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UNIVERSITY OF CALIFORNIA, SAN DIEGO

SAN DIEGO STATE UNIVERSITY

# Implicit socioemotional modulation of working memory brain activity in schizophrenia

A dissertation submitted in partial satisfaction of the requirements for the degree

Doctor of Philosophy

in

Clinical Psychology

by

Khalima Alicia Bolden

Committee in charge:

University of California San Diego

Professor Gregory G. Brown, Chair
Professor Kristin Cadenhead
Professor Elizabeth Twamley

San Diego State University

Professor Claire Murphy
Professor Ralph Axel Mueller

2016

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The Dissertation of Khalima Alicia Bolden is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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Chair

University of California, San Diego

San Diego State University

2016

# DEDICATION

I dedicate this work to my family and friends, without whom this accomplishment would not have been possible. In particular, I dedicate this work to my mother, because she has always taught me: Life for me ain't been no crystal stair…

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# ACKNOWLEDGEMENTS

This research was made possible by the VA San Diego Mental Illness Research, Education and Clinical Center, the University of California San Diego (UCSD) Center for Functional Magnetic Resonance Imaging, and the UCSD Laboratory of Cognitive Imaging. I would additionally like to thank select members of the Brown Lab for all of their help and support: Michael Thompson, Ph,D., Benjamin S. McKenna, Ph.D., MJ Meloy, Ph.D., and Peter Wirth. I would also like to express my gratitude to my dissertation committee members, Drs. Kristin Cadenhead, Claire Murphy, Ralph-Axel Mueller, and Elizabeth Twamley for their guidance and generous support. Lastly I would like to thank my committee chair, Dr. Gregory G. Brown, who has supported me, guided me, and encouraged me throughout my graduate career.

CURRICULUM VITA

## EDUCATION

**Doctor of Philosophy, Clinical Psychology,** San Diego State University/University of California San Diego, Joint Doctoral Program in Clinical Psychology, San Diego, CA, September 2016.

- Dissertation: *"Implicit socioemotional modulation of working memory brain activity in schizophrenia."*

**Master of Arts, Psychology,** Boston University, Boston, MA, May 2010.
**Bachelor of Science, Clinical Psychology, Minor; Child Development**, Tufts University, Medford, MA, May 2005.

## AWARDS and HONORS

2015-2016 PALA Grant, VISN 22 Mental Illness Research, Education and Clinical Center Awardee, "Implicit socioemotional modulation of working memory brain activity in schizophrenia." Status: Completed.
2012-2013 NIDA Training Grant Trainee, T32DA031098, "Training in Research on Addictions in Interdisciplinary NeuroAIDS (TRAIN)"
Summer 2010 Department of Health and Human Resources, 3R01MH050740-14S1, "Computerized Image Analysis of MR Scans in Schizophrenia"
2008-2010 Boston University NSF ADVANCE PAID Initiative Graduate Fellowship, "WIN: Women In Networks, Building Community and Gaining Voice"

## RELATED EXPERIENCE

***Research***

*08/2010 - present* *Graduate Student Researcher*
Laboratory of Cognitive Imaging, Department of Psychiatry, University of California San Diego, Veteran's Affairs Medical Center, San Diego, CA

- Perform MR image acquisition and analyses to assess the structural and functional correlates of schizophrenia spectrum disorders.
- Perform MR image analysis to assess white matter integrity in individuals diagnosed with HIV, individuals with a history of methamphetamine abuse, and healthy controls.
- Conduct clinical and neuropsychological assessments on patients diagnosed with schizophrenia spectrum disorders as well as healthy controls.
- Assess working memory in patients diagnosed with schizophrenia spectrum disorders and healthy controls.

*Supervisor: Gregory G. Brown, Ph.D.*

*07/2012 – 07/2013* *Training Grant Trainee*

Translational Methamphetamine AIDS Research Center, Department of Psychiatry, University of California San Diego, La Jolla, CA

- Performed neurobehavioral assessments on individuals diagnosed with the Human Immunodeficiency Virus (HIV), those with a history of methamphetamine abuse, and healthy controls.
- Examined correlates between neuropsychological functioning and neurological structure in individuals infected with HIV and those with a history of methamphetamine abuse.

*Supervisor Steven P. Woods, Psy.D.*

*02/2009 - 08/2010* *Research Assistant*

Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School Affiliate, Boston, MA February 2009 – August 2010

- Aided in the study of schizophrenia and schizophrenia spectrum disorders through the analysis of both structural and functional magnetic resonance mediums.
- Utilized image analysis software to assess white matter integrity in patients diagnosed with schizophrenia.
- Examined the structural integrity of medial temporal lobe structures in patients diagnosed with Post Traumatic Stress Disorder.

*Supervisor: Martha E. Shenton, Ph.D.*

*09/2008 – 05/2010* *Graduate Student Researcher*

Department of Psychology, Boston University, Boston, MA September 2008 – May 2010

- Assessed the disparities in the networks of women scientists in the STEM disciplines at Boston University.
- Aided in the development and implementation of programs seeking to improve professional networks for historically disadvantaged populations seeking tenure at Boston University.

*Supervisor: Deborah Belle, Ph.D.*

*09/2008 – 08/2009* *Graduate Student Researcher*

Department of Psychology, Boston University, Boston, MA September 2008 – August 2009

- Aided in the study of visual impairment in patients diagnosed with Alzheimer's and Parkinson's disease.
- Assisted in data analysis and management.

*Supervisor: Alice Cronin-Golomb, Ph.D.*

*06/2006 – 09/2008* *Research Coordinator*

Departments of Neurology and Radiology, Brigham and Women's Hospital, Harvard Medical School Affiliate, Boston, MA June 2006 – September 2008

- Performed MR image analysis for studies assessing the neuropathology of Multiple Sclerosis and HIV.
- Responsible for patient and subject recruitment for major studies ongoing within the lab. Collaborated with colleagues at the Partners Multiple Sclerosis Center to establish and maintain the best recruitment strategies possible for all studies.
- Administered neuropsychological assessments with patients enrolled in a Multiple Sclerosis study.
- Responsible for all IRB submissions.

*Supervisors: David F. Tate, Ph.D. and Charles R. G. Guttmann, M.D.*

***Clinical***

*07/2015 – 06/2016* *Psychology Intern*

UCLA Semel Institute for Neuroscience and Human Behavior Adolescent Serious Mental Illness Track, Los Angeles, CA

- Conduct clinical, psychodiagnostic, and neuropsychological assessments with adolescents and young adults suspected to experience symptoms associated with prodromal psychosis and individuals diagnosed with 22q11.2 deletion syndrome at the Center for Assessment and Prevention of Prodromal States (CAPPS).
- Provide Family Focused Therapy for adolescents diagnosed with mood and psychosis spectrum disorders at the Child and Adolescent Mood Disorders Program (CHAMP).
- Provide consultation and brief assessments for children and adolescents presenting in the UCLA Adolescent Medicine Clinic.
- Conduct clinical, psychodiagnostic, and neuropsychological assessments with children and adolescents with possible autism spectrum diagnoses.

*Supervisors: Carrie Bearden, Ph.D., David Miklowitz Ph.D., Angus Strachan, Ph.D., Sarah Marvin, Ph.D., C. Enjey Lin, Ph.D., and Brenda Bursch, Ph.D.*

*07/2014 – 06/2015* *Graduate Student Clinician*

Rady Children's Hospital Child and Adolescent Psychiatry Service (CAPS) Inpatient Unit, San Diego, CA

- Administer individualized and group evidenced based treatments to children and adolescents with serious mental illness who were admitted to the inpatient unit. Caseload 5 hours of direct service hours per week.
- Administered cognitive, neuropsychological, and psychodiagnostic assessments to children and adolescents on the inpatient unit.

*Supervisor: Sandra J. Brown, Ph.D.*

*07/2013 – 06/2014* *Graduate Student Clinician*

University of California San Diego Hospital Outpatient Psychiatry Clinic, San Diego, CA

- Provided intake assessments, individualized and group evidenced based treatments to clients with serious mental illness and personality disorders presenting the UCSD Adult Outpatient Psychiatry Clinic. Caseload 7 hours of direct service hours per week.
- Administered cognitive, neuropsychological, and psychodiagnostic assessments to clients throughout the clinic.

*Supervisors: Cynthia Gomes, Ph.D., Elizabeth Twamley, Ph.D., and Patricia Judd, Ph.D.*

*07/2012 – 06/2013* *Graduate Student Clinician*

Rady Children's Hospital Outpatient Psychiatry Clinic, San Diego, CA

- Administer evidenced based treatments to children and families presenting to the Child and Adolescent Outpatient Psychiatry Clinic. Caseload 8 hours of direct service hours per week.
- Administered cognitive, neuropsychological, and psychodiagnostic assessments to children presenting at the clinic.
- Consulted with scholastic and medical professionals involved with clients to provide coordinated care to clients being seen in the clinic.
- Participated in the AIM HI study introducing a new treatment for children with autism spectrum disorders.

*Supervisor: Katherine Williams, Ph.D., Lauren Brookman-Frazee, Ph.D., and Colby Cheblowski, Ph.D.*

*07/2011 – 06/2012* *Graduate Student Clinician*

San Diego State University Psychology Clinic, San Diego, CA

- Administer psychotherapy under the supervision of experienced licensed clinicians with specific experience in: Cognitive Behavior Therapy, Exposure Therapy, Parent and Child Interactive Therapy, and Social Skills

Training. Caseload of 4 patients for 10 hrs/week and 4 hrs/week of supervision. Experience in child & family, adult, and couples psychotherapy.

- Assessment experience including but not limited to; SCID, Wechsler scales, WRAT, KSADS-PL, CBCL Beck scales, MCMI, and the MMPI.

*Supervisors: Monica Ulibarri, Ph.D. and Emily Trask, Ph.D.*

***Teaching***

*09/2009 – 12/2009* *Teaching Assistant*
Boston University, Boston MA

- Functioned as a Teaching Assistant for a dual undergraduate and graduate course on the neuroplastic capabilities of the brain.

*Supervisor: Jacqueline Liederman, Ph.D.*

**RELATED SKILLS**

MRI image acquisition and analysis; Familiarity with Slicer, AFNI, FSL, Perl, EPRIME, Freesurfer, Matlab, Linux, SPSS, HTML editing and website development, Dreamweaver, and Wordpress.

**PUBLICATIONS**

***Journal Articles***

**K. A. Bolden**, G. G. Brown, S. P. Woods, K. Cadenhead, C. Murphy, I. Grant, & The TMARC Group. Assessing Callosal Fiber Tracts in HIV Infection and Methamphetamine Dependence: A Diffusion Tensor Imaging Study. *To be submitted to Psychiatry Research: Neuroimaging.*

J. E. Cattie, M. J. Marquine, **K. A. Bolden**, L. C. Obermeit, E. E. Morgan, D. R. Franklin, A. Umlauf, J. M. Beck, J. H. Atkinson, I. Grant, S. P. Woods, & The TMARC Group. (In Press). Predictors of Attrition in a Cohort Study of HIV Infection and Methamphetamine Dependence. *Journal of Substance Use.*

R. Kamat, G. G. Brown, **K. A. Bolden**, T. D. Marcotte, S. L. Letendre, R. J. Ellis, S. P. Woods, R. K. Heaton, I. Grant, and the TMARC Group. 2014. Apathy is associated with white matter abnormalities in anterior, medial regions in persons with HIV. *Journal of Clinical Experimental Neuropsychology.*

Q. R. Mano, G. G. Brown, H. Mirzakhanian, **K. A. Bolden**, K. S. Cadenhead, and G. Light. 2014. Not all distraction is bad: Working memory vulnerability to implicit emotional distraction correlates with negative symptoms and functional impairment in psychosis. *Schizophrenia Research and Treatment, 2014,* 320948.

L. C. Obermeit, J. E. Cattie, **K. A. Bolden**, M. Marquine, E. E. Morgan, D. R. Franklin, J. H. Atkinson, I. Grant, S. P. Woods, and the TMARC Group. Attention-Deficit/Hyperactivity Disorder among chronic methamphetamine

users: Frequency, persistence, and adverse effects on everyday functioning. *Addictive Behaviors, 38*(12), 2874-2878.

G. G. Brown, T. Turner, Q. R. Mano, **K. A. Bolden**, & M. L. Thomas. 2013. Experimental manipulation of working memory model parameters: An Exercise in construct validity. *Psychological Assessment, 25*(3), 844-858.

Q. R. Mano, G. G. Brown, **K. A. Bolden**, R. Aupperle, M. P. Paulus, M. B. Stein. 2012. Curvilinear relationship between phonological working memory load and social emotional modulation. *Cognition and Emotion, 27*(2), 283-204.

A. Mike, B. I. Glanz, P. G Hildenbrand, D. Meier, **K. A. Bolden**, M. Liguori, E. Dell'Oglio, B. C. Healy, R. Bakshi, C. R. G. Guttmann. 2011. Identification and clinical impact of multiple sclerosis cortical lesions as assessed by routine 3T MR imaging. *American Journal of Neuroradiology, 32,* 515-21.

***Abstracts***

R. Kamat, G. G. Brown, **K. A. Bolden**, T. D. Marcotte, S. L. Letendre, R. J. Ellis, S. P. Woods, R. K. Heaton, I. Grant, and the TMARC Group. 2014. Apathy is associated with white matter abnormalities in anterior, medial regions in persons with HIV. International Neuropsychological Society. February 12-15, 2014. Seattle, Washington.

G. G. Brown, M. Scadeng, R. Bussell, S. L. Archibald, C. L. Achim, S. Semenova, **K. A. Bolden**, J. P. Kesby, A. Markou, S. P. Woods, I. Grant, and The TMARC Group. 2013. Brain Diffusion Tensor Imaging in HIV Infected Subjects and the gp120 Transgenic Mouse Model. Society for Neuroscience. November 9-13, 2013. San Diego, CA.

L. C. Obermeit, J. E. Cattie, **K. A. Bolden**, M. Marquine, E. E. Morgan, D. R. Franklin, J. H. Atkinson, I. Grant, S. P. Woods, and the TMARC Group. 2013. Attention-Deficit/Hyperactivity Disorder among chronic methamphetamine users: Frequency, persistence, and adverse effects on everyday functioning. The College on Problems of Drug Dependence. June 15-20, 2013. San Diego, CA.

Q. R. Mano, G. G. Brown, H. Mirzakhanian, **K. A. Bolden**, K. S. Cadenhead, G. A. Light. 2013. Not all distraction is bad: Working memory vulnerability to implicit emotional distraction correlates with negative symptoms and functional impairment in psychosis. International Congress on Schizophrenia Research. April 21-25, 2013, Orlando, Fl.

**K. A. Bolden,** G. G. Brown, S. P. Woods, I. Grant, The TMARC Group. 2013. Assessing callosal fibers in methamphetamine dependence and HIV infection. International Neuropsychological Society. February 6-9, 2013, Waikoloa, HI.

**K. A. Bolden**, H. Mirzakhanian, K. S. Cadenhead, L. T. Eyler, G. G. Brown. 2012. White matter and clinical symptomatology in the early stages of schizophrenia. Schizophrenia International Research Society. April 5-9, 2012, Florence, Italy.

H. Mirzakhanian, **K. A. Bolden,** K. S. Cadenhead, L. T. Eyler, G. G. Brown. 2012. A Multimodal study of emotion processing in prodromal and first-episode

schizophrenia. Schizophrenia International Research Society. April 5-9, 2012, Florence, Italy.

G. G. Brown, J. B. Lohr, **K. A. Bolden**. 2011. Working memory in schizoaffective disorder: A Latent components analysis. International Congress on Schizophrenia Research Cognition Satellite Meeting, April 1-2, 2011, Colorado Springs, Colorado.

**K. A. Bolden**, J. S. Schneiderman, A. LaVenture, M. T. Vu, P. E. Pelavin, D. P. Terry, R. I. Mesholam-Gately, L. J. Seidman, J. M. Goldstein, R. W. McCarley, M. J. Lyons, M. Kubicki, M. E. Shenton. 2010. White matter differences in the inferior longitudinal fasciculus between first episode and chronic schizophrenia patients. The 18th Harvard Psychiatry Annual research Day, Sponsored by the Mysell Committee, Department of Psychiatry, Harvard Medical School, March 24, 2010, Boston, MA.

A. Mike, B. I. Glanz, P. G Hildenbrand, D. Meier, **K. A. Bolden**, E. Dell'Oglio, B. C. Healy, M. Liguori, R. Bakshi, C. R. G. Guttmann. 2010. 3T MRI frequency of MS cortical lesions and their relationship with cognitive performance. American Academy of Neurology, April 10-17, 2010, Toronto, ON, Canada.

**K. A. Bolden**, J. Conley, R. H. Paul, K. Coop, K. Tashima, T. Flannigan, C. R. G. Guttmann, D. F. Tate. 2008. Cognitive performance and medial temporal lobe volumes in HIV+ patients. International Neuropsychological Society, February 6-9, 2008, Waikoloa, HI.

J. Conley, **K. A. Bolden**, R. H. Paul, K. Coop, K. Tashima, T. Flannigan, C. R. G. Guttmann, D. F. Tate. 2008. Neurocognitive performance of HIV+ patients correlates with MRI volumetric measures of the basal ganglia. International Neuropsychological Society, February 6-9, 2008, Waikoloa, HI.

D. Tate, J. Conley, R. H. Paul, K. Coop, **K. A. Bolden**, D. H. Laidlaw, S. Zhang, T. Flannigan, K. Tashima. 2008. Hepatitis C Virus co-infection does not significantly worsen neuroimaging measures of diffusivity in HIV infected patients. The Conference on Retroviral and Opportunistic Infections, February 3-6, 2008, Boston, MA.

M. Berger, M. P. Sampat, Z. Liptak, A. Charil, O. Felsovalyi, B. C. Healey, **K. A. Bolden**, M. Polgar-Turcsanyi, R. Bakshi, S. J. Khoury, H. L. Weiner, C. R. G. Guttmann. 2007. Longitudinal study of medulla oblongata atrophy in Multiple Sclerosis. European Committee for Treatment and Research in Multiple Sclerosis, October 11-14, 2007, Prague, Czech Republic.

***Book Chapters***

J. Iudicello, **K. A. Bolden**, S. R. Griglak, & S. P. Woods. (2013). Neuropsychology of Methamphetamine Use. In D. N. Allen and S. P. Woods (Eds). *Neuropsychological aspects of substance use disorders: Evidence-based perspectives*. New York: Oxford University Press.

***Invited Presentations***

Cognitive Performance and Medial Temporal Lobe Volumes in HIV+ Patients. 36th Annual Meeting of the International Neuropsychological Society. 2008. *[Paper Presentation]*

Cognition and Structural Correlates with Medial Temporal Lobe Structures in HIV+ Patients. Brigham and Women's Hospital, Partners MS Center. 2008. *[Invited Lecture]*

**PROFESSIONAL ACTIVITIES**

*04/2014* *Invited Panelist*
"College Week Live" – a webcast event

*03/2012* *Invited Panelist*
"The Minority Graduate Experience at UCSD."

*02/2011* *Invited Panelist*
"UC Edge presents: Students of Color in the Social Sciences: Advice on Doctoral Admissions."

*11/2010* *Invited Panelist*
"Funding for Minority Students in the Social Sciences." 2010.

ABSTRACT OF THE DISSERTATION

Implicit socioemotional modulation of working memory brain activity in schizophrenia

by

Khalima Alicia Bolden

Doctor of Philosophy in Clinical Psychology

University of California San Diego, 2016
San Diego State University, 2016

Professor Gregory G. Brown, Chair

The neural substrate of interactions of working memory (WM) with socio-emotional processing is poorly understood in schizophrenia. This study builds on published papers using a delayed match to sample design to study the interaction of

WM load with type of distracter (socially relevant faces vs. socially irrelevant geometric designs [FvG]) presented briefly during the WM maintenance period. Based on previously published findings, we hypothesize: (1) The FvG difference in brain activity in the dorsolateral prefrontal cortex (DLPFC) in the task maintenance period will be largest at the highest WM load. (2) Among schizophrenia/ schizoaffective patients and healthy controls the magnitude of the face vs. geometric design (FvG) contrast in brain activity in the amygdala during the task maintenance period will follow a quadratic pattern across WM load when averaged over face type. (3) Among schizophrenia patients, the magnitude of the FvG contrast in brain activity in the amygdala and DLPFC at the greatest WM load will be correlated with negative symptoms.

Individuals between the ages of 18-55 diagnosed with schizophrenia/schizoaffective disorder (N = 12) and non-psychiatric controls (N = 20) matched with the patients on age, gender, paternal education and paternal socioeconomic status underwent structural and functional magnetic resonance imaging (fMRI). To assess the effect of implicit socioemotional modulation on brain activity during WM, the effect of facial distraction on brain activation was assessed for WM of pseudowords at three syllable loads (1, 2, and 3) across several face valence types and contrasted with the effect of a geometric distracter.

*Results:* Although patients performed significantly above chance, they were less accurate than controls with no difference in response latency. When the FvG contrast was tested for response latency, we observed a significant quadratic effect of

WM load in healthy controls ($F$[1,19] = 6.108, $p$ = .023, $\eta^2$ = .24) but a linear effect among patients ($F$[1,10] = 4.012, $p$ = .073, $\eta^2$ = .29). Similar patterns were found for response accuracy but were not statistically significant. With regard to neural activity, we found a significant bilateral linear trend of percent signal change on WM load for the FvG contrast in the DLPFC ($F$[1,19] = 5.818, $p$ = .026, MSE = .077, $\eta^2$ = .23). among controls, with brain activation to faces greater than activation to designs only at the highest WM load. In the amygdala we observed a significant bilateral quadratic effect of percent signal change on WM load for the FvG contrast in the control group ($F$[1,19] = 10.423, $p$ = .004, MSE = .121, $\eta^2$ = .35). We observed a significant difference in neural activation patterns in patients compared to controls in the DLPFC and the amygdala. Specifically, in patients, we observed a quadratic instead of a linear trend in the DLPFC but only in the right hemisphere (hemisphere x quadratic: $F$[1,11] = 9.362, $p$ = .011, $\eta$2 = .40). In the amygdala, the patients displayed a quadratic trend also only in the right hemisphere, (hemisphere x quadratic: F[1,11] = 10.442 p = .008, $\eta$2 = .49). In neither controls nor patients did individual differences in the quadratic effect of brain activity in the amygdala correlate with the quadratic effect in response time or accuracy. Although the correlation between the magnitude of the quadratic trend in the right amygdala at the highest WM load with general psychopathology was moderately large in patients, neither this effect nor any other brain activation effects were significantly correlated with psychopathology.

Confirming hypothesis one, controls showed the largest difference in brain activity of the FvG contrast in the DLPFC during the maintenance period at the highest WM load. However, in patients we saw significantly decreased percent signal change in DLPFC at the highest WM load on the FvG contrast in the maintenance period. For hypothesis two we observed a quadratic pattern of WM load on the FvG contrast in the maintenance period for both controls and patients, although this effect was only present in the right hemisphere of patients. Furthermore, contrary to hypothesis 3 we did not observe significant correlations between symptom severity and the magnitude of the FvG contrast in brain activity in the amygdala and DLPFC at the greatest WM load. These results suggest a separate process of social-discrimination is taking place in controls. However, this process appears to be impaired in individuals with schizophrenia. This disruption may be due to poor integration of different brain areas and interhemispheric communication.

## Introduction

Schizophrenia is a neuropsychiatric illness that is estimated to affect approximately 1.1% of the Unite States population with estimated direct and indirect costs ranging up to approximately $65 billion (Knapp, Mangalore, & Simon, 2004). Individuals with schizophrenia account for the largest percentage of psychiatric hospitalizations and associated health care costs (Sun, Liu, Christensen, & Fu, 2007). Schizophrenia is characterized by positive symptoms, or symptoms reflecting distortions of perception or behaviors that most people do not usually experience (e.g., hallucinations, delusions, disorganized speech and behavior) and negative symptoms, or symptoms showing the absence of behavior seen in neurotypical individuals (e.g., blunted or flat affect, anhedonia, avolition, alogia) and impairments in social functioning (American Psychiatric Association, 2013). Impairments in cognitive and social functioning have been demonstrated prior to illness onset and throughout the course of the disorder (Cornblatt et al., 2012; Couture, Penn, & Roberts, 2006; Lotzin, Haack-Dees, Resch, Romer, & Ramsauer, 2013; White, Schmidt, & Karatekin, 2010; White, Schmidt, Kim, & Calhoun, 2011) Social functioning has also been shown to be a predictor of treatment outcome (Ayesa-Arriola et al., 2013; Kee, Green, Mintz, & Brekke, 2003; Perlick, Mattis, Stastny, & Teresi, 1992; Pfammatter, Junghan, & Brenner, 2006). Additionally, cognitive and social deficits do not respond to standard pharmacological treatments of schizophrenia (Barch, 2005; Couture et al., 2006; Kee, Green, Mintz, & Brekke, 2003).

Researchers have reported multiple domains of cognitive and social dysfunction in individuals with schizophrenia. Deficits in working memory and emotion processing have been the most replicated, with both areas showing an association with symptom severity and functional outcomes (Barch, 2005; Barch & Ceaser, 2012; Barch & Smith, 2008; Bozikas, Kosmidis, Anezoulaki, Giannakou, & Karavatos, 2004; Burns, 2006; Couture et al., 2006; Green et al., 2008; Kee et al., 2003; Keefe et al., 2007; Kohler & Martin, 2006; Kohler, Walker, Martin, Healey, & Moberg, 2010; Li, Chan, McAlonan, & Gong, 2009; Pfammatter, Junghan, & Brenner, 2006). In most real-world situations working memory functions in the context of emotional perception; properly attending and managing information while also perceiving and cataloging another person's socioemotional cues. Social functioning involves perceiving, attending to, managing, and using a flowing stream of information while simultaneously processing and expressing socio-emotional information. Engaging in social interactions is likely affected by deficits in managing information (working memory processes) and perceiving and expressing socio-emotional information (emotion processing). Therefore, understanding the nature of working memory and emotion processing dysfunction both separately as well as their interaction, should be undertaken.

Before understanding this process in individuals diagnosed with schizophrenia, it is important to determine the neurophysiology associated with these processes in individuals without psychiatric disorders. To that end, functional activation studies of working memory and emotion processing have yielded

individual results. However, there has been little research on these co-occurring processes in healthy individuals.

## Working Memory

**Models of working memory.** Impairments in working memory in individuals with schizophrenia have been widely demonstrated. However, working memory is a complex cognitive processing involving different subcomponents. To understand the nature of these deficits it is important to examine the various processes involved in working memory as it relates to schizophrenia. Baddeley (2003) proposed four components of working memory: 1) the central executive, which supports the manipulation and transformation of information held within two storage buffers 2) the visual-spatial sketchpad storage buffer for visual information 3) the phonological loop storage buffer for verbal information and 4) the episodic buffer, which is an interface between the working memory subsystems and information contained in long-term memory. Baddeley (2003) further divides the central executive into two subcomponents: automatic and supervisory control. Baddeley (2003) describes automatic control as a more automatic process in which individuals behave in ways consistent with habits and schemas. Supervisory control was described as executive control associated with the task or goal-directed behavior, such as following novel instructions or unfamiliar sequences of steps. Researchers theorized that this particular subcomponent may be most responsible for impairments in working memory given that supervisory control is necessary across different working memory paradigms (Mano & Brown, 2012).

**Working memory impairments in schizophrenia.** Studies have shown consistent impairments in both buffer systems as well as the central executive component of working memory in individuals with schizophrenia. In particular deficits across the encoding, maintenance, and manipulation of information have been demonstrated in patients with schizophrenia (Barch, 2005; Barch & Ceaser, 2012; Barch & Smith, 2008; Brown et al., 2007; Fleming, Goldberg, Gold, & Weinberger, 1995; Hartman, Steketee, Silva, Lanning, & McCann, 2003; Hill, Griffin, Miura, Herbener, & Sweeney, 2010; Kim, Glahn, Nuechterlein, & Cannon, 2004; Lee & Park, 2005; Mayer & Park, 2012; Mazhari et al., 2010; Zilles, Gruber, Falkai, & Gruber, 2010). Another aspect considered is whether the nature of the stimuli involved in the working memory task, namely verbal or visuospatial in nature, has a differing effect on working memory. While there do not appear to be significant differences in performance deficits across the type of stimuli used in tasks, recent evidence suggests there may be a difference in the associated processes involved for verbal vs. visuospatial stimuli (Brown et al., 2007; Kim et al., 2004; Lee & Park, 2005; Zilles et al., 2010). Specifically, a study conducted by Brown et al. (2007) examined differences in working memory components for psychometrically matched verbal and visuospatial stimuli. Here the authors reported significant differences between individuals with schizophrenia and non-psychiatric controls on both verbal and visuoperceptual working memory tasks. Additionally, the authors reported that deficits in verbal working memory performance were associated with working

memory span, whereas deficits in visuospatial working memory performance were associated with attention and encoding.

A meta-analysis by Lee and Park (2005) included over 100 studies of working memory performance in individuals with schizophrenia in their analyses. The authors reported consistent evidence of working memory deficits in individuals with schizophrenia spectrum disorders. Importantly, they did not find a significant impact on the amount time the stimuli should be kept in working memory on effect sizes of working memory deficits in individuals with schizophrenia. The authors suggested this finding indicated greater impairments in encoding for individuals with schizophrenia. However, the authors note this finding does not mean there is an absence of impairments in the maintenance of information in individuals with schizophrenia. To better understand the nature of these specific deficits a greater range of time delays from the presentation of stimuli should be assessed. Studies specifically assessing deficits in item maintenance in schizophrenia have indeed shown consistent impairments in this subprocess as well (Barch & Smith, 2008; Brown et al., 2007; Fleming et al., 1995; Hartman et al., 2003; Hill et al., 2010; Kim et al., 2004; Mazhari et al., 2010; Zilles et al., 2010). Specifically, a study by Mazhari et al. (2010) the authors examined working memory maintenance across short delays to determine differences in working memory maintenance in participants with schizophrenia vs. non-psychiatric controls. The authors reported a greater slope of impairment over maintenance time in individuals with schizophrenia than non-psychiatric controls.

Deficits related to the central executive subcomponent have also been documented in individuals with schizophrenia. Researchers have reported significant deficits in the manipulation of items in working memory tasks (Barch & Smith, 2008; Hill et al., 2010; Kim et al., 2004). In addition to these deficits in manipulating information during working memory tasks, studies have reported significantly more impairment in the presence of distracters during the encoding and maintenance phases of working memory tasks (Barch & Smith, 2008; Fleming et al., 1995; Hill et al., 2010; Kim et al., 2004; Mayer & Park, 2012). For example, Kim et al. (2004) compared the performance in maintenance-only vs. maintenance-and-manipulation working memory tasks in individuals with schizophrenia and non-psychiatric controls. Here the investigators found maintenance and manipulation processes to be impaired in participants with schizophrenia, however, a steep decline in performance of the maintenance-and-manipulation condition in participants with schizophrenia.

**Neural activation associated with working memory.** Functional neuroimaging techniques have provided great insight into understanding relationships between neurological function and behavioral outcomes. Functional magnetic resonance imaging (fMRI) has become the method of choice in the decision neuroscience literature because of its excellent spatial resolution and non-invasive nature that can precisely localize the brain areas activated when subjects perform various human processes. MRI contrast stems from taking advantage of spin relaxation rates in different tissues and the presence of pathology (Pyket, 1982). fMRI is similar to structural MRI but uses the change in magnetization between

oxygen-rich and oxygen-poor blood as its basic measure (Huettel, Song, & McCarthy, 2004). Specifically, task-related fMRI maps the functional activation of the brain by detecting regional differences in blood-oxygenation-level-dependent (BOLD) signal due to changes in neuronal activity. When a participant undergoes a typical fMRI study, the scan maps the changes in blood flow, blood volume, and oxygen extraction (via the BOLD contrast) in response to changing behavioral activity due to altered task demands. Neuroimaging research has indicated the involvement of the prefrontal cortex (PFC), parietal cortex, and anterior cingulate cortex most consistently during working memory tasks (Baddeley, 2003; Bledowski, Kaiser, & Rahm, 2010).

A study by McKenna, Brown, Drummond, Turner, and Mano (2013) examined areas of activation during encoding and maintenance in a verbal working memory task amongst healthy controls. The study demonstrated a linear relationship between verbal working memory load (as measured by syllable load) and BOLD percent signal change; where increased working memory load was associated with increased percent signal change (see Figure 1).

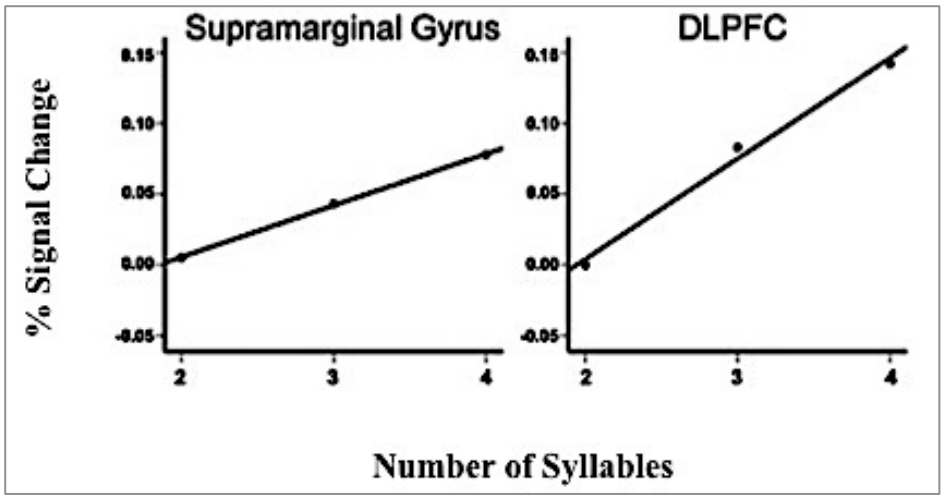



Figure 1. Reproduced from McKenna et al. (2013) showing the observed patterns of brain response (percent change in the BOLD signal) as a function of number of syllables in pseudowords to be learned during the maintenance task intervals for the supramarginal gyrus and dorsolateral prefrontal cortex (DLPFC).

**Neural activation of working memory in schizophrenia.** Concerning neurophysiology, WM dysfunction in schizophrenia has been linked with inefficiency of prefrontal cortex (PFC) functioning. Studies assessing the neurophysiological correlates of working memory in individuals with schizophrenia have shown disruptions in functional activation with the most replicated findings showing altered activation in the PFC. In a meta-analysis by Glahn et al. (2005), the authors analyzed neuroimaging studies that assessed working memory using an N-back task. The authors reported significant *hypoactivation* in the dorsolateral and rostral prefrontal cortices, left premotor cortex, and insula. Additionally, they reported *hyperactivation* in the left frontal pole, dorsomedial prefrontal cortex, and anterior cingulate cortex. However, while many studies have shown that this decreased activation in areas of the prefrontal cortex, recent studies have reported instances of *hyperfrontality*,

specifically in the dorsolateral prefrontal cortex (DLPFC). A subsequent meta-analysis conducted by Minzenberg, Laird, Thelen, Carter, and Glahn (2009) reported *hypoactivation* in the dorsolateral and ventrolateral prefrontal cortices, premotor cortex, and anterior cingulate cortex with *hyperactivation* in the insula, cingulate gyrus, and medial temporal areas. Studies have consistently reported decreased activation in the prefrontal cortex, leading to a theory of *hypofrontality* in this region. These findings indicate that there is no uniform decrease in activation throughout the prefrontal cortex and other areas involved in working memory performance in individuals with schizophrenia.

Further probing this variability in the prefrontal cortex, Callicott et al. (2003) assessed differences between individuals with schizophrenia and non-psychiatric controls in BOLD responses during a working memory functional magnetic resonance imaging (fMRI) task. The authors reported differences in BOLD responses between individuals with schizophrenia and non-psychiatric controls based on performance. Specifically, the authors split individuals with schizophrenia into low performing and high performing subgroups and reported pervasive *hypofrontality* in low-performing schizophrenia group throughout the DLPFC. In contrast the high-performing schizophrenia group showed areas of *hyperfrontality* (when compared to high-performing controls) as well as *hypofrontality*. The authors concluded that this difference in performance-based activation is indicative of bell-shaped activation x performance relationship. Additional neuroimaging studies have demonstrated increases in DLPFC activation as a function of working memory load until working

memory load exceeds an individual's capacity after which a decrease in DLPFC activity is observed (Manoach et al., 2003; Thermenos et al., 2005). In participants with schizophrenia, this bell-shaped relationship was shifted to the left, due to less-efficient or more effortful performance. Furthermore, when individuals with schizophrenia are matched on performance or relative difficulty to non-psychiatric controls, there is no significant difference in DLPFC activation (Jansma, Ramsey, van der Wee, & Kahn, 2004; Manoach, 2003; Manoach et al., 2000; Thermenos et al., 2005). Furthermore, these disruptions in activity during working memory tasks have been seen in adolescents at risk for psychosis (Alexander-Bloch et al., 2010; Bittner et al., 2014; Diwadkar et al., 2012; Seidman et al., 2006; Yaakub et al., 2013) and individuals experiencing prodromal symptoms (Jacobson et al., 2010; Yaakub et al., 2013), indicating altered activity prior to and at the onset of symptoms.

## Emotion-Processing

**Emotion-processing models.** Emotion-processing, particularly the components of perceiving and interpreting emotions expressed by others is an important function in navigating the world as these emotional signals indicate social approval and disapproval as well as general danger or safety. However, these processes appear to be impaired in individuals diagnosed with schizophrenia (Kohler & Martin, 2006; Li, Chan, McAlonan, & Gong, 2009; Mano & Brown, 2013). Emotion-processing is a somewhat broad neurocognitive domain. Therefore, researchers often divide this neurocognitive process into two larger subcomponents: the first level of processing involving emotion perception/recognition and the

secondary level of processing involving emotion regulation/expression (Pinkham, 2014). Though the bisection of emotion-processing is helpful in separating primary and secondary processes, investigators have long noted that a variety of processes exist within these levels.

Within the primary level of emotion-processing investigators have mostly agreed that visual processing of implicit/automatic and explicit emotion processes, auditory perception of emotions, and identifying/labeling emotions all play an important role (Green & Horan, 2010; Green et al., 2008; Mayer, Salovey, Caruso, & Sitarenios, 2001). Investigations examining implicit tasks differ from explicit tasks primarily with regards to the focus of the task. Specifically, explicit facial processing refers to tasks that focus on presenting faces representing emotions in which individuals are instructed to attend. Implicit emotion-processing tasks are those in which participants are directed to focus on non-emotional dimensions of facial stimuli with the idea that facial emotion stimuli are attended to automatically and therefore modulate performance on the non-emotional task. In this domain, investigators have consistently shown no marked differences in subjects with schizophrenia when compared to non-psychiatric controls (Aichert et al., 2013; Linden et al., 2010; Mano & Brown, 2012).

**Emotion-processing in schizophrenia.** Individuals with schizophrenia have shown impairments on tasks in which they are asked to recognize and label emotions from both visual and auditory emotional cues (Edwards, Jackson, & Pattison, 2002; Garrido-Vasquez, Jessen, & Kotz, 2011; Kohler, Walker, Martin, Healey, & Moberg,

2010; Marwick & Hall, 2008) as well as those involving the expression and regulation of emotions (Hoekert, Kahn, Pijnenborg, & Aleman, 2007; Kohler et al., 2010; Mandal, Pandey, & Prasad, 1998). Individuals with schizophrenia have demonstrated significant impairments in explicit facial processing with large effect sizes in both independent labeling and emotion discrimination tasks relative to non-psychiatric controls (Edwards, Jackson, & Pattison, 2002; Kohler et al., 2010; Marwick & Hall, 2008). A meta-analysis performed by Kohler et al. (2010), the investigators, reported consistent deficits in emotion perception with these deficits generalizing across different types of recognition tasks (identifying vs. differentiating emotions). While impairments in affective labeling generalize across task type, there may be differences with regards to the emotional valence of the faces used in tasks. In particular some studies have demonstrated greater impairments for perceiving and decoding negative emotions (Edwards, Pattison, Jackson, & Wales, 2001; Hall et al., 2008), while others show no difference based on valence (Kucharska-Pietura, David, Masiak, & Phillips, 2005; Mano & Brown, 2012; Marwick & Hall, 2008).

Implicit emotion processing tasks are seen in two forms: 1) implicit/automatic processing tasks, during which participants are directed to focus on non-emotional dimensions of facial stimuli 2) affective priming tasks during which participants are directed to perform cognitive tasks where emotional stimuli are presented fast to prevent conscious processing during the task. Implicit/automatic processing has been shown to be intact amongst individuals with schizophrenia compared to non-psychiatric controls (Aichert et al., 2013; Linden et al., 2010; Mano & Brown, 2012).

However, studies of affective priming have varied results, with some studies reporting significant differences on the effect of affective priming between participants with schizophrenia compared to non-psychiatric controls (Höschel & Irle, 2001) while others did not (Suslow, Droste, Roestel, & Arolt, 2003). Notably, in a study on affective priming by Suslow et al. (2003), the authors studied the effects of affective priming on judging the valence of Chinese ideographs. The investigators reported no differences in affective priming in participants with schizophrenia overall. However, an effect was seen in individuals with schizophrenia who experienced anhedonia and flat affect, specifically were more sensitive to the priming of sad (vs. happy or neutral) affective facial priming.

**Neural activation associated with implicit emotion-processing. F**unctional imaging studies have implicated a variety of brain regions involved in emotion processing: the amygdala and the orbitofrontal cortex (implicated in emotion recognition), prefrontal regions (implicated in emotion identification/regulation, and theory of mind), fusiform and temporal gyri (implicated in facial recognition), and the basal ganglia (implicated in detecting disgust; Abdi & Sharma, 2004; Adolphs, 2002; Straube, Mothes-Lasch, & Miltner, 2011). Studies have shown that these areas, particularly the amygdala, fusiform gyrus, and orbitofrontal cortex are involved in implicit emotion processing. Vuilleumier et al. (2001) assessed implicit/automatic emotion processing by presenting participants with a screen showing two faces and two houses aligned vertically and horizontally. Participants were instructed to attend to the faces or the houses by asking them whether the stimuli (face or house) were the

same. The authors reported activation in the amygdala regardless of whether participants were processing the faces explicitly or implicit. They reported activation in the fusiform gyrus during explicit emotion processing of faces. However, during implicit emotion processing only the right fusiform gyrus showed activation and only during the presentation of fearful (instead of neutral) faces. This pattern of amygdalar and fusiform activation was seen in further studies, showing consistent amygdalar activation during implicit emotion processing and affect dependent activation in areas in the fusiform gyrus (Matsuda et al., 2013). Furthermore, studies assessing implicit processing show continued activation in the amygdala regardless of stimulus type (e.g. affective words, prosody, body language, etc.; Flaisch, Imhof, Schmälzle, Wentz, Ibach, & Schupp 2015; Matsuda et al., 2013; Suslow et al., 2015).

**Neural activation of emotion-processing in schizophrenia.** During emotion perception tasks some studies reported *hypoactivation* of the amygdala (Anticevic et al., 2012; Li et al., 2009; Taylor et al., 2012). Li et al. (2009) conducted a meta-analysis and reported dampened activation in the amygdala and fusiform gyri in participants with schizophrenia compared to controls during explicit emotion perception tasks. However, they noted some studies (though fewer) reported amygdalar *hyperactivation*. Seeking to understand better this phenomenon, Anticevic, and colleagues (2012) examined the integrity of a neural network involving the amygdala and the prefrontal cortex during automatic emotion-processing of negative stimuli in patients with schizophrenia. During the fMRI scan participants performed a simple perceptual decision task where either aversive or neutral distracters were

presented. They reported finding an association between disrupted connections between the amygdala and the prefrontal cortex and task performance where aversive stimuli were presented. This was observed even though there were no statistically significant group differences in reaction time between negative vs. neutral stimuli, emotional ratings across groups, or amygdalar activation. The investigators reported a significant correlation between the amygdala-prefrontal cortex coupling during neutral distracters and negative symptom severity in participants with schizophrenia, particularly in regards to affective flattening. The authors interpret this evidence indicating that the prefrontal cortex-amygdalar network is engaged when one appraises situations in their environment, possibly assessing for relevant emotional information. When emotional stimuli are present, the amygdala is engaged while the prefrontal cortex is brought on to enervate amygdala responsiveness, particularly when the absence of emotional stimuli is found. Furthermore, this feedback between the prefrontal cortex and the amygdala may be disrupted in individuals with schizophrenia thus impairing their ability to process emotion information during cognitive tasks, thereby impairing social interactions.

In another study of automatic emotion-processing Mukherjee et al. (2012) examined neural networks during an implicit emotion-processing task using fearful stimuli. During the scan participants were presented with fearful or neutral facial images then instructed to select the gender for each image. The authors reported disrupted connectivity in the network involving the amygdala and parietal areas as well as the network involving the amygdala and parts of the middle and superior

temporal gyri compared to controls. The authors hypothesized that this disruption in amygdala-parietal and amygdala-temporal networks might indicate a problem with perceiving and recognizing a displayed emotion and connecting that with that person's internal emotional and mental state.

Additional studies of implicit emotion processing in patients with schizophrenia suggest a dysregulation between frontal and parietal areas and the amygdala (Das, et al. 2007; Leitman et al., 2008). Furthermore, researchers have reported findings that suggest disrupted network activation within the frontal lobe itself, particularly between the prefrontal cortex and the middle and inferior frontal cortices (Leitman et al., 2008; Mazza et al., 2013).

**Working Memory and Emotion Processing**

**Behavioral studies.** Assessing implicit socioemotional modulation of working memory is an essential step in understanding the social functioning impairments in individuals with schizophrenia. As stated previously, social interactions involve a variety of cognitive processes, notable, working memory. These working memory processes occur in the presence of implicit emotion processing, namely the simultaneous processing of socioemotional cues from those with whom one is interacting. Understanding the behavioral and neural processes during the interaction of working memory and implicit emotion processing is, therefore, a critical step towards understanding the social function deficits in individuals with schizophrenia. There is a breadth of literature on working memory and emotion processing in individuals with schizophrenia separately, however, there

is a dearth of studies examining affective priming in working memory in individuals with schizophrenia. Behavioral studies examining performance during tasks of working memory with implicit socioemotional modulation in healthy participants have shown an interesting interaction. In general, cognitive science has noted a linear relationship between working memory load and performance (Baddeley, Thomson, & Buchanan, 1975; Brown, Turner, Mano, Bolden, & Thomas, 2013). However, studies of working memory and implicit emotion processing have shown a curvilinear relationship. Mano et al. (2013) examined the relationship interaction between working memory and implicit socioemotional processing in healthy controls. The authors reported a curvilinear relationship between working memory load and performance in the presence of a socioemotional distractor. Specifically, they reported the longest reaction times and impaired accuracy at the intermediate working memory load, rather than at the highest working memory load when the performance associated with the geometric design was subtracted from that of the face stimuli (see Figure 2).

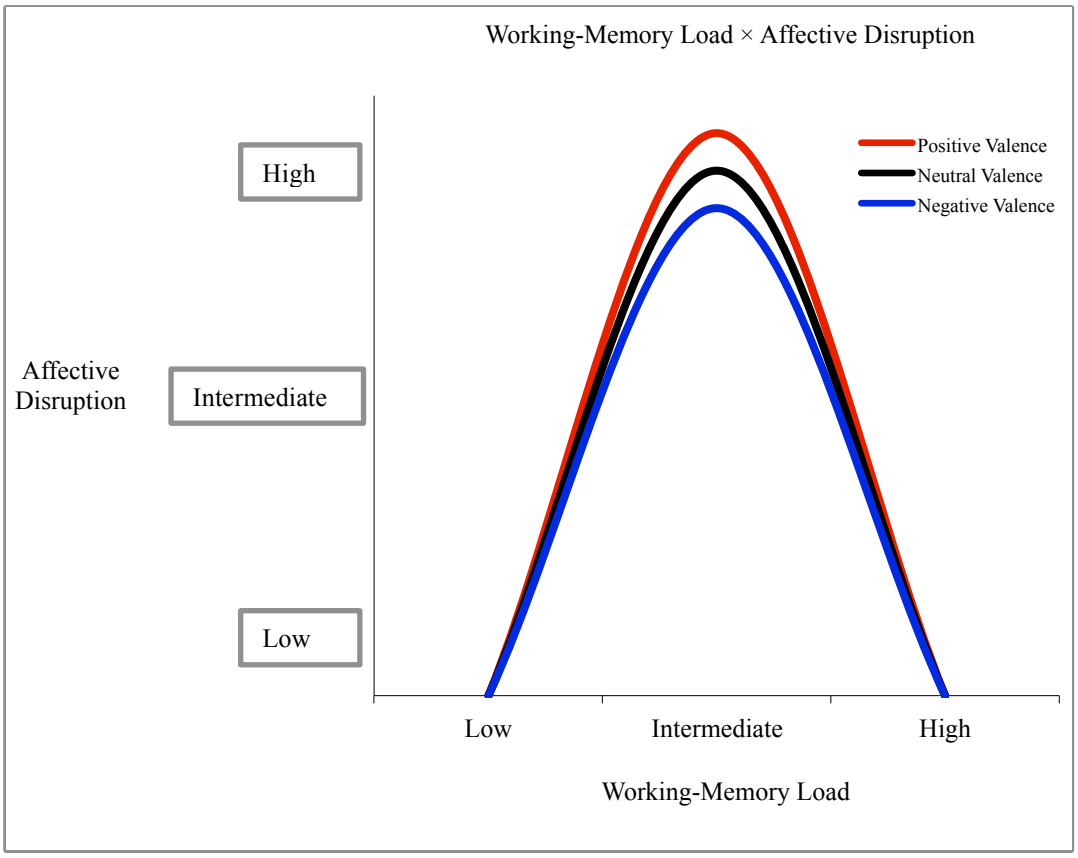



Figure 2. Reproduced from Mano et al. (2013). The effects of stimulus valence are displayed relative to non-affective geometric intrusions. The model recreates behavioral data from both Experiment 1 and 2, in which facial-distracters were disruptive to working memory during intermediate load processing (2-syllables) but not during low and high load processing (1-syllable, 3-syllables, respectively).

Interestingly, this effect was seen across valence type. Specifically, the authors conducted two phases of the experiment, the first using happy, sad, and neutral faces with the second phase, involving a new sample of subjects, replacing

sad faces with fearful ones. In both experiments, the curvilinear nature was observed averaged across face type (compared with a geometric shape) as well as with each type of affective face. This evidence of a curvilinear relationship between cognition and emotion processing indicate that the secondary task (for this paper this would be implicit emotion-processing) depends on the availability of cognitive resources. Generally speaking, the demand of the primary task (for this paper this would be working memory) correlates with whether the secondary task is completed or not.

**Working memory and emotion processing interactions in schizophrenia.** When investigating the interaction between cognition and emotion in individuals with schizophrenia, Mano et al. (2014) reported a similar curvilinear relationship between working memory load and performance (both reaction times and accuracy) in participants with schizophrenia which was similar to that observed in a previous study of non-psychiatric controls (see Figure 3).

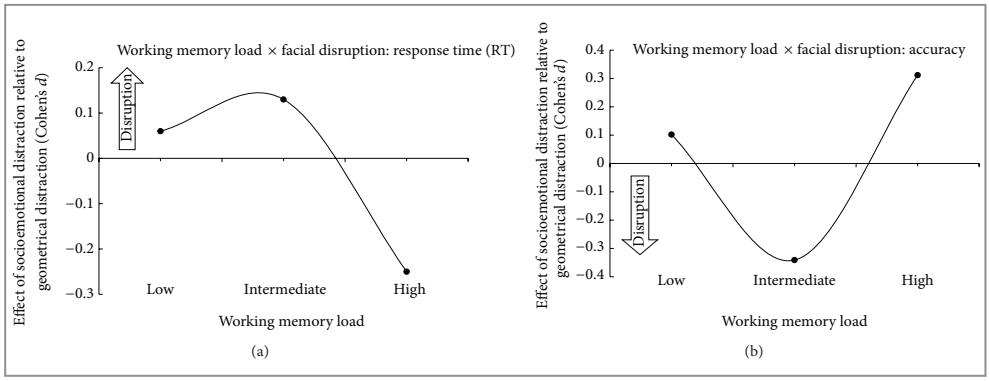



Figure 3. Reproduced from Mano et al. (2014) demonstrating the modulation effects of all facial distracters displayed relative to nonfacial geometric distracters. The zero axis value represents working memory performance in the context of nonfacial geometrical distracters. In (a) depicting response latencies relative to nonfacial geometrical distracters, positive effect sizes denote behavioral disruption while negative effect sizes denote behavioral facilitation. In (b) depicting accuracy relative to nonfacial geometrical distracters, positive effect sizes denote behavioral facilitation while negative effect sizes denote behavioral disruption.

Notably, the authors reported a relationship between affective distraction and symptomatology, with individuals reporting less severe symptoms and better global functioning showing greater distraction at the highest working memory load. The authors proposed that this association might indicate better or intact facial processing in individuals who report less severe symptoms; therefore, facial distracters are more likely to distract these individuals. It should be noted that this study did not include a control group and therefore did not address the question of whether the magnitude of these effects was normal. However, a comparison of effect sizes of the interactions showed a decreased magnitude of curvilinear pattern in individuals with schizophrenia compared to that observed in controls. Other studies assessing working

memory and emotion processing interactions have reported findings that suggest altered, interactions between cognitive and affective processes (Becerril & Barch, 2011; Diaz et al., 2011; Habel et al., 2010; Linden et al., 2010; Pauly et al., 2008; Strauss et al., 2012).

**Neural patterns of working memory and emotion processing.** Studies investigating emotion processing during working memory tasks suggest that neural activation associated with emotion processing is contingent upon working memory resources (Pessoa, McKenna, Gutierrez, & Ungerleider, 2002; Iordan, Dolcos, & Dolcos, 2013). Specifically, as cognitive demand increases, attentional resources are diverted from processing affective stimuli to meet the demands of the primary cognitive task (Hsu and Pessoa, 2007; Van Dillen et al., 2009; McRae, Hughs, Chopra, Gabrieli, Gross, Ochsner, 2010; Yates, Ashwin, & Fox 2010; Kanske and Kotz, 2011). In a study conducted by Pessoa, McKenna, Gutierrez, & Ungerleider (2002) the authors assessed activation patterns associated with emotion processing during a cognitive task. The authors reported decreased amygdalar activation when participants were attending to a primary cognitive task vs. when they attended to the emotion stimuli. Additional studies have further reported findings indicating decreased neural activation in areas associated with emotion processing as cognitive demand increases (Pessoa, 2008; Luo, Qin, Fernandez, Zhang, Klumpers, & Li, 2014).

**Neural patterns of working memory and emotion processing in schizophrenia.** In a study by Becerril and Barch (2011) assessed brain activation

during affective working memory in participants with schizophrenia and non-psychiatric controls. The authors reported similar amygdalar activation in both groups during the task. However, there was a noted decrease in activity in the DLPFC and hippocampus in individuals with schizophrenia compared to non-psychiatric controls. The results suggest that although emotional items are highly salient for healthy adults, however, to individuals with schizophrenia, emotional items are no more distracting than neutral ones.

Iordan, Dolcos, & Dolcos (2013) theorized that emotional distraction results in the activation of prefrontal and medial temporal lobe areas associated with emotion processing. However, to complete cognitive tasks the supervisory control process is activated, increasing activation areas of the prefrontal cortex to counteract the distraction of emotional stimuli associated with the decrease in medial temporal lobe activity. From this, it can be postulated that the top-down regulation of activation associated with emotion-processing takes place as the demand of the primary cognitive process increases. Concerning the task used in Mano et al. (2014) one could theorize that as working memory load increases, the demand placed on cognitive processes also increases. Therefore, activity associated with emotion processing is down-regulated by areas in the prefrontal cortex to allow for task-driven processes to be carried out.

**The Current Study**

Previous studies conducted in this laboratory have illustrated the distractive influence facial stimuli have on working memory. Mano et al. 2013 demonstrated

more interference when facial stimuli were distracters in comparison to a geometric stimulus, particularly at an intermediate WM load. In Mano's work, the core dependent variable was a contrast formed from response times or percent accuracy scores obtained when WM was tested following a short delay. The contrast involved subtracting a performance variable (response time or accuracy) when study words were followed by the brief presentation of a geometric distracter from the performance variable obtained when face distracters followed study words. Among healthy individuals and patients with psychosis, this contrast was small at the lowest WM load, large at the intermediate load, and small again at the highest WM load. This quadratic pattern is compatible with the working hypothesis that the face distracters diverted attention from WM processing but that this distraction did not alter performance until the WM load reached intermediate levels. As the WM load increased further, the distracting effect of the faces was suppressed. This hypothesis was supported by the post-study report of individuals that they did see faces briefly presented during the task.

Neuroimaging research has yielded evidence suggesting a dynamic interplay between prefrontal areas associated with working memory and cognitive control and the modulation of activity in areas related to affective processing. In other words, as cognitive demand increases, emotion processing decreases (Pessoa, 2008). Furthermore, neural activity in areas of the prefrontal cortex involved in cognitive control increases in response to cognitive demand whereas areas involved in implicit emotion processing decreases in response to the availability of cognitive resources

(Iordan, Dolcos, & Dolcos 2013).

The study examined the neural patterns of activity during a task that assessed working memory in the context of implicit socioemotional distraction. The aims of the study were based on the *distraction-suppression hypothesis* coupled with our understanding of the brain substrate modulating the pattern of neural activation during the interaction of emotional and cognitive processes. The literature reviewed above implicates the DLPFC, amygdala and fusiform face area as regions of interest where this interaction might occur when faces are presented. Moreover, the previous research suggested that the interaction of emotional and working memory processes is likely to unfold during the maintenance phase of working memory tasks (Mano et al., 2012). Neuroimaging research has also shown a strong relationship between prefrontal cortical activity and working memory load during the maintenance period of working memory (McKenna et al., 2013). Therefore, the primary focus of the dissertation results will be on functional brain activity during the maintenance phase of a previously validated socioemotional working memory task. More specifically:

**Aim 1.** Our first aim is to replicate findings from previous studies. In particular, we seek first to replicate the curvilinear relationship between working memory and implicit emotion processing reported in Mano et al. (2013) by examining response latency when the response latency for the geometric design is subtracted from the response latency of the face stimuli (FvG). Second, we will analyze the percent signal change associated with WM load to replicate the linear relationship reported in the supramarginal gyrus, and the dorsolateral prefrontal cortex (DLPFC)

described in McKenna et al. (2013).

**Aim 2.** Our second aim is to examine the effect of WM load on the brain response as measured by percent signal change for the FvG contrast in regions of interest (ROI) that are involved in working memory (i.e. the DLPFC), facial identification (i.e. the fusiform face area (FFA)), and emotion recognition (i.e. the amygdala) in healthy controls and patients. Additionally, we aim to understand the relationship between brain activity in the amygdala with performance in both patients and controls and psychopathology.

***Hypothesis 1.*** The FvG difference in brain activity in the DLPFC in the task maintenance period will be largest at the highest WM load in the control group. Schizophrenia patients will show altered activation in comparison to controls in the FvG difference in brain activity in the DLPFC during the maintenance period.

***Hypothesis 2.*** The FvG difference in brain activity in the FFA in the task study period will be largest at the intermediate syllable load for the control group. Schizophrenia patients will show altered activation in comparison to controls in the FvG difference in brain activity in the FFA during the study period.

***Hypothesis 3.*** Both groups will show a larger amygdala response when face distracters are presented during the WM maintenance period than when geometric designs were presented, although the control group will show a larger response than schizophrenia patients.

***Hypothesis 4.*** Among schizophrenia patients, the magnitude of the FvG contrast in brain activity in the amygdala and DLPFC at the greatest WM load will be

correlated with negative symptoms.

**Aim 3.** Our last aim is to perform an exploratory whole-brain voxel-wise analysis to investigate additional brain regions involved in the FvG contrast during the maintenance period.

## Methods

### Participants

This study was approved by the Institutional Review Board of the Veterans Administration San Diego Healthcare Systems, and all participants were given written consent prior to study enrollment. Participants were recruited from the San Diego area through a variety of methods, such as flyers and outpatient treatment clinics. We recruited right-handed individuals (handedness was confirmed with the Edinburgh Handedness Inventory; handedness quotient >_ 70; (Oldfield, 1971) between the ages of 18 and 55 who were diagnosed with schizophrenia or schizoaffective disorder, which was confirmed using the SCID-I/NP (First, Spitzer, Gibbon, & Williams, 2010) and non-psychiatric controls (history of primary psychiatric diagnoses were assessed using the SCID-I/NP; see Table 1). Participants from both groups were excluded 1) if they had a history of head injury with loss of consciousness greater than fifteen minutes; 2) current/past history of major medical illness (e.g., diabetes; exception was medication induced diabetes that was stable and well controlled for at least 1 year); 3) current/past history of chronic disorders of lung, heart, vasculature; 5) substance abuse within the previous three months; 6) history of stroke or transient ischemic attacks; 7) pregnant or trying to get pregnant (urine test required if pregnancy possible); 8) Migraines/ migraine treatment in last month (exception: sumatriptan-like medications for acute migraine care; not within 2 days of scan); 9) had less than 9 years of formal education; 10) were colorblind; 11) had a self-reported hearing-loss; and 12) were contraindicated for MR scan (per MRI

safety questionnaire). Prior to undergoing the MRI all participants completed a urine toxicology screen that looked for recent use of amphetamines, methamphetamine, cocaine, opiates, phenylcyclidine, and cannabis. If participants exhibited a positive urine toxicology screen with the exception of marijuana or prescription medications, the assessment was rescheduled. Participants were also asked not to use caffeine or tobacco products for at least 2 hours prior to testing, and marijuana products the day of the scan. Participants in the non-psychiatric control group were excluded if they 1) met criteria for any Axis I diagnoses as assessed by the SCID-I/NP or had substance use histories as assessed by the M.I.N.I. Neuropsychiatric Interview (Sheehan et al., 1998). , 2) scored 10 or higher on the Beck Depression Inventory-II (BDI-II; (Beck, Steer, & Brown, 1996) or 9 or higher on the Beck Anxiety Inventory (BAI; (Beck & Steer, 1993). Participants in the schizophrenia group were excluded if they 1) were taking benzodiazepines or medication that affects the neurovascular system, first generation antipsychotic medication, more than one second generation antipsychotic medication, more than one mood stabilizer, or more than one antidepressant; 2) received electroconvulsive therapy treatment in the last 6 months; 3) displayed significant extrapyramidal symptoms; 4) severe depression as indicated by a score of 28 or higher on the BDI-II; 5) severe anxiety as indicated by a score of 25 or higher on the BAI; and 6) significant social or vocational impairment caused by drug use within the past month. Diagnoses and substance use histories were assessed using the SCID-I/NP for patients.

A total of 72 participants were screened for this study (33 control and 39 patients). Of the 72 screened, 35 were excluded (8 due to administrative reasons, 7 due to current substance use or history of dependency, 5 due to diabetes of hypertension, 5 due to head injuries, 6 due to medication exclusions, 2 controls had primary depressive disorders, 1 woman was trying to get pregnant, and 1 control learned English 21-years-old), 3 did not complete the assessments and MRI (i.e. did not show up for their appointments and did not return), and 34 were included (22 non-psychiatric controls and 12 patients).

**Assessments of Neuropsychological Functioning and Symptom Severity**

All participants completed an approximately 1-hour neuropsychological battery comprised standardized clinical tests across several cognitive domains. Overall cognitive functioning was assessed using the Shipley Institute of Living Scale (Zachary, 1986), which is an assessment aimed to measure two aspects of cognition: that which is gained through education and experience; and the capacity to use logic to learn and acquire new information or solve problems and the Wechsler Test of Adult Reading (Holdnack, 2001) which is an assessment aimed at measuring intelligence before the onset of illness or injury. Phonologic decoding skills were assessed using the Word-Attack subtest of the Woodcock Johnson (Woodcock, Mather, & McGrew, 2001). Speed of information processing was measured using the Trail Making Test part A (Corrigan & Hinkeldey, 1987). Executive functioning was measured using the Trail Making Test Part B (Corrigan & Hinkeldey, 1987). Working memory was assessed using Letter-Number Span (Nuechterlein et al., 2008) which

aims to examine verbal working memory, and The Continuous Paired Associates Test (CPAT) program (Newton & Brown, 1985) which aims to assess verbal working memory. Emotion identification was assessed using the Emotion Recognition subtest of the University of Pennsylvania Computerized Neuropsychological Testing Battery (ER40; Gur, et al. 2002). This assessment presents target facial stimuli and asks participants to identify and select the affect being portrayed from an array of four options. Symptom severity for individuals with schizophrenia will be assessed using the Positive and Negative Syndrome Scale (PANSS; Kay, 1987).

**Implicit Facial-Affect and Working Memory Paradigm**

The facial-affect and working memory paradigm involved within-subjects factors including working memory load (1 vs. 2 vs. 3 syllables) and distractor primes (faces (happy, sad, and emotionally neutral) vs. nonfacial geometrical oval figure)). Stimuli included (1) pronounceable nonwords, (2) human faces (from the Radboud Faces Database; (Langner et al., 2010)), and a (3) nonfacial geometrical control. Each trial began with a cross (e.g., "+") presented at central fixation for 1000 ms and was comprised of three sequential phases. In the first period (study), participants were given one, two, or three syllables to subvocally read and memorize (2-second phase duration). Unbeknownst to participants, distracters were briefly presented (33ms) immediately after the pseudoword study phase. Distracters are task-irrelevant and presented at fixation. A non-facial neutral backward mask immediately replaces distracters and filled the duration of the maintenance period. (Participants were told the backward mask was a rehearsal indicator.) During this second period

(maintenance), participants were instructed to mentally rehearse the syllables presented in the first period, with the rehearsal interval duration varying among 8–16 seconds in two-second increments. The third period (recognition) consisted of a recognition test in which two sets of pseudowords were presented and the participant was instructed to indicate (using the keyboard number pad with dominant right hand) which set was from the study period (4-second study period duration) followed by a variable inter-trial period (4-8 seconds in two second increments; see Figure 4). The total duration of the computerized task lasted approximately 40 minutes, consisting of four runs of 24 trials lasting approximately 9 minutes and 42 seconds. Stimulus presentation and behavioral recordings were controlled using E-Prime (Psychology Software Tools, Inc., Pittsburgh, PA). Accuracy and speed were equally stressed. Dependent variables were response latencies and percentage correct.

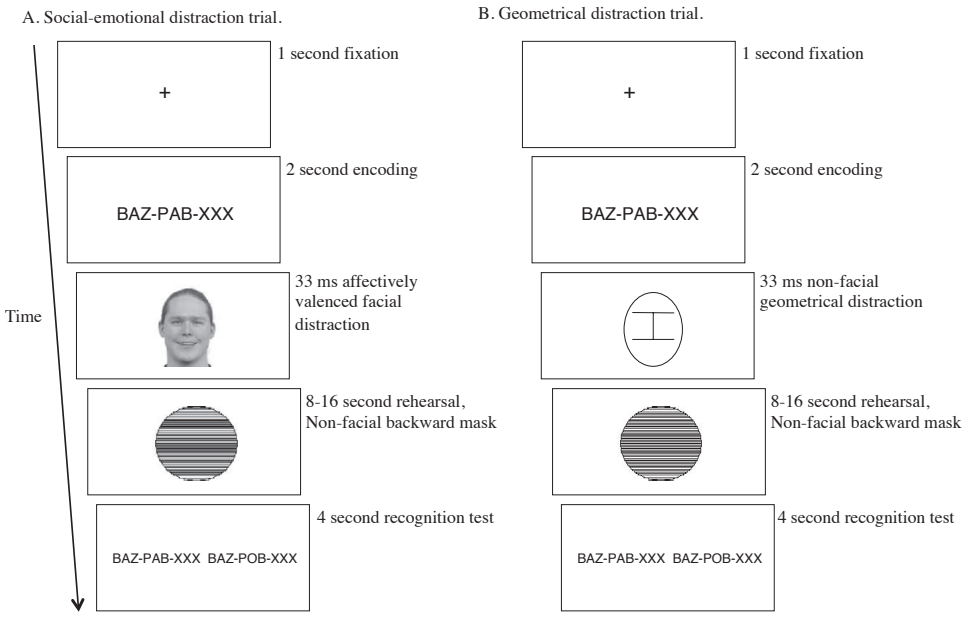



Figure 4. Task diagram. Notably, images and stimuli are not displayed to scale. For example, alphabetic stimuli subtend a much smaller visual angle than is projected on the display. Picture of happy face taken from Radboud Faces Database (Langner et al., 2010). Permissions to display picture of happy face were obtained from the copyright holder of the Radboud Faces Database and publisher of the image.

**Posttask Facial Affect Recognition Test**.

Following completion of the task, participants were asked in an open-ended manner whether they "noticed anything in the task." If a participant did not freely report detecting a face in the task, they were given a debriefing statement. If participants reported detecting a face during the task, they were given the facial affect recognition test prior to presentation of the debriefing statement. This test consisted of pictures of facial expressions representing each of the eight emotional expressions (angry, contemptuous, disgusted, fearful, happy, neutral, sad, and surprised) in the Radboud Faces Database. Participants were instructed to circle three emotions

potentially seen in the task to assess awareness of emotional expressions of facial distracters.

**Sample Size Justification.** We conducted a power analysis, which indicated a target sample size of 20-25 participants in each group to detect a .05 alpha level, 2-tailed test at a power level ranging from 0.72-0.8. Although we studied 20 healthy participants, we only studied 12 schizophrenia patients due to recruitment challenges.

**MRI Acquisition**

Following auto-shimming, participants were scanned on a GE Signa EXCITE 3.0 Tesla whole-body imaging system (gradient system: 50 mT/m amplitude; 200 T/m/s slew rate) at the UCSD Keck Center for Functional MRI. An eight channel head coil was used for parallel imaging with Asset scans acquired to correct for variations in coil sensitivity. Participants were asked to get eight hours of sleep the night before the scan, abstain from drinking coffee the day of the scan, and refrain from smoking cigarettes within two hours of the scan time. On the day of the scan participants were asked by investigators about these factors, in which all but one reported compliance with sleep and caffeine and tobacco intake. One participant reported smoking 1 hour prior to his scan.

Anatomical scans were acquired with a $T_1$-weighted (T1w) protocol utilizing a 3D inversion-recovery prepared, fast spoiled gradient echo pulse sequence (NEX = 1, TI = 450 ms, TE= minimum full, flip angle = $12^o$, receiver bandwidth = 31.25 Hz, 256 x 256 matrix, Field of View = 220 mm, in-plane resolution = 0.859 mm x 0.859 mm, 166 interleaved sagittal slices thickness=1.2 mm).

The functional scans were collected to be sensitive to the $T_2^*$-weighted blood oxygen level dependent (BOLD) signal using a raster-style protocol. Head movement was constrained using NOMOCO pillows (NOMOCO, Inc., San Diego, CA). We acquired four runs of the Implicit Facial-Affect and Working Memory Paradigm (WMrun1, WMrun2, WMrun3, WMrun4). Each of the four versions of the WM task lasted 9.7 minutes and possessed the same general structure as shown in Figure 4. The four versions differed in their pattern of temporal jittering during the maintenance period, temporal in the jittering between the recognition period and the next trial, and permutations in the pseudowords presented, and in the presentation order of the distracting stimuli (face type, control stimulus). The presentation order of the four versions was fixed over participants.

Thirty-one or 32 single shot, non-oblique, echoplanar 4 mm axial slices covering the whole brain were acquired using a gradient echo protocol (fat saturation, TR=2000 ms, TE=30 ms, flip angle = $77^o$, image matrix = 64 X 64, Field of View = 240 mm, 3.75 mm X 3.75 mm in-plane resolution, 291 time points) were acquired in an interleaved manner using a 2D gradient echo pulse sequence for each of four runs. An eight-minute task-free (so called resting-state) functional scan was also acquired using the same scan gradient echo protocol as described above as long as time permitted. However, there were 11 participants (8 controls and 3 patients) in which resting-state function scans were not acquired due to time constraints.

A single field map was collected at the same resolution as the functional gradient echo images. The field map was collected and applied to the functional

images in order to unwarp the echo-planar images in order to mitigate inhomogeneities in the magnetic field, especially those related to tissue susceptibility differences. For each functional scan we simultaneously collected pulse and respiratory data with additional monitoring equipment (Labview based Biopac system 7 controls; General Electric Built-in system remaining controls and all patients).

Diffusion weighted images were collected using the following protocol: 51 direction EPI series with a b-value of 1000 s/mm$^2$, axial slice thickness = 2.5 mm, NEX = 2, in-plane resolution=2 mm X 2 mm. In addition, ten brief single direction scans (b=1000 s/mm$^2$) were acquired prior to the 51-direction scan. While we were able to acquire diffusion scans for most participants, in the case of 8 participants (3 controls and 5 patients) this sequence was not collected due to time constraints. Because these scans were not relevant to testing the study's hypotheses, no diffusion data will be presented here.

**Image Processing and Analysis**

**Preprocessing.** In order to examine and analyze fMRI data the scans must be pre-processed to remove noise, increase the signal-to-noise ratio, and allow comparisons among different anatomical brains across subjects. Our preprocessing was done using tools from the Analysis of Functional NeuroImage library ((AFNI); Cox, 1996; Cox & Hyde, 1997) and the FMRIB Software Library ((FSL); Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; Smith et al., 2004; Woolrich et al., 2009). We developed Perl scripts calling AFNI and FSL routines to guarantee

uniform processing of each participant's scans. A Perl script created a fixed directory structure for each participant.

After their acquisition, all acquired images were transferred as gzipped tar files from the UCSD Center for fMRI to the server at the UCSD NeuroImaging and Behavioral Analysis Laboratory (NIBAL). The tar file was then unpacked with the user prompted to identify which scan series was to be associated with each image type (T1, WMrun1, etc). After scans slices were moved to their appropriate directories, they were assembled into AFNI BRIK and HEADER files.

One key weakness of functional imaging is low spatial resolution and poor anatomical contrast in the images produced. To improve the localization of the activation regions, the functional images were realigned with the T1w anatomical image that has higher spatial resolution. Prior to this alignment the T1w volume was skull stripped using AFNI's 3dSkullStrip routine to improve the remaining preprocessing steps. The anatomical volumes were then warped into Talairach space, a 3-dimensional coordinate system used to standardize the location of brain structures independent of individual differences in size and overall shape of the brain (Lancaster et al., 1997; Lancaster et al., 2000). The warping was done automatically using AFNI's @auto_tlrc routine with linear resampling. The transformation aligned a participant's T1w image with a Talairach version of the ICBM atlas. Once this conversion was completed each image was inspected by the primary investigator for noticeable anomalies in the skull stripped, warped images. Few anomalies were found but when they occurred the above steps were repeated with different routine

parameters. These images were saved for alignment with the functional images as described below. The Talairach transformation matrix was saved for warping the functional maps into standard space at a later stage of the image-processing pipeline.

For the functional images, we first created 4D volumes (3 spatial dimensions and one in time) as AFNI BRIK and HEADER pairs. Local magnetic field distortions were then corrected using the field map. This was accomplished with three files (ggfm, epidewarp4.ucsd, dicomrx) developed at the UCSD Center for fMRI. The core correction steps were accomplished using the FSL field map correction routine.

The functional scans in this sequence totaled 56 minutes and 50 seconds. While participants were asked to lie as still as possible and were constrained by the NOMOCO Pillow System, it was expected that some movement would occur given the length of these scans. Head motion can result in noticeable changes in signal intensity across voxels over time, thereby causing spurious brain activation patterns if accumulated over many images (Forman, 1995; Friston, 2002; Hajnal et al., 1994). As a first step in dealing with movement artifacts, we identified and replaced outlier volumes using AFNI's 3dDespike. The default options were accepted ignoring the first three image volumes. We then co-registered each EPI time series image to a base image volume that showed minimal movement artifact. Each base image was selected after visual inspection of the times series signal response graph using FSL's visualization tool, to enable the investigators to select an image representative of the dataset. While each base image varied across participants and across runs, the modal base image selected was 150 out of 291. AFNI's align_epi_anat.py aligned the base

image to the T1w image, using the Local Pearson Correlation cost function, and co-registered each of the 291 images in the time series to the aligned base image. The Local Pearson Coefficient cost function, which uses information from the ventricles as well as the brain images for alignment, has been shown to produce excellent alignment between structural and functional images (Saad et al., 2009). The alignment of the entire time series and the co-registration were completed in one resampling step. The adequacy of the alignment of the EPI base image with the T1w image was visualized using an edge detection algorithm (see AFNI's @AddEdge routine). This routine compared pre- and post-alignment images producing edges of the gyri in both the functional and structural images to facilitate the comparison of pre- and post-alignment images. The edges were visually inspected by the primary investigator in which the overlap of the post-alignment images to the structural image was compared with overlap of the unaligned images to the structural images in order to determine the goodness of fit of the alignment. If the fit was judged inadequate, the Perl script prompted the user to select another cost function and repeated the alignment.

The above steps produced a file containing the degree each time series volume needed to be moved in the 3 axes of rotation and 3 planes of translation to register with the base image. The align_epi_anat.py script also provided a distance statistic for each voxel in the brain based on the six movement parameters. In this instance, distance is defined as the maximum distance in mm that any voxel in a brain volume had to be moved in order to align it with the base image. We then examined the

maximum of these maxima and the median of the maxima, for each of the four runs and compared these values between patients and controls.

Some imaging researchers argue that functional scans should be corrected for differences in slice time acquisition due to the sequential nature of image acquisition in functional scans (Henson et al., 1999). However, we did not perform time slice-time correction because there is little consensus about the importance of this step and because temporal differences between slices combine with physiological and behavioral head motion to cause phase shifts that vary with slice position, complicating image adjustments related to the physiological covariates (http://afni.nimh.nih.gov/pub/dist/doc/program_help /3dTshift.html; Cheng & Puce, 2014). It is noteworthy that Poldrack, Mumford, and Nichols (2011, pp. 41-42) do not recommend slice-timing correction.

De-spiking then registering each volume in the fMRI time series with the base volume corrects for much of the misalignment that might occur during a run, however, sporadic variation in image alignment and image quality might occur. We performed an additional search for outlier time series volumes in order to create a censor file to be used at the general linear modeling step of image processing. We performed this step using AFNI's 3dtqual routine, which calculated a quality index as 1 - Spearmen coefficient of each volume with the 'median volume' (the median volume is composed of voxels with the median image intensity for the time series of that voxel). This process produced a graph and a file displaying the median and variation of the quality index across all volumes, which were then inspected by the

primary investigator to determine a threshold used to identify volumes that contained too many irregularities. Typically, a Spearman coefficient of .99 was used as the threshold to create a censor file, i.e., image volumes whose rank of signal intensity across voxels correlated less than .99 with the rank signal intensity of the median image were censored.

As previously stated, one source of signal noise is physiological movement, specifically cardiovascular-linked brain pulsations that are aliased into lower frequencies and respiration that are associated with small magnetic field variations (Polrack et al., 2011, p. 49). Cardiovascular-linked pulsations can result in signal change in regions of the brain near highly vascularized regions, near cerebrospinal fluid, and in gray matter areas (Glover, Li, & Ress (2000). Changes associated with respiration are less region specific, affecting the brain globally (Glover, Li, & Ress (2000). These sources of physiological noise can produce signal changes correlated with the signal changes driven by cognitive tasks, thereby reducing the statistical significance of task-associated activation signals or, more typically, they can add unwanted signal variation to the fMRI time series. Therefore, in order to analyze and interpret results validly, it is important to control for physiological noise in our signal analyses. In the present study we monitored and collected cardiovascular pulsations during the scan by placing a photopulse sensor on the index finger of the non-dominant (in the case of all participants this was the left) hand. Similarly, respiration was collected and monitored via placing a pneumatic belt on each participant's abdomen. The cardiac and respiratory levels were monitored while the scan was

conducted to ensure the equipment was working properly. In the case of 4 participants, there were technological difficulties and cardiac or respiratory information was not able to be collected. The cardiovascular data were recorded at a rate of 10 samples/s and the respiration data were recorded at a rate of 40 samples/s using a multichannel data logger connected to the scanner's analog gating outputs. The data logger was started by a trigger from the scanner to ensure time synchrony of the physiological data and the functional scans.

The physiological data were collected at a higher temporal frequency than the fMRI data. Yet the physiological data may be aliased into low frequencies of the fMRI task data. To correct for the aliasing, only lower order frequencies of the physiological data need to be considered. Glover and colleagues (2000) developed a method, RETROICOR, to correct retrospectively the EPI time series in image space, i.e., after the images had been reconstructed from k-space. Glover et al. (2000) found that adequate correction of the unwanted physiological frequencies could be obtained from the first two terms in the Fourier expansion of the physiological data. The linear coefficients obtained from the regression of the fMRI time series onto the first two terms of a Fourier expansion represents the contribution of the physiological data to the fMRI time series. The equation is:

$$S(t) = C_1\mathbf{cos}(\theta_c) + C_2\mathbf{sin}(\theta_c) + C_3\mathbf{cos}(2\theta c) + C_4\mathbf{sin}(2\theta c) + R_1\mathbf{cos}(\theta_r) + R_2\mathbf{sin}(\theta_r) + R_3\mathbf{cos}(2\theta r) + R_4\mathbf{sin}(2\theta r).$$

$S(t)$ is the fMRI signal at time t and $\theta_c$ and $\theta_r$ are phases for the cardiac and respiratory variables that are directly derived from the physiological data. Thus,

when both cardiac and respiratory data were successfully acquired, eight coefficients for each time point in the fMRI time series were estimated. The model coefficients, $C_1$, $C_2$, … $C_8$, are entered as temporal regressors in the general linear model (GLM). To estimate the coefficients, we used MATLAB scripts developed at the UCSD Center for fMRI. The RETROICOR coefficients were estimated for each axial slice of the fMRI data without de-convolving the hemodynamic response. We preferred slice wise correction to whole brain correction because physiological artifacts affect different regions of the brain differently (Glover, Li, & Ress, 2000; Lowe, Mock, & Sorenson, 1998).

**Activation Mapping.**

***General Linear Model (GLM).*** Because the amygdala is one of the target regions of interest, only a small amount of spatial smoothing (FWHM = 1.5 voxel widths) was used in order to avoid bleaching out the signal activation in this small structure. Investigators at NIBAL prefer to incorporate nuisance regressors into the general linear model (GLM) in order to account for temporal autocorrelations rather than prewhiten the time series before performing a GLM. Residuals from the GLM were saved in order to examine the extent of residual autocorrelations.

A GLM implemented with AFNI's 3dDeconvolve generated the amplitude of the BOLD response for each study effect. The within-participant analysis-design is complex, being comprised of three working memory loads and four stimulus types (Sad, neutral, and happy faces and geometric design). Additionally, the task unfolds over three periods (study, maintenance, and recognition). Thus, for each run, 36 event

effects were estimated (3 loads X 4 stimuli X 3 periods); 144 event timing files were created across the four runs. Given the complexity of the design matrix, derivatives were not included in the GLM. Perl scripts were developed to create correct event descriptions of each run and to use the appropriate task definitions in the general linear model. The timing files associated with the 36 explanatory variables were convolved with Mark Cohen's gamma function (Cohen, 1997). The additive constant from the GLM is the implied baseline, which reflects the signal components of the fMRI time series not explicitly coded as experimental events or nuisance covariates.

To correct for baseline drift, the contributions of a fourth order polynomial entered the model as nuisance parameters, as did the six movement parameters and the eight physiological parameters. Altogether 55 regression parameters were estimated for each brain voxel for each run. Figure 5 shows the timing of the experimental events (Event Regressor Set); Figure 6 shows the temporal pattern of the nuisance events (Baseline Regressor Set). An $R^2$ change value was calculated for each voxel for each run of each participant comparing the change in $R^2$ when the Event Regressor Set was added to the Baseline Regressor Set. The regression weights for each event reflected the direction and magnitude of the BOLD response to that stimulus event. Thus, the regression weights were the brain activation/de-activation markers.

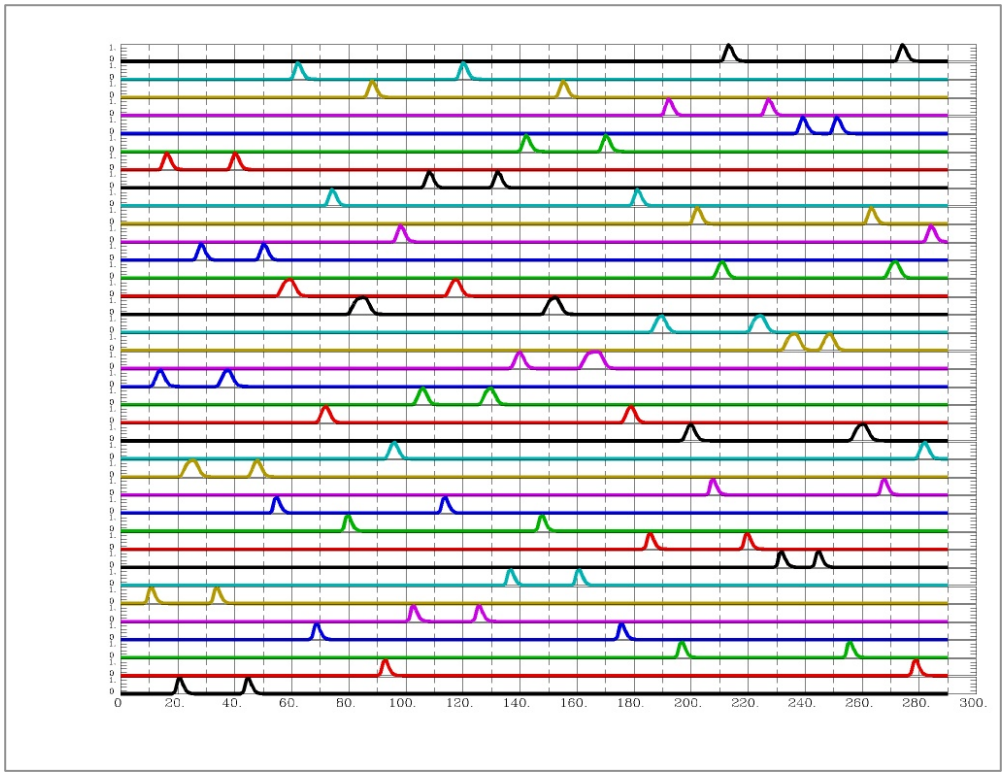



Figure 5. Temporal pattern of the event regressors used in the GLM for each participant.

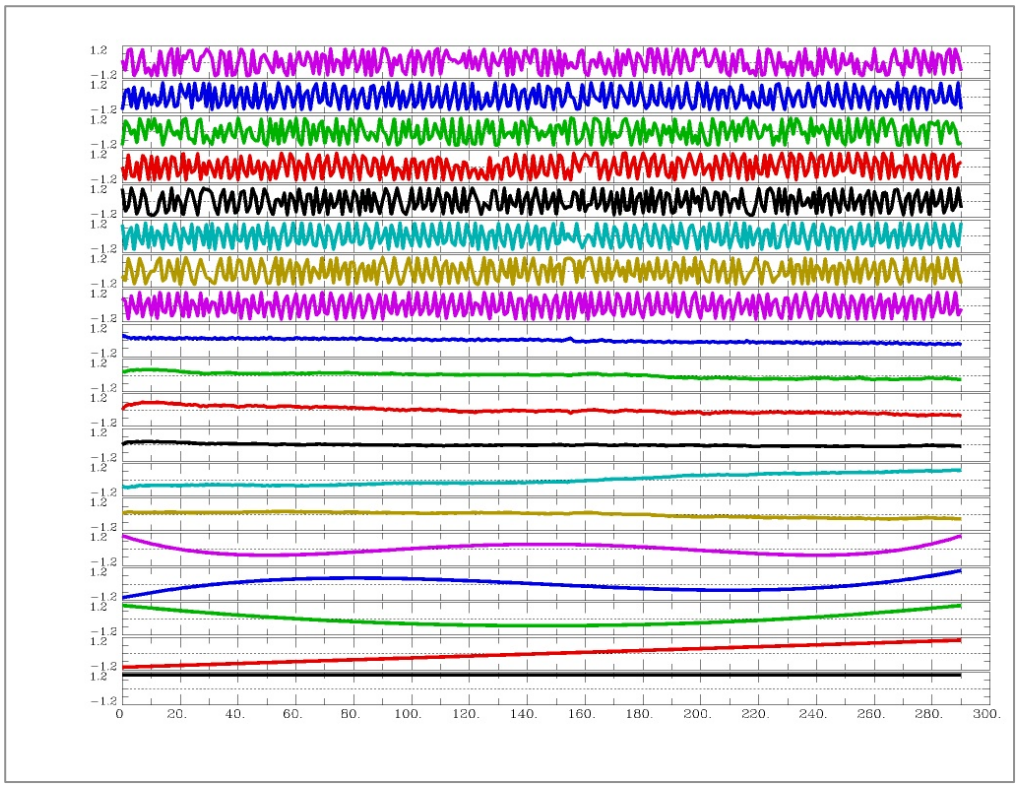



Figure 6. Example of the temporal pattern of the nuisance regressors used in the GLM for each participant.

Although all of these effects were coded within the design matrix, not all simple event effects and their interactions were used to test study hypotheses. Because we are interested in the simple effects of working memory load, each working memory load was averaged over the four prime types within the study and maintenance periods. To investigate aims related to the interaction of load with stimulus type, the effect of syllable load on the contrast of Faces vs. the Geometric design (FvG) was investigated. Although the recognition events were included in the GLM, we have no hypotheses about the recognition period.

The GLM was performed with AFNI's 3dDeconvolve. The model included the Event Regressor Set and the Baseline Regressor Set as described above. Outliers, also as described above, were used to censor the time series. Because physiological effects have a different impact at different levels of the brain, the GLM was separately performed for each slice along the inferior-superior axis to incorporate the slice-wise physiological regressors into the linear model. Regression weights from the GLM were divided by the additive constant in the linear model in order to calculate percent signal change as the primary study variable.

***Regions of Interest.*** The major aims of this study are to investigate the brain activation involved in WM and implicit emotion processing. We used the AFNI Talairach Daemon (Cox, 1996; Lancaster et al., 2000) to create ROIs, which were applied to the activation maps after the maps were transformed into Talairach space (see Figure 7). More specifically, the ROIs defined for the dorsolateral prefrontal cortex (DLPFC) and the supramarginal gyrus were those previously published in McKenna, et al. (2013). The amygdala mask, which has been shown to encompass brain regions that respond to face perception, was defined by the Talairach Daemon label (Brown et al., 2015; Lancaster et al., 2000). To create the fusiform face area we performed a literature review of methodologically sound studies identifying and validating this area. We then selected those using Talairach maps and averaged the reported coordinates from the selected studies. Following this the two primary investigators applied these coordinates to each participant and using validated

anatomical maps adjusted the coordinates as necessary. The placement of each ROI mask was visually inspected with manual corrections made as needed (see Figure 8).

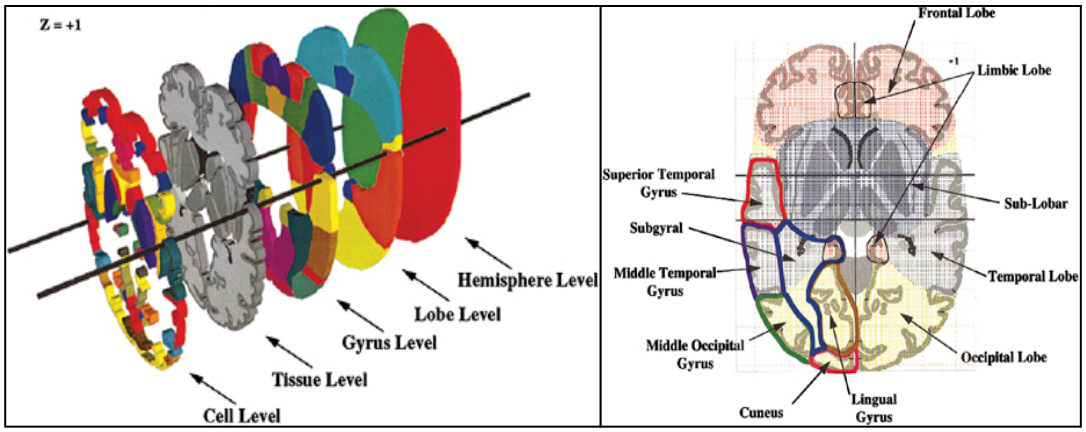



Figure 7. On the left: A typical set of three-dimensional data used to generate the volume occupancy Talairach labels around the *z*=+1 level. Openings in lobe through cell levels were provided to emphasize the three-dimensional nature of data at each level. (From Lancaster *et al* (2000), copyright © 2000. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.). On the right: An example of volume occupancy Talairach labels for a Talairach Atlas section image at the *z*=+1 level. Lobar levels are demarcated by patterned colors. Bold color outlines are used to demarcate gyral levels on the bottom left of the image. (From Lancaster *et al* (2000), copyright © 2000. Adapted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.).

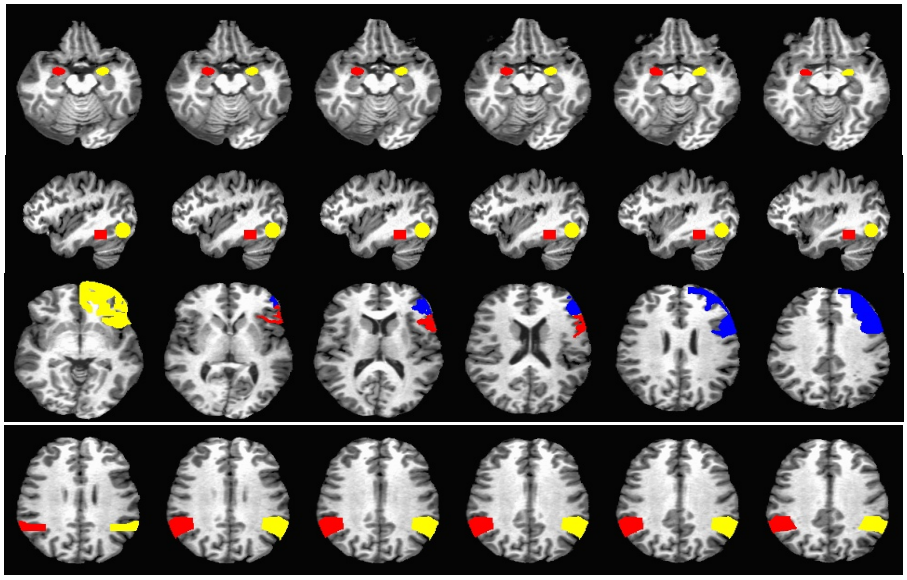


Figure 8. Manually correct ROI masks for the amygdala (top), fusiform face area (second), frontal areas (third), and supramarginal gyrus (bottom).

## Data Analysis

**Statistical analysis of task performance.** Each study hypothesis involves the contrast of all facial stimuli with the geometric stimulus (FvG). Performance was measured by response latency and accuracy (percent correct). These values were entered into an SPSS database to perform 4 (run) by 4 (faces) by 3 (memory load) analyses for each group followed by a to 2 (control vs. patient) by 3 (memory load) analysis of variance for the FvG contrast. The ANOVAs performed were hypothesis driven tests of linear and quadratic effects of syllables (Pedhazur, 1982).

**Statistical Analysis of Regions of Interest.** The first analyses conducted was aimed at replicating findings previously McKenna et al. (2013) which demonstrated a linear impact of WM load on BOLD response in the DLPFC and the supramarginal

gyrus. Effects of working memory load were tested with orthogonal linear (-1 0 1) and quadratic (1 -2 1) contrasts for each ROI (Pedhazur, 1982).

Each study hypothesis involves the contrast of all facial stimuli with the geometric stimulus (FvG). Six BOLD response variables for the FvG contrast were generated, one for each of the three working memory load conditions within the encode and maintenance periods. For each ROI, the mean BOLD percent signal change was averaged over the voxels within the ROI for each of these six conditions. These values were entered into an SPSS database to perform 4 (run) by 3 (memory load) by 2 (hemisphere) analyses for each group followed by a to 2 (control vs. patient) by 3 (memory load) by 2 (hemisphere) analysis of variance separately for the encode and maintenance periods for each ROI. The ANOVAs performed were hypothesis driven tests of linear and quadratic effects of syllables in each study ROIs (Pedhazur, 1982).

**Exploratory whole brain voxel-wise analyses.** Exploratory whole brain analyses were performed to test group differences in the FvG contrast during the maintain period. The analysis involved setting a t-value threshold corresponding to a two-tailed test at $p = .02$ for each image voxel, then correcting for multiple statistical tests across all voxels. The latter step needed to account for the spatial autocorrelations in the model residuals. The residuals were obtained as output from the GLM. We used AFNI's 3dFWHMx to obtain spatial smoothness parameters for the residuals. These parameters were imported into 3dClustSim, which was run with the -acf option for 10,000 simulations. This approach accounts for the long tails in

the non-Gaussian distributions of test statistics induced by correlated spatial noise. The correction for multiple statistical tests is experiment-wise, which along with the long-tailed test statistic gives a conservative result. By setting a voxel-wise $p = .02$ and a cluster-wise $p = .10$ for a bi-sided threshold in the exploratory analysis, all clusters with volumes of 3341 μl or larger were identified as statistically reliable.

# Results

## Sample

Table 1 shows the characteristics of the final sample, demonstrating that there were no significant differences between groups on age, parental education, or parental SES. We found significant group differences in highest level of completed education. In patients, our sample was evenly split regarding psychosis diagnoses (50% schizophrenia, 50% schizoaffective disorder). All patients were stable on medication and had confirmed diagnoses for at least one year. With regard to psychopathology in patients, we found that patients endorsed higher levels of negative symptoms compared to positive and general symptoms on the PANSS and no patients showed significant symptoms of mania (see Table 1). Additionally, we found statistically significant differences in depressive and anxiety symptoms between patients and controls.

Table 1. Demographic and psychopathology characteristics of the sample showing the mean and (SD) of each parameter.

| | **Controls (n=20)** | **Patients (n=12)** | **Effect Size (η2)** |
|---|---|---|---|
| | | | |
| **Age** | 39.37 (±10.1) | 40 (±8.4) | 0.002 |
| **Education **** | 15.58 (±1.62) | 13.38 (±1.5) | 0.408 |
| **Maternal Education** | 13.83 (±3.1) | 11.75 (±4.5) | 0.048 |
| **Paternal Education** | 14.1 (±3.1) | 13.5 (±3.3) | 0.016 |
| **Maternal SES** | 30210 (±28359) | 20090 (±24002) | 0.011 |
| **Paternal SES** | 74447 (±105207) | 49780 (±48336) | 0.023 |
| **BAI**** | 1.71 (±2.785) | 8.42 (±7.501) | .157 |
| **BDI**** | 2.64 (±4.72) | 9.25 (±10.54) | .287 |
| **PANSS Positive** | ----- | 13.33 (3.985) | ------ |
| **PANSS Negative** | ----- | 17 (4.178) | ------ |
| **PANSS General** | ----- | 26.17 (8.83) | ------ |
| **Age at first hospitalization** | ----- | 18.38 (7.891) | ------- |
| **Age at first diagnosis** | ----- | 20.2 (7.757) | ------- |
| **Number of hospitalizations** | ----- | 3.36 (2.767) | ------ |

With regard to neuropsychological functioning we did not find statistically significant group differences on most measures with the exception the Shipley Abstract T-score and Shipley estimated IQ (see Table 2).

Table 2. Sample characteristics of neuropsychological functioning showing the mean and (SD) for each measure.

| | Controls (n=20) | Patients (n=12) | Effect Size (η2) |
|---|---|---|---|
| | | | |
| **Word Attack** | 27.28 (±2.43) | 26.08 (±5.71) | 0.05 |
| **WTAR** | 37.85 (±4.75) | 34.583 (±10.95) | 0.138 |
| **Letter-Number** | 16 (±3.43) | 13.92 (±3.45) | 0.117 |
| **Trails A response time** | 23.84 (±7.18) | 27.81 (±8.29) | 0.071 |
| **Trails A Errors** | 0.857 (± 2.14) | 0.083 (±0.29) | 0.065 |
| **Trails B Response Time** | 55.46 (±19.77) | 80.4075 (±51.99) | 0.105 |
| **Trails B Errors** | 0.857 (±0.95) | 0.83 (±1.75) | 0 |
| **Shipley Vocabulary T score** | 50.84 (±6.23) | 43.83 (±10.01) | 0.208 |
| **Shipley Abstract T score **** | 55.6 (±8.15) | 49.5 (±11.15) | 0.387 |
| **Shipley IQ Estimate **** | 101 (±9.55) | 91.58 (±14.36) | 0.358 |
| **Post Task Recog Neutral **** | 0.095 (.001) | 0.0667 (.48) | 0.213 |

To understand performance on working memory and emotion recognition separately adjunctive to the performance on our task each participant was administered the CPAT and the Penn ER40 task respectively. On the CPAT we did not find statistically significant differences between groups on overall performance or reaction time, However, further exploration showed significant differences at different lag intervals, indicating lower performance in patients when lag times were increased (see Figure 9).

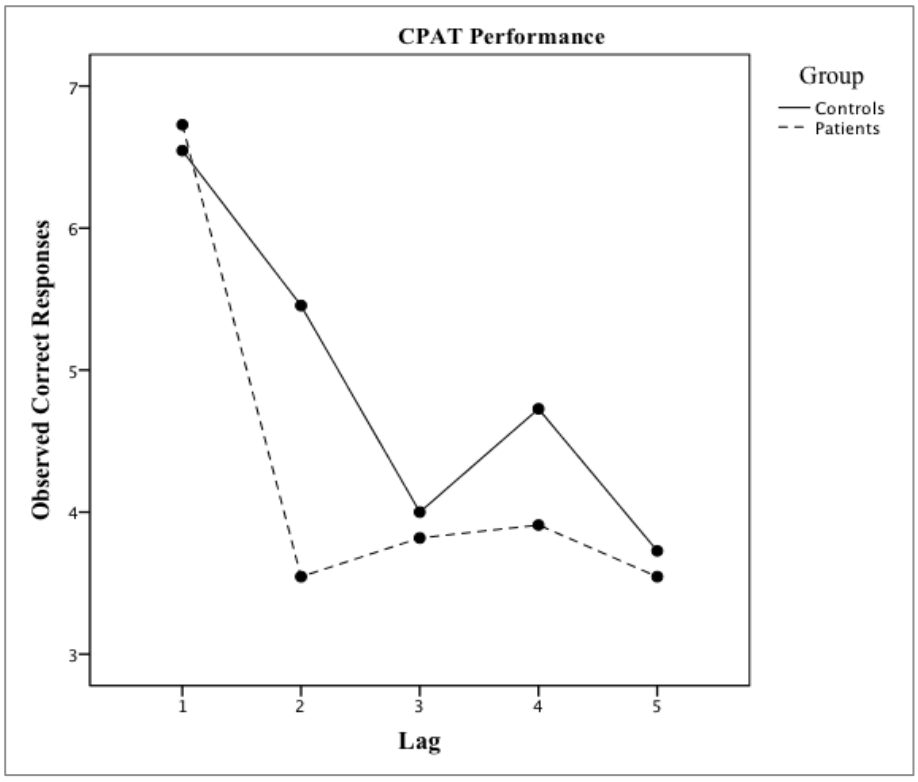



Figure 9. Observed correct responses on the CPAT by lag and group.

With regard to performance on the Penn ER40 task we saw statistically significant differences between groups overall on both measures of accuracy and reaction times, with patients showing decreased accuracy and longer reaction times (see Table 3). Interestingly, this was restricted to stimuli with negative valence, with no differences seen between groups on accuracy or reaction time for happy stimuli.

Table 3. Shows performance (mean and (SD)) on an emotion recognition task between controls and patients.

| | Performance on the ER40 Task | | |
|---|---|---|---|
| | **Controls (=9)** | **Patients (6)** | **Effect Size (η2 )** |
| **Overall %Correct **** | 0.85 (.09) | 0.675 (.02) | 0.279 |
| **Anger %Correct **** | 0.63 (0.167) | 0.375 (.25) | 0.298 |
| **Sad %Correct **** | 0.86 (.16) | 0.58 (.32) | 0.278 |
| **Fear %Correct **** | 0.90 (.14) | 0.73 (.27875) | 0.168 |
| **Happy %Correct** | 0.97 (.055) | 0.875 (.19) | 0.138 |
| **Neutral %Correct** | 0.875 (.18) | 0.8125 (.23) | 0.026 |

**Aim 1: fMRI Task Performance**

**Controls**. Performance on the fMRI task was examined to determine if participants were responding above chance. If participants responded below chance, those values were dropped from analyses and a mean imputation analyses was performed to replace missing values. In the control group only one participant responded below chance on one run during the fMRI task. The original task was administered in one session, lasting approximately 40 minutes (Mano et al. 2013). To accommodate fMRI scanning capabilities the task was broken down into 4 separate runs as detailed in the methods section. To replicate previous findings reported in Mano et al. (2013) we first analyzed performance in each run to assess the presence of fatigue or practice effects. We did not observe a run effect on either accuracy ($F$[3, 17] = 1.173, $p$ = .349; MSE = .015; $\eta^2$ = .08) or response latency ($F$[3,17] = .708, $p$ =

.561; MSE = .023; $\eta^2$ = .05). Additionally, we examined the overall effect of WM load on accuracy and response time. We found a significant effect of WM load on accuracy ($F$[2,18] = 29.596, $p$ < .001; MSE = .012; $\eta^2$ = .58), demonstrating a linear trend where responses were most accurate for the 1-syllable condition (M=97.6%; SD=8%), intermediately accurate for the 2-syllables condition (M=96.3%; SD=7%), and least accurate for the 3-syllable condition (M=86.4%; SD=21%). We found a similar linear effect on response latencies ($F$[2,18] = 331.948, $p$ < .001, MSE = 47.92, $\eta^2$ = .94).

To replicate the curvilinear relationship of WM load on response latency previously reported in Mano et al. (2013) we tested the quadratic trend of WM load on both response latency and accuracy in the FvG contrast. We did not see a significant quadratic trend of WM load on accuracy in the FvG contrast but observed a linear trend, though this trend was not statistically significant. Analysis of the FvG contrast in response latency showed a significant quadratic effect of working memory load ($F$[1,19] = 6.108, $p$ = .023, $\eta^2$ = .24; see Figure 10), replicating previous findings.

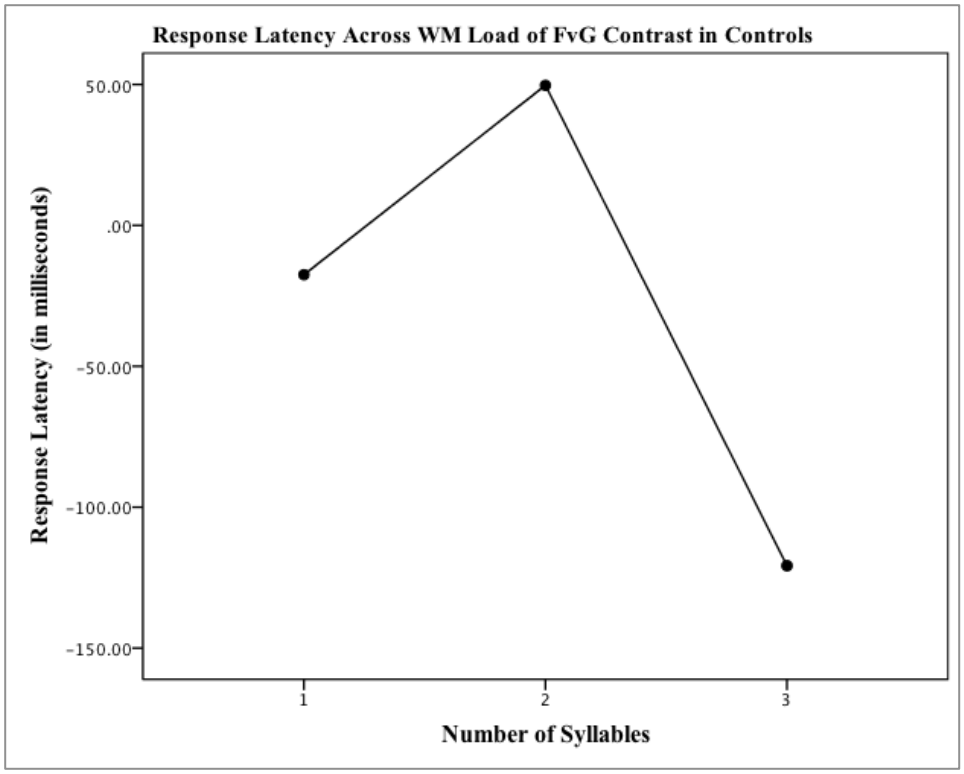



Figure 10. The Effect of WM load on response latency in FvG contrast in the control group.

In order to better understand the mechanisms underlying this relationship we probed the linear and quadratic effects for the facial and geometric stimuli. Facial distraction did not have a significant effect on accuracy ($F$[3,17] = 1.573, $p$ = .233; MSE = .012; $\eta^2$ = .14) or response latencies ($F$[3,17] = 1.470, $p$ = .260, MSE = 46.793, $\eta^2$ = .07). However, the interaction between load and stimulus distraction on accuracy was significant ($F$[6,14] = 3.503, $p$ = .025, MSE = 0.006, $\eta^2$ = .28). When this was probed further it was seen that the geometric design was the more disruptive at the intermediate working load than the face stimuli, however the face stimuli were

more disruptive at the highest WM load (see Figure 11). We also found a significant interaction between load and distractor type in response latency, showing a similar curvilinear trend observed in performance accuracy.

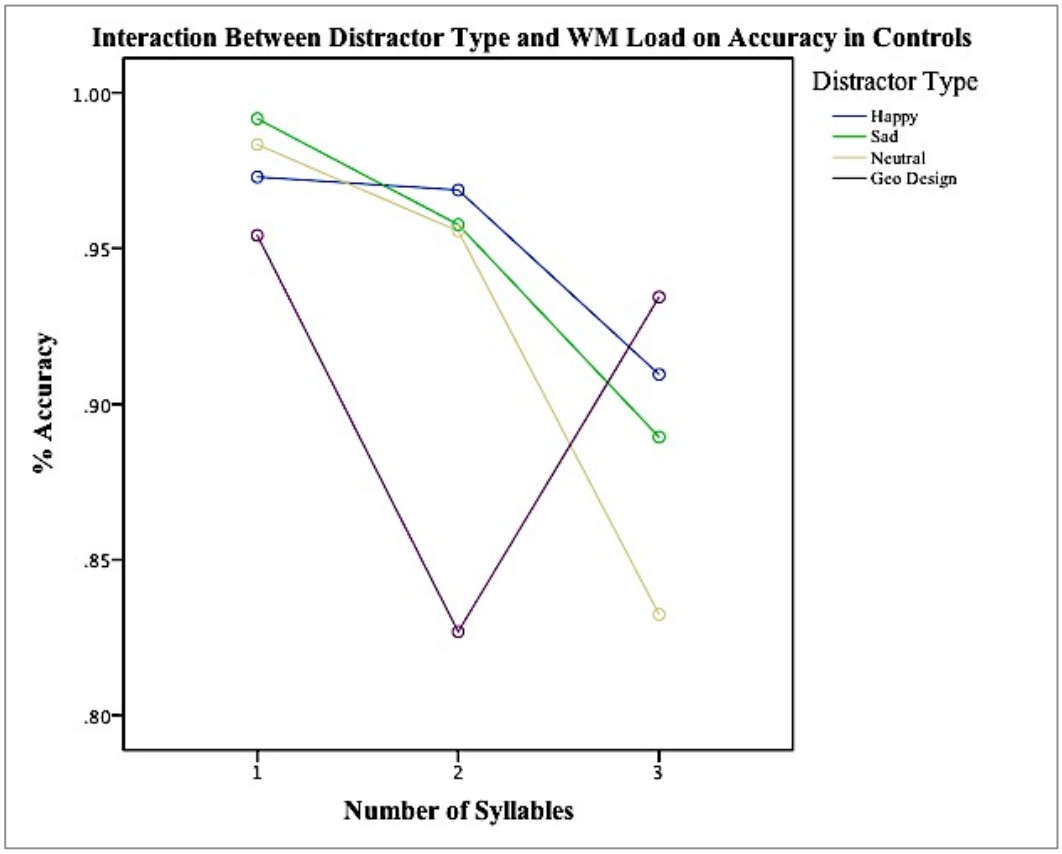



Figure 11. The effect of WM load on accuracy for each distractor type in the control group.

**Patients**. As with controls we examined performance on the fMRI task to ensure participants were responding above chance. In the patient group three participants had one run in which they responded below chance. Those values were dropped and a mean imputation analysis was completed. We analyzed performance in each run

against syllable load to determine main effects for run and load. We did not observe an effect of run ($F$[3,8] = 1.937, $p$ = .202; MSE = .030; $\eta^2$ = .13). We did observe a significant effect of working memory load on accuracy ($F$[2,9] = 20.646, $p$ < .001; MSE = .028; $\eta^2$ = .68), demonstrating a linear trend where responses were most accurate for the 1-syllable condition (M=87.1%; SD=6%), intermediately accurate for the 2-syllables condition (M=81%; SD=4.4%), and least accurate for the 3-syllable condition (M=74.4%; SD=4%). We found a similar linear effect on response latencies ($F$[2,9] = 40.008, $p$ < .001, MSE = 128.25, $\eta^2$ = .80).

To replicate findings previously reported in Mano et al (2014) we analyzed the quadratic effect of WM load on performance in the FvG contrast. We did not see a significant quadratic trend, but found a significant linear trend of WM load on accuracy in the FvG contrast among patients (F[2,9] = 4.402, p = .046, η2 = .49). In response latency we did not see a significant quadratic effect of working memory load, though review of the data showed a curvilinear pattern ($F$[1,10] = 4.012, $p$ = .073, $\eta^2$ = .29; see Figure 12).

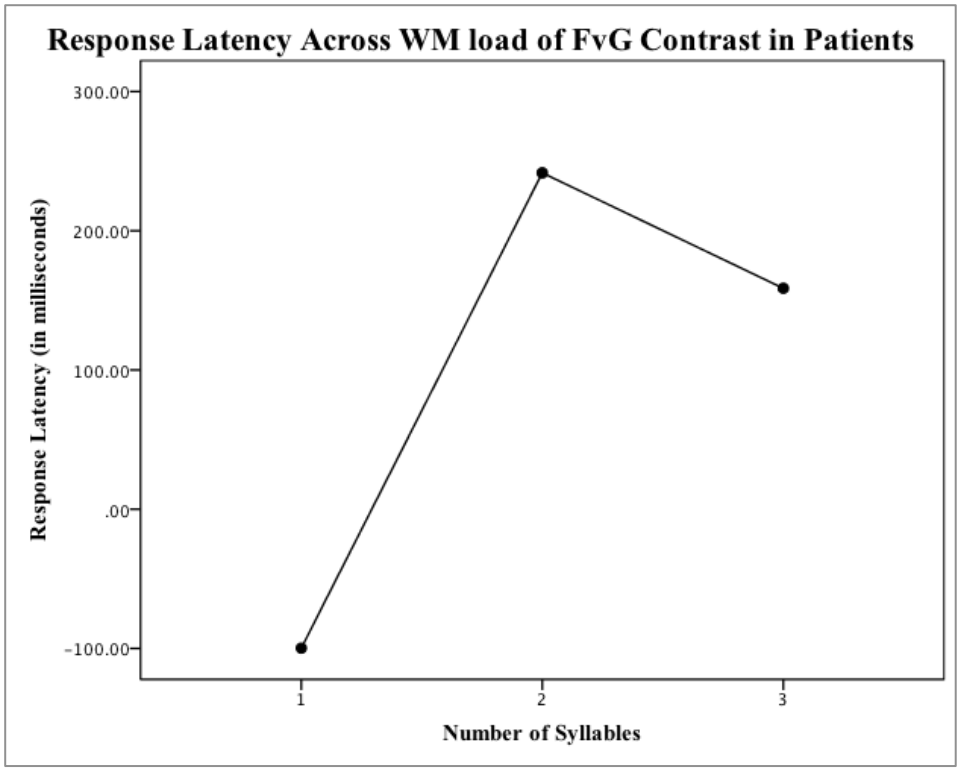



Figure 12. The effect of WM load on response latency in FvG contrast in the patient group.

In order to better understanding the mechanisms underlying this curvilinear relationship we probed the linear and quadratic effects for the affective and geometric stimuli. Facial distraction did not have a significant effect on accuracy ($F$[3,8] = 1.346, $p$ = .326; MSE = .027; $\eta^2$ = .11), however, we did see a significant linear effect on response latencies ($F$[1,10] = 40.176, $p$ < .001, MSE = 120.6, $\eta^2$ = .80). We did not find a significant interaction between load and facial distraction on accuracy

($F$[6,5] = 0.300, $p$ = .913, MSE = 0.039, $\eta^2$ = .07), nor did we observe a curvilinear trend. Further investigation showed a linear trend for across distractor types, without a significant difference between faces and the geometric distractor (see Figure 13). We did not find a significant interaction between load and distractor type in response latency either, though it did show a similar linear trend observed in performance accuracy.

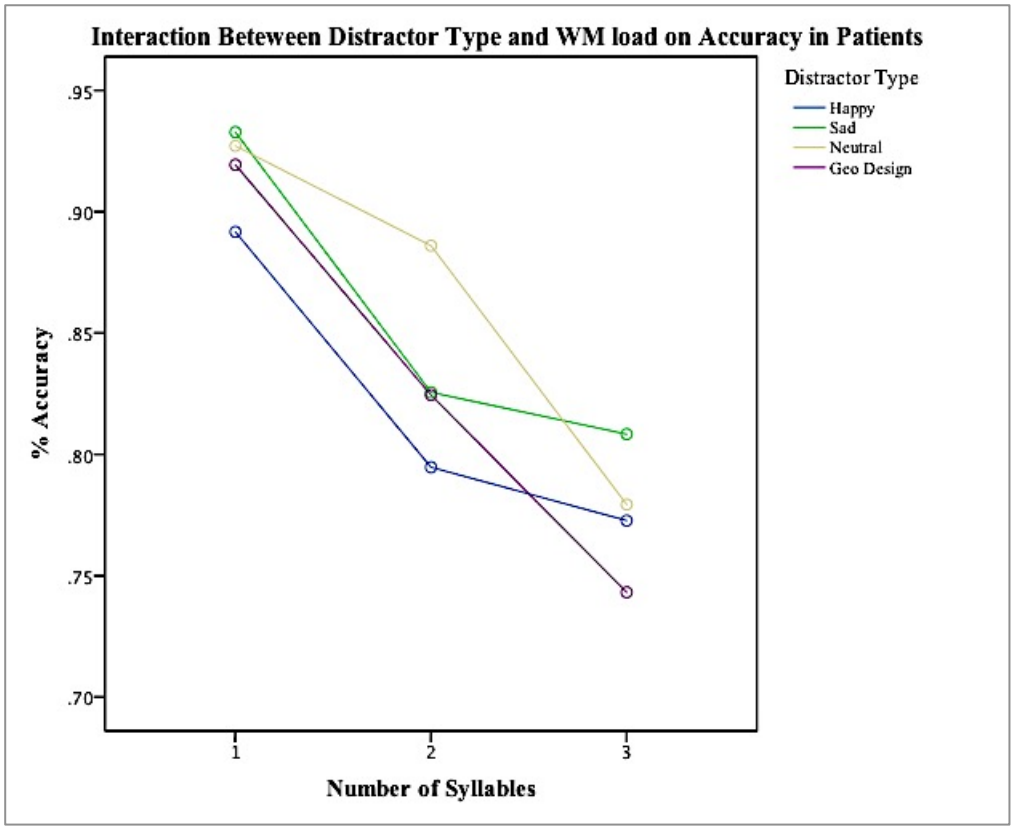



Figure 13. The effect of WM load on accuracy for each distractor type in the patient group.

**Controls vs Patients**. We assessed differences in accuracy and response latencies between patients and controls overall and found a significant difference in accuracy ($F$[1,29] = 14.118, $p$ = .001, MSE = .032, $\eta^2$ = .38) but not response latencies ($F$[1,29] = 2.52, $p$ = .144, MSE = 121.857, $\eta^2$ = .07). Specifically, patients were overall less accurate than controls and although they appeared slower this difference was not statistically significant. With regard to interactions between group differences and syllable load we did not observe a significant interaction for accuracy ($F$[2,28] = 23.697, $p$ = .242, MSE = .023, $\eta^2$ = .05) nor for response latency ($F$[2,28] = 2.171, $p$ = .133, MSE = 74.493, $\eta^2$ = .09). Similarly we did not observe a statistically significant interaction between group and stimulus distractor type for accuracy ($F$[3,27] = 1.195, $p$ = .330, MSE = .027, $\eta^2$ = .03) but we did observe a significant interaction between group and response latency ($F$[3,27] = 2.171, $p$ < .001, MSE = 74.493, $\eta^2$ = .16).

In the analysis of the FvG contrast we did not find a significant difference between groups in accuracy ($F$[1,29] = .355, $p$ = .556, MSE = .038, $\eta^2$ = .012) but did observe a statistically significant difference between groups in response latencies ($F$[1,29] = 6.213, $p$ = .019, MSE = 59.191, $\eta^2$ = .18). Specifically, the patient group showed greater disruption in response latency for facial stimuli in comparison to the geometric figure than control group demonstrated (See Figure 14).

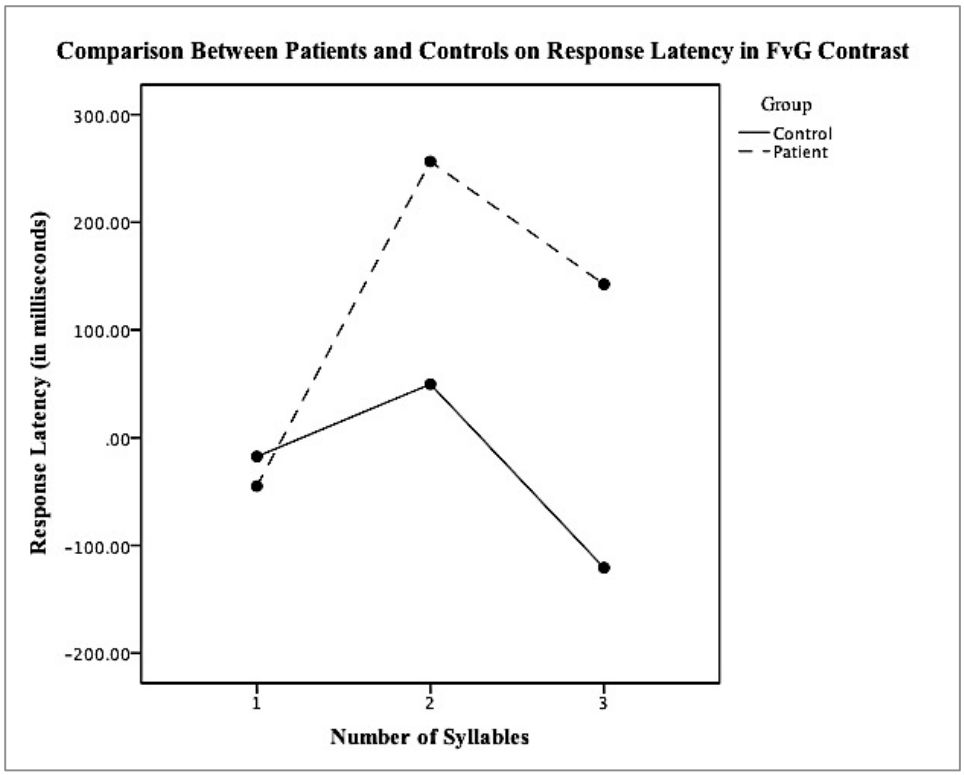



Figure 14. Comparison between controls and patients when response latency in the geometric distractor condition was subtracted from the mean response latency for face distracters.

**Aim 1: fMRI Analyses Replicating the Syllable Effect in Healthy Controls**

**DLPFC – Maintenance Period.** We found a significant effect of syllable load on the percent signal change in the DLPFC ($F$[2,18] = 12.587, $p$ < .001, MSE = .022, $\eta^2$ = .49). Specifically, we observed a linear increase as the syllable load increased. We did not observe a significant difference between hemispheres ($F$[1,19] = 3.150, $p$ = .092, MSE = .022, $\eta^2$ = .14; see Figure 15).

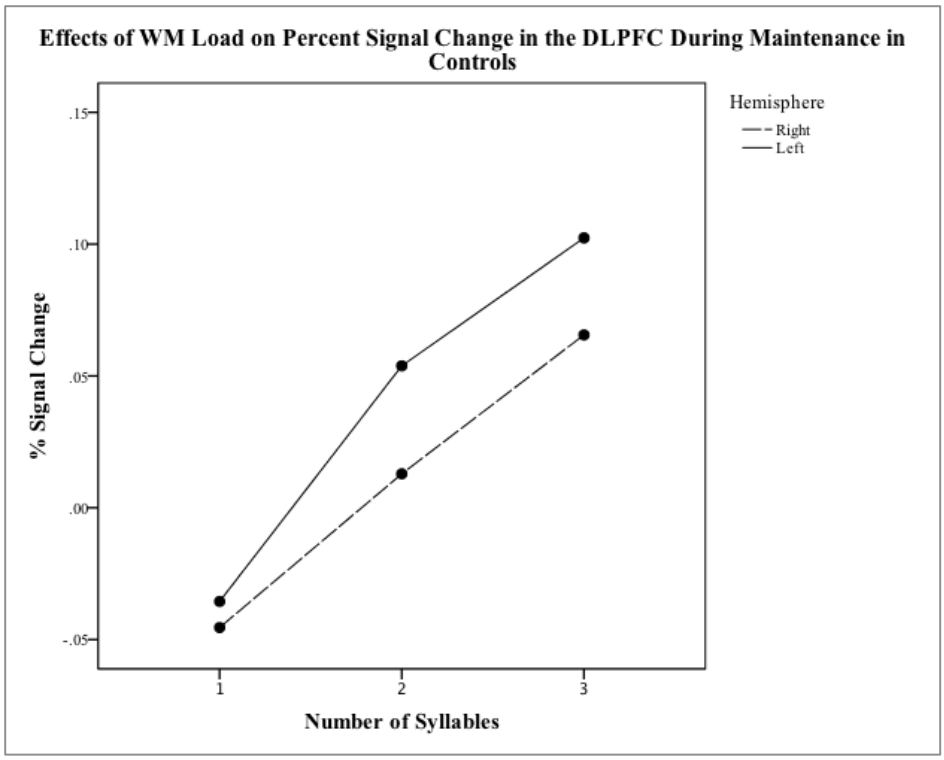



Figure 15. The percent signal change in response to working memory load in both the right and left hemisphere of the DLPFC in controls during the maintenance period of the fMRI task.

**Supramarginal Gyrus – Maintenance Period.** We found a significant effect of syllable load on the percent signal change in the supramarginal gyrus ($F$[2,18] = 10.333, $p < .001$, MSE = .0213, $\eta^2 = .34$). Specifically, we observed a linear increase as the syllable load increased. We did not observe a significant difference between percent signal change in the right vs. the left hemisphere ($F$[1,19] = 1.645, $p = .215$, MSE = .017, $\eta^2 = .08$).

**Aim 2: Faces - Geometric Design Contrast**

Prior to determining group differences on neural response to task conditions we first examined differences in movement parameters between patients and controls. We found statistically significant differences between groups ($F$[1,30] = 4.464, $p$ = .043, MSE = .161, $\eta^2$ = .130), indicating patients required more movement correction than controls.

**Hypothesis 1: FvG Contrast in the DLPFC.**

***FvG Contrast in DLPFC in Controls.*** We found a significant linear effect of WM load on percent signal change of the FvG contrast in the DLPFC in the control group ($F$[1,19] = 5.818, $p$ = .026, MSE = .077, $\eta^2$ = .23). Specifically, similar to the overall effect of WM load on percent signal change in the DLPFC reported in Aim 1, we found as WM load increased, the percent signal change of the FvG contrast increased. We did not see a significant difference between hemispheres ($F$[1,19] = .899, $p$ = .355, MSE = .036, $\eta^2$ = .05).

***FvG Contrast in DLPFC in Patients.*** We did not observe a significant effect of WM load on percent signal change in the FvG contrast of the DLPFC though we did find a medium to large effect size (**$F$**[2,10] =1.450, $p$ = .280, $\eta 2$ = .11; see Figure 16). Though we did not see a main effect of hemispheric differences we did observe a quadratic instead of a linear trend in the DLPFC but only in the right hemisphere (hemisphere x syllable: $F$[1,11] = 9.362, $p$ = .011, $\eta 2$ = .40).

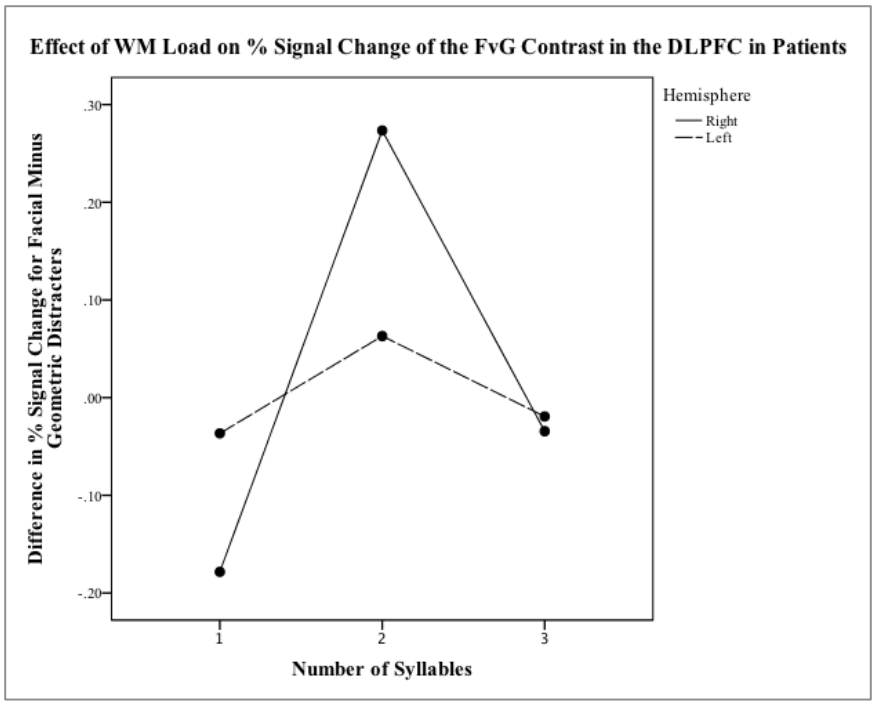



Figure 16. The percent signal change of the DLPFC in patients across WM load when average percent signal change in the geometric design was subtracted from the average percent signal change in the face stimuli.

***FvG Contrast in the DLPFC in controls vs. patients.*** We observed an interaction between syllables, hemisphere, and group in the DLPFC ($F$[2,29] = 5.584, $p$ = .005, MSE = .123, $\eta^2$ = .16). Specifically, in patients, we observed a quadratic instead of a linear trend in the DLPFC in the right hemisphere, with lower overall activation in the left DLPFC in patients vs. controls.

**Hypothesis 2: FvG Contrast in the FFA**

***FvG contrast in the FFA in controls.*** We did not find a significant effect of syllable load on the percent signal change of the FvG contrast in the FFA during the

maintenance ($F$[2,18] = 3.039, $p$ = .073, MSE = .081, $\eta^2$ = .12) or study periods ($F$[2,18] = .618, $p$ = .550, MSE = .083, $\eta^2$ = .06). However, we did find a significant difference between hemispheres averaged over syllable load in the study period ($F$[1,19] = 4.539, $p$ = .046, MSE = .043, $\eta^2$ = .19; see Figure 17). When this was explored further, we found a significant quadratic trend in the right hemisphere only (hemisphere x syllable: $F$[1,19] = 6.317, $p$ = .021, MSE = .043, $\eta^2$ = .25; see Figure 18).

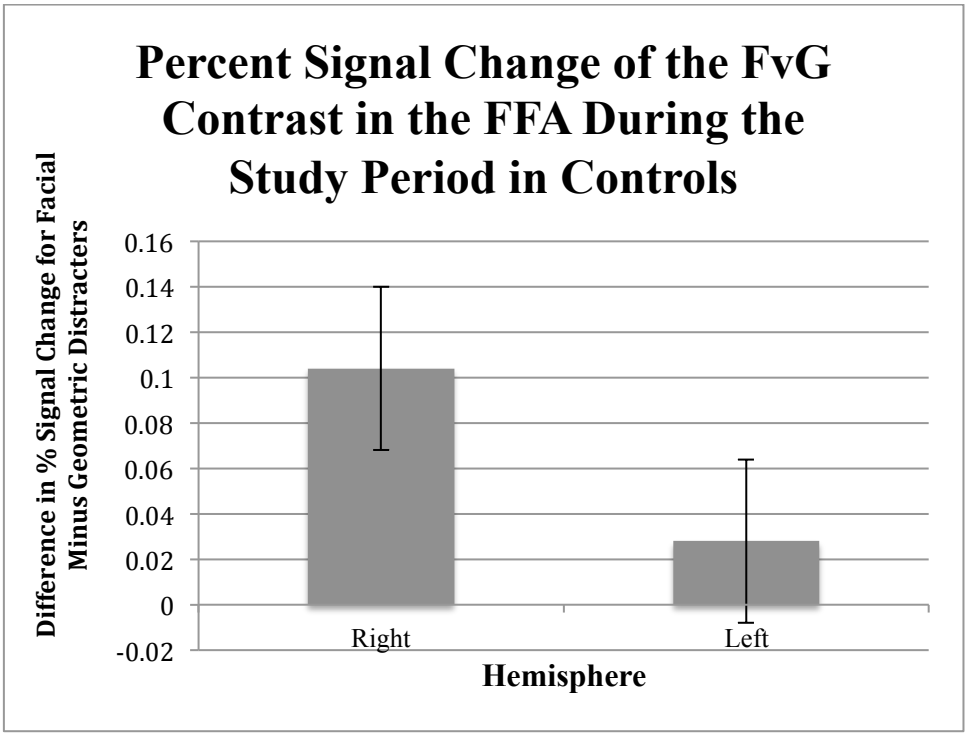



Figure 17. The percent signal change in the right and left hemisphere of the FFA of controls when average percent signal change in the geometric design was subtracted from the average percent signal change in the face stimuli.

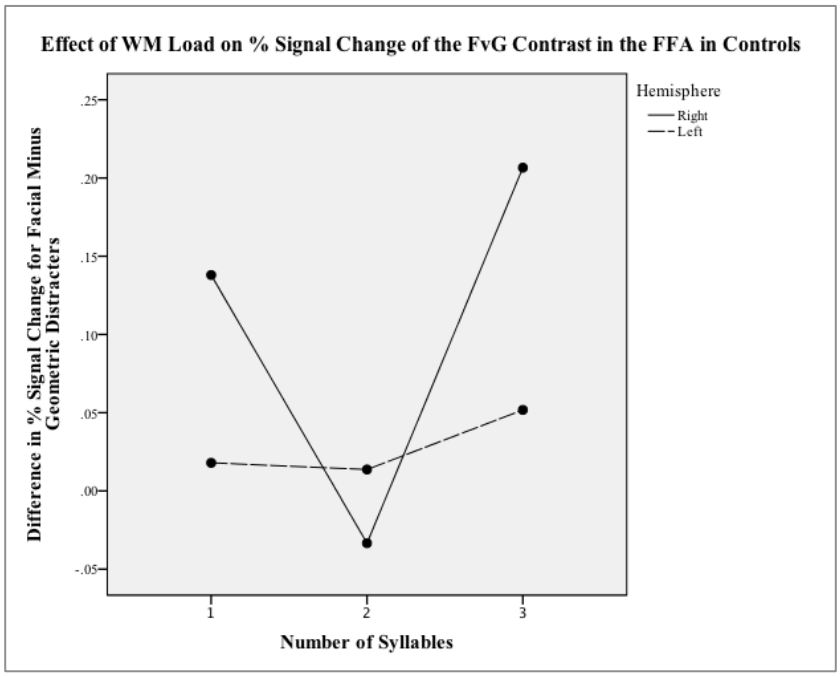



Figure 18. The percent signal change in the FFA of controls across WM load when average percent signal change in the geometric design was subtracted from the average percent signal change in the face stimuli during the study period.

***FvG Contrast in the FFA in patients.*** We did not find a significant effect of syllable load on the percent signal change of the FvG contrast in the FFA in the maintenance ($F$[2,10] = 2.893, $p$ = .102, MSE = .148, $\eta^2$ = .25) or study period ($F$[2,10] = .618, $p$ = .346, MSE = .148, $\eta^2$ = .10). However, a review of the data showed a quadratic trend where the largest difference was found at the intermediate

WM load. Additionally, we did not find a significant difference between hemispheres averaged over syllable load ($F$[1,11] = 2.483, $p$ = .143, MSE = .079, $\eta^2$ = .18).

***FvG Contrast in the FFA in controls vs. patients.*** We did not find a significant differences between groups overall, nor did we see a significant interaction between group and other variables in the FFA ($F$[1,30] = .314, $p$ = .580, MSE = .078, $\eta^2$ = .010).

**Hypothesis 3: FvG Contrast in the amygdala.**

***FvG Contrast in the amygdala in controls.*** In the amygdala we found a significant effect of WM load on percent signal change in the FvG contrast ($F$[2,18] = 6.299, $p$ = .008, MSE = .085, $\eta^2$ = .30). Interestingly, we saw the lowest percent signal change in the intermediate WM load and the highest percent signal change in the highest WM load producing a quadratic effect ($F$[1,19] = 10.423, $p$ = .004, MSE = .121, $\eta^2$ = .35; see Figure 19).

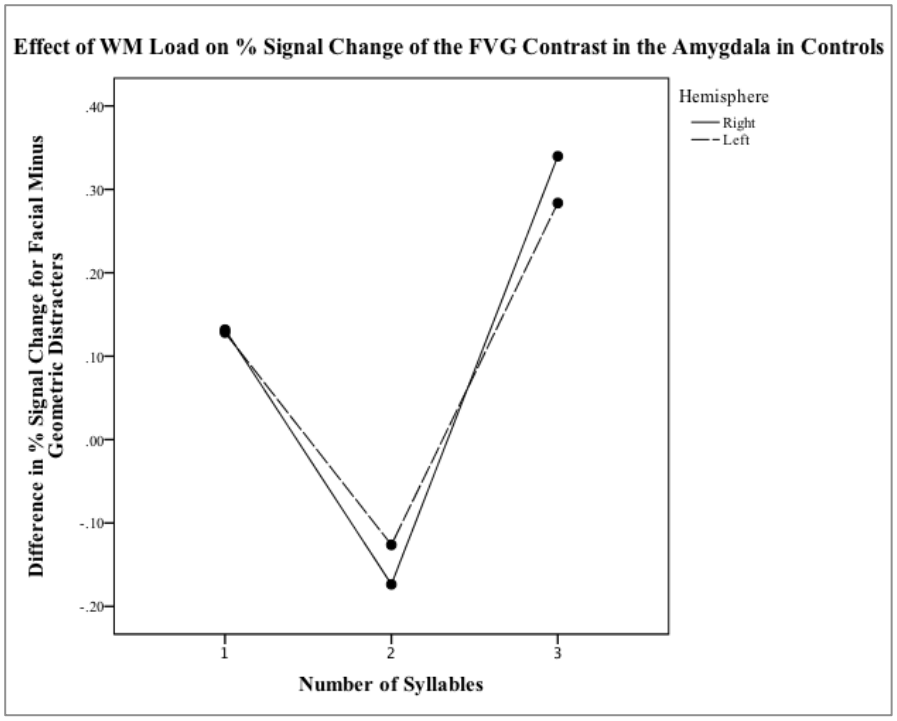



Figure 19. The percent signal change in the amygdala of controls across WM load when average percent signal change in the geometric design was subtracted from the average percent signal change in the face stimuli.

***FvG Contrast in the amygdala in patients.*** In the amygdala we did not find a significant effect of WM load on percent signal change in the overall omnibus analysis of the FvG contrast ($F$[2,10] = .189, $p$ = .831, MSE = .085, $\eta^2$ = .02). Nonetheless, we found a significant quadratic as seen in controls, however, this was in the opposite direction as that of controls and was only seen in the right hemisphere (hemisphere x syllable: F[1,11] = 10.442 p = .008, η2 = .49; see right hemisphere findings in Figure 20).

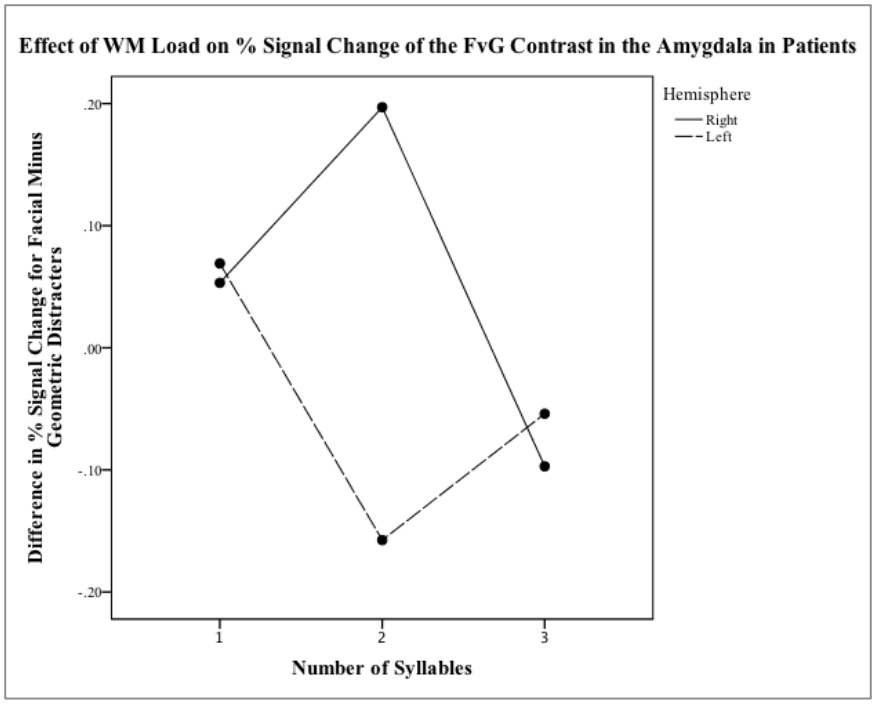



Figure 20. The percent signal change of the amygdala of patients across WM load when average percent signal change in the geometric design was subtracted from the average percent signal change in the face stimuli.

***FvG Contrast in the amygdala in controls vs. patients.*** We found a significant interaction between syllables, hemisphere and group in the amygdala ($F$[2,29] = 6.298, $p$ = .005, MSE = .099, $\eta^2$ = .18). Specifically, we saw an inverse quadratic trend in patients to that observed in controls in the right hemisphere, with lower overall activation in the left amygdala in patients vs. controls (see Figure 21).

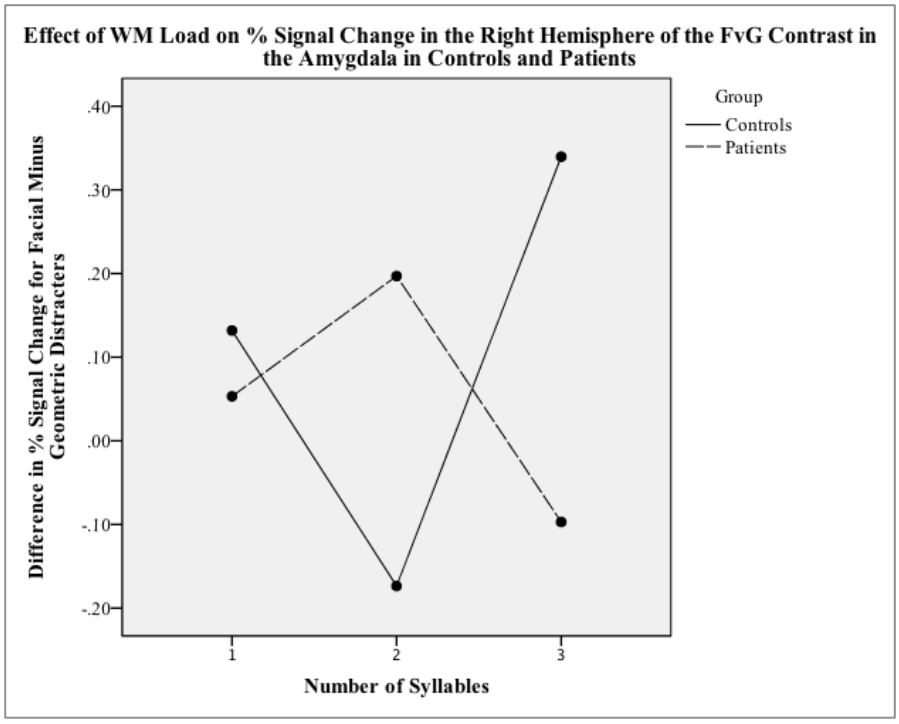



Figure 21. The percent signal change of the right hemisphere of the amygdala across WM load when average percent signal change in the geometric design was subtracted from the average percent signal change in the face stimuli for controls and patients.

***Additional amygdala analyses.*** In controls and patients we performed an exploratory analysis on the percent signal change associated with individual distracting stimuli. In controls we found that the percent signal change associated with the presentation of the geometric design in the amygdala during maintenance produced a quadratic trend similar to that evidenced in the FvG contrast of response latency (see Figure 22). However, pattern of signal change in the faces condition produced a decreasing linear trend (see Figure 23).

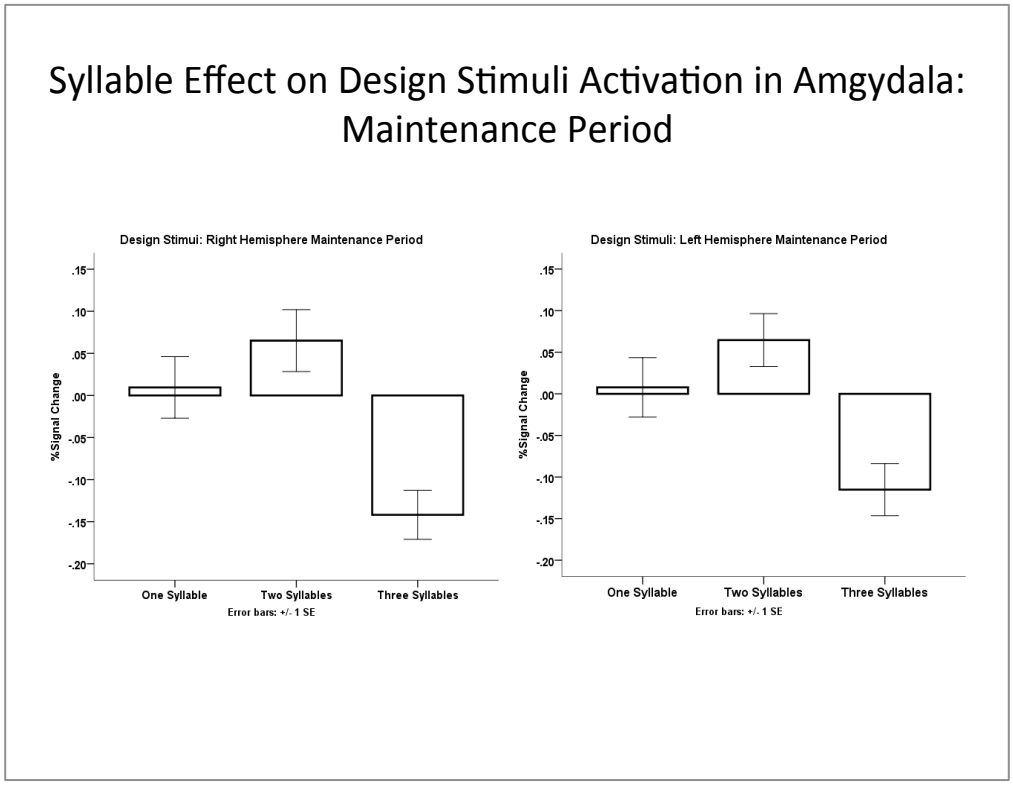



Figure 22. The effect of WM load in the geometric design on percent signal change in each hemisphere of the amygdala during the maintenance period. Here we see a curvilinear trend in percent signal change across WM load, indicating the highest activation at an intermediate WM load with the least activation at the highest WM load.

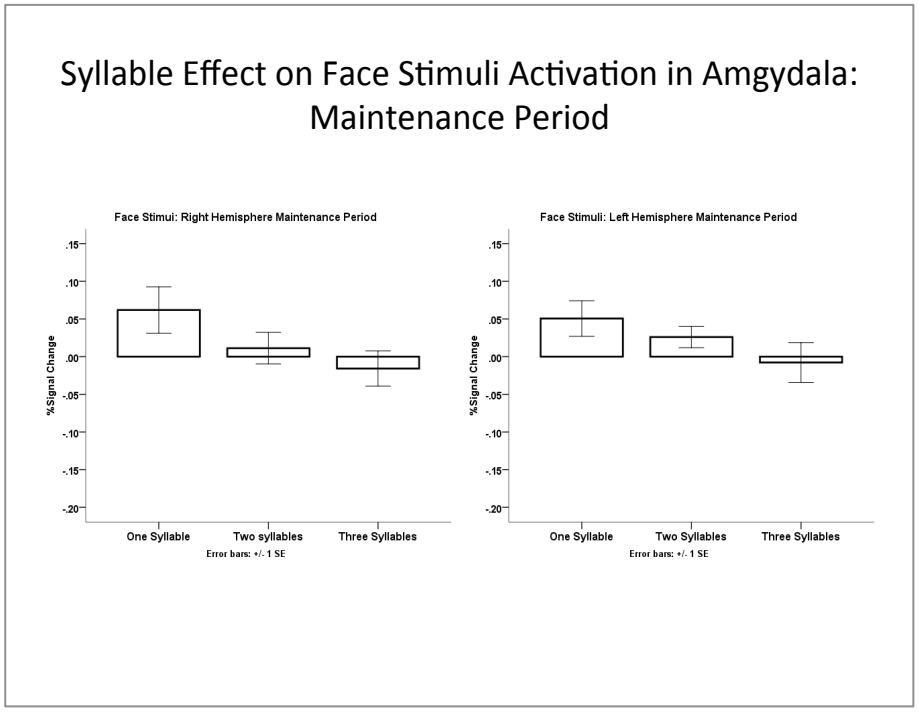



Figure 23. The effect of WM load in the face distracters on percent signal change in each hemisphere of the amygdala during the maintenance period. Here we see a decreasing linear trend in percent signal change across WM load.

In patients we found a pattern similar to that evidenced in the FvG contrast of response latency. Specifically, the percent signal change associated with the presentation of the geometric design and face stimuli in the amygdala during maintenance produced a quadratic trend (see Figures 24 & 25). However, the pattern of signal change in the right hemisphere in the design condition produced a slight decreasing linear trend, though there was no significant difference in percent signal change between working memory loads (see Figure 24).

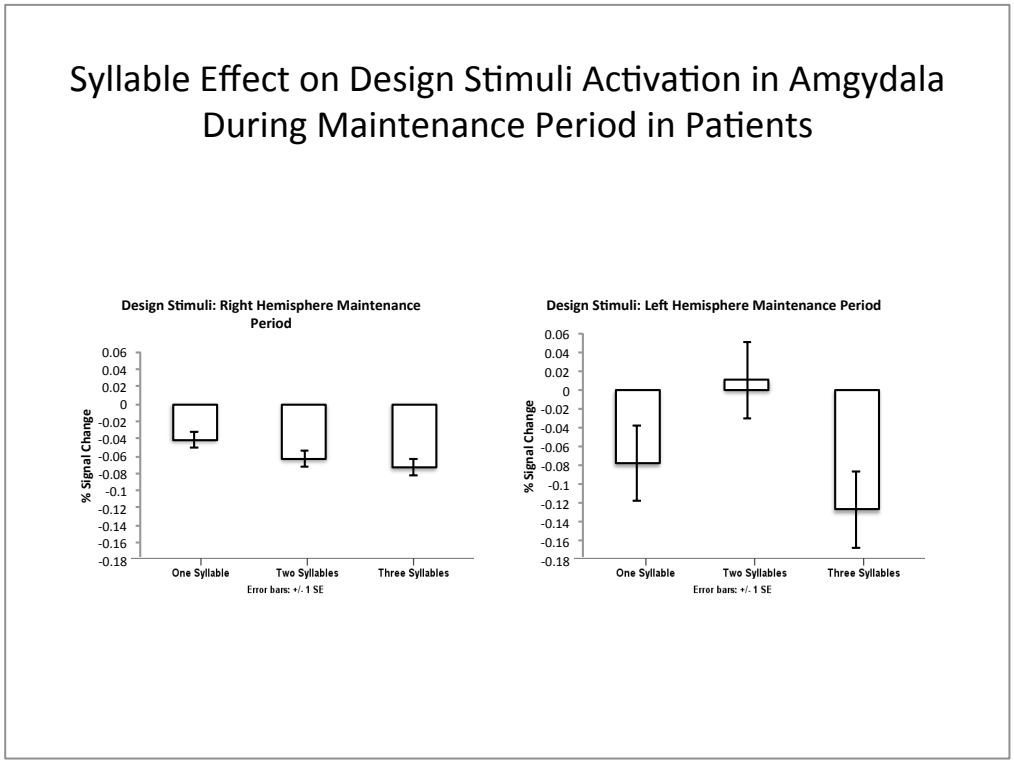



Figure 24. The effect of WM load in the geometric design on percent signal change in each hemisphere of the amygdala during the maintenance period. Here we see a curvilinear trend in percent signal change in the left hemisphere across WM load, indicating the highest activation at an intermediate WM load with the least activation at the highest WM load. However, in the right hemisphere we see a stable though slight linear decline.

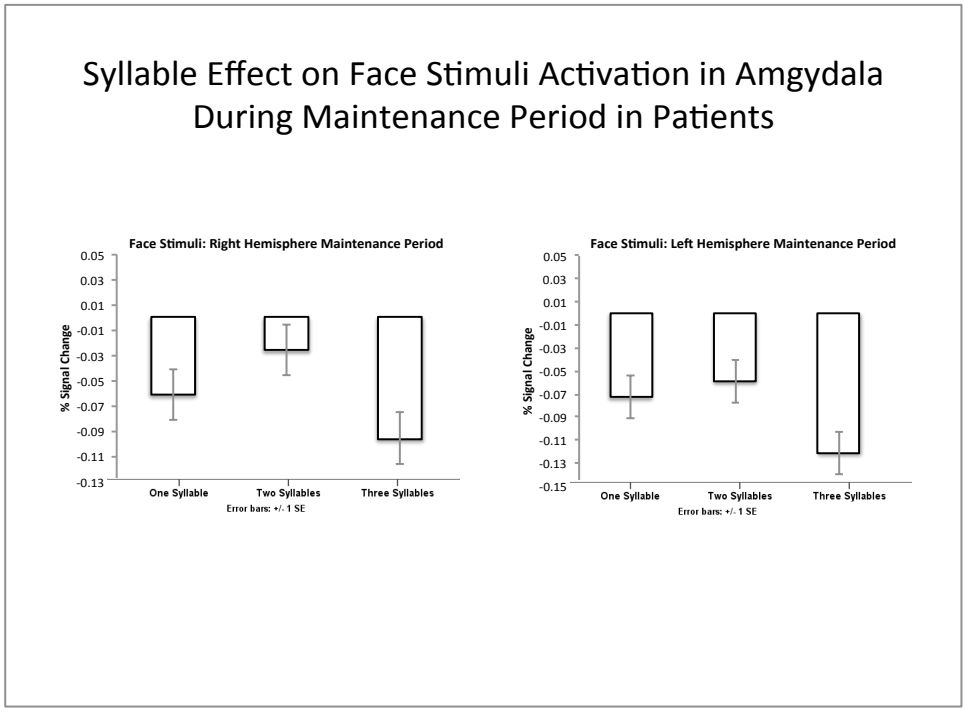



Figure 25. The effect of WM load in the face distracters on percent signal change in each hemisphere of the amygdala during the maintenance period. Here we see a curvilinear trend in percent signal change across WM load, indicating the highest activation at an intermediate WM load with the least activation at the highest WM load.

**Hypothesis 4: Correlation between performance, functional activation, and psychopathology in patients.** Although the correlation between the magnitude of the quadratic trend in the right amygdala at the highest WM load with general psychopathology was moderately large in patients, possibly because of the limited sample size this correlation did not reach statistical significance ($r$ = -.37). This correlation indicated as reported psychopathology increased, percent signal change of the FvG contrast in the amygdala at the highest WM load decreased. Similarly, we

saw large though not statistically significant correlations between the accuracy in the highest WM load of the FvG contrast for reported positive symptoms ($r$ = .43), reported negative symptoms ($r$ = .25), and reported general symptoms ($r$ = .55). This indicated that as the difference between accuracy between facial distracters and geometric design increased at the highest WM load, reported symptoms increased.

**Aim 3: Exploratory Whole Brain Analyses**

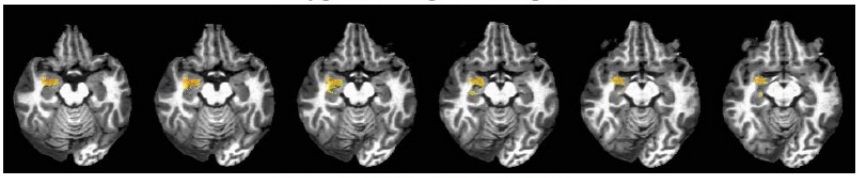
These analyses were performed to test group differences in the quadratic trend for syllable load on FvG contrast during the maintenance period. Plots of the between-group Cohen d values converted from the voxel-wise, between-group t-test maps for the statistically significant clusters are presented in the first three rows of Table 4. Three large clusters of between-group difference were found. The first cluster included the right amygdala and extended into the right subcallosal gyrus, lentiform nucleus, putamen, parts of the thalamus and along much of the extent of the right parahippocampal gyrus. A second cluster included several regions of the cerebellum, with the right more involved than the left, and extended into the lingual gyri, again right more than left. The third cluster encompassed portions of the body and anterior section of the cingulate cortex bilaterally and extended into the primary sensorimotor cortex of the left hemisphere. All three clusters of between group differences showed the same pattern. In both controls and patients, syllable load was quadratically related to the FvG contrast, although the patterns were inverted between the two groups, as in Figure 21. Recall that the quadratic contrast involves subtracting

twice a dependent variable value at syllable 2 from the sum of values associated with syllables 1 and 3. Therefore, whereas the faces minus geometric designs difference in percent signal change was smallest at syllable load 2 for controls, it was largest as syllable load 2 for patients. The last two rows of Table 4 show this pattern for the cingulate cortex, where within-group Cohen d values are positive for controls and negative for patients.

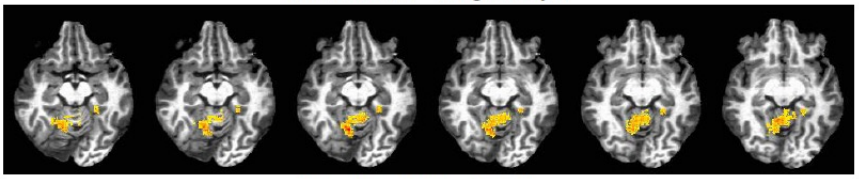
Table 4. Brain Location and Signed Effect Size Magnitude for Between Group and Within Group Tests Derived from a Whole Brain Analysis

**Between Group Effects**

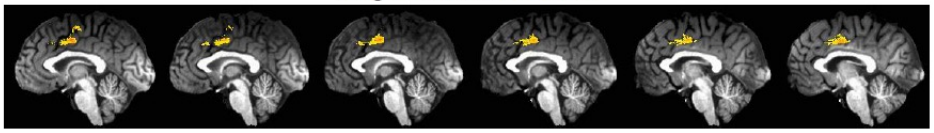
Amygdala – Right Hemisphere



Cerebellum – Lingual Gyri

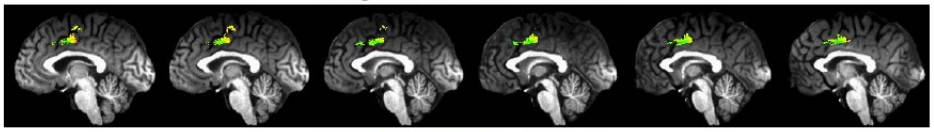


Cingulate-Motor Cortices

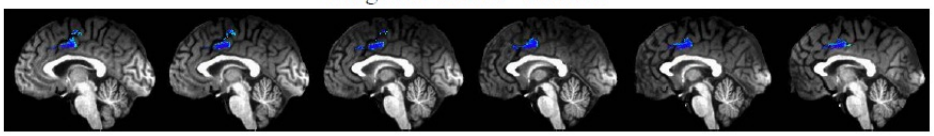


**Within Group Effects**

Cingulate Cortex – Controls



Cingulate Cortex - Patients



*Note*. The effect size is Cohen's d. For the between group difference the extreme colors are set equal to |d| = 2.0. For the within-group effect the extreme colors are set equal to |d| = 1.0. Images are presented in radiological orientation where the right hemisphere appears on the left side of the brain image.

## Discussion

Neuroscientific research regarding the interaction between cognition and emotion has produced findings that indicate a dynamic interplay between areas associated with cognitive control and those associated with affective perception and identification (Dolcos, Iordan, & Dolcos, 2011). In this study, we sought to elucidate the neural activation associated with the curvilinear trend previously seen in a study of emotion and working memory interaction. Findings from our previous studies indicated that processing faces during the maintenance period may detract attentional resources from the working memory maintenance process. This competition for attentional resources would not be seen at the lowest WM load, but would become evident at the intermediate load. We, therefore, postulated that this competition of resources may result in the executive (supervisory) system suppressing the attention process related to affective processing to allocate sufficient resources to maintain information in WM. Our results suggested that this competition for resources would be associated with increased neural response to faces compared with non-face stimuli at the intermediate working memory load. In the next section, we will discuss this working hypothesis in the context of this study's aims and hypotheses.

**Aim 1: Replication and Interpretation:**

We first sought to replicate previously reported behavioral findings for this task in both patients and controls. In controls, we found a significant curvilinear trend in response latencies of the FvG contrast similar to that previously produced by our laboratory (Mano et al. 2013 & 2014). However, concerning accuracy, we did not

observe the previously curvilinear trend (in the opposite direction of the curvilinear trend observed in response latency). To understand this difference we examined the effect of WM load on response accuracy for faces and the geometric design separately. In this analysis, we found the curvilinear trend reported by Mano et al. (2013) only for the geometric design. However, for facial distracters, we saw a decreasing linear trend. This difference in trends may suggest that the curvilinear pattern previously observed may be driven by the process of discriminating between stimuli, rather than interference by socially relevant stimuli.

In patients, we observed a quadratic trend of WM load on response latency in the FvG contrast, though this didn't reach the level of statistically significant. This trend is consistent with previous findings from this laboratory (Mano et al. 2014). However, with regards to accuracy, we did not observe a curvilinear trend but instead found a significant linear trend. As with controls, we investigated this further and found that all distracter types (facial and geometric) showed a decreasing linear trend of WM load on accuracy.

We also sought to replicate the BOLD signal change in the DLPFC. Cognitive research regarding neural activation associated with working memory has long implicated the DLPFC in WM attention and maintenance (Bledowski, Kaiser, & Rahm 2010). Previous studies from our lab confirmed this contribution of WM load on percent signal change in the DLPFC. Specifically, as WM load increased, activation in the DLPFC increased. In this study we replicated the previous findings reported by McKenna et al. (2013), demonstrating a linear increase in bilateral

percent signal change of the DLPFC in response to WM demands. This finding suggests that the DLPFC's pattern of activation in increasingly difficult working memory tasks is consistent even in the presence of task-irrelevant stimuli.

In addition to the linear trend in the DLPFC, previous findings showed a similar trend in the supramarginal gyri (McKenna et al. 2013). Research has indicated that neural activation in the supramarginal gyri is related to the phonological encoding and recoding of verbal stimuli. McKenna and colleagues (2013) concluded that the increasing linear activation trend in relation to WM load seen in the supramarginal gyri is the result of an increased demand to encode and recode a greater number of syllables within the temporary phonological storage system. In this study we found a significant increasing linear trend in the supramarginal gyri as previously reported, confirming the activation pattern associated with WM load in the supramarginal gyri for this task.

**Aim 2: BOLD Signal Change Associated with the Faces vs. Geometric Design Contrast**

**Hypothesis 1: FvG Contrast in the DLPFC.** We found evidence among controls that the linear trend previously discussed was observed in the FvG contrast. These results indicate that as WM load increases, the difference in percent signal change between facial distracters and geometric design also increases. These findings are consistent with literature regarding DLPFC activity in WM tasks in the presence of task-irrelevant distracters, as well as those reporting DLPFC activation in the presence of emotional distracters (Bledowski, Kaiser, & Rahm 2010). For example,

Sakai et al. (2002), reported findings that suggested the DLPFC was involved in preserving WM representations in the presence of task-irrelevant distracters in a delayed-match-to-sample task. They theorized these findings indicated that the DLPFC was involved in protecting working memory from distracting task-irrelevant stimuli. In this study, we find that there is more activation in the DLPFC associated with the facial distracters compare to the geometric design, especially at the highest WM load. This possibly indicates that the DLPFC is active in processing the facial distracters while maintaining WM representations as WM demands increase.

In patients, we found a significant quadratic, rather than a linear trend of WM load on activation in the FvG contrast of the DLPFC, but only in the right hemisphere. Here we saw that the discrepancy between activation associated with facial distracters compared to that of the geometric design was minimal in the left hemisphere. However in the right hemisphere, this contrast was greatest at the intermediate working memory load, suggesting more interference in activation associated with facial distracters. There was little to no difference in between activation of the facial distracters compared to the geometric design across WM load in the left hemisphere. Here we see evidence of a *distraction-suppression* effect; specifically, at intermediate working memory loads facial distracters interfere with WM processes, however, this process is suppressed when WM load increases.

**Hypothesis 2: FvG Contrast in the FFA.** Evidence has indicated that the fusiform face area is associated with identifying facial stimuli. Research shows that this process is performed primarily in the right hemisphere (Gauthier, Tarr, Moylan,

Skudlarski, Gore, & Anderson, 2000). In this study, we sought to examine the pattern of activation in the FFA when the percent signal change associated with the presentation of the geometric design was subtracted from that associated with the presentation of the facial distracters. In controls, we saw a slight curvilinear trend in the right hemisphere during the maintenance period. We then found a significant curvilinear relationship in the right hemisphere during the study period. This finding demonstrated that the largest discrepancy between facial and geometric distracters was at the highest WM load, rather than the intermediate WM load, contrary to our hypothesis suggesting there may be an alternate process that is engaged than the *distraction-suppression* process we hypothesized. In patients, we did not find significant differences between activation in the FFA of facial and geometric distracters across WM load during the study or maintenance periods. However, review of the data showed a curvilinear pattern in the study period, though this was in the opposite direction than that seen in controls. Specifically, we found the largest difference in activation between the facial and geometric distracters at the intermediate working memory load. This pattern, seen in patients is again consistent with our overarching *distraction-suppression* hypothesis. Though we found different patterns of activation in the FvG contrast between patients and controls, this was not statistically significant.

**Hypothesis 3: FvG Contrast in the amygdala.** Understanding the functional patterns of the amygdala in the context of cognition-emotion interactions continues to evolve. In this study, we postulated that the percent signal change in the amygdala

associated with the FvG contrast would show a pattern similar to previously reported behavioral findings demonstrating a curvilinear pattern in response latencies of the FvG contrast (Mano et al. 2013). In the present study, we did find a significant curvilinear trend. However, it was in the opposite direction of our hypotheses in controls. Specifically, we proposed that we would see high differential activation between face and design distraction in the amygdala at the lowest WM load, similar or higher differential activation at the intermediate WM load condition, and little no differential activation at the highest WM load in controls. However, we did find the lowest differential activation in the amygdala in the intermediate WM load condition and a significant increase at the highest WM load. To further understand this activation pattern among controls we examined the percent signal change in the amygdala for faces and geometric designs separately. In this analysis of the maintenance period, we found a linear reduction in activation for faces across WM load with a large activation in the amygdala at syllable one (see Figure 22). Interestingly, it appears that the quadratic trend seen in response latencies of the FvG contrast was mirrored in the activation associated with the geometric design (see Figure 23). As can be seen, there is increased activation at the two syllable compared with the one syllable load condition after the presentation of the geometric design. We then see the sharp decrease in activation after the presentation of the geometric design at syllable three. Notably, this pattern is very similar to that seen in response accuracy. Specifically, in response accuracy, we saw a decreasing linear trend in accuracy in response to WM load for the facial stimuli. However, in the for the

geometric design condition, we saw decreased accuracy at the intermediate WM load compared to both the low and high WM load conditions. This activation pattern, like that in the FFA, may indicate that these areas are expending some neural activity on alternate processes.

In patients, we found the curvilinear trend we hypothesized would be associated with the *distraction-suppression* hypotheses. Specifically, we found the highest activation at the intermediate WM load for both facial and geometric design. Notably, this was not seen for design stimuli in the right hemisphere only. These results, are also consistent with the *distraction-suppression* hypothesis indicating that patients may be processing socioemotional stimuli at low and intermediate WM loads but is suppressed at high WM loads. Additionally, we found moderate correlations between the magnitude of the difference in percent signal change of the FvG contrast in the right amygdala at the highest WM load with accuracy and positive and general psychopathology in patients. However, these correlations were not statistically significant, possibly because of the limited sample size this correlation did not reach statistical significance.

**Aim 3: Exploratory Analyses of the FvG Contrast.**

In the whole brain voxel-wise exploratory analysis we endeavored to explore other areas involved in the group difference in the FvG contrast. Here we found significant group differences in quadratic patterns in clusters involving the anterior cingulate cortex and cerebellar to lingual gyrus region that were similar to the quadratic patterns in the amygdala. Specifically, we found controls to have the lowest

difference in percent signal change between facial distracters and geometric designs at the intermediate WM load, whereas patients evidenced their largest difference in percent signal change between facial distracters and geometric designs at the intermediate WM load.

**Neural Patterns of Social Affect Discrimination in Controls**

The findings reported in this study of the neural patterns associated with the FvG contrast suggest an alternate hypothesis than the *distraction-suppression* hypothesis. In particular, across different regions, we found the largest difference between facial and geometric stimuli at the highest WM load. Neuroscientific research suggests that the amygdala is not only involved in processing and identifying emotional stimuli, but also in discriminating between socially relevant vs. irrelevant stimuli (Ousdal, Jensen, Server, Hariri, Nakstad, & Andreassen, 2008; Sander, Grafman, & Zalla, 2003). Furthermore, research shows that the processing of emotional and social relevant stimuli involves a neural network encompassing limbic, frontal, and temporal regions (Scharpf, Wendt, Lotze, & Hamm, 2010). The neural patterns reported in this study suggest that this process of discrimination between socially relevant and socially irrelevant stimuli is occurring in controls during the maintenance period. These neural patterns may indicate that when discrimination is difficult for the dorsal executive system, the efficient identification of socially relevant stimuli during the WM maintenance period declines and reduces maintenance efficiency, resulting in slower response time. Therefore, it is not the dominance of the neural response to affective stimuli that is responsible for

slower response time at intermediate WM loads, but the inability to discriminate socially relevant stimuli from socially irrelevant stimuli that drives the slower response times for faces. At the higher WM loads, we see increased neural activation in regions of the dorsal executive system, therefore, the appropriate discrimination of socially relevant to socially irrelevant stimuli is in balance again.

**Neural Patterns of Social Affect Discrimination in Patients**

As previously stated both WM and emotion processing are disrupted in patients with schizophrenia. There is less known about the performance of patients with schizophrenia during tasks involving cognition and emotion. The current research available does indicate impaired performance on tasks involving WM and implicit emotion processing (Diaz et al., 2011, Anticevic et al., 2012; Mano et al. 2014). In the present study, we sought to understand the neural activation patterns associated with the impairment in cognition-emotion interactions. In patients, we found significantly different activation patterns than those seen in controls. In the DLPFC we observed a quadratic rather than a linear trend in the FvG contrast of differential activation in the DLPFC in the right hemisphere with minimal differential activation in the left hemisphere. In the amygdala, the patients displayed a quadratic trend in the FvG contrast, also only in the right hemisphere again with minimal differential activation in the left hemisphere. Furthermore, concerning performance accuracy we saw a significantly different pattern in patients. Specifically, patients showed a decreasing linear trend in all faces as well as the geometric design. This difference in performance was also seen in response latency in the FvG contrast with

patients again showing a linear trend for all four distracter types. These findings are consistent with the *distraction-suppression* hypothesis, suggesting that to attend properly to demanding cognitive tasks, processing task-irrelevant stimuli is suppressed.

Overall, patients did not show neural activation patterns similar to controls. Specifically, in controls, we observed neural activation patterns that may indicate a *social-discrimination* process is taking place. One possible explanation for these differences in neural activation and subsequent cognitive processes may be the decreased interhemispheric interaction. In this study, we found significant differences between the neural patterns of the right and left hemisphere in both the amygdala and DLPFC in individuals with schizophrenia. In particular, we observed opposite quadratic trends between hemispheres (in the DLPFC) possible indicating poor interhemispheric interaction during WM maintenance. Research shows interhemispheric interaction is important in many cognitive processes (Schulte & Müller-Oehring, 2010). Interestingly, differences in interhemispheric interactions have been noted in individuals with schizophrenia (Hoptman et al., 2012; Whitford et al., 2011). This poor interhemispheric integration is evidenced in both structure and function. Specifically, patients have shown decreased structural integrity in the corpus callosum (one of the major structures connecting the right and left hemispheres) and decreased connectivity of this structure associated with delayed interhemispheric communication (Knochel, et al., 2012; Kubicki et al., 2008; Whitford et al., 2011; Whitford et al., 2012). This impairment in interhemispheric interaction may be

associated with symptomatology (Hoptman et al., 2012; Knochel et al., 2012; Ribolsi, Daskalakis, Siracusano, & Koch, 2014).

In addition to impaired interhemispheric interaction patients in this study showed differential lateralization. Specifically, in the DLPFC we found greater overall activation in the *right hemisphere.* However, in the control group, we found greater overall activation in the *left hemisphere*. Furthermore, this was evident when distracters were taken into account. Specifically, there were greater differences in percent signal change associated with facial vs. geometric distracters in the *right hemisphere* of patients but the *left hemisphere* of controls. Additionally, in the patient group we found bilateral activation in the FFA. However, there was a stronger trend in the *left hemisphere* whereas we found overall greater activation in the *right hemisphere* of controls, which is what was expected based on the literature (Grill-Spector, Knouf, & Kanwisher, 2004). This seemingly reversed asymmetry has been demonstrated in other studies. Angrili et al. (2009) reported decreased *left-hemispheric lateralization* in individuals with schizophrenia when performing a task of phonological and semantic word matching. Oertel et al. (2010) reported decreased left-right hemispheric asymmetry in frontotemporal areas was correlated with increased auditory hallucinations in individuals with schizophrenia.

**Summary**

Findings in the control group suggest *social-discrimination* processes interact with WM and cognitive control processes. It can be theorized that due to the significant importance of identifying social stimuli this process is carried out in social

contexts even as other cognitive processes are engaged. Therefore, as demands of these other cognitive processes increase, an integrated neural response is brought online in so that the *social-discrimination* processes can continue. This process seems disrupted in patients with schizophrenia. In particular, it appears that the neural activation patterns associated with *social-discrimination* may be significantly altered in patients. This alteration may be attributed to poor lateralization and impaired interhemispheric interaction. It can be inferred this process does take place, given that patients were just as likely to identify seeing faces during the task relative to patients, however, they may have more difficulty discriminating the social relevance between facial and geometric distractors.

**Limitations and Future Directions**

The results of this study indicate significant contributions to the literature on neural patterns of cognition-emotion interactions in both healthy controls and patients with schizophrenia. However, this study has several limitations. First, despite vigorous recruitment efforts, we had a small sample size, particularly in patients with schizophrenia. Furthermore, given our exclusion criteria in our patient population, our sample was physically healthier and more clinically stable than typical schizophrenia patients. Additionally, further understanding of the neural processes involved in *social-discrimination* and their integration with working memory would benefit from a block design task that would facilitate the use of functional connectivity analyses.

Understanding the neural patterns of cognition and emotion-processing in schizophrenia would have implications both for understanding the neural bases of in

schizophrenia, as well as providing information that may inform and improve treatment outcomes. Currently, the standard treatment for schizophrenia is pharmacotherapy, with socio-cognitive remediation therapies gaining in prominence and use (Bustillo, Lauriello, Horan, & Keith, 2001). These treatments could increase in efficacy with an understanding of disrupted functional processes involved in schizophrenia. Specifically, future functional imaging studies of cognition-emotion interactions would provide further information on the neural processes associated with schizophrenia, possibly enabling tailored and more effective treatments. With the introduction of social cognitive rehabilitation in the treatment of schizophrenia, clinicians would benefit from understanding the neural bases and networks of impaired cognition to better target these areas for rehabilitation, as well as utilize areas not affected by the disorder to better develop compensatory strategies. Additionally, identifying the systems involved with these pervasive emotional deficits would lead to investigations of the neurotransmitters involved in this system. This line of inquiry would then lead to a better understanding of the neurochemical mechanisms associated with these systems as well as the imbalance in these chemicals, thereby leading to improved pharmacological treatments for schizophrenia. In this way, functional network analyses can be used as measures of treatment impact and symptom progression or alleviation.

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