being asked to attend to, while automatic recognition or naming is not as prevalent when the stimuli are meaningless. This area has also been proposed to play a role in error detection (Chevrier, Noseworthy, & Schachar, 2007), so it may be involved in comparing predictions about stimuli to feature information coded by V1, though the directionality of the relationship conflicts with the theory of less prediction updating occurring for meaningful stimuli as proposed above. The area's potential role in working memory (Pochon et al., 2002; Raye, Johnson, Mitchell, Reeder, & Greene, 2002; Zhang, Leung, & Johnson, 2003) and spatial memory (Leung, Gore, & Goldman-Rakic, 2002; Slotnick & Moo, 2006) may also be related to predictive coding errors by holding the template that predictions are being compared to. Again, the direction of this relationship would suggest that stronger signaling is occurring between the medial frontal cortex and V1 for meaningful stimuli, which would be indicative of more comparisons and updating to the template in this condition.

Given the possible implications of the relationships between these areas identified by the gPPI analysis. the lack of between group differences in these regions is potentially in conflict with the idea of impaired feedback signaling in schizophrenia patients.

However, these gPPI ROIs were identified by whole brain analyses, so any areas where a between group difference had a large enough magnitude to cancel out when collapsing across groups would not be identified. Also, given our sample sizes, any small effects will be difficult to identify. The task that we asked participants to respond to, whether a shape was short and fat or tall and skinny, might have resulted in eye movements around the image, despite a fixation mark, which likely diluted the strength of activations in retinotopically organized regions like V1.

The results of this study suggest that greater understanding of visual processing abnormalities in psychosis may be found in studies of symptomatology as opposed to diagnosis. As such, it may be of value in the future to intentionally recruit participants that represent a range of behaviors or scores on symptom evaluations. It is also clear that there is a dearth of evidence examining object meaning beyond coherent shapes, with only one previous study that we know of looking at differences between objects and scrambled objects. Finally, the generalized PPI analysis done in this study has interesting implications for the general nature of iterative processing in vision, suggesting that this method of analysis may be a fruitful and important avenue in future studies of the visual system.

Chapter 3- Computational Modeling of the Tilt Illusion in Schizophrenia Patients and First-Degree Relatives

A substantial body of evidence indicates deficits in contextual modulation, a phenomenon in which response to a stimulus is somehow altered by other stimuli presented simultaneously or in close temporal proximity, in patients with schizophrenia (SZ). These deficits are observed across a range of both cognitive and sensory processing tasks, including working memory tasks (Macdonald, 2005), inhibition-related tasks (Cohen et al., 1999), social cognition (Baez et al., 2013), reward learning (Reinen et al., 2014), and vision (Dakin et al., 2005; Yoon et al., 2009; Dias et al., 2011; TIbber et al., 2013; Seymour et al., 2013, Yang et al., 2013; Schallmo et al., 2013). It may be that a single mechanism related to an inability to incorporate information from context underlies this group of deficits in SZ. In the visual domain, contextual modulation deficits in schizophrenia patients have been observed when manipulating contrast (Dakin et al., 2005; Schallmo et al., 2013; Yang et al., 2013; Tibber et al., 2013), orientation (Schallmo et al., 2013; Seymour et al., 2013; Yoon et al., 2009), and size (Tibber et al., 2013). Similar impairments, though typically not quite as severe, have also been observed in the first-degree relatives of SZ patients, suggesting that visual processing dysfunctions, and contextual modulation in particular, may represent a genetic vulnerability to the disorder (Avsar et al., 2011; Bedwell et al., 2003; Chkonia et al., 2010; Keri et al. 2005).

Visual contextual modulation often results in visual illusions, manifestations of contextual information altering our perceptions to no longer accurately reflect the physical properties of a stimulus. For example, when a center stimulus and a surround have only slightly offset orientations, the orientation of the center seems to be tilted away from the surround; when the two orientations are considerably different, the center orientation seems

to tilt toward the surround. This phenomenon is known as the tilt illusion, and has long been studied both behaviorally (Goddard, Clifford, & Solomon, 2008; Wenderoth & Johnstone, 1988; Westheimer, 1990) and neurally (Cavanaugh et al., 2002; Levitt & Lund, 1997; Li, Thier, & Wehrhahn, 2000; Sengpiel, Sen, & Blakemore, 1997). There is evidence that changes in tuning curves of individual orientation-selective neurons of the early visual system in presence of a surround may be driving this bias, but the underlying mechanism of these tuning curve shifts is currently unclear (Blakemore et al., 1970; Blakemore & Tobin, 1972; Clifford, Wenderoth, & Spehar, 2000; Gilbert & Wiesel, 1990; Schwartz, Hsu, & Dayan, 2007).

Most models for the tilt illusion incorporate some form of divisive normalization, an inhibitory mechanism in which the response of units in V1 is normalized by the pooled activity of similar units (Heeger, 1992). This inhibition occurs through local, horizontal connections within V1, though the strength of the gain pool may be determined by other factors. Divisive normalization accounts for the non-linear response patterns of neurons in early visual cortex by rescaling the input by the shared response of a neuronal population (Carandini & Heeger, 2012).

Models have also proposed some sort of long-range feedback signal from higher areas of the visual cortex. Schwartz et al. suggest that this signal functions to provide information on the probability that the center and the surround should be grouped and interpreted as a single element, which would affect the gain control pool by setting the gain control of the center and the surround to be the same (single element) or different (different elements) (2009). Reynolds and Heeger also included a long-range feedback term that determines gain control strength, but in their model it is determined by attentional resources

directed to an element. Typically attention is more focused at a central, foveal target than at the periphery, which would set different gain control parameters for center and surround (2012). Coen-Cagli et al.'s long-range feedback is related to the degree to which the center and the surround are perceived to be homogenous and helps define a flexible normalization model (2015).

These models offer a robust way of study orientation related contextual modulation deficits in schizophrenia. Traditional psychophysical and imaging experiments make it difficult to segregate the locus of abnormal responses; it is difficult to determine what atypical responses are being driven by long-range feedback from other areas of the visual system, strength of gain control driven by local inhibitory connections, or differences in tuning curve width. Computational modeling provides the ability to manipulate a variety of parameters in order to determine which ones are more likely to be driving observed deficits.

In schizophrenia, the canonical architecture of V1 allows for the study of not only visual processing deficits, but potentially generalized deficits that occur across domains. For example, contextual modulation is disrupted in the visual system in addition to a variety of more cognitive processing, suggesting that there may be some shared mechanism to these impairments. Models that are developed or applied in the visual system may be applicable to other areas of the brain and used to increase our understanding of neuronal variations in the disorder.

We fit an adapted version of Schwartz et al.'s computational model describing tilt biases as a function of grouping probability of the center and the surround. This model was fit to data collected from SZ patients, their first-degree relatives, and controls in an

effort to localize the disruptions occurring in SZ during orientation driven contextual modulation.

Methods

Thirty-three SZ patients, 21 first-degree relatives of schizophrenia patients, and 25 controls completed the experiment. Experimental protocols were approved by the University of Minnesota and Minneapolis VA Institutional Review Boards, and all participants signed a statement of informed consent and were monetarily compensated for their time. Exclusion criteria included English as a second language, mental retardation, current alcohol or drug dependence, current or past central nervous system condition, history of electroconvulsive therapy, history of head injury with skull fracture or substantial loss of consciousness, and age under 18 or over 60. All participants had normal or corrected to normal vision. Diagnostic category was determined by a doctoral level clinical psychologist.

Visual stimuli were generated using PsychoPy software (Peirce, 2007) and were presented on a high-resolution monitor (1280x1024 pixels, 60 Hz refresh rate, NEC MultiSync LCD 2190 uxi, NEC Corporation, Tokyo, Japan) connected to a Mac Mini (Apple, Inc., Cupertino, CA). Observers were seated 62 cm from the monitor. Subjects indicated their responses on a keyboard.

Procedures

Stimuli were presented in the center of the visual field, and subjects were asked to indicate via keyboard whether the orientation of the central grating was tilted clockwise or counterclockwise with respect to vertical. Presentation duration was 250 ms, and the

subject advanced to the next trial manually with a button response. Visual fixation was directed to the center of the screen with a fixation cross at all times.

Stimuli consisted of circular center gratings surrounded by a grated annulus (Figure 1). The relative orientations between the center and surround gratings varied between 0 and 90 degrees. The center grating had a diameter of 1° of visual angle, while the annulus grating had a diameter of 3°. Both gratings had a spatial frequency of 2 cycles per degree.
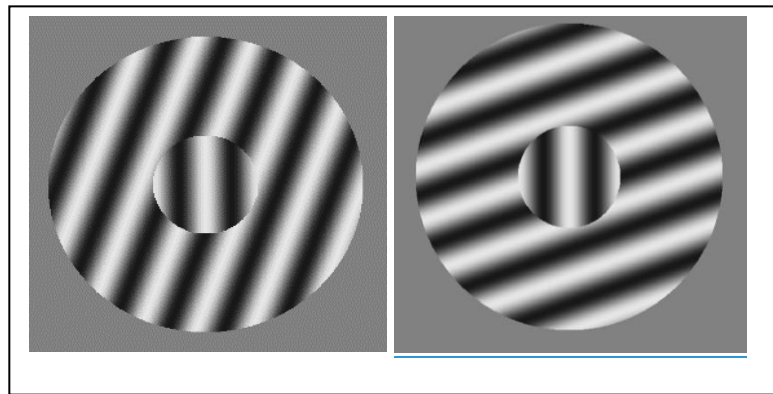

Figure 1. Stimuli examples for the tilt illusion task. Offset between center orientation and surround orientation varied between 0 and 90 degrees. Participants were asked to indicate whether the center grating was oriented to the left or right of vertical.

Subjective vertical was determined by manipulating the orientation of the center grating based on a double-staircase method. This method allowed for an estimate of bias from vertical. For each presentation of seven relative orientations, the psychophysically measured subjective vertical was compared to the subjective vertical obtained from the no surround condition, subtracting out the subject's inherent bias from true vertical. This difference was used as a measurement of the bias for a given orientation.

Data from each orientation for each diagnostic group were fit to a modified Schwartz model in an attempt to highlight parameters with different model estimates. This model accounts

for the role of divisive normalization and segmentation of the center and surround stimuli in determining the strength of modulation of the surround on perception of the center orientation. The estimate of the normalized neural response of the center is calculated by

$$E(g_{ci}|l_{ci}, l_{si}) = \frac{l_{ci}}{\sqrt{l}} \cdot \frac{B(\frac{n}{2} - \frac{1}{2}, l)}{B(\frac{n}{2} - 1, l)}$$

The second term in this equation is a modified Bessel function of the second kind, a solution for a differential equation that functions as a constant of proportionality in this equation. l_{ci} is a filter response of the central detector tuned to a preferred orientation ϕ_{ci} with a tuning curve width of ω.

$$l_{ci} = \exp(-(\phi_{ci} - \theta_c)^2/2\omega^2)$$

l_{si} is the response to the surround stimuli with an orientation of θ_s.

$$l_{si} = \exp(-(\phi_{ci} - \theta_s)^2/2\omega^2)$$

l represents the divisive normalization factor

$$l = \sqrt{l_{ci}^2 + (n-1)l_{si}^2 + k}$$

where n represents the strength of the surround's influence on the gain pool and k is an additive constant that represents the strength of gain control in the absence of any modulating factors.

The segmentation factor is determined by

$$p[g] = \frac{1}{\sqrt{2\pi\sigma^2}} \exp(-g^2/2\sigma^2)$$

Where σ^2 is a function of λ, which controls the steepness of the probability a neuron will assign a stimulus and surround to the same perceptual group.

Results

Seventeen participants were excluded on the basis of demonstrating no psychophysical tilt curves (SZ=3, SZR = 6, CTRL = 8). Although there were no significant differences between the magnitude of tilt repulsion bias (p>.176), there are differences in the shape of the curve between groups. Tilt bias reached a maximum at 15 degrees offset for the SZR group (mean = 3.09°), but peaked at 30 degrees for the SZ and CTRL groups (mean = 3.40°; mean = 2.87°). SZ and SZR groups also displayed more of a peak at the maximum tilt bias, while CTRL demonstrated more of a plateau pattern. All three groups displayed maximum tilt attraction at a 75 degree offset between center and surround orientation (Figure 2A).

The computational model of the tilt illusion proposed by Schwartz et al. (2009) relies on two groups of components to characterize center/surround interactions: probability of segmentation and divisive normalization. Probability of segmentation is determined by the relative orientations of the center and surround, which contributes to whether the center and surround are co-assigned to the same gain control pool. The divisive normalization term is comprised of several factors, including baseline strength of gain control, the relative sizes of the center and surround, and the tuning curve width.

Given that our experiment collected only seven points of data, we reduced the number of parameters in Schwartz's model in order to be able to fit the data. The stimulus properties were fixed and the same tuning curve width was assigned to both the center and

surround to represent orientation coding in V1. We allowed four free parameters to find the best fit of this model to describe our data. Three contributed to setting the divisive normalization curve and one contributed to segmentation probability. See Figure 2B for model estimations.

There was a significant between groups difference for λ, the parameter representing how sensitive to orientation the grouping term is ($p<.001$, F=11.96). This group difference was driven by the SZR group. Although the one-way ANOVA was not statistically significant, the *k* parameter, representing the baseline level of gain control, did significantly deviate from the control subject parameters for the SZ group (Figure 2C).
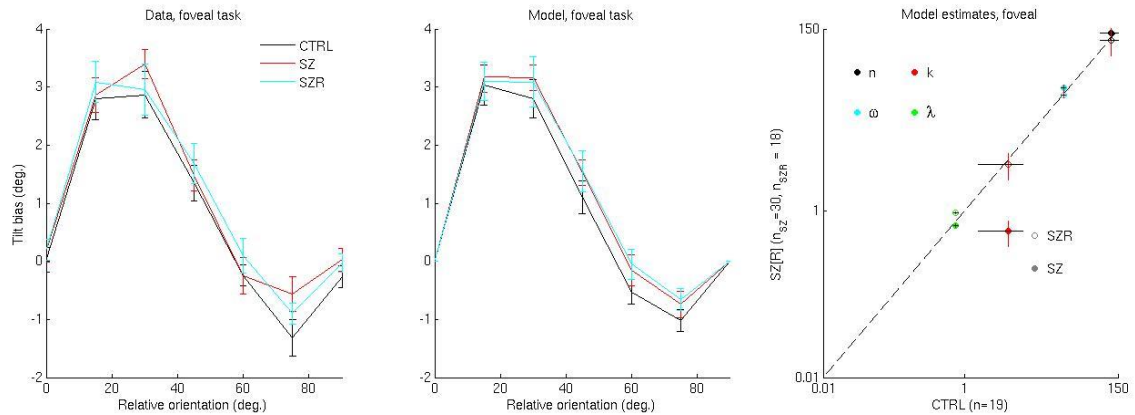

Figure 2. A- Actual tilt bias curves obtained from the psychophysical experiment. Colors represent diagnostic group. B- The predicted response curves for each group using the computational model described above. C- The estimates for each free parameter in the model. The-x axis represents the average fit parameters of the control group, while the y-axis represents the average fit parameters for the SZR and SZ groups. The dotted line indicates where parameter estimates are the same across groups; points that deviate from the line are parameters that have different estimated values for one of the clinical groups and controls.

Discussion

In order to understand mechanisms driving deficits in contextual modulation in schizophrenia patients, we applied a modified version of the Schwartz model to foveal tilt illusion data in patients, first-degree relatives, and controls. The SZR group was significantly more sensitive to orientation when determining the probability of grouping than either the SZ patients or the controls. The schizophrenia group deviated from the estimates of the control and SZR groups on the *k* parameter, an additive constant representing the general strength of divisive normalization.

The difference in the *k* parameter suggests that SZ patients experience a lower baseline level of divisive normalization, which is consistent with previous findings (Barch et al., 2012; Butler & Javitt, 2005; Slaghuis, 1998). Deficits in this stage may be indicative of dysfunctions in either the lateral geniculate nucleus or the input layer of V1 (Webb et al., 2005). Two main theories have been proposed for impaired gain control in schizophrenia: magnocellular visual pathway impairments and neurotransmitter imbalances. Visual processing deficits in SZ have been particularly noted with stimuli that bias processing toward the magnocellular pathway (Bedwell et al., 2003; Calderone et al., 2013; Martínez et al., 2008), which often carries information about low spatial frequency, low contrast, large stimuli (Steinman et al., 1997), though other results conflict with these findings (Skottun & Skoyles, 2007). Given the high contrast of our stimuli (70%), it is reasonable to assume that the magnocellular pathway would be saturated in this case and results are driven primarily by the high contrast, high spatial frequency parvocellular pathway (Jeffries et al., 2014). Neurons in the parvocellular pathway experience less gain control than to magnocellular neurons (Butler, Silverstein, & Dakin, 2008), so one potential interpretation of these data is that healthy controls are still experiencing magnocellularly

driven gain control due to cross-talk between the pathways, while under-responsive magnocellular pathways in SZ patients are influencing gain control less.

Lower baseline divisive normalization could also potentially be driven by disrupted neurotransmitter systems. N-methyl d-aspartate (NMDA), a glutamatergic receptor, has been implicated in gain control by enhancing both responses to isolated visual stimuli as well as lateral inhibition (Daw, Stein, & Fox, 1993). Introduction of an NMDA antagonist produces response curves very similar to those in SZ patients (Butler et al., 2007; Butler & Javitt, 2005; Fox, Sato, & Daw, 1990; Kwon et al., 1992). NMDA has consistently been proposed to be disrupted in SZ patients, with evidence stemming from NMDA receptor antagonist studies in animals (Bygrave et al., 2016; Javitt & Frusciante, 1997; Javitt, Jayachandra, Lindsley, Specht, & Schroeder, 2000; Newcomer et al., 1999; Olney, Newcomer, & Farber, 1999) and ketamine challenge studies in humans (Corlett, Honey, & Fletcher, 2016; de la Salle et al., 2016; Ebert, Haussleiter, Juckel, Brüne, & Roser, 2012; Powers, Gancsos, Finn, Morgan, & Corlett, 2015). Introduction of NMDA antagonists also results in downstream disruptions in in the inhibitory neurotransmitter γ-Aminobutyric acid (GABA) (Marsden, Beattie, Friedenthal, & Carroll, 2007; Xue et al., 2011), which has been shown to mediate lateral inhibition in contextual modulation (Cavanaugh et al., 2002; Meese, Summers, Holmes, & Wallis, 2007; Schwabe, Obermayer, Angelucci, & Bressloff, 2006). Reduced GABA has been noted in the visual system of SZ patients (Yoon et al., 2010). Parvalbumin-positive (PV+) GABAergic neurons appear to modulate early, un-tuned suppression, while Somatostatin-positive (SO+) neurons play more of a role in later-stage, specifically turned modulation (Adesnik, Bruns, Taniguchi, Huang, & Scanziani,

2012; Ma et al., 2010). A general deficit in gain control would likely be due to the effects of the untuned PV+ neurons.

Visual processing deficits have been suggested as an endophenotype of schizophrenia, a heritable biomarker that segregates with illness and has a higher rate within affected families (Gottesman; Keri 2006). The parameter estimates from this experiment, specifically the λ parameter is consistent with a large body of evidence proposing impairments in family members of patients (Avsar et al., 2011; Bedwell et al., 2003; Chkonia et al., 2010; Green, Nuechterlein, & Breitmeyer, 1997; Green, Nuechterlein, Breitmeyer, & Mintz, 2006). These results are indicative that generally deficient divisive normalization might represent a genetic vulnerability to SZ.

Because we collapsed the term for width of the tuning curves for the center and the surround into a single parameter, this model is only appropriate for responses originating in V1, where the widths of tuning curves are more consistent. If responses are originating from more mid-level or high-level areas, this model will fail to capture those nuances. The design of the stimuli, specifically keeping contrast stable between the center and the surround, means that the only segmentation cues being provided are those derived from orientation differences. Segmentation cues play a role in determining the probability of grouping term in the Schwartz model, which is conceivably at least partially driven by top-down mechanisms. Perceptual grouping has been shown to be disrupted in SZ (Johnson et al., 2005; Keane et al., 2014; Uhlhaas & Silverstein, 2005), however, there was no significant difference for the segmentation term between patients and controls. It is possible that solely using orientation as a segmentation cue was no enough to drive this effect; using contrast manipulations or depth cues to strengthen segmentation cues may

result in more opportunities to capture this difference (Qiu, Kersten, & Olman, 2013). There was a significant difference between first-degree relatives and the other two groups, suggesting that visual feedback signals might function as a biomarker of schizophrenia. Other models of contextual modulation have proposed alternative functions for feedback signaling, including homogeneity (Coen-Cagli et al., 2015) and attention (Reynolds and Heeger, 1999). There is a possibility that using segmentation cues to drive the feedback signaling may not be the most effective way of feedback differences.

In conclusion, the results from this study indicate that the overall strength of the gain control pool is weaker in patients with schizophrenia and their first-degree relatives. Functionally, this may manifest in reduced contextual modulation in these groups, and potentially explain a variety of observed dysfunctions across cognitive domains. These dysfunctions also offer potential as an endophenotype of schizophrenia, and further research should be done to characterize the effect in family members.

Chapter 4- Modulation of the Neural Correlates of Conditioned Fear Generalization by D-cycloserine

The generalization of classically conditioned fear, a phenomenon in which fear responses conditioned to one stimulus paired with an aversive outcome are extended to a range of similar stimuli, is a normative response to fearful situations that is seen to be an adaptive mechanism of avoiding potentially dangerous situations (Armony et al., 1997). Recent studies have begun to elucidate some of the neural mechanisms associated with fear generalization. Gradients of reactivity formed by BOLD responses to a conditioned danger cue, a conditioned safety cue, and parametrically varying intermediary stimuli, have been observed in the bilateral anterior insula, the dorsomedial prefrontal cortex, the right middle frontal gyrus, thalamus, anterior cingulate cortex, bilateral ventral hippocamus, ventromedial prefrontal cortex, and precuneus (Dunsmoor et al., 2011; Greenberg et al., 2013; Lissek et al., 2014). Similar gradients have also been observed in skin conductance response, startle magnitude, and behavioral anxiety ratings (Lissek et al, 2008; Dunsmoor et al., 2009).

Although fear generalization is adaptive, overgeneralization of conditioned fear to safe stimuli can be pathological and has been associated with panic disorder (Lissek et al., 2010), generalized anxiety disorder (Lissek et al., 2014; Greenberg et al., 2013), and posttraumatic stress disorder (Morey et al., 2015; Kasckurkin et al., 2017). Given this association, reducing overgeneralization of conditioned fear could be a potentially viable target of novel treatments for anxiety disorders. This type of treatment would not necessarily reduce fear to a specific threat cue, but would potentially reduce fear to a broad range of resembling stimuli.

Because overgeneralization of conditioned fear is a maladaptive form of learning, modulating the learning process may prove to be a fruitful avenue of research. On a synaptic level, learning is dependent on the N-methyl-D-aspertate receptor (NMDAR), a glutamatergic receptor that plays a vital role in synaptic plasticity (Collingridge, 1987). One pharmacological compound used to modulate NMDA-mediated learning is D-cycloserine, a partial agonist of the NMDAR glycine site that functions as a cognitive enhancer. DCS has been used to augment exposure therapy by facilitating learning during exposure sessions (Ressler et al., 2004; Guastella et al., 2007). In animals, it has been shown to increase fear learning if given just prior to acquisition, as well as reducing generalization of classical conditioning (Thompson and Disterhoft, 1997).

We applied a validated fMRI paradigm for the assessment of generalized conditioned fear, and tested the effects of DCS on behavioral and neural indices of generalization in healthy controls. Specifically, we administered DCS just prior to acquisition of conditioned fear, and assessed the drug's effects on generalization of conditioned fear 24 hours later. We hypothesized that the cognitive enhancing properties of D-cycloserine would strengthen acquisition of fear-conditioning, resulting in a decrease in fear generalization errors as measured both behaviorally and neurally.

Methods

Participants

Seventy-seven healthy college students (54 female) were recruited from the University of Minnesota's Research Experience Program participant pool and reimbursed for their time. The mean age was 21.5 (SD= 2.46), and the sample was 77.2% Caucasian.

Prior to testing, participants gave written informed consent that had been approved by the University of Minnesota IRB. Exclusion criteria for this study included (1) current Axis-I psychiatric diagnosis, as determined by self-report, (2) past diagnosis of an anxiety or depressive disorder, (3) currently taking any psychoactive medications or medications affecting central nervous system function, (4) medical condition that would increase risk, or conflict with the aims of the study, (5) pregnancy, (6) use of alcohol within the previous 24 hours, and (7) any standard magnetic resonance exclusions.

Generalization Paradigm

This study employed a version of a validated fMRI paradigm that has previously been used to study fear generalization and is described in detail elsewhere (Lissek et al, 2014).

Stimuli and trial structure

Five checkerboard textured counterphase-flickering (10 Hz) rings of parametrically increasing size, and one "V-shaped" stimulus of the same counterphase-flickering type served as conditioned stimuli (CS+, CS-) and generalization stimuli (GSs). Such stimuli were designed to activate the calcarine sulcus along a continuum of visual eccentricity (e.g., Murray et al., 2006) as part of a longer-range goal to use this generalization paradigm to retinotopically map representations of CSs and GSs in sensory cortex. Important for the purposes of the current paper is the size and shape of these stimuli rather than their retinotopic-mapping characteristics, as retinotopy was unsuccessful in this study.

The current paradigm included one CS+ and the following two CS-: 1) either the largest or smallest ring— referred to as the oCS-, and 2) a "V" shaped stimulus—referred

to as the vCS-. Though all subjects were conditioned with the same vCS-, the oCS- was the largest ring for 50% of subjects and the smallest ring for the remaining half. Subjects for whom the oCS- was the largest ring were conditioned with the smallest ring as CS+ and vice versa. The three intermediately-sized rings served as GSs (i.e., GS_1, GS_2, GS_3) and formed a continuum-of-size between the CS+ and oCS- with GS_3, GS_2, and GS_1 demarcating the GS with most to least similarity to the CS+ regardless of CS+ size. The vCS- was included to test the degree to which conditioned generalization occurss to all "ringed" stimuli following reinforcement of the ring-shaped CS+. That is, heightened activations in fear-related brain areas to all sized rings, relative to the v-shaped vCS-, would be identified as neural correlates of this broader form of generalization to all circular stimuli. Furthermore, the inclusion of the vCS- allows for an assessment of brain responses to the CS+ (vs. vCS-) that are independent of putative generalization effects to all ringed stimuli. Such an assessment is important because brain activations to the CS+ will be used as functional regions of interest in which to test gradients of fear generalization, and should thus be orthogonal to the generalization process. The CS+ versus vCS- contrast provides such an index of conditioning that is independent of generalization effects.

All CSs and GSs were presented for 4 s on a rear-projection viewing screen mounted at the foot of the scanner. Inter-trial-intervals for CSs and GSs were either 2.4- or 4.8-s, during which time participants focused their gaze on crosshairs in the center of the screen. The unconditioned stimulus (US) was a 100-ms electric shock (3-5mA) delivered to the right ankle. Prior to the start of the experiment, a sample shock procedure was performed during which participants received between 1-3 sample shocks, and a level of shock rated by participants as being 'highly uncomfortable or mildly painful' was established.

Behavioral Ratings

Throughout testing, a behavioral task developed to maintain visual gaze at the center of the visual field (Schwartz et al., 2005) was applied. This task consists of a string of colored crosshairs (blue, yellow, red, green, purple) presented serially for a duration of 800 ms each in a quasi-random order in the center of the viewing screen during 4 s presentation of CSs/GSs (5 crosshairs per stimulus). Participants were instructed to continuously monitor the stream of colored crosshairs and rate their perceived level of risk for shock as quickly as possible following each red-cross using a 3 button, fiber optic, response pad (Lumina LP-404 by Cedrus), where 0 = 'no risk', 1 = 'moderate risk', and 2 = 'high risk'. Risk ratings were recorded with Presentation software (Neurobehavioral Systems). For half of CS/GS trials, 1 of 5 crosshairs was red, and the remaining trials included no red crosshairs. Additionally, on reinforced CS+ trials, the red crosshair never appeared in the fourth or fifth position to avoid interference from shock on behavioral responses. Finally, self-reported anxiety to CS+, oCS-, and vCS- were retrospectively assessed following pre-acquisition, acquisition, and generalization sequences using 10-point Likert scales.

Design

The generalization paradigm included three phases: 1) *pre-acquisition—* consisting of 20 trials of each stimulus type (CS+, GS$_1$, GS$_2$, GS$_3$, oCS-, vCS-) all presented in the absence of any shock US; 2) *acquisition—* including 15 CS+, 15 oCS-, and 15 vCS-, with 12 of 15 CS+ co-terminating with shock (80% reinforcement schedule); and 3) *generalization test—* including 20 trials of each stimulus type (unreinforced CS+, GS$_1$, GS$_2$, GS$_3$, oCS-, vCS-), and an additional 10 CS+ co-terminating with shock (33% reinforcement schedule) to prevent extinction of the conditioned response during the

generalization sequence, while leaving 20 unreinforced CS+ to index responses uninfluenced by the shock US. Trials for all 3 phases of the study were arranged in quasi-random order such that no more than two stimuli of the same class occurred consecutively. An additional constraint for the generalization sequence was the arrangement of trials into 6 blocks of 13 trials (2 unreinforced CS+, 1 reinforced CS+, 2 oCS-, 2 vCS-, 2 GS_1, 2 GS_2, 2 GS_3) to ensure an even distribution of trial types throughout runs.

fMRI Data Acquisition

A 3T Siemens TRIO system equipped with a twelve-channel receive-only head coil was used to acquire functional T2*-weighted echo-planar images (EPIs) depicting the BOLD contrast (TR: 2300 ms, TE: 23 ms, flip: 90°). Whole-brain acquisitions consisted of 36 sagittally-oriented slices of 1.5 mm thickness and 1.5x1.5mm^2 in-plane resolution (matrix: 128×128, FOV: 22 cm). High-resolution T1-weighted magnetization-prepared rapid acquisition gradient-echo sequences (MP-RAGE) were obtained to serve as anatomical reference. Head movement was limited with foam pads during data acquisition.

Procedure

Upon arrival, participants were given either a 250 mg dose of DCS, a 500 mg dose of DCS, or a placebo, determined randomly. Experimenters were also blind to which condition each participant was in. After being given DCS, 90 minutes elapsed in order to allow the DCS to reach peak levels in the blood by the time the fear acquisition stage of the experiment had begun (van Berckel et al., 1997). Participants were not instructed of the CS/US contingency but were told they might learn to predict the shock if they attend to the presented stimuli. Shock electrodes were then attached and a shock workup procedure was completed. Participants next practiced using the button box to respond to

red crosshairs appearing both at the center of CSs and GSs. Participants were then placed in the magnet. Structural scans were acquired followed by the pre-acquisition and acquisition EPI runs. Twenty-four hours later, participants returned and completed EPI runs during the generalization test, in order to assess the effect of DCS on memory consolidation. Participants rated their anxiety responses to CS+, oCS-, and vCS- after preacquisition, acquisition, and generalization scans.

fMRI Data Analysis

Image analysis was completed with Analysis of Functional Neural Images (AFNI) software (Cox, 1996). Echo-planar time series data was time corrected, registered, spatially smoothed (FWHM= 4 mm), normalized, and concatenated. During individual-level analyses, functional activation maps were computed by regressing each voxel's fMRI response time-course onto an ideal response function consisting of a Gamma-variate function convolved with the time-series of each of 6 stimulus types (i.e., vCS-, oCS-, GS_1, GS_2, GS_3, unreinforced CS+) at pre-acquisition and generalization test separately. The acquisition phase was used to condition participants to CS+, oCS-, and vCS- and was not intended for image analysis due to the majority of CS+ trials being contaminated by US administrations, and because such data were not critical for testing central hypotheses of interest. Modeled as covariates of no interest were baseline drift, participant-specific movement, response time course (button presses), and the time-course of shock delivery. Subjects (n=7) with more than 3.0 mm of head motion in any dimension from one EPI brain volume to the next were removed.

Group-level analyses of generalization-test data were completed in two stages. First, brain areas sensitive to the conditioning manipulation were identified as functional

regions of interest (fROI). Specifically, whole brain analyses of the contrast between responses to the 20 unreinforced CS+ versus the 20 vCS- were conducted using a voxelwise probability of $p \leq .00001$ and a cluster probability of $p \leq .05$. A stringent voxelwise probability was necessary to achieve adequate demarcation between clusters. The probability of obtaining clusters of a particular size was estimated with the AFNI program AlphaSim. The vCS- rather than oCS- was contrasted against unreinforced CS+ because the CS+ versus vCS- contrast, but not CS+ versus oCS-, yields a measure of conditioning independent of fear generalization that may occur to all circular stimuli. In the second stage, beta weights averaged across voxels within these fROIs were plotted across conditioned and generalization stimuli and analyzed for effects of generalization as well as interactions between group and generalization. Such analyses began with one-way, repeated measures ANOVAs with 5 levels (oCS-, GS_1, GS_2, GS_3, unreinforced CS+). fROIs significantly instantiating generalization gradients were then subjected to 3 (Group: 250 mg, 500 mg, placebo) x 5 (Stimulus-type) repeated measure ANOVAs.

Results

Pre-acquisition: Neither the main effects of stimulus type and group membership nor the Group x Stimulus-type interaction were significant for either risk rating (p-values > .499) or retrospective ratings of anxiety (p-values > .214).

Acquisition: Successful acquisition of conditioned fear was evidenced by increases in online ratings of risk to CS+ (M= 1.56, SD= .41) versus either oCS- (M= .34, SD = .41) or vCS- (M=.34, SD=.39), p-values <.001. Online risk ratings did not differ between oCS- and vCS- (p= .966), but there was a trend toward a difference in retrospective anxiety (p =

.072).   No Group x Stimulus-type interactions were found for online risk ratings or retrospective anxiety (*p*-values >.389).

   Generalization: Online risk ratings and retrospective anxiety continued to be greater to CS+ versus both oCS- and vCS- (all p-values < .001), demonstrating the persistence of conditioned fear during the generalization sequence.   Additionally, generalization of conditioned fear was evidenced by main effects of stimulus type in placebo (p=.028), 250 mg DCS (p= .058), and 500 mg DCS (p=.037) groups, all deriving from downward gradients of perceived risk as the presented stimulus differentiated from CS+.   There were also no significant Group x Stimulus-type interactions for online risk ratings (p= .905), when looking at each group separately or when collapsing across drug group and defining group as drug versus placebo (p=.695).   The interaction was at the trend level for retrospective anxiety (*p*=.065) and became significant when collapsing across drug group (*p*=.015) (Figure 1).
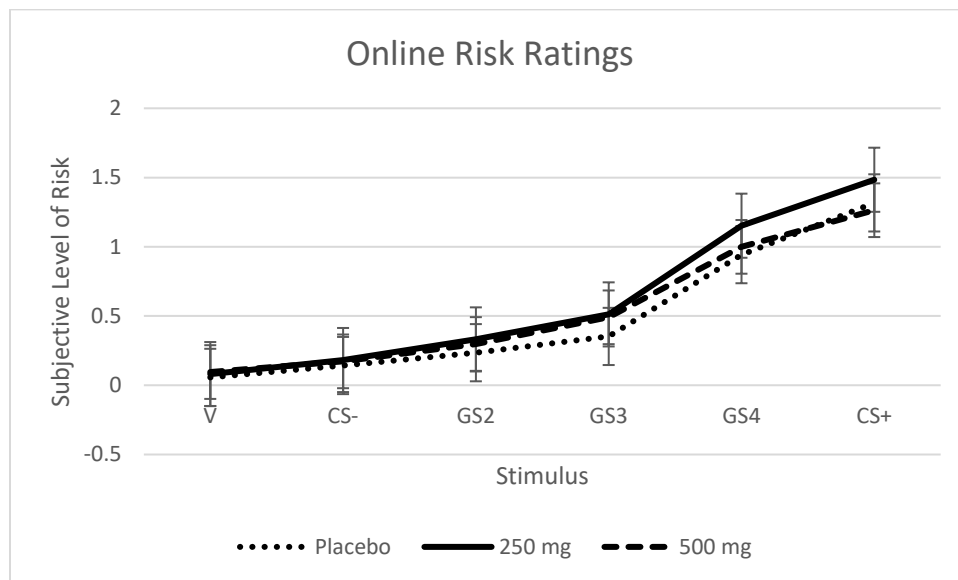

Online Risk Ratings

Figure 1- Online risk ratings to each stimulus size, by drug group. Error bars represent standard error.

Functional regions of interest (fROIs). Table 1 lists brain regions that were differentially activated to CS+ versus vCS- at voxelwise probability of p=.00001 and cluster probability of p=.05. A stringent voxelwise probability was necessary to achieve adequate discrimination between clusters. These areas served as fROIs within which linear and quadratic components of generalization gradients were tested both before and after acquisition training.

Pre-acquisition: Prior to conditioning, no fROIs showed a significant main effect of group (p values > .213), or a significant Group x Stimulus-type interaction (*p*-values > .07).

Generalization test. Twenty-four hours after acquisition, BOLD activations in several fROI's fell along linear and/or quadratic generalization gradients, with strongest responding to CS+ and gradual decreases to GS_3, GS_2, GS_1, oCS-, and vCS-. Replicating previous findings (Lissek et al, 2014; Kazckurkin et al, 2017), positive generalization gradients were found in the bilateral anterior insula, bilateral middle frontal gyrus (Brodmann area 32), bilateral fusiform gyrus, and right superior frontal gyrus. Also found were fROIs falling along negative gradients with strongest responding to the oCS- and degraded reactivity to GS_1, GS_2, GS_3, and CS+. Replicating past findings, the negative linear and/or quadratic gradients were instantiated in the vmPFC, dmPFC and left precuneus (Brodmann area 30).

Group effects at generalization. Next, the fifteen largest fROIs displaying significant linear gradients, as well as those selected *a priori* were subjected to further analysis to determine any group differences (Table 1*).* None of the fROIs revealed a main effect of group membership on average beta value regardless of whether each group was considered separately ($p >$.277) or collapsed across the drug condition ($p >$.328). No fROIs had significant group x stimulus type interactions ($p >$ .327). When considering the magnitude of difference between GS4 and CS- as a measure of generalization of elevated fear responding to the first approximation of the CS+, there are no significant group differences ($p >$ .334). When using a comparison of the average response to all ring shaped generalization stimuli to the V shape stimuli to capture any elevated responding to all ring shapes, there was a significant group difference in the left middle occipital gyrus ($p =$ .040), and a trends toward a group difference in the right inferior frontal gyrus ($p =$.068). We also considered the amount that the generalization gradient departed from a linear slope between CS+ and CS-, where the larger the departure, the less generalization the subject experienced, because it is indicative of a faster drop off than would be expected between the CS+ and CS- assuming that equal reduction in fear occurred between each approximation. Statistically significant group differences in this measure were found in Brodmann area 22 ($p =$ .032) and the right inferior frontal gyrus ($p =$ .004). Both of these significant results were driven primarily by differences between the 500 mg DCS group and the other two.

Brain Region	Direction		Volume (voxels)	X-coordinate	Y-coordinate	Z-coordinate
dmPFC/SMA (BA 6)	CS+ CS-	>	1570	-9.0	-24.0	+25.0
Posterior Cingulate	CS+ CS-	<	1460	-10.5	+42.0	+1.0

|						
vmPFC	CS+ CS-	<	1221	+0.0	-36.0	-14.0
Right anterior insula	CS+ CS-	>	1189	-40.5	-19.5	-8.0
Left anterior insula	CS+ CS-	>	1070	+30.0	-18.0	-5.0
Right caudate	CS+ CS-	>	307	-15.0	+1.5	-2.0
Left STG	CS+ CS-	>	298	+51.0	-6.0	+2.5
Thalamus	CS+ CS-	>	286	-4.5	+27.0	-5.0
Left SFG(BA9)	CS+ CS-	<	256	+7.5	-54.0	+28.0
Right middle occipital gyrus (BA 37)	CS+ CS-	<	243	-52.5	+58.5	-11.0
Left MTG	CS+ CS-	<	236	+48.0	+60.0	+20.5
Left inferior temporal gyrus	CS+ CS-	<	216	+48.0	+72.0	-3.5
Right inferior temporal gyrus (BA 9)	CS+ CS-	>	164	-42.0	-10.5	+20.5
Left cuneus (BA19)	CS+ CS-	<	144	+28.5	+81.0	+22.0
Left superior frontal gyrus	CS+ CS-	<	124	+16.5	-28.5	+44.5
Left Hippocampus	CS+ CS-	<	90	+16.5	+13.5	-20.0

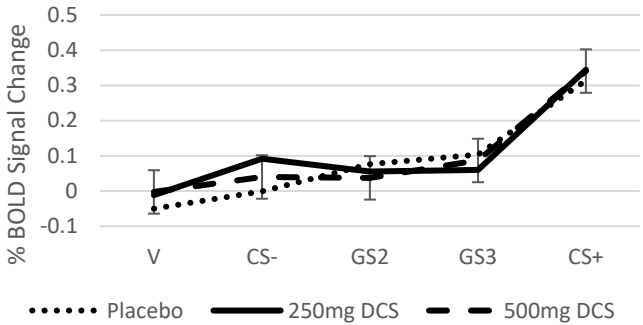*Table 1- The fifteen largest ROIs and a priori ROIs.*
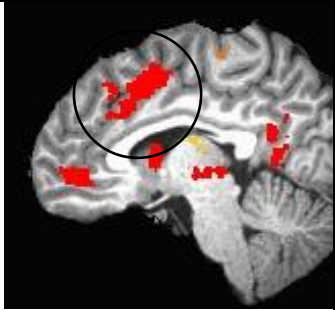
X = -9.0

dmPFC/SMA
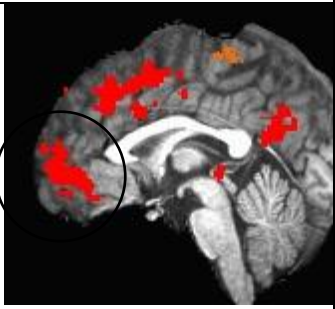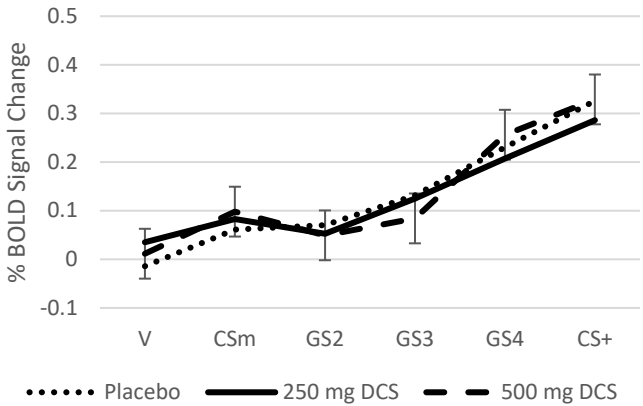
X = 0.0

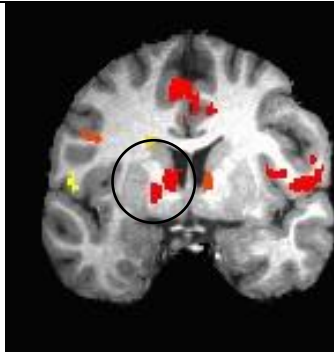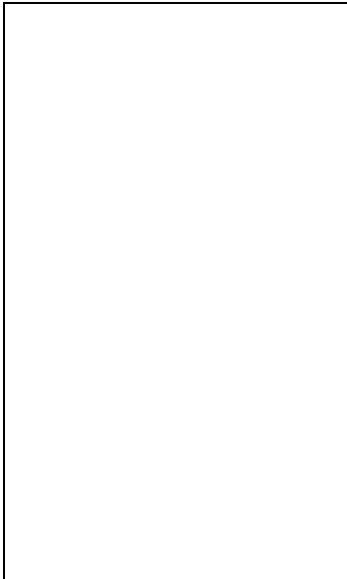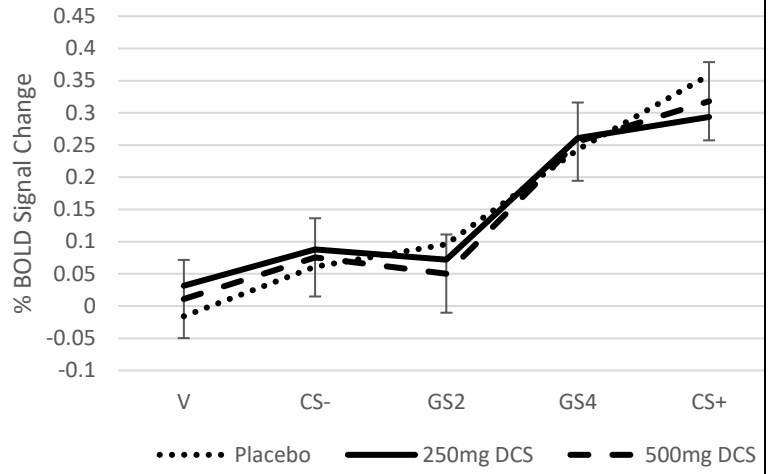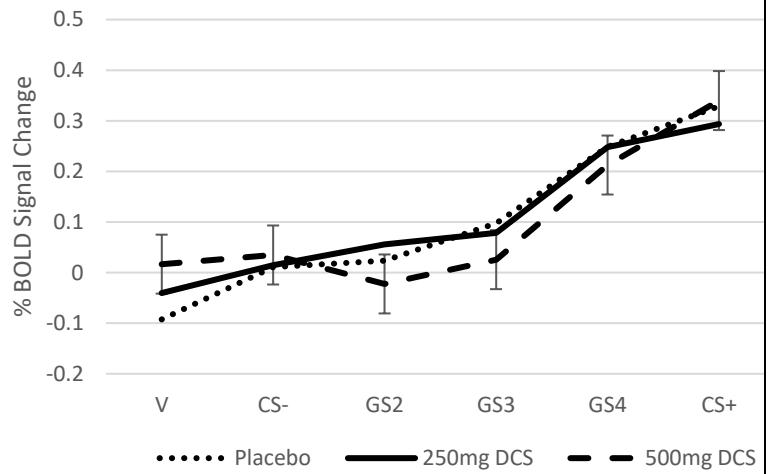vmPFC
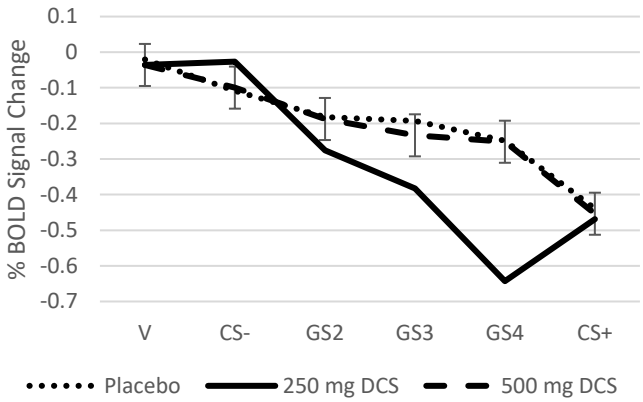
Z = -5.0

Right Anterior Insula

Left Anterior Insula

Right Caudate

Y = -15.0

Y = 13.5

X = -42
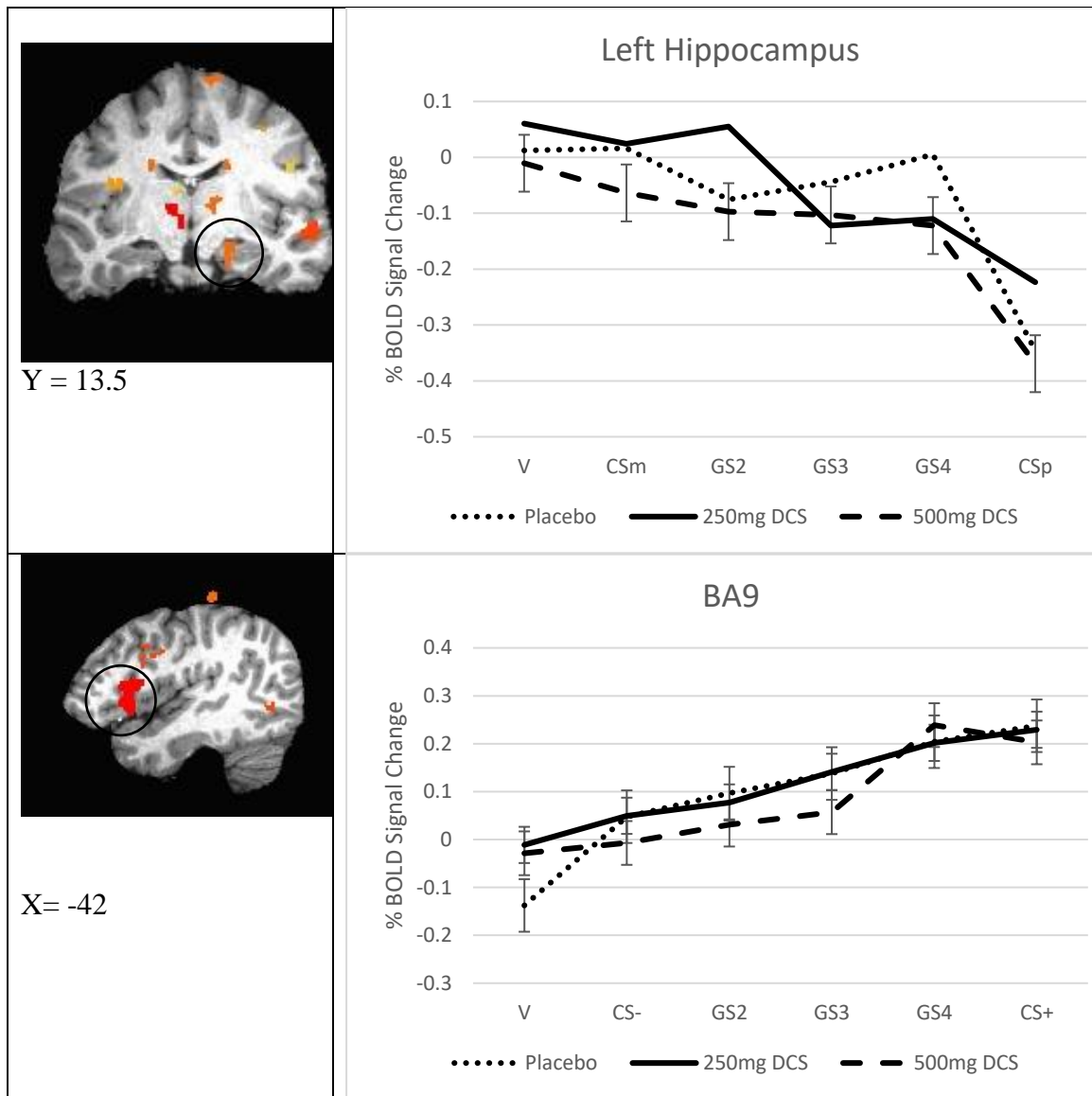
Figure 2- Percent change in BOLD signal response from baseline to each stimulus by group. Error bars represent standard error.

Discussion

This study showed no significant differences among DCS 500, DCS 250 and placebo groups on either behavioral or neural measures of generalized conditioned fear in healthy controls. When collapsing across groups, participants rated themselves as being at high risk of electric shock and feeling high anxiety when the CS+ appeared, and such ratings declined as the stimuli became less similar to the CS+. This is consistent with the

generalization gradients observed in other studies of fear generalization (for reviews, see Kalish, 1969; Mackintosh, 1974; Honing and Urciuoli, 1981).

Collapsing across groups revealed similar gradients in the BOLD signal in the bilateral anterior insula, consistent with previous studies (Dunsmoor et al., 2011; Greenberg et al., 2013b; Lissek et al, 2014; Kazcurkin et al., 2017). The insula has been implicated in fear conditioning, anticipatory responses, and salience evaluation (Lovero et al., 2009; Menon and Uddin, 2010; Nitschke et al., 2006; Paulus & Stein, 2006). These results suggest that fear generalization is associated with higher levels of anticipation, stimulus salience, fear processing, and interoceptive awareness of fear to stimuli resembling the CS+. Similar gradients are seen in the dmPFC, which is again consistent with previous studies, and may be indicative of heightened threat-appraisal or expression of negative emotion to the nearby approximations (Etkin et al., 2011). Given the location of the BOLD activation gradients in the dmPFC, it may also be related to the supplementary motor area, and may suggest the preparation for an escape-related motor response (Lissek et al., 2014; Schaefer et al., 2014).

Negative gradients in BOLD activation were seen in the left hippocampus, again consistent with previous research (Lissek et al, 2014; Dunsmoor et al., 2011; Kazcurkin et al., 2017, Greenberg et al., 2013b). The hippocampus has been suggested to play a role in schematic matching, which in this case would be necessary to discriminate CS+ from CS- (O'Reilly & Rudy, 2001; Otto & Eichenbaum, 1992; Sanders et al., 2005). Negative gradients in this area suggest that less pattern separation is needed the more similar the stimulus is to the CS+. Negative gradients were also observed in the vmPFC, consistent with previous findings (Lissek et al., 2014; Kazcurkin et al., 2017; Greenberg et al., 2013).

The vmPFC has long been thought to be associated with the inhibition of fear responses, particularly evident in terms of extinction learning (Milad et al., 2007; Phelps et al., 2004; Schiller et al., 2008). This negative gradient was indicative of a deactivation of BOLD response to the CS+, as opposed to elevated responding to the CS-, suggesting reduction in baseline levels of inhibition when the subject was feeling more at risk for shock.

Current results suggest that there are no group differences in generalized conditioned fear between DCS and placebo groups when DCS is given to healthy controls prior to acquisition. The lack of group differences may be related to a differential effect of DCS on fear acquisition versus fear extinction. The vast majority of studies identifying effects of DCS on fear learning, particularly in humans, have focused on the role of DCS in heightening and strengthening extinction learning. It may be that during fear acquisition, DCS may have no effect or actually increase fear responding due to increased learning (Hoffman, 2014). There is a general dearth of research on the effects of DCS on fear learning when given at acquisition. Several studies in animals have shown increases in fear learning, contextual learning, and associative learning in animals (Quartermain et al., 1994; Monahan et al., 1989; Land and Riccio, 1999). These increases in learning may only be evident within a few hours of training, and therefore would not still be apparent at the 24 hour time point (Steele et al., 1996). In human subjects, DCS given prior to acquisition has been shown to improve hippocampal-dependent declarative memory, but there has not been much exploration of the effect on fear acquisition (Onur et al., 2010). It is also possible that by performing this study in healthy controls, there was not enough variability in subjects' anxiety level to the CS+ post-conditioning to be able to see an effect of DCS. Indeed, other studies looking at the effect of DCS on extinction learning in healthy

populations have found no significant effects (Bailey et al., 2007; Guastella et al., 2007). Finally, given that some results seem to be trending toward significance, it may be that there is simply a small effect size that interfered with the ability to capture significant differences given our sample size. Given that the group differences in the departure from linear were driven primarily by the 500 mg DCS group, it is possible that higher doses may be necessary to see a result; however, this seems unlikely considering that differences in therapy outcomes between drug and placebo groups have been observed in previous studies with dosages as low as 50 mg. It follows that our selected dosages of 250 mg and 500 mg should have been enough to see differences if they exist (Ressler, 2004). The similarities between our results and other studies on the neural correlates of the generalization of conditioned fear suggest that the paradigm, study parameters, and analysis are valid and replicable. Future studies on the effect of DCS on fear generalization should attempt to tease apart some of these potential explanations for our results, beginning with looking at the effects on the generalization of fear extinction, and whether there is an effect in anxiety populations.

References

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

Adesnik, H., Bruns, W., Taniguchi, H., Huang, Z. J., & Scanziani, M. (2012). A neural circuit for spatial summation in visual cortex. *Nature*, *490*(7419), 226–231. https://doi.org/10.1038/nature11526

Alitto, H. J., & Usrey, W. M. (2004). Influence of contrast on orientation and temporal frequency tuning in ferret primary visual cortex. *Journal of Neurophysiology*, *91*(6), 2797–2808. https://doi.org/10.1152/jn.00943.2003

Altmann, C. F., Bülthoff, H. H., & Kourtzi, Z. (2003). Perceptual organization of local elements into global shapes in the human visual cortex. *Current Biology: CB*, *13*(4), 342–349.

Angelucci, A., & Bullier, J. (2003). Reaching beyond the classical receptive field of V1 neurons: horizontal or feedback axons? *Journal of Physiology, Paris*, *97*(2–3), 141–154. https://doi.org/10.1016/j.jphysparis.2003.09.001

Angelucci, A., Levitt, J. B., Walton, E. J. S., Hupe, J.-M., Bullier, J., & Lund, J. S. (2002). Circuits for local and global signal integration in primary visual cortex. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *22*(19), 8633–8646.

Armony, J. L., Servan-Schreiber, D., Romanski, L. M., Cohen, J. D., & LeDoux, J. E. (1997). Stimulus generalization of fear responses: effects of auditory cortex lesions in a computational model and in rats. *Cerebral Cortex*, *7*(2), 157–165. http://doi.org/10.1093/cercor/7.2.157

Atallah, B. V., Bruns, W., Carandini, M., & Scanziani, M. (2012). Parvalbumin-expressing interneurons linearly transform cortical responses to visual stimuli. *Neuron*, *73*(1), 159–170. https://doi.org/10.1016/j.neuron.2011.12.013

Avsar, K. B., Stoeckel, L. E., Bolding, M. S., White, D. M., Tagamets, M. A., Holcomb, H. H., & Lahti, A. C. (2011). Aberrant visual circuitry associated with normal spatial match-to-sample accuracy in schizophrenia. *Psychiatry Research*, *193*(3), 138–143. https://doi.org/10.1016/j.pscychresns.2011.03.008

Baez, S., Herrera, E., Villarin, L., Theil, D., Gonzalez-Gadea, M. L., Gomez, P., … Ibañez, A. M. (2013). Contextual Social Cognition Impairments in Schizophrenia and Bipolar Disorder. *PLoS ONE*, *8*(3), e57664. https://doi.org/10.1371/journal.pone.0057664

Bailey, J. E., Papadopoulos, A., Lingford-Hughes, A., & Nutt, D. J. (2007). d-Cycloserine and performance under different states of anxiety in healthy volunteers. *Psychopharmacology*, *193*(4), 579–585. http://doi.org/10.1007/s00213-007-0817-9

Barch, D. M., Carter, C. S., Dakin, S. C., Gold, J., Luck, S. J., Macdonald, A., … Strauss, M. E. (2012). The clinical translation of a measure of gain control: the contrast-contrast effect task. *Schizophrenia Bulletin*, *38*(1), 135–143. https://doi.org/10.1093/schbul/sbr154

Bedwell, J. S., Brown, J. M., & Miller, L. S. (2003). The magnocellular visual system and schizophrenia: what can the color red tell us? *Schizophrenia Research*, *63*(3), 273–284.

Blakemore, C., Carpenter, R. H., & Georgeson, M. A. (1970). Lateral inhibition between orientation detectors in the human visual system. *Nature*, *228*(5266), 37–39.

Blakemore, C., & Tobin, E. A. (1972). Lateral inhibition between orientation detectors in the cat's visual cortex. *Experimental Brain Research*, *15*(4), 439–440.

Bodatsch, M., Ruhrmann, S., Wagner, M., Müller, R., Schultze-Lutter, F., Frommann, I., … Brockhaus-Dumke, A. (2011). Prediction of psychosis by mismatch negativity. *Biological Psychiatry*, *69*(10), 959–966. https://doi.org/10.1016/j.biopsych.2010.09.057

Butler, P. D., Abeles, I. Y., Silverstein, S. M., Dias, E. C., Weiskopf, N. G., Calderone, D. J., & Sehatpour, P. (2013). An event-related potential examination of contour integration deficits in schizophrenia. *Frontiers in Psychology*, *4*. https://doi.org/10.3389/fpsyg.2013.00132

Butler, P. D., DeSanti, L. A., Maddox, J., Harkavy-Friedman, J. M., Amador, X. F., Goetz, R. R., … Gorman, J. M. (2003). Visual backward-masking deficits in schizophrenia: relationship to visual pathway function and symptomatology. *Schizophrenia Research*, *59*(2–3), 199–209.

Butler, P. D., & Javitt, D. C. (2005). Early-stage visual processing deficits in schizophrenia. *Current Opinion in Psychiatry*, *18*(2), 151–157.

Butler, P. D., Martinez, A., Foxe, J. J., Kim, D., Zemon, V., Silipo, G., … Javitt, D. C. (2007). Subcortical visual dysfunction in schizophrenia drives secondary cortical impairments. *Brain: A Journal of Neurology*, *130*(Pt 2), 417–430. https://doi.org/10.1093/brain/awl233

Butler, P. D., Schechter, I., Zemon, V., Schwartz, S. G., Greenstein, V. C., Gordon, J., … Javitt, D. C. (2001). Dysfunction of early-stage visual processing in schizophrenia. *The American Journal of Psychiatry*, *158*(7), 1126–1133. https://doi.org/10.1176/appi.ajp.158.7.1126

Butler, P. D., Silverstein, S. M., & Dakin, S. C. (2008). Visual perception and its impairment in schizophrenia. *Biological Psychiatry*, *64*(1), 40–47. https://doi.org/10.1016/j.biopsych.2008.03.023

Bygrave, A. M., Masiulis, S., Nicholson, E., Berkemann, M., Barkus, C., Sprengel, R., … Kätzel, D. (2016). Knockout of NMDA-receptors from parvalbumin interneurons sensitizes to schizophrenia-related deficits induced by MK-801. *Translational Psychiatry*, *6*, e778. https://doi.org/10.1038/tp.2016.44

Cadenhead, K. S. (2002). Vulnerability markers in the schizophrenia spectrum: implications for phenomenology, genetics, and the identification of the schizophrenia prodrome. *The Psychiatric Clinics of North America*, *25*(4), 837–853.

Calderone, D. J., Martinez, A., Zemon, V., Hoptman, M. J., Hu, G., Watkins, J. E., … Butler, P. D. (2013). Comparison of psychophysical, electrophysiological, and fMRI assessment of visual contrast responses in patients with schizophrenia. *NeuroImage*, *67*, 153–162. https://doi.org/10.1016/j.neuroimage.2012.11.019

Cannon, M. W., & Fullenkamp, S. C. (1991). Spatial interactions in apparent contrast: inhibitory effects among grating patterns of different spatial frequencies, spatial positions and orientations. *Vision Research*, *31*(11), 1985–1998.

Carandini, M., & Heeger, D. J. (2012). Normalization as a canonical neural computation. *Nature Reviews. Neuroscience*, *13*(1), 51–62. https://doi.org/10.1038/nrn3136

Cavanaugh, J. R., Bair, W., & Movshon, J. A. (2002). Selectivity and spatial distribution of signals from the receptive field surround in macaque V1 neurons. *Journal of Neurophysiology*, *88*(5), 2547–2556. https://doi.org/10.1152/jn.00693.2001

Chen, Y., Norton, D., McBain, R., Ongur, D., & Heckers, S. (2009). Visual and cognitive processing of face information in schizophrenia: detection, discrimination and working memory. *Schizophrenia Research*, *107*(1), 92–98. https://doi.org/10.1016/j.schres.2008.09.010

Chen, Y., Norton, D., & Ongur, D. (2008). Altered center-surround motion inhibition in schizophrenia. *Biological Psychiatry*, *64*(1), 74–77. https://doi.org/10.1016/j.biopsych.2007.11.017

Chevigny, H., & Braverman, S. (1950). *The adjustment of the blind*. Yale University Press.

Chevrier, A. D., Noseworthy, M. D., & Schachar, R. (2007). Dissociation of response inhibition and performance monitoring in the stop signal task using event-related fMRI. *Human Brain Mapping*, *28*(12), 1347–1358. https://doi.org/10.1002/hbm.20355

Chkonia, E., Roinishvili, M., Makhatadze, N., Tsverava, L., Stroux, A., Neumann, K., … Brand, A. (2010). The shine-through masking paradigm is a potential endophenotype of schizophrenia. *PloS One*, *5*(12), e14268. https://doi.org/10.1371/journal.pone.0014268

Choi, S.-H., Lee, H., Ku, J., Yoon, K. J., & Kim, J.-J. (2014). Neural basis of anhedonia as a failure to predict pleasantness in schizophrenia. *The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry*, *15*(7), 525–533. https://doi.org/10.3109/15622975.2013.819121

Cimmer, C., Szendi, I., Csifcsák, G., Szekeres, G., Ambrus Kovács, Z., Somogyi, I., … Kéri, S. (2006). Abnormal neurological signs, visual contrast sensitivity, and the deficit syndrome of schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *30*(7), 1225–1230. https://doi.org/10.1016/j.pnpbp.2006.03.021

Cisler, J. M., Bush, K., & Steele, J. S. (2014). A comparison of statistical methods for detecting context-modulated functional connectivity in fMRI. *NeuroImage*, *84*, 1042–1052. https://doi.org/10.1016/j.neuroimage.2013.09.018

Clifford, C. W., Wenderoth, P., & Spehar, B. (2000). A functional angle on some after-effects in cortical vision. *Proceedings. Biological Sciences*, *267*(1454), 1705–1710. https://doi.org/10.1098/rspb.2000.1198

Coen-Cagli, R., Kohn, A., & Schwartz, O. (2015). Flexible Gating of Contextual Influences in Natural Vision. *Nature Neuroscience*, *18*(11), 1648–1655. https://doi.org/10.1038/nn.4128

Coffman, B. A., Haigh, S. M., Murphy, T. K., & Salisbury, D. F. (2016). Event-related potentials demonstrate deficits in acoustic segmentation in schizophrenia.

Schizophrenia Research, *173*(1–2), 109–115.
https://doi.org/10.1016/j.schres.2016.03.012

Cohen, J. D., Barch, D. M., Carter, C., & Servan-Schreiber, D. (1999). Context-processing deficits in schizophrenia: Converging evidence from three theoretically motivated cognitive tasks. *Journal of Abnormal Psychology*, *108*(1), 120–133. https://doi.org/10.1037/0021-843X.108.1.120

Collingridge, G. (1987). The role of NMDA receptors in learning and memory. *Nature*, *330*(6149), 604–605. http://doi.org/10.1038/330604a0

Corlett, P. R., Honey, G. D., & Fletcher, P. C. (2016). Prediction error, ketamine and psychosis: An updated model. *Journal of Psychopharmacology (Oxford, England)*, *30*(11), 1145–1155. https://doi.org/10.1177/0269881116650087

Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research, an International Journal*, *29*(3), 162–173.

Dakin, S., Carlin, P., & Hemsley, D. (2005). Weak suppression of visual context in chronic schizophrenia. *Current Biology: CB*, *15*(20), R822-824. https://doi.org/10.1016/j.cub.2005.10.015

Davenport, N. D., Sponheim, S. R., & Stanwyck, J. J. (2006). Neural anomalies during visual search in schizophrenia patients and unaffected siblings of schizophrenia patients. *Schizophrenia Research*, *82*(1), 15–26. https://doi.org/10.1016/j.schres.2005.09.011

Daw, N. W., Stein, P. S., & Fox, K. (1993). The role of NMDA receptors in information processing. *Annual Review of Neuroscience*, *16*, 207–222. https://doi.org/10.1146/annurev.ne.16.030193.001231

Deabler, H. L., & Saucer, R. T. (1956). Perception of apparent motion in organics and schizophrenics. *Journal of Consulting Psychology*, *20*(5), 385–389.

de la Salle, S., Choueiry, J., Shah, D., Bowers, H., McIntosh, J., Ilivitsky, V., & Knott, V. (2016). Effects of Ketamine on Resting-State EEG Activity and Their Relationship to Perceptual/Dissociative Symptoms in Healthy Humans. *Frontiers in Pharmacology*, *7*, 348. https://doi.org/10.3389/fphar.2016.00348

DeAngelis, G. C., Anzai, A., Ohzawa, I., & Freeman, R. D. (1995). Receptive field structure in the visual cortex: does selective stimulation induce plasticity? *Proceedings of the National Academy of Sciences of the United States of America*, *92*(21), 9682–9686.

Deserno, L., Heinz, A., & Schlagenhauf, F. (2016). Computational approaches to schizophrenia: A perspective on negative symptoms. *Schizophrenia Research*. https://doi.org/10.1016/j.schres.2016.10.004

Diamond, R., & Carey, S. (1986). Why faces are and are not special: an effect of expertise. *Journal of Experimental Psychology. General*, *115*(2), 107–117.

Di Russo, F., Martínez, A., Sereno, M. I., Pitzalis, S., & Hillyard, S. A. (2002). Cortical sources of the early components of the visual evoked potential. *Human Brain Mapping*, *15*(2), 95–111.

Dias, E. C., Butler, P. D., Hoptman, M. J., & Javitt, D. C. (2011). Early sensory contributions to contextual encoding deficits in schizophrenia. *Archives of*

General Psychiatry, *68*(7), 654–664.
https://doi.org/10.1001/archgenpsychiatry.2011.17

Dima, D., Dietrich, D. E., Dillo, W., & Emrich, H. M. (2010). Impaired top-down processes in schizophrenia: a DCM study of ERPs. *NeuroImage*, *52*(3), 824–832. https://doi.org/10.1016/j.neuroimage.2009.12.086

Doniger, G. M., Foxe, J. J., Murray, M. M., Higgins, B. A., & Javitt, D. C. (2002). Impaired visual object recognition and dorsal/ventral stream interaction in schizophrenia. *Archives of General Psychiatry*, *59*(11), 1011–1020.

Dowd, E. C., Frank, M. J., Collins, A., Gold, J. M., & Barch, D. M. (2016). Probabilistic Reinforcement Learning in Patients With Schizophrenia: Relationships to Anhedonia and Avolition. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *1*(5), 460–473. https://doi.org/10.1016/j.bpsc.2016.05.005

Dumoulin, S. O., & Hess, R. F. (2006). Modulation of V1 activity by shape: image-statistics or shape-based perception? *Journal of Neurophysiology*, *95*(6), 3654–3664. https://doi.org/10.1152/jn.01156.2005

Dunsmoor, J. E., Mitroff, S. R., & LaBar, K. S. (2009). Generalization of conditioned fear along a dimension of increasing fear intensity. *Learning & Memory*, *16*(7), 460–469. http://doi.org/10.1101/lm.1431609

Dunsmoor, J. E., Prince, S. E., Murty, V. P., Kragel, P. A., & LaBar, K. S. (2011). Neurobehavioral mechanisms of human fear generalization. *NeuroImage*, *55*(4), 1878–1888. http://doi.org/10.1016/j.neuroimage.2011.01.041

Durant, S., & Clifford, C. W. G. (2006). Dynamics of the influence of segmentation cues on orientation perception. *Vision Research*, *46*(18), 2934–2940. https://doi.org/10.1016/j.visres.2006.02.027

Ebert, A., Haussleiter, I. S., Juckel, G., Brüne, M., & Roser, P. (2012). Impaired facial emotion recognition in a ketamine model of psychosis. *Psychiatry Research*, *200*(2–3), 724–727. https://doi.org/10.1016/j.psychres.2012.06.034

Edden, R. A. E., Muthukumaraswamy, S. D., Freeman, T. C. A., & Singh, K. D. (2009). Orientation discrimination performance is predicted by GABA concentration and gamma oscillation frequency in human primary visual cortex. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *29*(50), 15721–15726. https://doi.org/10.1523/JNEUROSCI.4426-09.2009

Etkin, A., Egner, T., & Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends in Cognitive Sciences*, *15*(2), 85–93. http://doi.org/10.1016/j.tics.2010.11.004

Fahrenfort, J. J., Scholte, H. S., & Lamme, V. a. F. (2007). Masking disrupts reentrant processing in human visual cortex. *Journal of Cognitive Neuroscience*, *19*(9), 1488–1497. https://doi.org/10.1162/jocn.2007.19.9.1488

Feigenson, K. A., Keane, B. P., Roché, M. W., & Silverstein, S. M. (2014). Contour integration impairment in schizophrenia and first episode psychosis: state or trait? *Schizophrenia Research*, *159*(2–3), 515–520. https://doi.org/10.1016/j.schres.2014.09.028

Feldman, H., & Friston, K. J. (2010). Attention, uncertainty, and free-energy. *Frontiers in Human Neuroscience*, *4*, 215. https://doi.org/10.3389/fnhum.2010.00215

Felleman, D. J., & Van Essen, D. C. (1991). Distributed hierarchical processing in the primate cerebral cortex. *Cerebral Cortex (New York, N.Y.: 1991)*, *1*(1), 1–47.

Feuerriegel, D., Churches, O., Hofmann, J., & Keage, H. A. D. (2015). The N170 and face perception in psychiatric and neurological disorders: A systematic review. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *126*(6), 1141–1158. https://doi.org/10.1016/j.clinph.2014.09.015

Fletcher, P. C., & Frith, C. D. (2009). Perceiving is believing: a Bayesian approach to explaining the positive symptoms of schizophrenia. *Nature Reviews. Neuroscience*, *10*(1), 48–58. https://doi.org/10.1038/nrn2536

Fogelson, N., Litvak, V., Peled, A., Fernandez-del-Olmo, M., & Friston, K. (2014). The functional anatomy of schizophrenia: A dynamic causal modeling study of predictive coding. *Schizophrenia Research*, *158*(1–3), 204–212. https://doi.org/10.1016/j.schres.2014.06.011

Force, R. B., Venables, N. C., & Sponheim, S. R. (2008). An auditory processing abnormality specific to liability for schizophrenia. *Schizophrenia Research*, *103*(1–3), 298–310. https://doi.org/10.1016/j.schres.2008.04.038

Fox, K., Sato, H., & Daw, N. (1990). The effect of varying stimulus intensity on NMDA-receptor activity in cat visual cortex. *Journal of Neurophysiology*, *64*(5), 1413–1428.

Georgeson, M. A. (1973). Spatial frequency selectivity of a visual tilt illusion. *Nature*, *245*(5419), 43–45.

Gibson, J. J. (1937). Adaptation, After-Effect, and Contrast in the Perception of Tilted Lines. II. Simultaneous Contrast and the Areal Restriction of the After-Effect. *Journal of Experimental Psychology*, *20*(6), 553.

Gilbert, C. D. (1992). Horizontal integration and cortical dynamics. *Neuron*, *9*(1), 1–13.

Gilbert, C. D., & Wiesel, T. N. (1990). The influence of contextual stimuli on the orientation selectivity of cells in primary visual cortex of the cat. *Vision Research*, *30*(11), 1689–1701.

Goddard, E., Clifford, C. W. G., & Solomon, S. G. (2008). Centre-surround effects on perceived orientation in complex images. *Vision Research*, *48*(12), 1374–1382. https://doi.org/10.1016/j.visres.2008.02.023

Goto, N., Yoshimura, R., Moriya, J., Kakeda, S., Ueda, N., Ikenouchi-Sugita, A., … Nakamura, J. (2009). Reduction of brain gamma-aminobutyric acid (GABA) concentrations in early-stage schizophrenia patients: 3T Proton MRS study. *Schizophrenia Research*, *112*(1–3), 192–193. https://doi.org/10.1016/j.schres.2009.04.026

Gottesman, I. I., & Gould, T. D. (2003). The endophenotype concept in psychiatry: etymology and strategic intentions. *The American Journal of Psychiatry*, *160*(4), 636–645. https://doi.org/10.1176/appi.ajp.160.4.636

Green, M. F., Glahn, D., Engel, S. A., Nuechterlein, K. H., Sabb, F., Strojwas, M., & Cohen, M. S. (2005). Regional brain activity associated with visual backward masking. *Journal of Cognitive Neuroscience*, *17*(1), 13–23. https://doi.org/10.1162/0898929052880011

Green, M. F., Lee, J., Cohen, M. S., Engel, S. A., Korb, A. S., Nuechterlein, K. H., … Glahn, D. C. (2009). Functional neuroanatomy of visual masking deficits in schizophrenia. *Archives of General Psychiatry*, *66*(12), 1295–1303. https://doi.org/10.1001/archgenpsychiatry.2009.132

Green, M. F., & Nuechterlein, K. H. (1999). Backward masking performance as an indicator of vulnerability to schizophrenia. *Acta Psychiatrica Scandinavica. Supplementum*, *395*, 34–40.

Green, M. F., Nuechterlein, K. H., & Breitmeyer, B. (1997). Backward masking performance in unaffected siblings of schizophrenic patients. Evidence for a vulnerability indicator. *Archives of General Psychiatry*, *54*(5), 465–472.

Green, M. F., Nuechterlein, K. H., Breitmeyer, B., & Mintz, J. (2006). Forward and backward visual masking in unaffected siblings of schizophrenic patients. *Biological Psychiatry*, *59*(5), 446–451. https://doi.org/10.1016/j.biopsych.2005.06.035

Green, M. F., Wynn, J. K., Breitmeyer, B., Mathis, K. I., & Nuechterlein, K. H. (2011). Visual masking by object substitution in schizophrenia. *Psychological Medicine*, *41*(7), 1489–1496. https://doi.org/10.1017/S003329171000214X

Greenberg, T., Carlson, J. M., Cha, J., Hajcak, G., & Mujica-Parodi, L. R. (2013). Neural reactivity tracks fear generalization gradients. *Biological Psychology*, *92*(1), 2–8. http://doi.org/10.1016/j.biopsycho.2011.12.007

Greenberg, T., Carlson, J. M., Cha, J., Hajcak, G., & Mujica-Parodi, L. R. (2013b). Ventromedial prefrontal cortex reactivity is altered in generalized anxiety disorder during fear generalization. *Depression and Anxiety*, *30*(3), 242–250. http://doi.org/10.1002/da.22016

Griffiths, O., Langdon, R., Le Pelley, M. E., & Coltheart, M. (2014). Delusions and prediction error: re-examining the behavioural evidence for disrupted error signalling in delusion formation. *Cognitive Neuropsychiatry*, *19*(5), 439–467. https://doi.org/10.1080/13546805.2014.897601

Guastella, A. J., Lovibond, P. F., Dadds, M. R., Mitchell, P., & Richardson, R. (2007). A randomized controlled trial of the effect of D-cycloserine on extinction and fear conditioning in humans. *Behaviour Research and Therapy*, *45*(4), 663–672. http://doi.org/10.1016/j.brat.2006.07.005

Hansen, T., & Neumann, H. (2008). A recurrent model of contour integration in primary visual cortex. *Journal of Vision*, *8*(8), 8.1-25. https://doi.org/10.1167/8.8.8

Harvey, P.-O., Lee, J., Cohen, M. S., Engel, S. A., Glahn, D. C., Nuechterlein, K. H., … Green, M. F. (2011). Altered dynamic coupling of lateral occipital complex during visual perception in schizophrenia. *NeuroImage*, *55*(3), 1219–1226. https://doi.org/10.1016/j.neuroimage.2010.12.045

Heeger, D. J. (1992). Normalization of cell responses in cat striate cortex. *Visual Neuroscience*, *9*(2), 181–197.

Heninger, G., & Speck, L. B. (1966). Visual evoked responses and mental status of schizophrenics. *Archives of General Psychiatry*, *15*(4), 419–426.

Herrmann, M. J., Ellgring, H., & Fallgatter, A. J. (2004). Early-stage face processing dysfunction in patients with schizophrenia. *The American Journal of Psychiatry*, *161*(5), 915–917. https://doi.org/10.1176/appi.ajp.161.5.915

Herzog, M. H., Roinishvili, M., Chkonia, E., & Brand, A. (2013). Schizophrenia and visual backward masking: a general deficit of target enhancement. *Frontiers in Psychology*, *4*, 254. https://doi.org/10.3389/fpsyg.2013.00254

Hofmann, S. G. (2014). D-cycloserine for Treating Anxiety Disorders: Making Good Exposures Better and Bad Exposures Worse. *Depression and Anxiety*, *31*(3), 175–177. http://doi.org/10.1002/da.22257

Honig, W. K., & Urcuioli, P. J. (1981). The legacy of Guttman and Kalish (1956): Twenty-five years of research on stimulus generalization. *Journal of the Experimental Analysis of Behavior*, *36*(3), 405–445. http://doi.org/10.1901/jeab.1981.36-405

Horga, G., Schatz, K. C., Abi-Dargham, A., & Peterson, B. S. (2014). Deficits in predictive coding underlie hallucinations in schizophrenia. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *34*(24), 8072–8082. https://doi.org/10.1523/JNEUROSCI.0200-14.2014

Hubel, D. H., & Wiesel, T. N. (1968). Receptive fields and functional architecture of monkey striate cortex. *The Journal of Physiology*, *195*(1), 215–243.

Hughes, G., Desantis, A., & Waszak, F. (2013). Attenuation of auditory N1 results from identity-specific action-effect prediction. *The European Journal of Neuroscience*, *37*(7), 1152–1158. https://doi.org/10.1111/ejn.12120

Hupé, J. M., James, A. C., Payne, B. R., Lomber, S. G., Girard, P., & Bullier, J. (1998). Cortical feedback improves discrimination between figure and background by V1, V2 and V3 neurons. *Nature*, *394*(6695), 784–787. https://doi.org/10.1038/29537

Ishikawa, K. (1968). Studies on the visual evoked responses to paired light flashes in schizophrenics. *The Kurume Medical Journal*, *15*(3), 153–167.

Javitt, D. C. (2010). Glutamatergic theories of schizophrenia. *The Israel Journal of Psychiatry and Related Sciences*, *47*(1), 4–16.

Javitt, D. C., & Frusciante, M. (1997). Glycyldodecylamide, a phencyclidine behavioral antagonist, blocks cortical glycine uptake: implications for schizophrenia and substance abuse. *Psychopharmacology*, *129*(1), 96–98.

Javitt, D. C., Jayachandra, M., Lindsley, R. W., Specht, C. M., & Schroeder, C. E. (2000). Schizophrenia-like deficits in auditory P1 and N1 refractoriness induced by the psychomimetic agent phencyclidine (PCP). *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *111*(5), 833–836.

Jeffries, A. M., Killian, N. J., & Pezaris, J. S. (2014). Mapping the primate lateral geniculate nucleus: a review of experiments and methods. *Journal of Physiology, Paris*, *108*(1), 3–10. https://doi.org/10.1016/j.jphysparis.2013.10.001

Johnson, S. C., Lowery, N., Kohler, C., & Turetsky, B. I. (2005). Global-local visual processing in schizophrenia: evidence for an early visual processing deficit. *Biological Psychiatry*, *58*(12), 937–946. https://doi.org/10.1016/j.biopsych.2005.04.053

Joshua, N., & Rossell, S. (2009). Configural face processing in schizophrenia. *Schizophrenia Research*, *112*(1–3), 99–103. https://doi.org/10.1016/j.schres.2009.03.033

Kalish HI. Stimulus generalization. (1969). In: Marx MH, editor. Learning: Processes.Oxford, England: Macmillan

Kapadia, M. K., Ito, M., Gilbert, C. D., & Westheimer, G. (1995). Improvement in visual sensitivity by changes in local context: parallel studies in human observers and in V1 of alert monkeys. *Neuron*, *15*(4), 843–856.

Katzner, S., Busse, L., & Carandini, M. (2011). GABAA inhibition controls response gain in visual cortex. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *31*(16), 5931–5941. https://doi.org/10.1523/JNEUROSCI.5753-10.2011

Kazckurkin, A.N., Burton P.C., Chazin, S.M., Sponheim S.R., Lissek, S. (2016). Neural Substrates of Over-generalized Conditioned-Fear in Posttraumatic Stress Disorder. *American Journal of Psychiatry*

Keane, B. P., Erlikhman, G., Kastner, S., Paterno, D., & Silverstein, S. M. (2014). Multiple forms of contour grouping deficits in schizophrenia: What is the role of spatial frequency? *Neuropsychologia*, *65*, 221–233. https://doi.org/10.1016/j.neuropsychologia.2014.10.031

Keane, B. P., Paterno, D., Kastner, S., & Silverstein, S. M. (2016). Visual integration dysfunction in schizophrenia arises by the first psychotic episode and worsens with illness duration. *Journal of Abnormal Psychology*, *125*(4), 543–549. https://doi.org/10.1037/abn0000157

Keane, B. P., Silverstein, S. M., Barch, D. M., Carter, C. S., Gold, J. M., Kovács, I., … Strauss, M. E. (2012). The spatial range of contour integration deficits in schizophrenia. *Experimental Brain Research*, *220*(3–4), 251–259. https://doi.org/10.1007/s00221-012-3134-4

Kéri, S., Kelemen, O., Benedek, G., & Janka, Z. (2004). Vernier threshold in patients with schizophrenia and in their unaffected siblings. *Neuropsychology*, *18*(3), 537–542. https://doi.org/10.1037/0894-4105.18.3.537

Koreki, A., Maeda, T., Fukushima, H., Umeda, S., Takahata, K., Okimura, T., … Kato, M. (2015). Behavioral evidence of delayed prediction signals during agency attribution in patients with schizophrenia. *Psychiatry Research*, *230*(1), 78–83. https://doi.org/10.1016/j.psychres.2015.08.023

Kourtzi, Z., Tolias, A. S., Altmann, C. F., Augath, M., & Logothetis, N. K. (2003). Integration of local features into global shapes: monkey and human FMRI studies. *Neuron*, *37*(2), 333–346.

Kovács, I. (1996). Gestalten of today: early processing of visual contours and surfaces. *Behavioural Brain Research*, *82*(1), 1–11.

Kübler, A., Dixon, V., & Garavan, H. (2006). Automaticity and reestablishment of executive control-an fMRI study. *Journal of Cognitive Neuroscience*, *18*(8), 1331–1342. https://doi.org/10.1162/jocn.2006.18.8.1331

Kwon, Y. H., Nelson, S. B., Toth, L. J., & Sur, M. (1992). Effect of stimulus contrast and size on NMDA receptor activity in cat lateral geniculate nucleus. *Journal of Neurophysiology*, *68*(1), 182–196.

Lamme, V. A., & Roelfsema, P. R. (2000). The distinct modes of vision offered by feedforward and recurrent processing. *Trends in Neurosciences*, *23*(11), 571–579.

Land, C., & Riccio, D. C. (1999). d-Cycloserine: Effects on Long-Term Retention of a Conditioned Response and on Memory for Contextual Attributes. *Neurobiology of Learning and Memory*, *72*(3), 158–168. http://doi.org/10.1006/nlme.1998.3897

Lavigne, K. M., Menon, M., & Woodward, T. S. (2016). Impairment in subcortical suppression in schizophrenia: Evidence from the fBIRN Oddball Task. *Human Brain Mapping*, *37*(12), 4640–4653. https://doi.org/10.1002/hbm.23334

Lee, M., Sehatpour, P., Hoptman, M. J., Lakatos, P., Dias, E. C., Kantrowitz, J. T., … Javitt, D. C. (2017). Neural mechanisms of mismatch negativity dysfunction in schizophrenia. *Molecular Psychiatry*. https://doi.org/10.1038/mp.2017.3

Leung, H.-C., Gore, J. C., & Goldman-Rakic, P. S. (2002). Sustained mnemonic response in the human middle frontal gyrus during on-line storage of spatial memoranda. *Journal of Cognitive Neuroscience*, *14*(4), 659–671. https://doi.org/10.1162/08989290260045882

Levitt, J. B., & Lund, J. S. (1997). Contrast dependence of contextual effects in primate visual cortex. *Nature*, *387*(6628), 73–76. https://doi.org/10.1038/387073a0

Li, W., Thier, P., & Wehrhahn, C. (2000). Contextual influence on orientation discrimination of humans and responses of neurons in V1 of alert monkeys. *Journal of Neurophysiology*, *83*(2), 941–954.

Lissek, S., Bradford, D. E., Alvarez, R. P., Burton, P., Espensen-Sturges, T., Reynolds, R. C., & Grillon, C. (2013). Neural substrates of classically conditioned fear-generalization in humans: a parametric fMRI study. *Social Cognitive and Affective Neuroscience*. http://doi.org/10.1093/scan/nst096

Lissek, S., Kaczkurkin, A. N., Rabin, S., Geraci, M., Pine, D. S., & Grillon, C. (2014). Generalized Anxiety Disorder is Associated with Overgeneralization of Classically Conditioned-Fear. *Biological Psychiatry*, *75*(11), 909–915. http://doi.org/10.1016/j.biopsych.2013.07.025

Lissek, S., Rabin, S., Heller, R. E., Lukenbaugh, D., Geraci, M., Pine, D. S., & Grillon, C. (2010). Overgeneralization of Conditioned Fear as a Pathogenic Marker of Panic Disorder. *The American Journal of Psychiatry*, *167*(1), 47–55. http://doi.org/10.1176/appi.ajp.2009.09030410

Lovero, K. L., Simmons, A. N., Aron, J. L., & Paulus, M. P. (2009). Anterior Insular Cortex Anticipates Impending Stimulus Significance. *NeuroImage*, *45*(3), 976–983.

Lynn, S. K., & Salisbury, D. F. (2008). Attenuated modulation of the N170 ERP by facial expressions in schizophrenia. *Clinical EEG and Neuroscience*, *39*(2), 108–111. https://doi.org/10.1177/155005940803900218

Ma, W., Liu, B., Li, Y., Huang, Z. J., Zhang, L. I., & Tao, H. W. (2010). Visual representations by cortical somatostatin inhibitory neurons--selective but with weak and delayed responses. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *30*(43), 14371–14379. https://doi.org/10.1523/JNEUROSCI.3248-10.2010

MacDonald, A. W., Carter, C. S., Kerns, J. G., Ursu, S., Barch, D. M., Holmes, A. J., … Cohen, J. D. (2005). Specificity of Prefrontal Dysfunction and Context Processing Deficits to Schizophrenia in Never-Medicated Patients With First-Episode Psychosis. *American Journal of Psychiatry*, *162*(3), 475–484. https://doi.org/10.1176/appi.ajp.162.3.475

Mackintosh NJ. (1974). The Psychology of Animal Learning. New York, NY: Academic Press.

Maeda, T., Takahata, K., Muramatsu, T., Okimura, T., Koreki, A., Iwashita, S., … Kato, M. (2013). Reduced sense of agency in chronic schizophrenia with predominant negative symptoms. *Psychiatry Research*, *209*(3), 386–392. https://doi.org/10.1016/j.psychres.2013.04.017

Malach, R., Reppas, J. B., Benson, R. R., Kwong, K. K., Jiang, H., Kennedy, W. A., … Tootell, R. B. (1995). Object-related activity revealed by functional magnetic resonance imaging in human occipital cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *92*(18), 8135–8139.

Marsden, K. C., Beattie, J. B., Friedenthal, J., & Carroll, R. C. (2007). NMDA Receptor Activation Potentiates Inhibitory Transmission through GABA Receptor-Associated Protein-Dependent Exocytosis of GABAA Receptors. *Journal of Neuroscience*, *27*(52), 14326–14337. https://doi.org/10.1523/JNEUROSCI.4433-07.2007

Martínez, A., Hillyard, S. A., Dias, E. C., Hagler, D. J., Butler, P. D., Guilfoyle, D. N., … Javitt, D. C. (2008). Magnocellular pathway impairment in schizophrenia: evidence from functional magnetic resonance imaging. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *28*(30), 7492–7500. https://doi.org/10.1523/JNEUROSCI.1852-08.2008

McBain, R., Norton, D., & Chen, Y. (2010). Differential roles of low and high spatial frequency content in abnormal facial emotion perception in schizophrenia. *Schizophrenia Research*, *122*(1–3), 151–155. https://doi.org/10.1016/j.schres.2010.03.034

McCleery, A., Lee, J., Joshi, A., Wynn, J. K., Hellemann, G. S., & Green, M. F. (2015). Meta-analysis of face processing event-related potentials in schizophrenia. *Biological Psychiatry*, *77*(2), 116–126. https://doi.org/10.1016/j.biopsych.2014.04.015

McClure, R. K. (2001). The visual backward masking deficit in schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *25*(2), 301–311.

McDonald, J. S., Mannion, D. J., Goddard, E., & Clifford, C. W. G. (2010). Orientation-selective chromatic mechanisms in human visual cortex. *Journal of Vision*, *10*(12), 34. https://doi.org/10.1167/10.12.34

McLaren, D. G., Ries, M. L., Xu, G., & Johnson, S. C. (2012). A Generalized Form of Context-Dependent Psychophysiological Interactions (gPPI): A Comparison to Standard Approaches. *Neuroimage*, *61*(4), 1277. https://doi.org/10.1016/j.neuroimage.2012.03.068

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure & Function*, *214*(5-6), 655–667. http://doi.org/10.1007/s00429-010-0262-0

Meduri, R. (1969). On chromatic discrimination during some psychiatric syndromes and some recognized cerebral lesions. *Rivista Oto-Neuro-Oftalmologica*, *44*(1), 35–60.

Meese, T. S., Summers, R. J., Holmes, D. J., & Wallis, S. A. (2007). Contextual modulation involves suppression and facilitation from the center and the surround. *Journal of Vision*, *7*(4), 7–7. https://doi.org/10.1167/7.4.7

Milad, M. R., Wright, C. I., Orr, S. P., Pitman, R. K., Quirk, G. J., & Rauch, S. L. (2007). Recall of Fear Extinction in Humans Activates the Ventromedial Prefrontal

Cortex and Hippocampus in Concert. *Biological Psychiatry*, *62*(5), 446–454. http://doi.org/10.1016/j.biopsych.2006.10.011

Monahan, J. B., Handelmann, G. E., Hood, W. F., & Cordi, A. A. (1989). D-cycloserine, a positive modulator of the N-methyl-D-aspartate receptor, enhances performance of learning tasks in rats. *Pharmacology Biochemistry and Behavior*, *34*(3), 649–653. http://doi.org/10.1016/0091-3057(89)90571-6

Morey, R. A., Dunsmoor, J. E., Haswell, C. C., Brown, V. M., Vora, A., Weiner, J., … LaBar, K. S. (2015). Fear learning circuitry is biased toward generalization of fear associations in posttraumatic stress disorder. *Translational Psychiatry*, *5*(12), e700. http://doi.org/10.1038/tp.2015.196

Morris, R. W., Vercammen, A., Lenroot, R., Moore, L., Langton, J. M., Short, B., … Weickert, T. W. (2012). Disambiguating ventral striatum fMRI-related BOLD signal during reward prediction in schizophrenia. *Molecular Psychiatry*, *17*(3), 235, 280–289. https://doi.org/10.1038/mp.2011.75

Mumford, D. (1992). On the computational architecture of the neocortex. II. The role of cortico-cortical loops. *Biological Cybernetics*, *66*(3), 241–251.

Murray, J. D., Anticevic, A., Gancsos, M., Ichinose, M., Corlett, P. R., Krystal, J. H., & Wang, X.-J. (2014). Linking microcircuit dysfunction to cognitive impairment: effects of disinhibition associated with schizophrenia in a cortical working memory model. *Cerebral Cortex (New York, N.Y.: 1991)*, *24*(4), 859–872. https://doi.org/10.1093/cercor/bhs370

Murray, S. O., Kersten, D., Olshausen, B. A., Schrater, P., & Woods, D. L. (2002). Shape perception reduces activity in human primary visual cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *99*(23), 15164–15169. https://doi.org/10.1073/pnas.192579399

Murray, S. O., Schrater, P., & Kersten, D. (2004). Perceptual grouping and the interactions between visual cortical areas. *Neural Networks: The Official Journal of the International Neural Network Society*, *17*(5–6), 695–705. https://doi.org/10.1016/j.neunet.2004.03.010

Nassi, J. J., Lomber, S. G., & Born, R. T. (2013). Corticocortical feedback contributes to surround suppression in V1 of the alert primate. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *33*(19), 8504–8517. https://doi.org/10.1523/JNEUROSCI.5124-12.2013

Nazimek, J. M., Hunter, M. D., & Woodruff, P. W. R. (2012). Auditory hallucinations: expectation-perception model. *Medical Hypotheses*, *78*(6), 802–810. https://doi.org/10.1016/j.mehy.2012.03.014

Newcomer, J. W., Farber, N. B., Jevtovic-Todorovic, V., Selke, G., Melson, A. K., Hershey, T., … Olney, J. W. (1999). Ketamine-induced NMDA receptor hypofunction as a model of memory impairment and psychosis. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *20*(2), 106–118. https://doi.org/10.1016/S0893-133X(98)00067-0

Nienborg, H., Hasenstaub, A., Nauhaus, I., Taniguchi, H., Huang, Z. J., & Callaway, E. M. (2013). Contrast dependence and differential contributions from somatostatin- and parvalbumin-expressing neurons to spatial integration in mouse V1. *The*

Journal of Neuroscience: The Official Journal of the Society for Neuroscience, *33*(27), 11145–11154. https://doi.org/10.1523/JNEUROSCI.5320-12.2013

Niendam, T. A., Lesh, T. A., Yoon, J., Westphal, A. J., Hutchison, N., Daniel Ragland, J., … Carter, C. S. (2014). Impaired context processing as a potential marker of psychosis risk state. *Psychiatry Research*, *221*(1), 13–20. https://doi.org/10.1016/j.pscychresns.2013.09.001

Nitschke, J. B., Sarinopoulos, I., Mackiewicz, K. L., Schaefer, H. S., & Davidson, R. J. (2006). Functional neuroanatomy of aversion and its anticipation. *NeuroImage*, *29*(1), 106–116. http://doi.org/10.1016/j.neuroimage.2005.06.068

Olney, J. W., Newcomer, J. W., & Farber, N. B. (1999). NMDA receptor hypofunction model of schizophrenia. *Journal of Psychiatric Research*, *33*(6), 523–533.

Onitsuka, T., Spencer, K. M., Lucia, L. C., Shenton, M. E., McCarley, R. W., & Niznikiewicz, M. A. (2009). Abnormal asymmetry of the face n170 repetition effect in male patients with chronic schizophrenia. *Brain Imaging and Behavior*, *3*(3), 240–245. https://doi.org/10.1007/s11682-009-9066-3

Onur, O. A., Schlaepfer, T. E., Kukolja, J., Bauer, A., Jeung, H., Patin, A., … Hurlemann, R. (2010). The N-Methyl-D-Aspartate Receptor Co-agonist D-Cycloserine Facilitates Declarative Learning and Hippocampal Activity in Humans. *Biological Psychiatry*, *67*(12), 1205–1211. http://doi.org/10.1016/j.biopsych.2010.01.022

O'Reilly, R. C., & Rudy, J. W. (2001). Conjunctive representations in learning and memory: Principles of cortical and hippocampal function. *Psychological Review*, *108*(2), 311–345. http://doi.org/10.1037/0033-295X.108.2.311

Otto, T., & Eichenbaum, H. (1992). Neuronal activity in the hippocampus during delayed non-match to sample performance in rats: Evidence for hippocampal processing in recognition memory. *Hippocampus*, *2*(3), 323–334. http://doi.org/10.1002/hipo.450020310

Ozeki, H., Finn, I. M., Schaffer, E. S., Miller, K. D., & Ferster, D. (2009). Inhibitory stabilization of the cortical network underlies visual surround suppression. *Neuron*, *62*(4), 578–592. https://doi.org/10.1016/j.neuron.2009.03.028

Pascual-Leone, A., & Walsh, V. (2001). Fast backprojections from the motion to the primary visual area necessary for visual awareness. *Science (New York, N.Y.)*, *292*(5516), 510–512. https://doi.org/10.1126/science.1057099

Paulus, M. P., & Stein, M. B. (2006). An Insular View of Anxiety. *Biological Psychiatry*, *60*(4), 383–387. http://doi.org/10.1016/j.biopsych.2006.03.042

Peirce, J. W. (2007). PsychoPy--Psychophysics software in Python. *Journal of Neuroscience Methods*, *162*(1–2), 8–13. https://doi.org/10.1016/j.jneumeth.2006.11.017

Pettet, M. W. (1999). Shape and contour detection. *Vision Research*, *39*(3), 551–557.

Pevzner, A. I. (1969). [On disorders of color vision in schizophrenic patients]. *Zhurnal Nevropatologii I Psikhiatrii Imeni S.S. Korsakova (Moscow, Russia: 1952)*, *69*(1), 83–87.

Phelps, E. A., Delgado, M. R., Nearing, K. I., & LeDoux, J. E. (2004). Extinction Learning in Humans: Role of the Amygdala and vmPFC. *Neuron*, *43*(6), 897–905. http://doi.org/10.1016/j.neuron.2004.08.042

Pochon, J. B., Levy, R., Fossati, P., Lehericy, S., Poline, J. B., Pillon, B., … Dubois, B. (2002). The neural system that bridges reward and cognition in humans: an fMRI study. *Proceedings of the National Academy of Sciences of the United States of America*, *99*(8), 5669–5674. https://doi.org/10.1073/pnas.082111099

Polat, U., & Sagi, D. (2007). The relationship between the subjective and objective aspects of visual filling-in. *Vision Research*, *47*(18), 2473–2481. https://doi.org/10.1016/j.visres.2007.06.007

Powers, A. R., Gancsos, M. G., Finn, E. S., Morgan, P. T., & Corlett, P. R. (2015). Ketamine-Induced Hallucinations. *Psychopathology*, *48*(6), 376–385. https://doi.org/10.1159/000438675

Qiu, C., Burton, P. C., Kersten, D., & Olman, C. A. (2016). Responses in early visual areas to contour integration are context dependent. *Journal of Vision*, *16*(8), 19. https://doi.org/10.1167/16.8.19

Qiu, C., Kersten, D., & Olman, C. A. (2013). Segmentation decreases the magnitude of the tilt illusion. *Journal of Vision*, *13*(13), 19. https://doi.org/10.1167/13.13.19

Quartermain, D., Mower, J., Rafferty, M. F., Herting, R. L., & Lanthorn, T. H. (1994). Acute but not chronic activation of the NMDA-coupled glycine receptor with D-cycloserine facilitates learning and retention. *European Journal of Pharmacology*, *257*(1–2), 7–12. http://doi.org/10.1016/0014-2999(94)90687-4

Quintana, J., Lee, J., Marcus, M., Kee, K., Wong, T., & Yerevanian, A. (2011). Brain dysfunctions during facial discrimination in schizophrenia: selective association to affect decoding. *Psychiatry Research*, *191*(1), 44–50. https://doi.org/10.1016/j.pscychresns.2010.09.005

Rao, R. P., & Ballard, D. H. (1999). Predictive coding in the visual cortex: a functional interpretation of some extra-classical receptive-field effects. *Nature Neuroscience*, *2*(1), 79–87. https://doi.org/10.1038/4580

Raye, C. L., Johnson, M. K., Mitchell, K. J., Reeder, J. A., & Greene, E. J. (2002). Neuroimaging a single thought: dorsolateral PFC activity associated with refreshing just-activated information. *NeuroImage*, *15*(2), 447–453. https://doi.org/10.1006/nimg.2001.0983

Reinen, J., Smith, E. E., Insel, C., Kribs, R., Shohamy, D., Wager, T. D., & Jarskog, L. F. (2014). Patients with schizophrenia are impaired when learning in the context of pursuing rewards. *Schizophrenia Research*, *152*(1), 309–310. https://doi.org/10.1016/j.schres.2013.11.012

Rentzsch, J., Shen, C., Jockers-Scherübl, M. C., Gallinat, J., & Neuhaus, A. H. (2015). Auditory mismatch negativity and repetition suppression deficits in schizophrenia explained by irregular computation of prediction error. *PloS One*, *10*(5), e0126775. https://doi.org/10.1371/journal.pone.0126775

Ressler, K. J., Rothbaum, B. O., Tannenbaum, L., Anderson, P., Graap, K., Zimand, E., … Davis, M. (2004). Cognitive enhancers as adjuncts to psychotherapy: use of D-cycloserine in phobic individuals to facilitate extinction of fear. *Archives of General Psychiatry*, *61*(11), 1136–1144. http://doi.org/10.1001/archpsyc.61.11.1136

Reynolds, J. H., & Heeger, D. J. (2009). The Normalization Model of Attention. *Neuron*, *61*(2), 168–185. https://doi.org/10.1016/j.neuron.2009.01.002

Robol, V., Tibber, M. S., Anderson, E. J., Bobin, T., Carlin, P., Shergill, S. S., & Dakin, S. C. (2013). Reduced crowding and poor contour detection in schizophrenia are consistent with weak surround inhibition. *PloS One*, *8*(4), e60951. https://doi.org/10.1371/journal.pone.0060951

Roelfsema, P. R., Lamme, V. A. F., & Spekreijse, H. (2004). Synchrony and covariation of firing rates in the primary visual cortex during contour grouping. *Nature Neuroscience*, *7*(9), 982–991. https://doi.org/10.1038/nn1304

Sanders, M. J., Wiltgen, B. J., & Fanselow, M. S. (2003). The place of the hippocampus in fear conditioning. *European Journal of Pharmacology*, *463*(1–3), 217–223. http://doi.org/10.1016/S0014-2999(03)01283-4

Saucer, R. T. (1958). A further study of the perception of apparent motion by schizophrenics. *Journal of Consulting Psychology*, *22*(4), 256–258.

Schaefer, H. S., Larson, C. L., Davidson, R. J., & Coan, J. A. (2014). Brain, body, and cognition: Neural, physiological and self-report correlates of phobic and normative fear. *Biological Psychology*, *98*, 59–69. http://doi.org/10.1016/j.biopsycho.2013.12.011

Schaefer, J., Giangrande, E., Weinberger, D. R., & Dickinson, D. (2013). The global cognitive impairment in schizophrenia: consistent over decades and around the world. *Schizophrenia Research*, *150*(1), 42–50. https://doi.org/10.1016/j.schres.2013.07.009

Schallmo, M.-P., Sponheim, S. R., & Olman, C. A. (2013). Abnormal contextual modulation of visual contour detection in patients with schizophrenia. *PloS One*, *8*(6), e68090. https://doi.org/10.1371/journal.pone.0068090

Schallmo, M.-P., Sponheim, S. R., & Olman, C. A. (2015). Reduced contextual effects on visual contrast perception in schizophrenia and bipolar affective disorder. *Psychological Medicine*, *45*(16), 3527–3537. https://doi.org/10.1017/S0033291715001439

Schiller, D., Levy, I., Niv, Y., LeDoux, J. E., & Phelps, E. A. (2008). From Fear to Safety and Back: Reversal of Fear in the Human Brain. *The Journal of Neuroscience*, *28*(45), 11517–11525. http://doi.org/10.1523/JNEUROSCI.2265-08.2008

Scholte, H. S., Jolij, J., Fahrenfort, J. J., & Lamme, V. A. F. (2008). Feedforward and recurrent processing in scene segmentation: electroencephalography and functional magnetic resonance imaging. *Journal of Cognitive Neuroscience*, *20*(11), 2097–2109. https://doi.org/10.1162/jocn.2008.20142

Schwabe, L., Obermayer, K., Angelucci, A., & Bressloff, P. C. (2006). The role of feedback in shaping the extra-classical receptive field of cortical neurons: a recurrent network model. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *26*(36), 9117–9129. https://doi.org/10.1523/JNEUROSCI.1253-06.2006

Schwartz, O., Hsu, A., & Dayan, P. (2007). Space and time in visual context. *Nature Reviews. Neuroscience*, *8*(7), 522–535. https://doi.org/10.1038/nrn2155

Schwartz, O., Sejnowski, T. J., & Dayan, P. (2009). Perceptual organization in the tilt illusion. *Journal of Vision*, *9*(4), 19.1-20. https://doi.org/10.1167/9.4.19

Schwartz, S., Vuilleumier, P., Hutton, C., Maravita, A., Dolan, R. J., & Driver, J. (2005). Attentional Load and Sensory Competition in Human Vision: Modulation of

fMRI Responses by Load at Fixation during Task-irrelevant Stimulation in the Peripheral Visual Field. *Cerebral Cortex*, *15*(6), 770–786. http://doi.org/10.1093/cercor/bhh178

Sehatpour, P., Dias, E. C., Butler, P. D., Revheim, N., Guilfoyle, D. N., Foxe, J. J., & Javitt, D. C. (2010). Impaired visual object processing across an occipital-frontal-hippocampal brain network in schizophrenia: an integrated neuroimaging study. *Archives of General Psychiatry*, *67*(8), 772–782. https://doi.org/10.1001/archgenpsychiatry.2010.85

Sengpiel, F., Sen, A., & Blakemore, C. (1997). Characteristics of surround inhibition in cat area 17. *Experimental Brain Research*, *116*(2), 216–228.

Seymour, K., Stein, T., Sanders, L. L. O., Guggenmos, M., Theophil, I., & Sterzer, P. (2013). Altered contextual modulation of primary visual cortex responses in schizophrenia. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *38*(13), 2607–2612. https://doi.org/10.1038/npp.2013.168

Shagass, C., & Schwartz, M. (1965). VISUAL CEREBRAL EVOKED RESPONSE CHARACTERISTICS IN A PSYCHIATRIC POPULATION. *The American Journal of Psychiatry*, *121*, 979–987. https://doi.org/10.1176/ajp.121.10.979

Shergill, S. S., White, T. P., Joyce, D. W., Bays, P. M., Wolpert, D. M., & Frith, C. D. (2014). Functional magnetic resonance imaging of impaired sensory prediction in schizophrenia. *JAMA Psychiatry*, *71*(1), 28–35. https://doi.org/10.1001/jamapsychiatry.2013.2974

Shin, Y.-W., Na, M. H., Ha, T. H., Kang, D.-H., Yoo, S.-Y., & Kwon, J. S. (2008). Dysfunction in configural face processing in patients with schizophrenia. *Schizophrenia Bulletin*, *34*(3), 538–543. https://doi.org/10.1093/schbul/sbm118

Shushruth, S., Mangapathy, P., Ichida, J. M., Bressloff, P. C., Schwabe, L., & Angelucci, A. (2012). Strong recurrent networks compute the orientation tuning of surround modulation in the primate primary visual cortex. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *32*(1), 308–321. https://doi.org/10.1523/JNEUROSCI.3789-11.2012

Silverstein, S. M., All, S. D., Kasi, R., Berten, S., Essex, B., Lathrop, K. L., & Little, D. M. (2010). Increased fusiform area activation in schizophrenia during processing of spatial frequency-degraded faces, as revealed by fMRI. *Psychological Medicine*, *40*(7), 1159–1169. https://doi.org/10.1017/S0033291709991735

Silverstein, S. M., Harms, M. P., Carter, C. S., Gold, J. M., Keane, B. P., MacDonald, A., … Barch, D. M. (2015). Cortical contributions to impaired contour integration in schizophrenia. *Neuropsychologia*, *75*, 469–480. https://doi.org/10.1016/j.neuropsychologia.2015.07.003

Silverstein, S. M., & Keane, B. P. (2011). Perceptual organization impairment in schizophrenia and associated brain mechanisms: review of research from 2005 to 2010. *Schizophrenia Bulletin*, *37*(4), 690–699. https://doi.org/10.1093/schbul/sbr052

Silverstein, S. M., Kovács, I., Corry, R., & Valone, C. (2000). Perceptual organization, the disorganization syndrome, and context processing in chronic schizophrenia. *Schizophrenia Research*, *43*(1), 11–20.

Silverstein, S. M., & Rosen, R. (2015). Schizophrenia and the eye. *Schizophrenia Research. Cognition*, *2*(2), 46–55. https://doi.org/10.1016/j.scog.2015.03.004

Silverstein, S. M., & Thompson, J. L. (2015). A vision science perspective on schizophrenia. *Schizophrenia Research. Cognition*, *2*(2), 39–41. https://doi.org/10.1016/j.scog.2015.05.003

Skottun, B. C., & Skoyles, J. R. (2007). Contrast sensitivity and magnocellular functioning in schizophrenia. *Vision Research*, *47*(23), 2923–2933. https://doi.org/10.1016/j.visres.2007.07.016

Skottun, B. C., & Skoyles, J. R. (2010). On using Vernier acuity to assess magnocellular sensitivity. *Brain and Cognition*, *72*(2), 165-166-168. https://doi.org/10.1016/j.bandc.2009.07.001

Slaghuis, W. L. (1998). Contrast sensitivity for stationary and drifting spatial frequency gratings in positive- and negative-symptom schizophrenia. *Journal of Abnormal Psychology*, *107*(1), 49–62.

Slaghuis, W. L. (2004). Spatio-temporal luminance contrast sensitivity and visual backward masking in schizophrenia. *Experimental Brain Research*, *156*(2), 196–211. https://doi.org/10.1007/s00221-003-1771-3

Slotnick, S. D., & Moo, L. R. (2006). Prefrontal cortex hemispheric specialization for categorical and coordinate visual spatial memory. *Neuropsychologia*, *44*(9), 1560–1568. https://doi.org/10.1016/j.neuropsychologia.2006.01.018

Speck, L. B., Dim, B., & Mercer, M. (1966). Visual evoked responses of psychiatric patients. *Archives of General Psychiatry*, *15*(1), 59–63.

Spencer, K. M. (2008). Visual gamma oscillations in schizophrenia: implications for understanding neural circuitry abnormalities. *Clinical EEG and Neuroscience*, *39*(2), 65–68. https://doi.org/10.1177/155005940803900208

Spencer, K. M., Nestor, P. G., Perlmutter, R., Niznikiewicz, M. A., Klump, M. C., Frumin, M., … McCarley, R. W. (2004). Neural synchrony indexes disordered perception and cognition in schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(49), 17288–17293. https://doi.org/10.1073/pnas.0406074101

Sponheim, S. R., Sass, S. M., Noukki, A. L., & Hegeman, B. M. (2013). Fragile early visual percepts mark genetic liability specific to schizophrenia. *Schizophrenia Bulletin*, *39*(4), 839–847. https://doi.org/10.1093/schbul/sbs041

Spratling, M. W. (2011). A single functional model accounts for the distinct properties of suppression in cortical area V1. *Vision Research*, *51*(6), 563–576. https://doi.org/10.1016/j.visres.2011.01.017

Steele, R. J., Dermon, C. R., & Stewart, M. G. (1996). D-cycloserine causes transient enhancement of memory for a weak aversive stimulus in day-old chicks (Gallus domesticus). *Neurobiology of Learning and Memory*, *66*(2), 236–240. http://doi.org/10.1006/nlme.1996.0064

Steinman, B. A., Steinman, S. B., & Lehmkuhle, S. (1997). Transient visual attention is dominated by the magnocellular stream. *Vision Research*, *37*(1), 17–23.

Sterzer, P., Mishara, A. L., Voss, M., & Heinz, A. (2016). Thought Insertion as a Self-Disturbance: An Integration of Predictive Coding and Phenomenological Approaches. *Frontiers in Human Neuroscience*, *10*, 502. https://doi.org/10.3389/fnhum.2016.00502

Supèr, H., Spekreijse, H., & Lamme, V. A. (2001). Two distinct modes of sensory processing observed in monkey primary visual cortex (V1). *Nature Neuroscience*, *4*(3), 304–310. https://doi.org/10.1038/85170

Thompson, L. T., & Disterhoft, J. F. (1997). Age- and dose-dependent facilitation of associative eyeblink conditioning by D-cycloserine in rabbits. *Behavioral Neuroscience*, *111*(6), 1303–1312.

Tibber, M. S., Anderson, E. J., Bobin, T., Antonova, E., Seabright, A., Wright, B., … Dakin, S. C. (2013). Visual surround suppression in schizophrenia. *Frontiers in Psychology*, *4*, 88. https://doi.org/10.3389/fpsyg.2013.00088

Tolhurst, D. J., & Thompson, P. G. (1975). Orientation illusions and after-effects: inhibition between channels. *Vision Research*, *15*, 967–972.

Uhlhaas, P. J., Phillips, W. A., & Silverstein, S. M. (2005). The course and clinical correlates of dysfunctions in visual perceptual organization in schizophrenia during the remission of psychotic symptoms. *Schizophrenia Research*, *75*(2–3), 183–192. https://doi.org/10.1016/j.schres.2004.11.005

Uhlhaas, P. J., & Silverstein, S. M. (2005). Perceptual organization in schizophrenia spectrum disorders: empirical research and theoretical implications. *Psychological Bulletin*, *131*(4), 618–632. https://doi.org/10.1037/0033-2909.131.4.618

Uhlhaas, P. J., & Singer, W. (2006). Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. *Neuron*, *52*(1), 155–168. https://doi.org/10.1016/j.neuron.2006.09.020

Van Berckel, B. N., Lipsch, C., Timp, S., Gispen-de Wied, C., Wynne, H., van Ree, J. M., & Kahn, R. S. (1997). Behavioral and neuroendocrine effects of the partial NMDA agonist D-cycloserine in healthy subjects. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *16*(5), 317–324. http://doi.org/10.1016/S0893-133X(96)00196-0

Wacongne, C. (2016). A predictive coding account of MMN reduction in schizophrenia. *Biological Psychology*, *116*, 68–74. https://doi.org/10.1016/j.biopsycho.2015.10.011

Wenderoth, P., & Johnstone, S. (1988). The different mechanisms of the direct and indirect tilt illusions. *Vision Research*, *28*(2), 301–312.

Westheimer, G. (1990). Simultaneous orientation contrast for lines in the human fovea. *Vision Research*, *30*(11), 1913–1921.

Williams, A. L., Singh, K. D., & Smith, A. T. (2003). Surround modulation measured with functional MRI in the human visual cortex. *Journal of Neurophysiology*, *89*(1), 525–533. https://doi.org/10.1152/jn.00048.2002

Wokke, M. E., Vandenbroucke, A. R. E., Scholte, H. S., & Lamme, V. A. F. (2013). Confuse your illusion: feedback to early visual cortex contributes to perceptual completion. *Psychological Science*, *24*(1), 63–71. https://doi.org/10.1177/0956797612449175

Wynn, J. K., Green, M. F., Engel, S., Korb, A., Lee, J., Glahn, D., … Cohen, M. S. (2008). Increased extent of object-selective cortex in schizophrenia. *Psychiatry Research*, *164*(2), 97–105. https://doi.org/10.1016/j.pscychresns.2008.01.005

Xing, J., & Heeger, D. J. (2000). Center-surround interactions in foveal and peripheral vision. *Vision Research*, *40*(22), 3065–3072.

Xue, J.-G., Masuoka, T., Gong, X.-D., Chen, K.-S., Yanagawa, Y., Law, S. K. A., & Konishi, S. (2011). NMDA receptor activation enhances inhibitory GABAergic transmission onto hippocampal pyramidal neurons via presynaptic and postsynaptic mechanisms. *Journal of Neurophysiology*, *105*(6), 2897–2906. https://doi.org/10.1152/jn.00287.2010

Yang, E., Tadin, D., Glasser, D. M., Hong, S. W., Blake, R., & Park, S. (2013). Visual context processing in schizophrenia. *Clinical Psychological Science: A Journal of the Association for Psychological Science*, *1*(1), 5–15. https://doi.org/10.1177/2167702612464618

Yeap, S., Kelly, S. P., Sehatpour, P., Magno, E., Javitt, D. C., Garavan, H., … Foxe, J. J. (2006). Early visual sensory deficits as endophenotypes for schizophrenia: high-density electrical mapping in clinically unaffected first-degree relatives. *Archives of General Psychiatry*, *63*(11), 1180–1188. https://doi.org/10.1001/archpsyc.63.11.1180

Yoon, J. H., D'Esposito, M., & Carter, C. S. (2006). Preserved function of the fusiform face area in schizophrenia as revealed by fMRI. *Psychiatry Research*, *148*(2–3), 205–216. https://doi.org/10.1016/j.pscychresns.2006.06.002

Yoon, J. H., Maddock, R. J., Rokem, A., Silver, M. A., Minzenberg, M. J., Ragland, J. D., & Carter, C. S. (2010). GABA concentration is reduced in visual cortex in schizophrenia and correlates with orientation-specific surround suppression. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *30*(10), 3777–3781. https://doi.org/10.1523/JNEUROSCI.6158-09.2010

Yoon, J. H., Rokem, A. S., Silver, M. A., Minzenberg, M. J., Ursu, S., Ragland, J. D., & Carter, C. S. (2009). Diminished orientation-specific surround suppression of visual processing in schizophrenia. *Schizophrenia Bulletin*, *35*(6), 1078–1084. https://doi.org/10.1093/schbul/sbp064

Yoshino, A., Kawamoto, M., Yoshida, T., Kobayashi, N., Shigemura, J., Takahashi, Y., & Nomura, S. (2006). Activation time course of responses to illusory contours and salient region: a high-density electrical mapping comparison. *Brain Research*, *1071*(1), 137–144. https://doi.org/10.1016/j.brainres.2005.11.089

Yu, D., Ponomarev, A., & Davis, R. L. (2004). Altered representation of the spatial code for odors after olfactory classical conditioning; memory trace formation by synaptic recruitment. *Neuron*, *42*(3), 437–449.

Zhang, J. X., Leung, H.-C., & Johnson, M. K. (2003). Frontal activations associated with accessing and evaluating information in working memory: an fMRI study. *NeuroImage*, *20*(3), 1531–1539.

Zheng, Y., Li, H., Ning, Y., Ren, J., Wu, Z., Huang, R., … She, S. (2016). Sluggishness of Early-Stage Face Processing (N170) Is Correlated with Negative and General Psychiatric Symptoms in Schizophrenia. *Frontiers in Human Neuroscience*, *10*, 615. https://doi.org/10.3389/fnhum.2016.00615