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The Effects of Naltrexone on Neural Responses to Methamphetamine Cues

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy
in Psychology

by

Kelly Elizabeth Courtney

2016

ABSTRACT OF THE DISSERTATION

The Effects of Naltrexone on Neural Responses to Methamphetamine Cues

by

Kelly Elizabeth Courtney

Doctor of Philosophy in Psychology

University of California, Los Angeles, 2016

Professor Lara Allison Ray, Chair

Background: Despite multiple legislative attempts to restrict access, methamphetamine remains a widely used drug in the United States, and a significant number of individuals develop methamphetamine problems following repeated use of the drug. No medications are currently approved by the FDA for the treatment of methamphetamine use disorders; yet, preclinical and clinical evidence advances naltrexone, an opioid receptor antagonist, as a promising candidate. Naltrexone is thought to reduce drug reinforcement via blocking dopamine-release in the mesolimbic dopamine system, primarily driven by the pathway from the ventral tegmental area (VTA) to the nucleus accumbens (NAcc); however, this theory has not been directly tested and other pathways may also be involved. Thus, the present dissertation investigated the effects of naltrexone on functional magnetic resonance imaging (fMRI) measures of functional connectivity during methamphetamine cue processing and subjective craving for methamphetamine.

Methods: A final sample of 23 non-treatment seeking individuals with methamphetamine use disorders (74% male, mean age = 34.70 [SD = 8.95]) were enrolled within a randomized, placebo controlled, within-subject design and underwent two blood-oxygen-level dependent (BOLD) methamphetamine cue-reactivity paradigms following three days of naltrexone treatment (50mg) and matched time for placebo. fMRI analyses tested naltrexone-induced differences in BOLD activation associated with methamphetamine and control cues, resting-state cerebral blood flow (CBF), and functional connectivity (using psychophysiological interaction [PPI] analysis) during methamphetamine cue processing.

Results: Analyses revealed that (1) the novel methamphetamine cues task employed was successful in eliciting cue-induced craving and relevant regional activation, (2) greater subjective methamphetamine craving is related to enhanced recruitment of prefrontal regions, (3) naltrexone moderates methamphetamine cue-reactivity in sensorimotor regions, (4) the BOLD results are not a reflection of global CBF changes induced by naltrexone, (5) reduced activation of sensorimotor regions during methamphetamine cue processing by naltrexone is related to functional connectivity of dorsal striatum, VTA, periaqueductal gray (PAG), and precuneus with visual, sensory, and motor-related regions, (6) naltrexone enhances dorsal striatum, VTA, and sensorimotor region functional connectivity with the frontal cortex during methamphetamine cues processing , and (7) naltrexone weakens the associations between subjective craving and precuneus functional connectivity with sensorimotor regions and strengthens the associations between subjective craving and dorsal striatum and precuneus connectivity with frontal regions during methamphetamine cue processing, as compared to placebo.

Conclusions: The results of this study provide the first evidence of naltrexone-induced changes in BOLD measures of methamphetamine cue-induced craving. Functional connectivity with

NAcc was not found to be modulated by naltrexone, and instead the results suggest that naltrexone may be functioning to reduce the salience of the methamphetamine cues by reducing sensorimotor processing and integration, and by engaging greater frontal regulation of salience attribution via dopaminergic, glutamatergic, and/or GABAergic pathways linking the dorsal striatum, midbrain, and precuneus to frontal, dorsal striatal, and sensorimotor regions during methamphetamine cue processing. The knowledge of these neurobiological pathways may prove to be useful in the prediction of clinical outcomes and aid in the development and application of medications such as naltrexone for the treatment of methamphetamine use disorders.

The dissertation of Kelly Elizabeth Courtney is approved.

Edythe Danick London

James David Jentsch

Martin M. Monti

Dara Ghahremani

Lara Allison Ray, Committee Chair

University of California, Los Angeles

2016

Dedication

This dissertation is dedicated to my mother who inspired me to pursue a career in psychology, to my father for teaching me to be curious and skeptical, to my brother for his help with increasing my distress tolerance, and to my wonderful husband who supported me in so many ways throughout the process.

Table of Contents

Introduction.....	1
History of Methamphetamine Use in the United States	1
Current Rates of Abuse and Dependence.....	3
Burden of Care Associated with Methamphetamine Use	4
Pharmacology of Methamphetamine	6
Neurocognitive Functioning Associated with Chronic Methamphetamine Use	14
Clinical Presentation of Methamphetamine Use Disorders	17
Craving as a Translational Intermediate Phenotype for Methamphetamine Addiction	20
Treatment of Methamphetamine Use Disorders	24
The Dissertation	32
Methods.....	33
Participants	33
Measures.....	37
Neuroimaging Procedures	41
Data Analysis Procedures	43
Data Preprocessing.....	43
Initial Task Analyses.....	44
Analysis of Specific Aims.....	45
Results.....	48

Demographic and Initial Task Results	48
Results of Specific Aims	49
Discussion	53
BOLD Task Results: Methamphetamine Cues versus Control Cues	56
Naltrexone Effects on Cerebral Blood Flow and Cue Processing	58
Naltrexone Effects on Functional Connectivity	59
Summary of functional connectivity results.....	66
Clinical Significance and Future Directions	68
Study Strengths and Limitations	72
Summary and Conclusions.....	73
References	75

List of Tables

Table 1. Diagnostic and Statistical Manual of Mental Disorders, versions IV and 5, criteria for methamphetamine use disorder.....	75
Table 2. Sample Characteristics of Study Completers	76
Table 3. Locations of Methamphetamine (MA) Cue > Control Cue activation averaged across medication conditions (A), within the placebo (PLAC) condition (B), and within the naltrexone (NTX) condition (C).	78
Table 4. Locations showing a moderation effect of medication (placebo [PLAC] > naltrexone [NTX]) on Methamphetamine (MA) Cue > Control Cue activation	81
Table 5. Locations of significant positive Methamphetamine (MA) Cue > Control Cue activation correlations with average in-scanner self-reported methamphetamine craving averaged across medication condition (A), and within the placebo (PLAC) condition (B)	82
Table 6. A priori region of interest (ROI) parameter estimates and significance tests from the Methamphetamine (MA) Cue > Control Cue contrast across medication conditions (A), within the placebo (PLAC) condition (B), and within the naltrexone (NTX) condition (C).....	83
Table 7. Locations showing a moderation effect of medication (placebo [PLAC] > naltrexone [NTX]) on periaqueductal gray (PAG) functional connectivity within the Methamphetamine (MA) Cue > Control Cue contrast	84
Table 8. Locations showing a moderation effect of medication (placebo [PLAC] > naltrexone [NTX]) on precuneus functional connectivity within the Methamphetamine (MA) Cue > Control Cue contrast	85

Table 9. Locations showing a moderation effect of medication (naltrexone [NTX] > placebo [PLAC]) on ventral tegmental area (VTA) functional connectivity within the Methamphetamine (MA) Cue > Control Cue contrast.	86
Table 10. Locations showing a moderation effect of medication (naltrexone [NTX] > placebo [PLAC]) on dorsal striatum functional connectivity within the Methamphetamine (MA) Cue > Control Cue contrast	87
Table 11. Locations showing a moderation effect of medication (naltrexone [NTX] > placebo [PLAC]) on slope values predicting dorsal striatal functional connectivity within the Methamphetamine (MA) Cue > Control Cue contrast from average self-reported MA craving during the task.....	88
Table 12. Locations showing a moderation effect of medication (placebo [PLAC] > naltrexone [NTX], [A]; NTX > PLAC, [B]) on slope values predicting precuneus functional connectivity within the Methamphetamine (MA) Cue > Control Cue contrast from average self-reported MA craving during the task.....	89

List of Figures

Figure 1. Study and recruitment flowchart	90
Figure 2. Examples of the methamphetamine (MA) and control cue visual stimuli within the three picture subtypes used for the Methamphetamine Cues Task.....	91
Figure 3. Schematic of the Methamphetamine Cues Task.....	92
Figure 4. A priori region of interest (ROI) masks.....	93
Figure 5. Line plot of self-reported craving during the Methamphetamine Cues Task within medication conditions	94
Figure 6. Methamphetamine (MA) Cue > Control Cue activation averaged across medication conditions.....	95
Figure 7. Methamphetamine (MA) Cue > Control Cue activation within the placebo (PLAC) condition	96
Figure 8. Methamphetamine (MA) Cue > Control Cue activation within the naltrexone (NTX) condition	97
Figure 9. Grey matter cerebral blood flow (CBF) estimates within the placebo and naltrexone conditions.....	98
Figure 10. Methamphetamine (MA) Cue > Control Cue activation that is moderated by medication (placebo [PLAC] > naltrexone [NTX]).....	99
Figure 11. Effect size estimates (in Cohen's d) for medication-moderated Methamphetamine (MA) Cue > Control Cue activation	100

Figure 12. Methamphetamine (MA) Cue > Control Cue activation averaged across medication conditions that is positively correlated with average self-reported methamphetamine craving .	101
Figure 13. Methamphetamine (MA) Cue > Control Cue activation averaged within the placebo (PLAC) condition that is positively correlated with average self-reported methamphetamine craving.....	102
Figure 14. Bar graph of a priori region of interest (ROI) parameter estimates from the Methamphetamine (MA) Cue > Control Cue contrast averaged across medication conditions and within the placebo and naltrexone condition	103
Figure 16. Regions of medication moderated (placebo [PLAC] > naltrexone [NTX]) precuneus functional connectivity within the Methamphetamine (MA) Cue > Control Cue contrast	105
Figure 17. Regions of medication moderated (naltrexone [NTX] > placebo [PLAC]) ventral tegmental area (VTA) functional connectivity within the Methamphetamine (MA) Cue > Control Cue contrast	106
Figure 18. Regions of medication moderated (naltrexone [NTX] > placebo [PLAC]) dorsal striatum functional connectivity with the Methamphetamine (MA) Cue > Control Cue contrast	107
Figure 19. Regions of dorsal striatum functional connectivity within the Methamphetamine (MA) Cue > Control Cue contrast that correlated with average self-reported methamphetamine craving and differed between medication conditions.	108
Figure 20. Scatterplot depicting the relationships between medication-moderated dorsal striatum functional connectivity (naltrexone [NTX] > placebo [PLAC]) and average self-reported methamphetamine craving within the Methamphetamine (MA) Cue > Control Cue contrast...	109

Figure 21. Regions of precuneus functional connectivity within the Methamphetamine (MA) Cue > Control Cue contrast that correlated with average self-reported methamphetamine craving and differed between medication conditions	110
Figure 22. Scatterplot depicting the relationships between medication-moderated precuneus functional connectivity (placebo [PLAC] > naltrexone [NTX]) and average self-reported methamphetamine craving within the Methamphetamine (MA) Cue > Control Cue contrast	111
Figure 23. Scatterplot depicting the relationships between medication-moderated precuneus functional connectivity (naltrexone [NTX] > placebo [PLAC]) and average self-reported methamphetamine craving within the Methamphetamine (MA) Cue > Control Cue contrast	112
Figure 24. Scatterplot depicting the within-subject trends between differences in dorsal striatum functional connectivity between medication conditions (naltrexone [NTX] - placebo [PLAC]) and differences in self-reported methamphetamine craving between conditions (NTX – PLAC) within the Methamphetamine (MA) Cue > Control Cue contrast	113
Figure 25. Scatterplot depicting the within-subject trends between differences in precuneus functional connectivity between medication conditions (naltrexone [NTX] - placebo [PLAC]) and differences in self-reported methamphetamine craving between conditions (NTX – PLAC) within the Methamphetamine (MA) Cue > Control Cue contrast	114
Figure 26. Scatterplot depicting the within-subject trends between differences in precuneus functional connectivity between medication conditions (placebo [PLAC] - naltrexone [NTX])	

and differences in self-reported methamphetamine craving between conditions (PLAC – NTX)	
within the Methamphetamine (MA) Cue > Control Cue contrast	115
Figure 27. Simplified depiction of the functional connectivity results.....	116
Figure 28. Simplified depiction of the correlated relationships between self-reported, subjective	
methamphetamine craving and functional connectivity results.....	117

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Dr. Lara Ray served as the study sponsor on the project.

Curriculum Vita

EDUCATION

- 2010-2016 (expected)** **Doctor of Philosophy, Psychology**, University of California, Los Angeles, CA
Major: Clinical Psychology
Minors: Quantitative Psychology & Behavioral Neuroscience
Dissertation: *The Effects of Naltrexone on Neural Responses to Methamphetamine Cues*
2nd Year Thesis: *Neural Markers of Response Inhibition in Alcohol Dependence*
Advisor: Lara Ray, Ph.D.
Clinical Internship: VA San Diego Healthcare System (2015-2016)
- 2007-2009** **Masters of Arts, Psychology**, San Diego State University, San Diego, CA
Emphasis: Cognition and Behavior
Thesis: *Binge Drinking in Young Adults: Neuroelectric Assessments*
Advisor: John Polich, Ph.D.
- 2000-2006** **Bachelor of Arts, Psychology**, California State University, Long Beach, CA

SELECTED AWARDS AND HONORS

- 2014** Charles E. & Sue K. Young Graduate Fellowship, UCLA, CA
2013 National Research Service Award, National Institutes of Health (NIDA)
2013 Charles Y. Nakamura Scholarship, UCLA, CA
2012 Stanley Sue Distinguished Research Award, UCLA, CA
2006 Graduation with Distinction in Psychology, CSU, Long Beach, CA
2004 Mt. Garfield Scholarship, Mesa State College, Grand Junction, CO

COMPLETED GRANT FUNDING

F31 DA035604 - NIDA	Courtney (PI)	10/2013-07/2015
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UCLA Graduate Summer Research Mentorship		06/2012-08/2012
UCLA Graduate Research Mentorship		08/2011-06/2012
UCLA Graduate Summer Research Mentorship		06/2011-08/2011
UCLA Distinguished University Fellowship		08/2010-06/2011
University of Utah Biology Student Research Grant	Courtney (PI)	08/2002-05/2003

POSITIONS

- 2010-2015** **Graduate Student**, UCLA Addictions Laboratory – Advisor: Lara Ray, Ph.D.
University of California, Los Angeles, Department of Psychology
- 2007-2010** **Senior Research Assistant/Graduate Student**, Cognitive Electrophysiology Laboratory
– Advisor: John Polich, Ph.D.
The Scripps Research Institute, La Jolla, CA, MIND
- 2005** **Research Assistant** – Advisor: Dale Jorgenson, Ph.D.
California State University, Long Beach, CA, Department of Psychology
- 2002** **Research Assistant** – Advisor: Leslie Sieburth, Ph.D.
University of Utah, Salt Lake City, UT, Department of Biology

SELECTED PUBLICATIONS

- Courtney, K.E.,** Schacht, J.P., Hutchison, K., Roche, D.J.O., & Ray, L.A. (2015). Neural substrates of cue-reactivity: Association with treatment outcomes and relapse. *Addiction Biology*. Advance online publication. doi: 10.1111/adb.12314. PMCID: in process.

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Book Chapters

- Courtney, K.E.,** & Ray, L.A. (2016). Clinical Neuroscience of Amphetamine Type Stimulants: From Basic Science to Treatment Development. In H. Ekhtiari, & M. Paulus (Eds.), *Neuroscience for Addiction Medicine: From Prevention to Rehabilitation - Constructs and Drugs* (Vol. 223, pp. 295-310). Progress in Brain Research, UK: Elsevier.
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Introduction

Methamphetamine use remains a significant public health concern in the United States, and the world more broadly. Estimates from 2012 suggest over 12 million people in the U.S., ages 12 years and older (4.7% of total responders) have used methamphetamine in their lifetimes, 1.2 million people (0.4 %) reported using methamphetamine in the past year, and approximately 440,000 (0.2%) of those identified as past month users (Substance Abuse and Mental Health Services Administration (SAMHSA), 2013). Amphetamine-type stimulants (ATS), of which methamphetamine is the most frequently used, are the second most commonly used class of illicit drugs worldwide (United Nations Office on Drugs and Crime (UNODC), 2012); approximately 0.7 percent of the global population (33.8 million people) aged 15-64 years-old, reported using an ATS in 2010 (UNODC, 2013). Importantly, these estimates appear to be growing, as stated in the 2013 World Drug Report, “The market for ATS appears to be expanding in terms of locations of manufacture and trafficking routes, as well as in terms of demand” (UNODC, 2013, p. 58).

History of Methamphetamine Use in the United States

ATS have a long history of use in the U.S., going as far back as World War II when soldiers used ATS to reduce fatigue and suppress appetite. ATS were widely prescribed in the 1950s and 1960s as a medication for depression and obesity, reaching a peak of 31 million prescriptions in the U.S. in 1967 (Anglin, Burke, Perrochet, Stamper, & Dawud-Noursi, 2000), with a roughly estimated 9.7 million Americans identified as past-year users of amphetamines in 1970 (Linnman, Moulton, Barmettler, Becerra, & Borsook, 2012). The rates of ATS use declined following the passage of the Comprehensive Drug Abuse Prevention and Control Act of 1970, which reclassified amphetamine to a more restrictive schedule, thereby limiting its accepted

medical use (Gonzales, Mooney, & Rawson, 2010). After amphetamine was rescheduled, illicit manufacturers began making methamphetamine using phenyl-2-propanone (“P2P”) and methylamine. However, after P2P became a Schedule II controlled substance in 1980, ephedrine and pseudoephedrine became the predominant precursors and large quantities of these chemicals were smuggled from Mexico into the U.S. (Jane Carlisle Maxwell & Brecht, 2011). The increase in production was followed by a dramatic increase in use, with methamphetamine specifically increasing in popularity during the 1990s and early 2000s (Rawson, Anglin, & Ling, 2002). For example, estimates from the 2002 U.S. National Survey on Drug Use and Health (NSDUH) suggest that over 210,000 individuals ages 12 and older tried methamphetamine for the first time in 1991, whereas 454,000 individuals did so in 1998 (SAMHSA, 2003). Following the passage of the Combat Methamphetamine Epidemic Act in 2005 which restricted public access to products containing pseudoephedrine, the rates of methamphetamine use finally began to decrease (Gonzales, et al., 2010; Jane Carlisle Maxwell & Brecht, 2011; J. C. Maxwell & Rutkowski, 2008), as evinced by a drop to 192,000 of new methamphetamine users in 2005 (SAMHSA, 2006).

This decline in methamphetamine use estimates was short lived however, as illicit manufacturers of methamphetamine began to use the P2P processes once again (Jane Carlisle Maxwell & Brecht, 2011). Estimates from the 2012 NSDUH identify over 130,000 individuals as new methamphetamine users in 2012, and the number of past month users in 2012 (440,000 people or 0.2%) remained consistent with reports from the last five years (0.1-0.2%) (SAMHSA, 2013).

Recent reports of production and supply indicate a probable rise of methamphetamine use in the near future. For example, the number of methamphetamine laboratories reported in the

U.S. quadrupled from 2,754 in 2010 to 11,116 in 2011, and the amount of methamphetamine seized by the U.S. government increased from 15 tons in 2010 to 23 tons in 2011 (UNODC, 2013). Furthermore, production methods are refined on an ongoing basis to produce purer and more potent forms of methamphetamine, and at lower costs. Analysis of data from the System to Retrieve Information on Drug Evidence (STRIDE), which reflects evidence submitted to DEA laboratories for analysis from July 2007 through September 2010, indicates that the price per pure gram of methamphetamine decreased 61%, from \$270.10 to \$105.49, while the purity increased 114%, from 39% to 83% (Jane Carlisle Maxwell & Brecht, 2011). Together, the culmination of recent prevalence, production, and supply data forewarn of an impending increase in methamphetamine use in the years to come.

Current Rates of Abuse and Dependence

Although the prevalence rates of current methamphetamine use have been relatively stable over the past five years, the rates of methamphetamine use disorders in the U.S. are on the rise. In 2012, 535,000 (0.2%) individuals were estimated to meet the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., DSM–IV; American Psychiatric Association, 1994) criteria of stimulant abuse or dependence, a significant increase from the 329,000 (0.1%) in 2011 (SAMHSA, 2013). This increase was especially pronounced among individuals aged 18-25 years, with 0.5% meeting criteria in 2012, up from 0.3% in 2011. Over 379,000 of individuals were estimated to meet dependence criteria for methamphetamine in 2012, as compared to 252,000 in 2011 (SAMHSA, 2013).

Estimates from the Treatment Episode Data Set (TEDS), which provides information on admissions to substance abuse treatment facilities that are licensed or certified by state substance abuse agencies, suggest that treatment admissions for primary methamphetamine increased from

78,248 individuals ages 12 or older (4.4% of admissions) in 2001 to 154,364 individuals (8.1%) in 2005, but then decreased to 102,384 individuals (5.6%) in 2011 (SAMHSA, 2013). The recently released TEDS data report a slight increase for 2012, with 116,090 individuals (6.6%) being admitted for primary methamphetamine-related problems (SAMHSA, 2015). The rates of methamphetamine dependence appear to be roughly equivalent in men compared to women, with 53% of primary methamphetamine/amphetamine admissions being male. Further, the majority of individuals admitted to treatment were non-Hispanic White (69%), followed by individuals of Mexican origin (12%; SAMHSA, 2015). Thus, methamphetamine dependence is largely a disorder of the White population; however, this may be a byproduct of the regional variability in methamphetamine use, which is currently greatest in the West and parts of the Midwest (NIDA, 2012).

Burden of Care Associated with Methamphetamine Use

In 2009, the RAND Corporation published the first national estimate of the economic burden of methamphetamine use based on information available for 2005. Their conclusion was, "... in the case of meth abuse, we should be cautious interpreting evidence from national household surveys and school-based studies as indicators of the problem. Clearly, the burden of methamphetamine abuse is substantial, far exceeding what would be implied by simple prevalence measures from either of these populations" (Nicosia, Pacula, Kilmer, Lundberg, & Chiesa, 2009, p. xvi). They estimated the economic burden of methamphetamine use in the United States to be approximately \$23.4 billion, which includes the costs associated with drug treatment, other health costs, the intangible burden of addiction and premature death, lost productivity, crime and criminal justice costs, child endangerment, and harms resulting from production. They further report that the intangible cost of addiction makes up a substantial

portion of the overall cost, at approximately \$12.6 billion; which includes the costs associated with drug treatment at approximately \$545 million, almost all of it being delivered in the community-based specialty treatment sector (\$491 million; Nicosia, et al., 2009). These high costs are consistent with the TEDS data, which indicates that primary methamphetamine/amphetamine admissions were more likely than all drug treatment admissions combined to receive long-term rehabilitation/residential treatment (16 % vs. 7 %; SAMHSA, 2013).

The RAND report identifies crime and criminal justice costs associated with methamphetamine use and production as the second-largest category of costs at approximately \$4.2 billion, including the costs associated with processing offenders for the possession and sale of methamphetamine (\$2.4 billion), methamphetamine-induced violent and property crimes (\$1.8 billion), and parole and probation violations for methamphetamine offenses (\$70 million) (Nicosia, et al., 2009). These estimates are again consistent with the TEDS data, which reported that primary methamphetamine/amphetamine admissions were more likely than all admissions combined to be referred to treatment by the criminal justice system (50% vs. 34%; SAMHSA, 2013). An independent report found that methamphetamine use is highly predictive of self-reported violent criminal behavior and recidivism among parolees, with 82% of methamphetamine users (versus 54% of nonusers) returning to custody within 12 months (Cartier, Farabee, & Prendergast, 2006), providing further support of the substantial crime-related costs of methamphetamine use.

An additional \$351 million was estimated to be spent in 2005 for the health care costs associated with methamphetamine use (Nicosia, et al., 2009). This estimate is in line with data from 2011, whereby methamphetamine use/abuse accounted for about 103,000 Emergency Department visits (Substance Abuse and Mental Health Services Administration, 2013), 3,273

total poison exposures, and 55 deaths (Bronstein, Spyker, Cantilena, Rumack, & Dart, 2012), suggestive of the significant toxicity of the substance.

In summary, methamphetamine use and the associated disorders constitute a significant monetary and judicial burden to society. Furthermore, the substantial time and resources devoted to the treatment of methamphetamine use disorders in the United States is indicative of the need for more efficacious, cost effective, and easily deliverable treatments.

Pharmacology of Methamphetamine

Chemistry of methamphetamine. Methamphetamine, also known as metamfetamine, N-methylamphetamine, methylamphetamine, and desoxyephedrine, is a psychostimulant of the phenethylamine and amphetamine class of psychoactive drugs. Methamphetamine exists in two stereoisomers, the l- and d- forms. D-methamphetamine, or the dextrorotary enantiomer, is a more powerful psychostimulant, with 3-5 times the central nervous system (CNS) activity as compared to l-methamphetamine, or the levorotary enantiomer (Ciccarone, 2011); however, both enantiomers influence dopamine release and can induce stereotypy (i.e., persistent mechanical repetition of speech or movement) and psychosis at high doses (Kuczenski, Segal, Cho, & Melega, 1995). Illicitly, methamphetamine may be sold as pure d-methamphetamine (dextromethamphetamine) or in a racemic mixture, and presents as powder or crystalline form, the latter commonly referred to as “ice” or “crystal meth” (Cruickshank & Dyer, 2009). Crystalline methamphetamine typically refers to a highly purified form of d-methamphetamine which is intended for smoking, with similar effects to that from an intravenous dose (Cho, 1990). Further, crystalline methamphetamine is associated with an increased incidence of dependence, as compared to the lower purity forms (McKetin, Kelly, & McLaren, 2006).

Molecular pharmacology of methamphetamine. Methamphetamine is a cationic lipophilic molecule which stimulates the release, and partially blocks the reuptake, of newly synthesized catecholamines in the CNS (Cho & Melega, 2002). Due to its structural similarity, methamphetamine interacts with the dopamine transporter (DAT), noradrenaline transporter (NET), serotonin transporter (SERT), and vesicular monoamine transporter-2 (VMAT-2) and reverses their endogenous function, thereby redistributing monoamines from storage vesicles into the cytosol. This process results in the release of dopamine, noradrenaline, and serotonin into the synapse, which then stimulate postsynaptic monoamine receptors (Cruickshank & Dyer, 2009). Methamphetamine also attenuates the metabolism of monoamines by inhibiting monoamine oxidase (Sulzer, Sonders, Poulsen, & Galli, 2005), further enabling the buildup of excess monoamines in the synapse.

The monoamines released due to the presence of methamphetamine act on the major dopaminergic, noradrenergic, and serotonergic pathways of the brain. In the case of dopamine, methamphetamine activates the mesolimbic, mesocortical circuit, and the nigrostriatal pathways, which have been related to the euphoric effects observed immediately after the ingestion of the drug (Homer et al., 2008). The medial basal forebrain, the hippocampus, and the prefrontal cortex (PFC) represent noradrenergic regions of interest, with various functions related to arousal, memory consolidation, and cognitive processing, respectively (C. W. Berridge & Waterhouse, 2003). Affected serotonergic neurons are dispersed throughout the brain, regulating diverse functions such as respiration, pain perception, sexual drive, reward, and higher-order cognitive processing (Hornung, 2003). However, the wide distribution of monoamines throughout the CNS, interactions between the monoamine pathways, baseline dopamine (and likely other monoamine) functioning, and peripherally mediated effects of methamphetamine

add to the complexity of methamphetamine's effect on the monoamine systems (Cruickshank & Dyer, 2009).

The potentiation of dopaminergic neurotransmission within the mesocorticolimbic circuit is thought to underlie the reinforcing properties of drugs of abuse, although evidence is accumulating on a converging role of the endogenous opioid systems in the establishment of reinforcement (Boutrel, 2008). Three families of endogenous opioid peptides have been identified (dynorphins, endorphins and enkephalins), each associated with a distinct polypeptide precursor (prodynorphin, proopiomelanocortin, and proenkephalin). These precursors produce a number of active ligands including β -endorphin, met- and leu-enkephalin, dynorphins, and neo-endorphins (Kieffer & Gavériaux-Ruff, 2002). Each ligand expresses a different affinity for each opioid receptor; for example, β -Endorphin binds with higher affinity to μ - than δ - or κ -opioid receptors (Mansour, Hoversten, Taylor, Watson, & Akil, 1995).

Anatomically speaking, endogenous opioid receptors are widely distributed throughout the CNS, with differential distributions per opioid receptor type. Importantly, opioid receptors and peptides are highly expressed in brain areas involved in reward and motivation, such as the ventral tegmental area (VTA) and striatum (Mansour, Fox, Akil, & Watson, 1995).

Administration of classical exogenous opioids facilitates dopamine release in the mesolimbic reward system by activating μ - and δ -opioid receptors in the nucleus accumbens (NAcc; Hirose et al., 2005; Murakawa et al., 2004), and by decreasing GABA-inhibition via μ - and κ -opioid receptors, which are mainly located on GABA interneurons in the VTA (Bonci & Williams, 1997; Shoji, Delfs, & Williams, 1999). Further, administration of κ -opioid receptor agonists impedes dopamine release in the mesocortical pathway linking the VTA to the PFC (Margolis et al., 2006), suggesting the presence of separate pathways by which opioids influence the reward

and motivation system. Many non-opioid drugs of abuse are also known to interact with the endogenous opioid system (for a review see Trigo, Martin-García, Berrendero, Robledo, & Maldonado, 2010). For example, preclinical studies in rats have shown that ethanol, cocaine, and d-amphetamine increase extracellular levels of endorphins in the NAcc (Olive, Koenig, Nannini, & Hodge, 2001), and that ethanol-induced increases in extracellular levels of dopamine in the NAcc are modulated by endogenous opioid system processes (e.g., Acquas, Meloni, & Di Chiara, 1993; Y. K. Lee et al., 2005). In humans, the rewarding effects of alcohol have been shown to be mediated by alcohol-induced endogenous opioid release in the NAcc and orbitofrontal cortex (OFC; Mitchell et al., 2012). Further, tobacco use, nicotine dependence severity, and nicotine craving were associated with reduced binding potential of a μ -opioid receptor agonist ($[^{11}\text{C}]$ -carfentanil) in a number of mesolimbic regions in an alcohol dependent sample (Weerts et al., 2012). Together, these reports are suggestive of a general mediating role for the endogenous opioid system in the reinforcing properties of multiple drugs of abuse.

ATSs have also been shown to affect the endogenous opioid system, which may mediate some of the rewarding properties associated with acute ATS use (Boutrel, 2008). For example, acute amphetamine administration has been linked with increased β -endorphin levels in the NAcc (Olive, et al., 2001), increased striato-nigral dynorphin-like immunoreactivity (Bustamante et al., 2002; Hanson, Merchant, Letter, Bush, & Gibb, 1988), and changes in the endogenous opioid mRNA expression in the striatum (Hurd & Herkenham, 1992; Smith & McGinty, 1994; J. Q. Wang & McGinty, 1995). Further, preclinical data suggest that the endogenous opioid system is involved in the induction and expression of methamphetamine-induced behavioral (locomotor) sensitization (Chiu, Ma, & Ho, 2006), analogous to compulsive drug seeking behavior in humans

(i.e., drug craving; Itzhak & Ali, 2002b), through its modulatory actions of the mesolimbic dopamine system (Ford, Mark, & Williams, 2006).

In sum, methamphetamine has pervasive effects not only on the dopaminergic system, but also on noradrenergic, serotonergic, and opioidergic neurotransmitter systems throughout the brain. It is through the culmination of these complex neurochemical modulations that significant behavioral and cognitive changes result.

Clinical pharmacokinetics of methamphetamine. Methamphetamine is commonly smoked, injected, ingested, snorted, dissolved sublingually, taken rectally, or solubilized and consumed as a liquid. Smoking, the most common route of administration (National Institute on Drug Abuse, 2012), and intravenous injection result in the near-immediate euphoric sensation which typically lasts for several minutes, as opposed to intranasal and oral ingestion which take approximately 5 and 20 minutes to reach peak euphoric state, respectively. The “high” through intranasal and oral methods, however, is reported to last 8 to 12 hours (Meredith, Jaffe, Ang-Lee, & Saxon, 2005). When smoked, methamphetamine exhibits 90.3% bioavailability, compared to 67.2% for oral ingestion (Caldwell, Dring, & Williams, 1972).

Methamphetamine is largely metabolized in the liver, resulting in metabolites including amphetamine, 4-hydroxymethamphetamine, norephedrine, hippuric acid, 4-hydroxyamphetamine, and 4-hydroxynorephedrine (Caldwell, et al., 1972). The metabolites of methamphetamine are unlikely to contribute to clinical effects, as the amphetamine metabolite reaches substantially lower plasma levels compared to that of the ingested drug and peaks after 12 hours, at which time the acute effects are minimal (Cook et al., 1993). Methamphetamine is then excreted by the kidneys, with approximately 70% of a single oral dose excreted in the urine within 24 hours. When taken orally, the majority of the dose is excreted as unchanged

methamphetamine (30-50%), followed by up to 15% as 4-hydroxymethamphetamine, and 10% as amphetamine (Cook, et al., 1993; Kim, Oyler, Moolchan, Cone, & Huestis, 2004). With repeated dosing, methamphetamine can accumulate in the urine, with one study showing detection 7 days after a regimen of four daily 10-mg oral doses (Oyler, Cone, Joseph, Moolchan, & Huestis, 2002).

Clinical response and withdrawal of methamphetamine. Methamphetamine is a potent CNS stimulator. As such, the clinical response to methamphetamine administration at low to moderate doses (5–30mg) includes euphoria, arousal, reduced fatigue, euphoria, positive mood, tachycardia, hypertension, pupil dilation, peripheral hyperthermia, reduced appetite, behavioral disinhibition, short-term improvement in cognitive domains, and anxiety (for a review see Cruickshank & Dyer, 2009). At frequent and high doses, there is also evidence that methamphetamine can induce psychotic episodes (Hermens, Lubman, Ward, Naismith, & Hickie, 2009; Ujike & Sato, 2004).

Frequent use of methamphetamine results in a depletion of presynaptic monoamine stores, down-regulation of receptors, and neurotoxicity (Barr et al., 2006; Meredith, et al., 2005), resulting in significant psychiatric withdrawal symptoms following abrupt cessation after periods of regular use. Symptoms of methamphetamine withdrawal include anhedonia, hypersomnia, irritability, anxiety, aggression, and intense cravings for methamphetamine (Cantwell & McBride, 1998; Meredith, et al., 2005). Depressive symptomatology has been considered the hallmark of methamphetamine withdrawal, with depressive symptoms lasting beyond two weeks of abstinence (Zorick et al., 2010). The severity of the withdrawal syndrome appears to be related to the frequency of use, yet methamphetamine withdrawal largely resolves spontaneously (Newton, Kalechstein, Duran, Vansluis, & Ling, 2004), and usually within 14 days of abstinence

(Zorick, et al., 2010). Protracted withdrawal from methamphetamine may in turn take several weeks to resolve and poses a large obstacle to sustained recovery.

Neurotoxicity associated with chronic methamphetamine use. Repeated exposure to moderate to high levels of methamphetamine has been related to neurotoxic effects on the dopaminergic and serotonergic systems, leading to potentially irreversible loss of nerve terminals and/or neuron cell bodies (Cho & Melega, 2002). Although the precise mechanisms remain unclear, the culmination of evidence suggests that the high level of cytoplasmic dopamine released as a result of methamphetamine use leads to the accumulation of reactive oxygen species and severe oxidative stress on the neuron (S. Berman, O'Neill, Fears, Bartzokis, & London, 2008). Results of non-human primates given doses of methamphetamine roughly equivalent to a typical human abuse pattern of use (0.5-2mg/kg given four times at 2-hour intervals), indicate that methamphetamine at this (typical) level of use produces long-term reductions in dopaminergic axonal markers in the brain, including decreased striatal DAT density (Villemagne et al., 1998). Human studies using positron emission tomography (PET) and magnetic resonance imaging (MRI) data also provide support for prolonged neurotoxicity following repeated methamphetamine use. Reductions in striatal DAT site density (McCann et al., 1998; Volkow, Chang, Wang, Fowler, Franceschi, Sedler, Gatley, Miller, et al., 2001; Volkow, Chang, Wang, Fowler, Leonido-Yee, et al., 2001), D2 receptor availability (Volkow, Chang, Wang, Fowler, Ding, et al., 2001), VMAT-2 density (Johanson et al., 2006), and SERT density (Sekine et al., 2006), have all been reported, with some markers (i.e., DAT density) showing improvement following prolonged (greater than 12 months) abstinence (Volkow, Chang, Wang, Fowler, Franceschi, Sedler, Gatley, Miller, et al., 2001). Neurotoxic effects have been associated with behavioral and cognitive changes, such as memory deficits and impaired

psychomotor coordination associated with reduced DAT site density (Volkow, Chang, Wang, Fowler, Leonido-Yee, et al., 2001), and increased aggression associated with reduced SERT density (Sekine, et al., 2006). Chronic abuse of methamphetamine is also associated with reduced markers of neuronal integrity and increased markers of glial content, possibly indicating the proliferation of glial cells following neural damage (Chang, Alicata, Ernst, & Volkow, 2007; Ernst, Chang, Leonido-Yee, & Speck, 2000).

Structural brain abnormalities among frequent methamphetamine users as compared to healthy controls have also been observed, including, but not limited to, reduced white-matter integrity and/or organization associated with depression severity and positive psychiatric symptoms (Tobias et al., 2010), reduced gray matter in the cingulate, limbic, and paralimbic cortices (Thompson et al., 2004), reduced hippocampal volumes associated with poorer memory performance (Thompson, et al., 2004), altered shape of the corpus callosum (Oh et al., 2005), and increased volumes of the putamen and globus pallidus (interpreted as a compensatory effect; Chang et al., 2005). As noted by Berman and colleagues (2008), lower cortical gray matter density or volume is the most consistently reported structural abnormality in amphetamine users, and studies assessing striatal gray matter report larger volumes in amphetamine abusers when compared to healthy controls, although the latter may reflect a compensatory response to initial neurotoxicity (S. Berman, et al., 2008).

A number of functional brain abnormalities have been observed in recently abstinent chronic abusers of methamphetamine. Using glucose metabolism as a marker of functional activity, regions of abnormally high relative activity include the amygdala, ventral striatum, and lateral OFC, whereas abnormally low activity was observed in the medial PFC and cingulate cortex (London et al., 2004). Furthermore, glucose metabolism in the anterior and middle

cingulate gyrus and the insula was negatively correlated with error rates on an auditory vigilance task in recently abstinent (4 to 7 days) methamphetamine abusers (London et al., 2005). Relative higher global and parietal cortex glucose metabolism has been noted to accompany continued abstinence (S. M. Berman et al., 2008; Volkow, Chang, Wang, Fowler, Franceschi, Sedler, Gatley, Hitzemann, et al., 2001), along with relatively lower metabolism in striatal and thalamic regions (Volkow, Chang, Wang, Fowler, Franceschi, Sedler, Gatley, Hitzemann, et al., 2001; G. J. Wang et al., 2004). Importantly, some degree of recovery has been observed in the neocortical regions (S. M. Berman, et al., 2008) and thalamus (G. J. Wang, et al., 2004) following one and nine months of abstinence, respectively.

Neurocognitive Functioning Associated with Chronic Methamphetamine Use

Chronic methamphetamine use has been associated with discrepancies in numerous cognitive processes dependent upon fronto-striatal and limbic circuits. However, differentiating preexisting deficits from methamphetamine-induced cognitive deficits poses significant challenges (Dean, Groman, Morales, & London, 2013), and concerns regarding the interpretation of these discrepancies and their clinical significance have been raised (Hart, Marvin, Silver, & Smith, 2012). Despite this, the preponderance of evidence from preclinical, cross-sectional human, and brain imaging studies supports the assertion that methamphetamine abuse does indeed cause cognitive decline in at least some individuals (i.e., individuals at the age of early-to-middle adulthood; Dean, et al., 2013) and that some cognitive/behavioral changes may be the result of methamphetamine neurotoxicity (Bortolato et al., 2009). Further, individual difference variables such as age, education level, and genotype appear to moderate the relationship between methamphetamine use and cognitive deficits (Dean, et al., 2013).

With respect to the specific cognitive domains potentially affected, a meta-analysis of 18 studies found medium effects of methamphetamine use disorders on processes including episodic memory, executive functions (e.g., response inhibition, novel problem solving), complex information processing speed, and psychomotor functions. Small, yet significant, effects were also observed on measures of attention/working memory, language, and visuoconstruction (Scott et al., 2007).

A small number of these cognitive processes have been further examined using functional neuroimaging procedures in chronic methamphetamine users (for a review see Aron & Paulus, 2007). For example, the brain correlates of learning and cognitive control in methamphetamine abusers have been investigated using a color-word Stroop task administered during functional magnetic resonance imaging (fMRI). On this task, methamphetamine abusers display reduced reaction-time (RT) adjustments and reduced PFC activity following conflict (i.e., incongruent) trials (Salo, Fassbender, Buonocore, & Ursu, 2013; Salo, Ursu, Buonocore, Leamon, & Carter, 2009), and reduced RT, increased error rate, and reduced activation of the right inferior frontal gyrus (IFG), supplementary motor cortex/anterior cingulate gyrus, and the anterior insular cortex during the incongruent condition (Nestor, Ghahremani, Monterosso, & London, 2011). Using a reversal learning task and PET in a preclinical sample, vervet monkeys given a chronic, escalating-dose regimen of methamphetamine revealed associations between the change in response to positive feedback and individual differences in the change in dopamine D₂-like receptor availability in the striatum, assessed pre- and post-methamphetamine regimen (Groman et al., 2012); thus advancing D₂ specific alterations of the dopaminergic system as a plausible neurobiological pathway subserving some of the disturbances in learning observed with repeated methamphetamine use.

Methamphetamine use disorders are associated with differential brain activity during decision-making, as assessed via fMRI. Methamphetamine abusers displayed reduced activation in the right IFG and the left medial frontal gyrus (MFG) during a two-choice prediction task (where only 50% of the responses are reinforced with a correct response outcome), and a decrease in dorsolateral PFC (dlPFC) and right OFC activity in the active compared to control conditions, as opposed to the increase of activation in these areas observed in the healthy controls (Paulus et al., 2002). In a follow-up study using the same task, recently abstinent (average 25 days) individuals with methamphetamine dependence displayed reduced activation of the OFC, dlPFC, anterior cingulate cortex (ACC), and parietal cortex irrespective of the outcome, and attenuation of specific “success-related” patterns of brain activation as compared to healthy controls (Paulus, Hozack, Frank, Brown, & Schuckit, 2003). Furthermore, the degree of activation in the right MFG, middle temporal gyrus, and posterior cingulate cortex (PCC) during the two-choice prediction task in early remission (3-4 weeks abstinent) was predictive of relapse during a one-year follow-up (Paulus, Tapert, & Schuckit, 2005).

Methamphetamine dependence has also been associated with maladaptive reward-related decision-making, as indexed via steeper rates of temporal discounting (“delay discounting”) (Hoffman et al., 2006). Contrasting “hard choices”, where roughly equivalent preference is obtained for the immediate and delayed reward choices, and “easy choices”, in which the choices differ dramatically in value and preference, revealed less activation in the precuneus, right caudate nucleus, ACC, and dlPFC in recently abstinent (2-8 weeks) individuals with methamphetamine dependence (Hoffman et al., 2008), and less activation of the left dlPFC and right intraparietal sulcus in active methamphetamine abusers (Monterosso et al., 2007), as compared to healthy controls. Furthermore, methamphetamine dependent individuals undergoing

treatment display disrupted risk-related processing, a component of decision-making, on the Risky Gains Task in both the ACC and insula (Gowin et al., 2013).

In summary, methamphetamine use disorders are associated with specific task-related behavioral and neural processing differences across a number of cognitive domains, which appear to be moderated by individual difference variables. Importantly, evidence is accumulating to suggest some of these differences are associated with altered dopaminergic processing (Groman, et al., 2012) and clinically meaningful outcomes (Paulus, et al., 2005), suggestive of a functional role for these cognitive differences in the development and perpetuation of methamphetamine addiction.

Clinical Presentation of Methamphetamine Use Disorders

A methamphetamine use disorder represents a complex psychiatric condition characterized by a set of maladaptive behaviors which result in clinically significant functional impairment (American Psychiatric Association, 1994, 2013). A diagnosis made using the DSM-IV criteria necessitates the experience of at least 1 symptom of abuse or 3 symptoms of dependence occurring within a 12-month period (American Psychiatric Association, 1994), whereas the fifth edition of the DSM (DSM-5) combines these criterion (with a few notable changes) to form a single “methamphetamine use disorder” with an added severity specification (American Psychiatric Association, 2013). The DSM-specified criteria include maladaptive behaviors such as “continued use despite persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of methamphetamine”, the development of “tolerance” and “withdrawal,” and “persistent desire or unsuccessful efforts to stop or cut down or control methamphetamine use” (see **Table 1** for a full list of criteria).

The two most notable changes to the DSM-5 criteria include the removal of “legal problems” and the addition of “drug craving” to the symptom list. The addition of “craving” as a possible symptom represents an effort to increase consistency between DSM-5 and the International Classification of Diseases (ICD-10; World Health Organization, 2010), as well as acknowledgment of a vast amount of scientific research highlighting the importance of craving in the perpetuation of the disorder (see section on craving below). Regardless of the precise criterion used as the basis for diagnosis, methamphetamine addiction, along with all other drug addictions, is considered a chronic and relapsing disorder characterized by neurobiological changes that subserve the observed functional impairment in the individual (Koob et al., 2004).

Neurobiological theories of addiction. Many theories attempt to explain how and why a specific individual makes the transition from infrequent, casual use of a drug to a more habitual and even compulsive use pattern despite the associated negative consequences. For the purposes of this proposal, a biopsychosocial model of psychiatric disorders has been adopted. Specifically, the biopsychosocial model applied to methamphetamine use disorders posits that the etiology of methamphetamine addiction represents a complex interplay between psychosocial (e.g., cognitions, personality traits, and environmental variables such as peer groups and norms) and biological (e.g., genetics and neurobiology) factors. Methamphetamine addiction, as with all complex diseases, can be conceptualized as a clinical outcome resulting from the net product of numerous biological and psychosocial risk and protective factors. Furthermore, there are likely multiple pathways both leading to methamphetamine addiction and to recovery, such that no two individuals with a methamphetamine use disorder will necessarily experience the same symptoms or a similar efficacy with a single treatment.

The allostatic and incentive salience models represent two more prominent biological models of addiction development. The allure of the allostatic model of addiction includes its integration of the neurobiology associated with the drug's acute rewarding/positively reinforcing effects and the negative reinforcement associated with withdrawal and stress (Koob, et al., 2004; Koob & Le Moal, 2001; Koob & Moal, 1997). This model describes a three-stage cycle by which drug-taking behavior progresses from impulsivity to compulsivity: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation (Koob & Moal, 1997). Conceptually, the development of addiction under this model is characterized as a process that involves neuroadaptation in reward and stress circuits in response to the frequent presence of the drug that results in the establishment of a new allostatic set point. Withdrawal of the drug from the system thus results in significant dysregulation, including changes in reward neurotransmitters (i.e., dopamine, serotonin, and opioid peptides) opposite to those experienced during positive reinforcement, and the recruitment of brain stress systems that oppose the hedonic effects of the drug, particularly within the basal forebrain macrostructure of the extended amygdala. Therefore, allostasis in this context is defined as, "the process of maintaining apparent reward function stability through changes in reward and stress system neurocircuitry" (Koob, et al., 2004, p. 748).

In contrast, the incentive salience model of addiction, although not necessarily mutually exclusive to the allostatic model, focuses on the motivational properties and craving associated with the use of drugs of abuse (K. C. Berridge & Robinson, 2003; Terry E. Robinson & Kent C. Berridge, 1993; Robinson & Berridge, 2001). This model posits that addiction is the largely caused by progressive neuroadaptation that results in an increase of effects, or "sensitization," following repeated drug use. This sensitization process is implicated to occur within the dopaminergic pathways that subserve attribution of motivational salience to mental

representations of stimuli and actions (e.g., drug ingestion), thus rendering these stimuli highly salient, and ultimately “wanted” or craved. Following sensitization of these pathways, the expression of incentive salience (i.e., craving) can be activated by the release of dopamine that is initiated in response to drug cues or priming doses of the drug itself (de Wit, 1996; Stewart, de Wit, & Eikelboom, 1984). In sum, “by this view, drug craving and addictive behavior are due specifically to sensitization of incentive salience” (Terry E. Robinson & Kent C. Berridge, 1993, p. 249). Furthermore, this view suggests a distinction between the neural systems subserving the “wanting” (craving) and “liking” (reward) of a drug, and emphasizes the role of drug craving, as opposed to rewarding properties of the drug, as the driving force behind addiction development.

Craving as a Translational Intermediate Phenotype for Methamphetamine Addiction

The increasingly recognized heterogeneity of diagnostic phenotypes has led to the study of more narrow and homogeneous intermediate phenotypes for psychiatric disorders (Gottesman & Gould, 2003; Gould & Gottesman, 2006), including addiction (Hines, Ray, Hutchison, & Tabakoff, 2005; Ray, Mackillop, & Monti, 2010). Specific to the study of drug addiction, craving appears to be a particularly valuable intermediate phenotype as it is widely held to be essential for understanding the pathogenesis and maintenance of addiction, as highlighted by the incentive salience model (Terry E. Robinson & Kent C. Berridge, 1993; Robinson & Berridge, 2001), and by the inclusion of craving as a criterion for a substance use disorder in the DSM-5 (American Psychiatric Association, 2013) and the International Classification of Diseases (ICD-10; World Health Organization, 2010). In fact, a longitudinal study found that alcohol craving was associated with the highest relative risk of all ICD-10 criteria for alcohol dependence (de Bruijn, van den Brink, de Graaf, & Vollebergh, 2005), and tobacco craving was found to compliment the other diagnostic symptoms in a unidimensional severity continuum (Shmulewitz

et al., 2011). Craving has also been consistently found to predict substance consumption in a number of laboratory studies (e.g., R.F. Leeman, Corbin, & Fromme, 2009; R. F. Leeman, O'Malley, White, & McKee, 2010; MacKillop & Lisman, 2005; O'Malley, Krishnan-Sarin, Farren, Sinha, & Kreek, 2002), and the amelioration of craving is a common target of treatment (Pavlick, Hoffman, & Rosenberg, 2009) as moderate to intense cravings are reported by substantial proportions of patients (Oslin, Cary, Slaymaker, Collieran, & Blow, 2009; Yoon, Kim, Thuras, Grant, & Westermeyer, 2006).

Specific to methamphetamine addiction, research suggests individuals with this disorder exhibit cognitive performance deficits that are more pronounced during exposure to methamphetamine-related cues (Tolliver et al., 2012), and that level of craving for methamphetamine is associated with neural and behavioral measures of self-control (Tabibnia et al., 2011), together suggestive of a strong neural relationship between craving and clinically relevant behavioral markers of addiction. Furthermore, methamphetamine craving has been observed to be present for at least 5 weeks into abstinence and is a significant predictor of subsequent use during outpatient treatment (Galloway & Singleton, 2009; Hartz, Frederick-
Osborne, & Galloway, 2001). Craving beliefs, or interpretations and decisions about cravings, have also been shown to predict relapse in a sample of regular methamphetamine users (N. K. Lee, Pohlman, Baker, Ferris, & Kay-Lambkin, 2010). On this basis, methamphetamine craving has been advanced as a surrogate marker of methamphetamine dependence (Galloway & Singleton, 2009).

Several lines of research have proposed a relationship between methamphetamine craving and the negative mood and other psychiatric symptoms that often accompany methamphetamine withdrawal. In particular, depressive symptomatology appears to have a strong relationship with

level of craving, as positive correlations have been observed between measures of methamphetamine craving post detoxification and multiple measures of depression (Nakama et al., 2008; Zorick, et al., 2010), even after controlling for previous methamphetamine usage (W. Shen, Liu, Li, Zhang, & Zhou, 2012). Along with the clinically significant depressive symptomatology, the intense cravings for methamphetamine during acute withdrawal appear to render the user particularly vulnerable to relapse during 7 to 14 days of abstinence (Zorick, et al., 2010).

In the human laboratory, craving for abused substances is commonly measured using a cue-exposure paradigm. This paradigm typically consists of systematically presenting individuals with drug and control cues (e.g., visual, smell, taste cues) while recording subjective and physiological changes associated with the urge to use the substance. The cue-exposure paradigm is largely grounded in associative learning principles in that repeated pairing of drug cues with consumption produce conditioned reinforcement such that drug cues become conditioned stimuli capable of eliciting drug craving. The translational value of this paradigm to the naturalistic environment is highlighted in the incentive salience model, in so much that relapse to drug use is often precipitated by exposure to drug-related cues which provokes craving (O'Brien, Childress, McLellan, & Ehrman, 1992).

Cue-induced craving has been shown to be reliably measurable in methamphetamine dependent individuals in the laboratory (Tolliver et al., 2010). Although baseline methamphetamine craving has been shown to decrease as a function of abstinence length (Galloway & Singleton, 2009; Hartz, et al., 2001; G. Wang et al., 2013), cue-induced craving for methamphetamine was observed to increase up to 3 months into abstinence (G. Wang, et al., 2013). Cue-induced methamphetamine craving has been associated with psychophysiological

changes, including altered heart rate variability (Culbertson et al., 2010), and greater levels of blood-oxygen-level dependent (BOLD) activation in the ACC, as compared to healthy controls, during pictorial methamphetamine-cue presentation (Yin et al., 2012).

Dopaminergic functioning in the striatum has been proposed as a possible neural substrate subserving the experience of drug craving (Volkow et al., 2006). In theory, the processing of drug cues shifts from ventral (NAcc) to dorsal (caudate/putamen) striatum during the transition from goal-directed to habitual and compulsive alcohol use (Vollstadt-Klein et al., 2010). This is consistent with the incentive-sensitization model of addiction, whereby compulsive drug use is under control of the dorsal striatum (B. J. Everitt & Robbins, 2005). There is some evidence to support this striatal shift in the existent literature (Ray et al., 2013; Volkow, et al., 2006), yet the consensus of the fMRI drug cue-reactivity literature suggests other brain regions may also be playing a large role during cue-processing in dependent individuals. Meta-analyses of neuroimaging studies including cue-exposure tasks have identified a small set of regions, not including the striatum, that appear to be selectively affected by drug cues in dependent individuals. Specifically, the precuneus was identified, along with the PCC and superior temporal gyrus, as selectively affected by alcohol-cue presentation in samples of alcohol-dependent individuals (Schacht, Anton, & Myrick, 2013b), and the precuneus was also implicated in response to smoking cues in samples of daily smokers (Engelmann et al., 2012). Further, emerging evidence suggests that the PFC is involved in the regulation of craving in response to drug cues (Goldstein & Volkow, 2011; Kober et al., 2010), and altered fronto-striatal connectivity has been observed in individuals with alcohol dependence (Ray, et al., 2013), cocaine use disorders (Wilcox, Teshiba, Merideth, Ling, & Mayer, 2011), and heroin users (Liu et al., 2011), in response to drug versus control cue exposure. Transcranial magnetic stimulation

(TMS) over the left dlPFC transiently increases cue-induced craving in individuals with methamphetamine dependence, suggesting that this technique functioned to inhibit prefrontal control and/or activate regions involved in craving via the dlPFC (Li et al., 2013). To that end, this project focuses on the neural markers of craving as an intermediate phenotype for methamphetamine dependence.

Treatment of Methamphetamine Use Disorders

At present, few effective options exist for individuals seeking treatment for methamphetamine use disorder, and to date these options have been limited to psychosocial interventions. Twelve-Step programs, such as Narcotics Anonymous, remain a common intervention pursued by many individuals with methamphetamine use concerns (Galanter, Dermatis, Post, & Santucci, 2013) despite a lack of evidence supporting the efficacy of these programs as a stand-alone treatment (Donovan & Wells, 2007; Shearer, 2007). There is some, albeit modest, evidence to suggest that other psychological interventions are effective for stimulant users (Knapp, Soares, Farrel, & Lima, 2007; Shearer, 2007; Vocci & Montoya, 2009). However, the majority of the treatment efficacy research has been done with cocaine abusing populations, and given the known differences between individuals seeking treatment for methamphetamine versus cocaine (i.e., age of first use, route of administration, frequency of use, demographics, and prior exposure to treatment; Huber et al., 1997), it remains unclear whether the efficacy of these interventions is generalizable to individuals with a methamphetamine use disorder.

Psychosocial Treatments. A systematic review of cognitive and behavioral treatments as applied specifically to methamphetamine use disorders concluded that good clinical outcomes are achieved with Cognitive-Behavioral Treatment (CBT; with and without Motivational

Interviewing [MI]) and Contingency Management (CM) therapies involving the systematic use of reinforcement (Nicole K. Lee & Rawson, 2008). A number of caveats must be considered when interpreting these conclusions however, such as the durability of treatment effects (especially with respect to CM programs). Furthermore, the effectiveness of psychosocial interventions is compromised by poor rates of treatment induction and retention (Shearer, 2007), and methamphetamine-related cognitive deficits in executive functioning, particularly those related to inhibitory control, have been hypothesized to potentially render heavily cognitive-based treatments ineffective (Baicy & London, 2007).

Pharmacologic Treatments. Given these important caveats of psychosocial interventions, and the heavy focus on the neurobiology of methamphetamine dependence, attention has shifted to the development of efficacious pharmacotherapies for methamphetamine addiction (NIDA, 2005). At present, no medication is approved by the U.S. Food and Drug Administration (FDA) for use in methamphetamine dependence. Numerous classes of medication are currently under study, primarily in small clinical trials (for a recent focused review see Brensilver, Heinzerling, & Shoptaw, 2013). Medications presumed to have potential for the treatment of methamphetamine addiction frequently target dopaminergic, serotonergic, GABAergic, and/or glutamatergic brain pathways (for a review see Vocci & Appel, 2007), as well as opioidergic pathways (e.g., Brensilver, et al., 2013). Additionally, cognitive enhancing medications such as modafinil (an analeptic drug with known cognitive-enhancing properties) have garnered attention given the known cognitive deficits associated with chronic methamphetamine use (e.g., Ghahremani et al., 2011).

A focused review on pharmacological treatments for methamphetamine/amphetamine dependence identified only three double-blind placebo-controlled trials that have shown positive

results for reducing use of the substance (Karila et al., 2010). The first two trials found treatment effects within a specific subpopulation of users; namely bupropion was associated with a reduction of methamphetamine use among baseline light, but not heavy, methamphetamine users (identified in a posthoc analysis; Shoptaw et al., 2008), and modafinil combined with CBT was associated with reduced methamphetamine use within a small sample of HIV+ gay men dependent on methamphetamine (McElhiney, Rabkin, Rabkin, & Nunes, 2009), although recent trials have not found strong support for a direct effect of modafinil on abstinence outcomes (e.g., Murty et al., 2014; Y. Zhang, Brady, & Smith, 2001). The third trial found support for reduced amphetamine use and greater abstinence rates with naltrexone treatment (50mg) in a sample of amphetamine-dependent individuals (Jayaram-Lindstrom, Hammarberg, Beck, & Franck, 2008). Since the review, an additional study has found support for the use of implant naltrexone for the treatment of problematic amphetamine use, noting patients with high levels of naltrexone (≥ 2 ng/ml) in their blood were 2.27 times more likely to be abstinent than patients with low naltrexone blood levels (< 2 ng/ml; Grant, Odlaug, & Kim, 2010). Despite these initial positive results, the efficacy of naltrexone for use in methamphetamine dependent individuals remains understudied and the neurobiological mechanisms associated with naltrexone's therapeutic efficacy are unclear.

Given the putative role of craving in the maintenance of addiction, numerous medications have also been tested for their ability to alleviate methamphetamine craving. These medications include ondansetron (Johnson et al., 2008), methylphenidate (Miles et al., 2013), a combination of flumazenil, gabapentin and hydroxyzine (Ling et al., 2012), modafinil (Shearer et al., 2009), topiramate (Johnson et al., 2007), aripiprazole (Newton et al., 2008), sertraline (Zorick, Sugar, Hellemann, Shoptaw, & London, 2011), and isradipine (Johnson et al., 2005). Unfortunately,

none of these medications have shown associated reductions in subjective methamphetamine craving, and two of these medications, namely aripiprazole and sertraline, have even been associated with increased (Newton, et al., 2008) or sustained (Zorick, et al., 2011) craving following treatment, respectively.

Nevertheless, a few medications have shown potential to reduce methamphetamine craving. Treatment with dextroamphetamine, as a potential substitution therapy, has been shown to reduce craving, but not methamphetamine use, in treatment seeking individuals with methamphetamine dependence (Galloway et al., 2011). Rivastigmine, a cholinesterase inhibitor, was observed to reduce participant's endorsement of "Likely to Use Meth" when exposed to acute methamphetamine via intravenous infusion in a sample of non-treatment seeking methamphetamine dependent individuals (De La Garza et al., 2012). Bupropion, an antidepressant which inhibits the reuptake of dopamine and norepinephrine, has also been associated with reduced methamphetamine craving in response to video cues in a laboratory model of non-treatment seeking individuals with a methamphetamine use disorder (Newton et al., 2006); although, preclinical work suggests that the effect of bupropion may be more general within the appetitive/reward system of the brain rather than having complete specificity for methamphetamine (Reichel, Linkugel, & Bevins, 2008). Nicotine has also shown promise in rodent models of craving. Specifically, methamphetamine-seeking behavior was found to be attenuated by repeated nicotine administration during methamphetamine withdrawal. Further, this attenuating effect was antagonized by the nicotinic antagonist mecamylamine (Hiranita, Anggadiredja, Fujisaki, Watanabe, & Yamamoto, 2004).

Naltrexone pharmacotherapy for the reduction of methamphetamine craving. While the rewarding and positive reinforcing effects of drugs of abuse are thought to be primarily

mediated by dopamine, opioid receptors are known to modulate dopaminergic activity and have been advanced as a plausible pharmacologic target for the treatment of various substance use disorders (Brensilver, et al., 2013). Naltrexone is an opioid antagonist with greatest affinity for the μ - and κ -opioid receptors in humans and non-human primates (Emmerson, Liu, Woods, & Medzihradsky, 1994; Toll et al., 1998). Specifically, reported K_i (nM) values for naltrexone at cloned human receptors expressed on Chinese hamster ovary cells are 0.2 at μ , 0.4 at κ , and 10.8 at δ (Toll, et al., 1998), which are similar to the values measured in monkey brain cortex homogenates (Emmerson, et al., 1994). Approved by the FDA for the treatment of alcohol and opioid dependence, naltrexone was found to be superior to placebo in reducing alcohol drinking outcomes when delivered in combination with medical management (Anton et al., 2006), and in reducing risk for relapse to opioid use (Syed & Keating, 2013). Furthermore, naltrexone shows promise as an efficacious treatment for nicotine dependence when combined with bupropion and the nicotine patch (Krishnan-Sarin, Meandzija, & O'Malley, 2003; O'Malley et al., 2006), and possibly as a stand-alone smoking-cessation treatment (A. C. King et al., 2012), particularly among heavy-drinking smokers (A. King, Cao, Vanier, & Wilcox, 2009). As reviewed above, preliminary evidence suggests naltrexone is also useful for the reduction of amphetamine use in amphetamine dependent populations (Jayaram-Lindstrom, Hammarberg, et al., 2008; Kelty, Thomson, Carlstein, Sinclair, & Hulse, 2013), as well as reduced heroin and amphetamine use in individuals with dual dependence on both substances (Tiihonen et al., 2012). Further, intramuscular injections of naltrexone (0.01-1 mg/kg) were associated with dose-dependent decreases in d-amphetamine and alcohol self-administration in a sample of adult rhesus monkeys (Jimenez-Gomez, Winger, Dean, Deaver, & Woods, 2011), and pre-treatment with naltrexone significantly attenuated amphetamine-induced reinstatement with no effect on food taking

behavior in the rat (Haggkvist, Lindholm, & Franck, 2009). Together, these results implicate a functional role for opioid receptors in modulating amphetamine seeking behavior and suggestive of naltrexone's potential utility for the treatment of methamphetamine dependence.

The reduction of drug craving is one plausible mechanism subserving the efficacy of naltrexone in the treatment of various substance use disorders. Numerous studies have observed a reduction of drug craving associated with naltrexone treatment (e.g., Krupitsky et al., 2011; Miranda et al., 2013; Monterosso et al., 2001; Monti et al., 1999; Ray et al., 2008; Subbaraman, Lendle, van der Laan, Kaskutas, & Ahern, 2013; Syed & Keating, 2013), although there is some evidence to suggest this effect may be moderated by opioid (i.e., OPRM1) and dopaminergic (i.e., D4 receptor) genes (Ashenhurst, Bujarski, & Ray, 2012; Ray, Bujarski, Chin, & Miotto, 2012; Ray et al., 2010; Schacht, Anton, Voronin, et al., 2013). In addition to the increased abstinence rates and reduction of amphetamine use as reviewed above, naltrexone treatment (50mg) was associated with reduced amphetamine (Jayaram-Lindstrom, Hammarberg, et al., 2008) and dexamphetamine craving in amphetamine dependent patients (Jayaram-Lindstrom et al., 2008), although no effect of naltrexone on craving was observed in individuals with dual dependence on heroin and amphetamine as craving decreased substantially in both naltrexone and placebo treatment groups (Tiihonen, et al., 2012). Naltrexone (12.5 and 50mg) was associated with a decrease in cocaine craving, but not positive subjective effects, during acute cocaine and d-amphetamine (versus placebo) administration in a sample comprised of predominant cocaine users. In addition, naltrexone was observed to reduce cocaine craving during the placebo administration, suggesting the effect of the medication is not specific to priming effects of the drug (Comer et al., 2013). Further, preclinical work has shown that naltrexone attenuates drug- and cue-induced locomotor behavior in amphetamine-conditioned

rats, by inhibiting the sensitized locomotor response (i.e., craving; Itzhak & Ali, 2002a) to amphetamine challenge following a 10-day drug-free period and by blocking the conditioned locomotor response when the amphetamine conditioned animals were placed in the previously amphetamine-paired context (Haggkvist et al., 2011).

With respect to methamphetamine craving specifically, evidence from the larger parent study from which the majority of the present sample was obtained supports a blunting effect of naltrexone on cue-induced craving for methamphetamine, in addition to naltrexone-induced reductions of several hedonic subjective effects of methamphetamine, such as stimulation and craving, during controlled methamphetamine (30mg) administration (Ray, Bujarski, et al., 2015). Further, preclinical work suggests naltrexone inhibits reinstatement of drug-seeking behavior, a plausible marker of drug craving in the animal, induced by methamphetamine-associated cues in mice following 12 days of methamphetamine self-administration and extinction (Anggadiredja, Sakimura, Hiranita, & Yamamoto, 2004). These results were related to the changes in dopamine and dopamine metabolite levels (Lan, Ma, Lin-Shiau, Liu, & Ho, 2008), as well as to the binding of a D1 agonist and D2 antagonist (SKF38393 and sulpiride, respectively) to dopamine receptors in the striatum (Tien, Ho, Loh, & Ma, 2007). Naltrexone was found to have no effect on methamphetamine-priming-induced reinstatement in these rodents, possibly indicating a separate pathway for drug priming effects (Anggadiredja, et al., 2004). Further, μ -opioid receptor knockout mice are unaffected by methamphetamine-induced behavioral sensitization (X. Shen et al., 2010), suggestive of naltrexone's mechanism of action in craving instatement. The blockage of methamphetamine-induced dopamine release in the mesolimbic dopamine system has been proposed as the neural mechanism underlying naltrexone's effect on drug reinforcement (Benjamin, Grant, & Pohorecky, 1993; Y. K. Lee, et al., 2005; Naleid, Grace, Cummings, &

Levine, 2005; Widdowson & Holman, 1992), however, no study to date has been conducted in humans to test this hypothesis.

Neural markers of treatment effects. Functional neuroimaging is often used to assess the effectiveness of addiction treatments, given the strong evidence for neurological alterations at the basis of drug dependence (e.g., Goldstein & Volkow, 2011; Parvaz, Alia-Klein, Woicik, Volkow, & Goldstein, 2011; Volkow, Wang, Fowler, & Tomasi, 2012). Functional neuroimaging provides an objective and quantifiable measure for evaluating changes with treatment beyond what can be gathered from self-report or behavior alone (Menossi et al., 2013). Using activation likelihood estimation (ALE), a meta-analysis identified the left ventral striatum, right IFG, and right OFC as commonly affected by a range of pharmacological and cognitive-based strategies for addiction treatment (Konova, Moeller, & Goldstein, 2013). Intervention in these regions was speculated to serve to reduce drug-seeking and impulsive behavior, and/or to normalize disturbances related to withdrawal and negative mood. Further, evidence from this meta-analysis suggests that cognitive-based interventions affect regions generally involved in top-down control processes (i.e., right ACC, right MFG, and left precuneus/PCC) more so than pharmacologic interventions, which may exert the majority of their effects via bottom-up processes such through the mediation of craving (Konova, et al., 2013).

Neuroimaging protocols which include cue-exposure paradigms may be particularly useful in elucidating the effects of addiction treatments due to the strong learning and memory components involved in addiction neurobiology, and cue-reactivity in particular (Kalivas & Volkow, 2005; T. E. Robinson & K. C. Berridge, 1993). The presentation of drug cues appears to reliably produce activation of neural circuits involved in learning and memory, as well as brain regions associated with the reward/reinforcement network, such as the striatum, amygdala,

PFC, cingulate, precuneus, and the insula (Camara, Rodriguez-Fornells, Ye, & Munte, 2009; Engelmann, et al., 2012; Schacht, Anton, & Myrick, 2013a). In sum, fMRI based cue-reactivity paradigms are well positioned to advance our understanding of the involvement of neurobiological pathways subserving the reward/reinforcement system in addiction and offer a translational platform by which interventions can be tested (Ray, Courtney, Roche, & Miotto, in press).

Thus, it was posited that functional neuroimaging of the pharmacologic intervention naltrexone on cue-induced meth craving would provide insight as to the pathways by which craving is instated. In addition, the use of a neuroimaging approach provides an objective and validated measure which links the therapeutic action of naltrexone to its neural mechanisms. Knowledge of these pathways provides a platform by which other new compounds under development can be evaluated.

The Dissertation

Methamphetamine addiction remains a significant burden to society with few effective options for remediation. Craving for methamphetamine represents an important translational intermediate phenotype for methamphetamine addiction, with promise as a viable treatment target. The literature reviewed above suggests that naltrexone is likely to affect methamphetamine cue-induced craving in individuals with methamphetamine dependence. Neuroimaging analyses, such as indices of functional connectivity, have proven useful in investigating functional pathways of pharmacologic and cognitively-mediated processes, and as such may be useful in assessing the pathways which regulate cue-induced craving (Hommer, 1999). Thus, the objective of this dissertation was to investigate the neurobiological effects of naltrexone on methamphetamine cue-reactivity. Twenty-three non-treatment seeking individuals

with a methamphetamine use disorder were treated with naltrexone (50mg) and placebo (counterbalanced within-subjects), and underwent an fMRI sequence which included a methamphetamine cues task designed to induce craving for methamphetamine. The following were the specific aims of the project: (1) To determine whether naltrexone (50mg) versus placebo moderates BOLD measures of methamphetamine cue processing (i.e., cue-reactivity), and (2) to determine whether naltrexone's effect on methamphetamine cue-reactivity is associated with differential functional connectivity from reward-/reinforcement-related regions (ventral and dorsal striatum, VTA), regions expressing high opioidergic receptor site densities (VTA, PAG), and previously determined cue-reactive (precuneus) regions during methamphetamine cue processing, as compared to placebo. Additional exploratory aims included: (1) To determine the effect of naltrexone (50mg) on cerebral blood flow (CBF), as any CBF alterations by the medication represent a potential confound on the fMRI analyses, and (2) to determine whether subjective reports of cue-induced methamphetamine craving are related to the neural markers of methamphetamine cue processing.

Methods

Participants

Non-treatment seeking individuals with methamphetamine dependence were recruited from the Los Angeles community through advertisements in online sources (i.e., Craigslist), newspapers (i.e., LA Weekly), community locations (e.g., phone booths, bus bench advertisement, and family health clinics), and through referrals from past research participants.

Interested individuals who phoned the lab for study information were informed about the nature of the study and received an individual telephone screen for self-reported inclusion and exclusion criteria following verbal informed consent. Those who were eligible were scheduled

for an in-person screening session in which written informed consent was obtained followed by a psychiatric diagnostic interview and a battery of individual differences measures (see baseline measures section below). A physical examination including a blood draw for a comprehensive metabolic panel was completed at the UCLA Clinical & Translational Research Center (CTRC) to ensure medical eligibility, as described in the exclusionary criteria. Medically eligible participants then received the first dose of double-blind medication (naltrexone or placebo), and returned to the lab on days two and three for medication (assuming the production of a negative toxicology screen for all drugs besides marijuana on each day). Participants underwent the first neuroimaging session on day three (at target dose) of the initial medication (see medication procedures below). A seven-day or more washout period was then instated, and participants returned to the lab daily for another three days to receive the second medication (naltrexone or placebo) and underwent the second neuroimaging session on day three. An overview of the study visits is presented in **Figure 1**. These procedures are consistent with those of the completed project from which the first 16 subjects' data are being culled. Therefore, the sample collected herein is well suited to be combined with the completed project sample for a final sample of 23 completers in the crossover medication design.

Inclusion and exclusion criteria. Criteria for inclusion in the study was as follows: (1) age between 18 and 50; (2) current DSM-IV diagnosis for methamphetamine abuse/dependence (as verified by the Structured Clinical Interview for DSM-IV); (3) fluency in English; (4) pass a physical exam and laboratory tests for medical eligibility; and (5) agree to abstain from methamphetamine use during the study, as evidenced by methamphetamine-negative urines obtained in the lab during daily medication visits.

Participants were excluded if any of the following criteria were met: (1) current treatment for methamphetamine dependence or a history of treatment in the 30 days before enrollment or are treatment seeking; (2) current (last 12 months) DSM-IV diagnosis of dependence on any psychoactive substances other than nicotine; (3) lifetime DSM-IV diagnosis of schizophrenia, bipolar disorder, or any psychotic disorder; (4) current major depressive disorder with suicidal ideation; (5) current use of psychoactive drug, other than marijuana and methamphetamine, as determined by self-report or urine toxicology screen; (6) clinically significant physical abnormalities as indicated by physical examination, hematological assessment, or bilirubin concentration; (7) currently taking any medications that could interact adversely with naltrexone, such as opioid pain medications; (8) pregnancy, nursing, or refusal to use reliable method of birth control, if female; (9) MRI contraindications (e.g., braces, claustrophobia); and (10) left handedness.

Participant flow. A total of 891 phone screens were conducted, 463 of which were determined to be initially eligible (see **Figure 1** for a detailed breakdown of recruitment flow). Of those, 203 came in for in-person screens and 117 were deemed eligible for the experimental portion of the study. Fifty-nine physical examinations were conducted, 49 of which were determined to be medically safe to commence study medication and undergo the MRI procedures. Study attrition from in-person screen to physical examination was primarily due to participant drop out ($n = 58$), failing to meet eligibility criteria based on the SCID (either not meeting methamphetamine abuse/dependence criteria or meeting criteria for other exclusionary psychological conditions; $n = 31$), inability to produce a positive methamphetamine urine to verify use history ($n = 23$), and positive urine test for other exclusionary substances ($n = 12$). Twenty-eight individuals (67.9% male, mean age = 33.68 [SD = 8.76]) were randomized to

medication and completed at least one scanning session, 24 of whom completed both scanning sessions, one while at naltrexone target dose and the other on matched placebo. One subject was dropped from the analyses due to excessive motion during scanning (exceeding 3mm translation), resulting in a final sample of 23 participants (74% male, mean age = 34.70 [SD = 8.95]).

Of the four participants that dropped during the experimental protocol, two self-withdrew (lost contact with the study team) and two were dropped by the experimenter (one due to inability to follow experimenter directions and one due to pregnancy). No participants tested positive for methamphetamine or other exclusionary substances once randomized to study medication.

The outpatient study was proportionally similar to the parent inpatient study on exclusionary factors and number of drop-outs during experimental procedures, and no differences in participant demographics were observed between studies (see **Table 2**). Given the comparableness of sample characteristics across the two studies, all further analyses are combined across the two study samples.

Medication procedures. Naltrexone and matched placebo tablets were converted to the appropriate dose and placed in identical opaque gelatin capsules. Participants received a 25mg dose on day one and 50mg doses on days two and three during the naltrexone arm of the study. The titration schedule aimed to minimize adverse events with the potential to impact the variables of interest (O'Malley, Krishnan-Sarin, Farren, & O'Connor, 2000). At least a seven-day washout period between medication conditions was required to reduce medication carry-over effects.

To ensure compliance of the medication procedures, participants took the medication under the Principal Investigator's supervision during their daily medication visits to the lab. During this time they were also assessed for medication side effects and all effects above a moderate severity level were immediately reported to the study physician. Participants were also given direct contact information for the study physician and were encouraged to discuss any side effects with her.

Participant compensation. Participants received \$30 for completion of the in-person screening visit, \$20 for completion of the physical exam, \$10 for each day they returned to the lab for medication (disbursed on day 3 of each scanning session), and \$50 for completion of each scanning session.

Measures

Participants completed a number of self-report and neurocognitive measures throughout the study. Responses on these measures were used to determine the characteristics of the sample.

Baseline measures. During the in-person screening session, participants completed a battery of individual difference measures: (1) A Demographics Questionnaire to collect information on age, sex, marital status, socioeconomic status, occupation, income, education, and ancestry; (2) The Shipley Institute of Living Scale-Revised to estimate IQ scores (Zachary, 1991); (3) The Digit Span task, a subscale from the Wechsler Adult Intelligence Scale (WAIS-IV) to assess short-term verbal memory (Wechsler, 2008); (4) The Beck Depression Inventory-II (BDI-II) to screen out individuals with current feelings of active suicidality (A. T. Beck, Steer, Ball, & Ranieri, 1996); (5) The Beck Anxiety Inventory (BAI), to assess anxiety symptomatology including physical and cognitive indicators of anxious mood (A. T. Beck, Epstein, Brown, & Steer, 1988); (6) The Inventory of Depression and Anxiety Symptoms

(IDAS), to provide an additional measure of depression and anxiety symptomatology (Watson et al., 2007); and (7) An Attention Deficit Hyperactivity Disorder (ADHD) scale, to assess both childhood and current ADHD symptoms.

To assess for methamphetamine, alcohol, nicotine, and other drug use/abuse, participants completed: (1) The Timeline Follow-Back (TLFB), to measure the use of alcohol, methamphetamine and alcohol for the 30 days prior to the screening visit (Sobell & Sobell, 1992); (2) The Methamphetamine Withdrawal Questionnaire (MAWQ), to assess methamphetamine withdrawal (Zorick, et al., 2010); (3) The Methamphetamine Urge Questionnaire (MAUQ), adapted from the Alcohol Urge Questionnaire (Bohn, Krahn, & Staehler, 1995) to assess methamphetamine craving; (4) A Route of Methamphetamine Administration questionnaire, to index preferred method of methamphetamine use (i.e., smoking, eating, IV, intranasal); (5) The Alcohol Consumption Questionnaire (ACQ), to assess lifetime drinking history such as current drinking pattern, age of onset, and number of attempts to quit/reduce drinking (Raabe, Grusser, Wessa, Podschus, & Flor, 2005); (6) The Alcohol Use Disorders Identification Test (AUDIT), to measure symptoms of alcohol abuse/dependence (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993); (7) The Smoking History Questionnaire (SHQ), to collect detailed history of frequency and quantity of nicotine use and quit attempts (Tiffany & Drobes, 1991); (8) The Fagerström Test of Nicotine Dependence (FTND), to assess nicotine dependence severity (T. F. Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991); (9) A Drug Use Questionnaire (DUQ), to assess individual behavior with regard to frequency and quantity of drug use; and (10) The Family Tree Questionnaire (FTQ), to identify blood relatives with alcohol and/or drug problems (Mann, Sobell, Sobell, & Pavan, 1985). The Structured Clinical Interview for DSM-IV (SCID) was also administered by trained

Masters' level clinicians to assess methamphetamine dependence as well to as screen out those with a diagnosis of major depression with suicidal ideation, bipolar disorder, or any psychotic disorder (First et al., 1995). DSM-5 diagnosis of a methamphetamine use disorder was also determined by summing the symptoms of methamphetamine abuse and dependence (excluding the "recurrent legal problems" criterion) acquired from the SCID and adding in a dichotomous craving item, determined by endorsement of craving on the MAUQ.

Given the literature linking impulsivity and drug use/abuse (e.g., Courtney et al., 2012; Dawe & Loxton, 2004; Jentsch & Taylor, 1999; Verdejo-Garcia, Lawrence, & Clark, 2008), the following self-report and neurocognitive measures of the impulsivity domains were also assessed: (1) The Barratt Impulsiveness Scale V11 (BIS-11) to measure trait impulsivity (Patton, Stanford, & Barratt, 1995); (2) The Monetary Choice Questionnaire/Delayed Discounting Task (MCQ/DDT), to assess for temporal discounting of rewards (Kirby, Petry, & Bickel, 1999); (3) The Domain Specific Risk Taking scale (DOSPERT), to measure risk taking on five content domains: financial (separately for investing versus gambling), health/safety, recreational, ethical, and social (Weber, Blais, & Betz, 2002); (4) The Balloon Analog Risk Task (BART), to measure risky behavior within rewarding conditions (Lejuez et al., 2002); (5) A computer version of the Stroop Color Word Interference Test, to measure focused attention and response inhibition (Stroop, 1935); and (6) The Stop Signal Task (SST), to measure response inhibition and activational responding (Logan, 1994).

Medication visit measures. At each medication visit, participants completed the Positive and Negative Affect Schedule (PANAS), a measure of the two primary dimensions of mood (Watson, Clark, & Tellegen, 1988), as well as the MAUQ and MAWQ. Immediately prior to the first administration of each medication, participants were asked about their methamphetamine

use since last seen in the laboratory using the TLFB. On days two and three of each medication they also completed the Systematic Assessment for Treatment Emergent Effects (SAFTEE) questionnaire to assess for medication-related subjective effects (Levine & Schooler, 1986).

Pre- and post-scan self-report measures. Immediately before and after each scanning session, participants were asked to again complete the three measures designed to assess dimensions of methamphetamine craving and withdrawal: the MAUQ, the MAWQ, and the PANAS.

Primary scanning measure. The visual Methamphetamine Cues Task was developed by the author of this dissertation to induce methamphetamine craving in the scanner in individuals with methamphetamine use disorders. A comprehensive literature search was conducted to locate successful studies that include the presentation of drug cue stimuli in the context of neuroimaging. Although no accessible methamphetamine cue studies were found, the task design was developed to maximize the potential for signal acquisition based on the result of this literature search (i.e., number of stimuli, inter-trial intervals, block versus event-related design, etc.). Methamphetamine cue stimuli for the task were acquired through extensive internet searches for un-copyrighted images of three picture types: methamphetamine itself, methamphetamine use (e.g., individuals smoking or snorting methamphetamine), and methamphetamine paraphernalia. Control stimuli were acquired through the same manner, with the goal of matching on non-drug related content of the images across the three picture types (i.e., the presence of people, intensity of color, etc.). Over 130 images were found and subjected to de-identified ratings of relatedness to methamphetamine by 15 staff and undergraduate research assistants in Dr. Lara Ray's Addictions Laboratory. These individuals were asked to rate each methamphetamine and control image on "How much does this picture remind you of

methamphetamine?” on an 11-point Likert-type scale (0 being not at all and 10 being very much). The ratings were averaged and only the control images with a mean rating less than 4 and the methamphetamine images with a mean rating of greater than 6 were kept for inclusion in the task. This resulted in the retention of 32 images from each condition, balanced across the three picture types (**Figure 2**). The final task was programmed using Matlab (Mathworks, Natick, MA) and Psychtoolbox (www.psychtoolbox.org). The task was then piloted in two healthy individuals, followed by two individuals with methamphetamine dependence. Subjective reports from the individuals with methamphetamine dependence gave assurance that the task was effective in eliciting methamphetamine craving.

Neuroimaging Procedures

Participants completed two neuroimaging sessions. Both sessions took place after three days of study medication, thus at target dose of naltrexone, or matched time for placebo.

Data acquisition. Neuroimaging was conducted using a 3 Tesla Siemens Trio MRI scanner at the UCLA Staglin IMHRO Center for Cognitive Neuroscience (CCN). The protocol began with initial structural scans followed by two runs of the Methamphetamine Cues Task and an arterial spin labeling (ASL) scan (described below). During data acquisition, the head was restrained using a foam pillow and pads. The presentation of the visual cues stimuli and response collection was programmed using MATLAB (Mathworks, Natick, MA) and Psychtoolbox (www.psychtoolbox.org) on a PC running Windows 7. Visual stimuli were presented using MRI compatible goggles (Resonance Technologies, Van Nuys, CA).

Structural scans. A T2-weighted, high resolution, matched-bandwidth (MBW), anatomical scan (TR, 5s; TE, 34ms; FOV, 192mm; matrix, 128x128; sagittal plane; slice thickness, 4mm; 34 slices) and a magnetization-prepared rapid-acquisition gradient echo scan

(MPRAGE; TR, 1.9s; TE, 2.26ms; FOV, 250mm; matrix, 256×256; sagittal plane; slice thickness, 1mm; 176 slices) were acquired for each subject to enable registration. The orientation for MBW and echoplanar image (EPI) scans was oblique-axial to maximize brain coverage.

Arterial spin labeling perfusion sequence (ASL). Quantification of cerebral blood flow (CBF) was measured using pseudo-continuous ASL (pCASL). Thirty slices of pCASL data were obtained in the oblique-axial plane (slice thickness, 5 mm; TR, 4s; TE, 22.62 ms; FOV, 220 mm; matrix, 64x64).

Methamphetamine cues task. The Methamphetamine Cues scan included 150 functional T2*-weighted EPIs (slice thickness, 4mm; 34 slices; TR, 2s; TE, 30ms; flip angle, 90°; matrix, 64 x 64; FOV, 192mm; voxel size, 3x3x4mm³). The Methamphetamine Cues Task involved two runs, each approximately six minutes in length, in which participants viewed four blocks of methamphetamine cue pictures and four blocks of control cue pictures, pseudo-randomly presented. Each block consisted of four pictures, presented for five seconds each, for a total of 32 pictures from each condition (**Figure 3**). The cue pictures within each block were randomly selected from the three picture types (i.e., drug, pipes, and consumption). Participants were asked to press a button at the presentation of each stimulus to ensure adequate attention during the task. Following each block of pictures, a craving question was presented on the screen prompting participants to rate their current urge to use methamphetamine using the four buttons on the response box corresponding to a four-item urge scale (1=no urge, 2=low urge, 3=moderate urge, 4=high urge). Feedback indicating their response was presented immediately after the rating for two seconds, with the remaining rating time (total 10 seconds possible) added to the following 10 second rest period; thus, the duration of the urge rating period was varied based on response time. Participants were instructed on the task prior to scanning.

Data Analysis Procedures

Data Preprocessing

ASL data preprocessing. FSL 5.0 (www.fmrib.ox.ac.uk/fsl) was used for all imaging analyses. The pCASL sequence described above resulted in control and label images, which were then motion corrected separately using the Motion Correction Linear Image Registration Tool (McFLIRT, Version 5.0) and brain-extracted using the Brain Extraction Tool (BET). An in-house MATLAB script was used to quantify cerebral blood flow (CBF) images using simple subtraction of label and control images, according to a one-compartment perfusion model (delay time 1.2s, label time 1.2s, label efficiency 0.9, blood/tissue compartment [λ] 0.9, T1-blood 1650ms). Mean CBF images were then generated by averaging all CBF images within each participant and medication condition. The mean CBF images were first registered to the MBW, then to the MPRAGE using affine linear transformations, and into standard space (Montreal Neurological Institute, MNI avg152 template) using FLIRT. The co-registered CBF images were then smoothed using a full width at half maximum (FWHM) Gaussian kernel (6mm). Grey matter masks were created for each participant separately on the MPRAGE images using FSL's Automated Segmentation Tool (FAST; Y. Zhang, et al., 2001), and then applied to the mean CBF images to enable extraction of spatial mean global grey matter CBF estimates for each participant and medication condition.

fMRI data preprocessing. The first six volumes collected for each EPI were discarded to allow for T1 equilibrium effects. Motion correction was carried out using McFLIRT, with the estimated motion parameters entered as covariates in the general linear model. Non-brain tissue/skull removal was conducted with BET. The images were smoothed using a FWHM Gaussian kernel (5mm) and high-pass filtered (100s cutoff) in the temporal domain using a

Gaussian weighted straight line with the FMRI Expert Analysis Tool (FEAT, Version 5.63). The EPI images were first registered to the MBW, then to the MPRAGE using affine linear transformations, and into standard space (Montreal Neurological Institute, MNI avg152 template). Registration to standard space was refined by FSL's FNIRT nonlinear registration.

Initial Task Analyses

Self-reported craving. In-scanner methamphetamine and control cue-induced craving ratings were analyzed using a repeated measures analysis of variance (ANOVA) including cue type (2 levels: methamphetamine, control) and medication condition (2 levels: placebo, naltrexone) as repeated factors. Post hoc tests on cue-type across the length of the scan were conducted using paired t-tests.

BOLD Methamphetamine Cue > Control Cue. Whole-brain statistical analysis was performed using a multi-stage approach to implement a mixed-effects model treating medication condition as a fixed-effects variable and participants as a random-effects variable. Explanatory variables for the Methamphetamine Cues Task were created by convolving delta functions representing the onset of experimental events of interest (i.e., Methamphetamine Cues and Control Cues, each with 20 second duration from stimulus onset) with a double-gamma hemodynamic response function in FEAT. The main contrast of interest, Methamphetamine Cue > Control Cue, was specified in the first-level models and temporal derivatives were included as covariates to improve statistical sensitivity. Second-level analyses averaged the Methamphetamine Cue > Control Cue contrast images across the two runs for each participant and medication condition separately. Third-level 'main effect' analyses averaging participants within medication conditions (medication) and across medication conditions (task) were then conducted on the second-level Methamphetamine Cue > Control Cue contrast images. Z-statistic

images were thresholded with cluster-based corrections for multiple comparisons based on the theory of Gaussian Random Fields first with a cluster-forming threshold of $Z > 2.3$ and a cluster-probability threshold of $p < 0.05$ (Worsley, 2001). Anatomical localization of peak voxels within each cluster (maximum Z statistics and MNI coordinates) was obtained by searching within maximum likelihood regions from the FSL Harvard-Oxford probabilistic atlas.

Analysis of Specific Aims

Exploratory Aim 1. To determine whether naltrexone (50mg) alters cerebral blood flow (CBF) as compared to placebo. Extracted mean global grey matter CBF estimates within each medication condition were analyzed using a paired samples t -test.

Aim 1. To determine whether naltrexone (50mg) versus placebo moderates the BOLD measures of methamphetamine cue processing. A second set of third-level analyses were run on the second-level Methamphetamine Cue > Control Cue contrast images averaged across runs (described above) which specified the medication contrasts (placebo > naltrexone, naltrexone > placebo) per participant. A fourth-level ‘interaction’ analysis was then conducted which averaged the medication contrasts (placebo > naltrexone, naltrexone > placebo) over participants. Z -statistic images from this fourth-level ‘interaction’ analysis were thresholded as described above using a cluster-forming threshold of $Z > 2.3$ and a cluster-probability threshold of $p < 0.05$.

Aim 2. To determine whether naltrexone’s effect on methamphetamine cue-reactivity is associated with differential functional connectivity from reward-/reinforcement-related regions (ventral and dorsal striatum, VTA), regions expressing high opioidergic receptor site densities (VTA, PAG), and previously determined cue-reactive (precuneus) regions during cue processing, as compared to placebo. Five a priori seed

regions of interest (ROIs) were selected (**Figure 4**) based on literature indicating their involvement in reinforcement and opiodergic functioning (i.e., ventral and dorsal striatum, ventral tegmental area, periaqueductal gray; Halladay & Blair, 2012; Mansour, Fox, et al., 1995; Ray, et al., 2013; Spetea, Asim, Wolber, & Schmidhammer, 2013) and involvement in cue-processing and drug dependence severity (i.e., precuneus; Courtney, Ghahremani, London, & Ray, 2014; Engelmann, et al., 2012; Schacht, Anton, et al., 2013b). The ventral striatum was anatomically defined using the bilateral nucleus accumbens (NAcc) regions from the Harvard-Oxford probabilistic atlas in FSL. The dorsal striatum was anatomically defined using the bilateral caudate regions from the Harvard-Oxford probabilistic atlas, and further functionally constrained by the activation from the Methamphetamine Cue > Control Cue contrast averaged across participants and medication conditions. Similarly, the bilateral precuneus was anatomically defined by the right and left precuneus regions from the Harvard-Oxford probabilistic atlas, and further functionally constrained by the activation from the Methamphetamine Cue > Control Cue contrast. The ventral tegmental area (VTA) was anatomically defined using a midbrain probabilistic atlas developed by Murty and colleagues (2014). For the periaqueductal gray (PAG), a 3mm radius sphere was created around bilateral peak coordinates obtained from a large review on human neuroimaging studies that reported PAG involvement ($x=-4/4$, $y=-29$, $z=-12$; Linnman, et al., 2012). Parameter estimates from these five seed ROIs within the Methamphetamine Cue > Control Cue contrast were extracted from each participant, and for each medication condition, and one-sample *t*-tests were conducted on these estimates to determine the presence of significant regional activation during methamphetamine cue processing across and within medication conditions. Paired *t*-tests were

also conducted on these estimates to determine regional differences between medication conditions (except when statistically prohibited; i.e., “double dipping”).

Functional connectivity was assessed using psychophysiological interaction (PPI) analysis (Gitelman, Penny, Ashburner, & Friston, 2003; O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012) which measures coupling of brain regions during specific task conditions. To examine medication related differences in functional connectivity during methamphetamine cues processing, the coupling of the different seed ROIs with the rest of the brain within the Methamphetamine Cue > Control Cue contrast were analyzed. The average time course of the seed ROIs were extracted from motion-corrected, high-pass filtered image data. The first-level model was identical to the first-level model described above in Aim 1 with the inclusion of four additional regressors: the main ‘psychological’ regressor to model the difference in task conditions (Methamphetamine Cues - Control Cues, convolved with a hemodynamic response function), a second ‘psychological’ regressor to account for the shared variance between task conditions (Methamphetamine Cues + Control Cues, convolved with a hemodynamic response function), a ‘physiological’ regressor to model the seed time course, and the ‘psychophysiological interaction’ regressor which is the product of the main ‘psychological’ (zero centered) and ‘physiological’ (mean centered) regressors. A whole-brain contrast image for each seed PPI was computed from these models and submitted for higher-level task ‘main effect’ and medication ‘interaction’ analyses as described above. Z-statistic images were first thresholded as described above using the conservative cluster-forming threshold of $Z > 2.3$ and a cluster-probability threshold of $p < 0.05$, and then tested at the lower standard $Z > 1.96$ cluster-forming threshold, if indicated.

Exploratory Aims 2A and 2B. To determine whether subjective reports of cue-induced methamphetamine craving are related to the BOLD measures of methamphetamine cue processing (2A) and functional connectivity during cue processing (2B). In order to model potential correlations between subjective reports of cue-induced methamphetamine craving and BOLD markers of methamphetamine cue-reactivity, participants' self-reported methamphetamine craving immediately following the presentation of methamphetamine cues during the task, averaged across medication conditions, was entered as a covariate of interest in separate higher-level analyses paralleling all models described above, and included the second-level ('main effect') or third-level ('interaction') contrast images for each participant. Within-subject differences in self-reported craving between medication conditions were also tested in the same manner. Self-reported craving was mean centered within medication condition for the 'main effect' analyses modeling activation within and across medication conditions and mean centered across medication conditions for the 'interaction' analyses modeling medication differences.

Results

Demographic and Initial Task Results

Sample Demographics. Twenty-three individuals (74% male, mean age = 34.70 [SD = 8.95]) completed the within-subjects scanning protocol and provided useable data for analysis (see **Table 2** for detailed sample characteristics). All 23 individuals met DSM-IV and DSM-5 criteria for a current (i.e., past month) methamphetamine use disorder (DSM-IV dependence/abuse: 20/3; DSM-5 severity: 1 mild, 6 moderate, 16 severe). All participants reported extensive experience smoking methamphetamine.

Self-Reported Methamphetamine Craving. Repeated measures ANOVAs revealed a significant effect of cue type on self-reported methamphetamine and control cue-induced methamphetamine craving during the fMRI Methamphetamine Cues Task ($F[1,22] = 35.96, p < 0.001$). No significant effects for medication condition or for the interaction of medication condition and cue type were observed ($ps > 0.8$). Post hoc tests on cue type across scanning blocks revealed that methamphetamine cues were associated with higher self-reported craving ratings than control cues, across the entire scan ($ps < .002$; **Figure 5**).

BOLD Methamphetamine Cue > Control Cue. The main contrast of interest, Methamphetamine Cue > Control Cue, on the 23 individuals averaged across medications (i.e., main effect of task) was associated with the activation of a broad set of regions including mesocorticolimbic areas such as the ventral and dorsal striatum and inferior frontal gyrus (IFG). Additional areas of activation were found in the frontal lobe (dorsolateral PFC, superior frontal gyrus), parietal lobe (precuneus), thalamus, hippocampus, and occipital areas (**Table 3A; Figure 6**). Similar results were observed when averaging Methamphetamine Cue > Control Cue activation within the placebo condition only (**Table 3B; Figure 7**), and to a lesser extent within the naltrexone condition only (**Table 3C; Figure 8**; note that the results reported in **Table 3** were thresholded at $Z > 3.7$ to enable separation of clusters).

Results of Specific Aims

Exploratory Aim 1. To determine whether naltrexone (50mg) alters cerebral blood flow (CBF) as compared to placebo. Spatial mean global grey matter CBF estimates (**Figure 9**) were not found to significantly differ between placebo ($M = 51.348$) and naltrexone ($M = 52.564$) conditions ($t [22] = -0.825, p = 0.418$). Thus, CBF estimates were not included as covariates in BOLD analyses.

Aim 1. To determine whether naltrexone (50mg) versus placebo moderates BOLD measures of methamphetamine cue processing. Contrasting the placebo and naltrexone conditions within the Methamphetamine Cue > Control Cue contrasts revealed significantly less activation associated with the naltrexone condition in sensorimotor areas (bilateral precentral and postcentral gyri), and occipital regions (left superior lateral occipital cortex; **Table 4; Figure 10**). Effect size estimates (in Cohen's *d*) for the medication contrasts are depicted in **Figure 11**.

Exploratory Aim 2A. To determine whether subjective reports of cue-induced methamphetamine craving are related to BOLD measures of methamphetamine cue processing. Exploratory analyses examining the correlation between self-reported methamphetamine craving and activation within the Methamphetamine Cue > Control Cue contrast, averaged across medications, revealed significant positive correlations between craving and activation of the precuneus and occipital regions (lingual gyrus, intracalcarine cortex) during methamphetamine cue processing (**Table 5A, Figure 12**). Positive correlations were also observed between craving and methamphetamine cue-related activation of left frontal regions (dlPFC, middle frontal gyrus [MFG], and IFG) and right occipital regions (lingual gyrus, intracalcarine cortex) within the placebo condition (**Table 5B, Figure 13**). No positive correlations were observed within the naltrexone condition, and no negative correlations were observed in any of the models. Further, no significant correlations were observed between self-reported craving and medication differences from the 'interaction' model contrasting placebo and naltrexone.

Aim 2. To determine whether naltrexone's effect on methamphetamine cue-reactivity is associated with differential functional connectivity from reward-/reinforcement-related regions (ventral and dorsal striatum, VTA), regions expressing high

opioidergic receptor site densities (VTA, PAG), and previously determined cue-reactive (precuneus) regions during cue processing, as compared to placebo. Of the three a priori seed regions of interest (ROIs) that could be appropriately tested given how the ROIs were defined (i.e., not functionally constrained by the contrast of interest; NAcc, VTA, and PAG), the VTA and PAG were found to exhibit significant activation (as compared to 0) within the Methamphetamine Cue > Control Cue contrast, averaging over medication condition ($ps < 0.006$). All ROI parameter estimates except the NAcc were significantly active within the naltrexone condition ($ps < 0.034$), and only the PAG, dorsal striatum (caudate), and precuneus were found to be significantly active within the placebo condition ($ps < 0.002$; **Table 6; Figure 14**). No difference between medication conditions was observed for any ROIs ($ps > 0.2$).

No regions of significant Methamphetamine Cue > Control Cue activation were observed when averaging across medication conditions for any of the seed ROIs in the PPI analyses; however, functional connectivity within each seed region analysis, with the exception of the ventral striatum (NAcc), was found to differ between medication conditions. Specifically, naltrexone was associated with weaker connectivity between the PAG and occipital regions, as compared to placebo, during methamphetamine cue processing (**Table 7, Figure 15**). At the second threshold tested ($Z > 1.96$), naltrexone was also associated with weaker connectivity between the precuneus and fronto-parietal regions including the precentral and postcentral gyri (**Table 8, Figure 16**), stronger connectivity between the VTA and prefrontal, temporal, and parietal regions (**Table 9, Figure 17**), and stronger connectivity between the caudate and prefronto-occipital regions (**Table 10, Figure 18**). No significant results were observed for precuneus, VTA, or caudate functional connectivity at a cluster-forming threshold of $Z > 2.3$.

Exploratory Aim 2B. To determine whether subjective reports of cue-induced methamphetamine craving are related to functional connectivity during methamphetamine cue processing. Of the five seed ROIs investigated, only the dorsal striatum (caudate) and precuneus were found to exhibit correlated functional connectivity during methamphetamine cues processing (Methamphetamine Cue > Control Cue) and average self-reported methamphetamine craving that differed between medication conditions (at a threshold of $Z > 1.96$). Specifically, naltrexone was associated with stronger positive correlations between average subjective craving and caudate functional connectivity to fronto-parietal regions during methamphetamine cue processing (**Table 11, Figures 19 and 20**). Naltrexone was also associated with weaker positive correlations between average self-reported craving and precuneus functional connectivity to parietal regions and stronger positive correlations between average self-reported craving and precuneus functional connectivity to frontal regions during methamphetamine cue processing, as compared to placebo (**Table 12, Figures 21, 22, and 23**). Although not statistically significant, visual inspection of the correlations between differences in self-reported methamphetamine craving between medication conditions and differences in functional connectivity parameter estimates between medication conditions suggests that stronger functional connectivity between frontal regions and the caudate (**Figure 24**) and precuneus (**Figure 25**) in the naltrexone (versus placebo) condition is trending towards an association with greater reductions in self-reported methamphetamine craving in the naltrexone (versus placebo) condition during methamphetamine cue processing. Further, stronger functional connectivity between the precuneus and parietal regions in the placebo (versus naltrexone) condition is trending towards an association with greater methamphetamine craving in the placebo (versus naltrexone) condition (**Figure 26**).

Discussion

Despite multiple legislative attempts to restrict access, methamphetamine remains a widely used drug in the United States, and a significant number of individuals develop methamphetamine problems following repeated use of the drug (SAMSHA, 2013). Psychosocial treatments for methamphetamine use disorders are modestly effective, but these treatments are extremely costly (Nicosia, et al., 2009) and hindered by clinically important caveats such as poor retention rates and the prerequisite of intact executive functioning abilities in the user (Baicy & London, 2007; Shearer, 2007). Given the profound evidence of biological alterations subserving the development of addiction, there is a great need for effective psychopharmacological treatments that target methamphetamine-affected pathways, yet no medications are currently approved by the FDA for the treatment of methamphetamine use disorder. A number of medications are currently under study; however, only a few have shown promise in early trials (Karila, et al., 2010).

The paucity of positive clinical outcomes in these pharmacological trials may be, in part, due to the heterogeneity of the methamphetamine use disorder diagnostic phenotype. Psychiatric research, including addiction research, has increasingly recognized the importance of studying more narrow and homogeneous intermediate phenotypes to circumvent the diagnostic heterogeneity issue (Gottesman & Gould, 2003; Gould & Gottesman, 2006; Hines, et al., 2005; Ray, Mackillop, et al., 2010). Specific to the study of drug addiction, craving appears to be a particularly valuable intermediate phenotype as it is widely held to be essential for understanding the pathogenesis and maintenance of addiction, as highlighted by the incentive salience model (Terry E. Robinson & Kent C. Berridge, 1993; Robinson & Berridge, 2001), and by the inclusion of craving as a criterion for a substance use disorder in the DSM-5 (American Psychiatric

Association, 2013) and the International Classification of Diseases (ICD-10; World Health Organization, 2010). Importantly, cue-induced craving has been shown to be reliably measurable in methamphetamine dependent individuals in the laboratory (Tolliver, et al., 2010) and appears to increase up to 3 months into abstinence (G. Wang, et al., 2013). Cue-induced methamphetamine craving has also been associated with psychophysiological changes, including altered heart rate variability (Culbertson, et al., 2010) and greater levels of blood-oxygen-level dependent (BOLD) activation in the anterior cingulate cortex (ACC), as compared to healthy controls, during pictorial methamphetamine-cue presentation (Yin, et al., 2012). Thus, drug cue-exposure paradigms implemented in the human laboratory represent an important tool for probing the clinical significance of drug craving and have high translational value to the naturalistic environment in so much that relapse to drug use is often precipitated by exposure to drug-related cues which provokes craving (O'Brien, et al., 1992).

The incentive salience model posits that addiction is largely caused by progressive neuroadaptation that results in sensitization following repeated drug use. This sensitization process is implicated to occur within the dopaminergic pathways that subserve attribution of motivational salience to mental representations of stimuli and actions (e.g., drug ingestion), thus rendering these stimuli highly salient and ultimately “wanted” or craved (K. C. Berridge & Robinson, 2003; Terry E. Robinson & Kent C. Berridge, 1993; Robinson & Berridge, 2001). Following sensitization of these pathways, the expression of incentive salience (i.e., craving) can be activated by the release of dopamine that is initiated in response to drug cues or priming doses of the drug itself (de Wit, 1996; Stewart, et al., 1984). Dopaminergic functioning within the striatum, particularly the dorsal striatum (B. J. Everitt & Robbins, 2005), is thought to be critically important for the development of incentive salience or craving for drugs (Volkow, et

al., 2006; Vollstadt-Klein, et al., 2010); however, functional interactions between the endogenous opioid and dopaminergic systems have also been implicated in the development of behavioral sensitization (including higher locomotor activity and stereotyped behaviors) to many drugs of abuse. With respect to methamphetamine specifically, increases in preproenkephalin mRNA expression and decreases in μ -opioid receptor levels in the dorsal and ventral striatum were observed in sensitized wild-type mice following 7 days of daily intraperitoneal injection (i.p.) methamphetamine injections, while no changes were observed in μ -opioid receptor knockout mice. These opioidergic changes were associated with altered dopaminergic functioning in the same striatal regions (Tien, et al., 2007) and highlight potential mechanisms by which the two systems interact to result in the experience of drug craving.

Naltrexone, an opioid receptor antagonist with greatest affinity for the μ - and κ -opioid receptors in humans (Emmerson, et al., 1994; Toll, et al., 1998), is arguably one of the most promising pharmacological treatments for methamphetamine use disorders given its associated effects on amphetamine addiction clinical outcomes (<2 ng/ml; Grant, et al., 2010; Jayaram-Lindstrom, Hammarberg, et al., 2008; Jayaram-Lindstrom, Konstenius, et al., 2008; Kelty, et al., 2013) and on behavioral markers of methamphetamine craving in preclinical samples (Anggadiredja, et al., 2004). Furthermore, the larger parent study ($n = 30$) from which the majority of the present sample was obtained demonstrated naltrexone-induced attenuation of cue-induced methamphetamine craving and reductions of several hedonic subjective effects of methamphetamine, such as stimulation and craving, as compared to placebo, during controlled methamphetamine (30mg) administration (Ray, Bujarski, et al., 2015). The reduction of drug craving has been advanced as a plausible mechanism subserving the efficacy of naltrexone in the treatment of various substance use disorders (e.g., Krupitsky, et al., 2011; Miranda, et al., 2013;

Monterosso, et al., 2001; Monti, et al., 1999; Ray, et al., 2008; Subbaraman, et al., 2013; Syed & Keating, 2013). Naltrexone is thought to modulate reward-/reinforcement-driven behavior via blocking dopamine release in the mesolimbic dopamine system, primarily driven by the pathway from the VTA to the NAcc (Benjamin, et al., 1993; Y. K. Lee, et al., 2005; Naleid, et al., 2005; Widdowson & Holman, 1992); however, this theory has not been directly tested in cue-induced craving, and other pathways may also be involved.

The present study is the first to employ a methamphetamine cue-exposure paradigm in humans as a tool for investigating neurological changes associated with methamphetamine addiction treatment. The primary aims of the present study were: (1) To determine whether naltrexone (50mg) versus placebo moderates BOLD measures of methamphetamine cue processing (i.e., cue-reactivity) and (2) to determine whether naltrexone's effect on methamphetamine cue-reactivity is associated with differential functional connectivity from reward-/reinforcement-related regions (ventral and dorsal striatum, ventral tegmental area [VTA]), regions expressing high opiodergic receptor site densities (VTA, periaqueductal gray [PAG]), and previously determined cue-reactive (precuneus) regions during methamphetamine cue processing, as compared to placebo. Additional exploratory aims included: (1) To determine the effect of naltrexone (50mg) on cerebral blood flow (CBF), as any CBF alterations by the medication represent a potential confound for the fMRI analyses and (2) to determine whether subjective reports of cue-induced methamphetamine craving are related to the neural markers of methamphetamine cue processing.

BOLD Task Results: Methamphetamine Cues > Control Cues

Given the lack of available methamphetamine cue-exposure paradigms for use in the functional magnetic resonance imaging (fMRI) environment, the present study developed a novel

pictorial methamphetamine cue-reactivity paradigm that was designed to elicit methamphetamine craving in individuals with methamphetamine use disorders, while also controlling for extraneous visual related processing. The increases in self-reported, subjective methamphetamine craving during the presentation of methamphetamine as compared to control cues during this paradigm highlight the initial efficacy of the task in generating cue-induced methamphetamine craving. Furthermore, the primary BOLD results depicted greater methamphetamine cue-elicited activation in regions that are commonly seen to be cue-reactive for other substances in dependent populations (e.g., middle frontal gyrus [MFG], ACC, posterior cingulate cortex [PCC]/precuneus, thalamus, insula, middle temporal gyrus [MTG], postcentral gyrus, inferior occipital cortex, and brain stem), as compared to control cue activation (Engelmann, et al., 2012; Schacht, Anton, et al., 2013b), suggestive of the effectiveness of this novel paradigm in producing relevant drug cue-elicited activation. In addition, commonly described “reward”- or “reinforcement”-related regions were also found to be activated to a greater extent during methamphetamine versus control cue presentation, including the left ventral striatum (NAcc), bilateral dorsal striatum (caudate, putamen), ventral tegmental area (VTA), hippocampus, and amygdala. These regions primarily rely on dopamine, GABA, opioid, and glutamate signaling and are theoretically important for the development of incentive salience (Kalivas & Volkow, 2005; Kauer & Malenka, 2007; Nestler, 2005).

The significant correlations observed between average self-reported, subjective methamphetamine craving and BOLD measures of methamphetamine cue-reactivity within the placebo condition add to the validity of the paradigm. Specifically, greater average subjective methamphetamine craving was associated with greater activation of prefrontal regions implicated in the regulation of motivational drives, including the inferior frontal gyrus (IFG) and

dorsolateral prefrontal cortex (dlPFC; Bechara, 2005; Koob & Volkow, 2010). Given that correlations between BOLD cue-reactivity and subjective craving are not reliably observed in the fMRI cue-reactivity literature (e.g., Courtney & Ray, 2014; Due, Huettel, Hall, & Rubin, 2002; Filbey et al., 2008; Heinz et al., 2004), the present results provide further evidence for this paradigm as an effective and naturalistic probe of methamphetamine cue-induced craving in individuals with methamphetamine use disorders.

Naltrexone Effects on Cerebral Blood Flow and Cue Processing

fMRI is becoming an increasingly popular tool for the investigation of pharmacological manipulations on functional brain processing due to its noninvasiveness, relatively wide availability, and lower cost as compared to positron emission tomography (PET; Ray, et al., in press; D. J. Wang, Chen, Fernandez-Seara, & Detre, 2011; Wise et al., 2002). However, BOLD fMRI is the result of a complex interaction between cerebral blood volume, oxygen consumption, and CBF, and pharmacologic manipulation can potentially occur at any or all of these levels (D. J. Wang, et al., 2011). In the present study, pseudo-continuous arterial spin labeling (pCASL) perfusion MRI, which is methodologically similar to ^{15}O -water PET, was used to detect potential changes in CBF due to the naltrexone manipulation. Importantly, no alterations in global grey matter CBF were observed on baseline brain functioning at target dose (50mg) of naltrexone when compared to placebo. This result adds credence to the interpretation of any observed naltrexone-induced BOLD effects as being the result of changes in oxygen consumption, presumably due to underlying pharmacological alterations in brain processing.

In fact, naltrexone was found to modulate cue-reactivity such that naltrexone treatment was associated with attenuated activation in sensorimotor (i.e., precentral and postcentral gyri) and visual (i.e., occipital cortex) regions during methamphetamine-cue processing, as compared

to placebo. Of the two studies that have directly compared naltrexone to placebo effects on whole-brain BOLD measures of drug cue-reactivity in alcohol and nicotine dependent samples, both reported naltrexone-induced changes in the precentral and postcentral gyri (Lukas et al., 2013; Ray, Courtney, et al., 2015), suggestive of the reliability of these naltrexone results in drug cue-reactivity paradigms across substances of abuse.

Naltrexone Effects on Functional Connectivity

Functional connectivity analyses offer a unique advantage over simple, main effects, BOLD fMRI analyses in that they allow for the observation of interactions between brain areas in addition to functional localization. Thus, the goal of functional connectivity analysis is to observe how information flows within brain networks across time or under different behavioral conditions (O'Reilly, et al., 2012). In the present study, psychophysiological interaction (PPI) analysis was used to probe the methamphetamine cue-reactivity networks that are affected by naltrexone.

Naltrexone-induced differences in functional connectivity during methamphetamine cue-processing were observed with a number of the a priori seed regions (i.e., PAG, VTA, precuneus, and caudate, but not NAcc). These regions were selected as seeds due to their purported roles in the reward/reinforcement network (i.e., NAcc and VTA; Camara, et al., 2009; Nestler, 2005; Ray, et al., 2013), high density of opioid receptor sites - the target of naltrexone (i.e., NAcc, PAG, and VTA; Halladay & Blair, 2012; Mansour, Fox, et al., 1995), and replicable involvement in neuroimaging studies of drug cue-reactivity (i.e., precuneus; Courtney, et al., 2014; Engelmann, et al., 2012; Schacht, Anton, et al., 2013b).

Periaqueductal gray (PAG) connectivity. Of the four a priori seed regions, only PAG functional connectivity was found to be modulated by naltrexone at the conservative statistical

threshold first tested (cluster-corrected $Z > 2.3$). Specifically, weaker connectivity between the PAG and occipital regions was observed in the naltrexone, as compared to placebo, condition during methamphetamine cue processing. Preclinical data suggests that the PAG innervates the majority of the cerebral cortex to varying degrees, including the occipital cortex (Herrero, Insausti, & Gonzalo, 1991), and that glutamatergic innervations from the occipital cortex to the PAG may be relevant for PAG functionality (Beitz, 1989). Either of these directional pathways may be affected in the present sample, as PPI analysis does not make inferences about the direction of information flow (O'Reilly, et al., 2012). For example, it is possible that naltrexone may be attenuating the ability of the PAG to communicate with the occipital cortex, or that normal glutamatergic communication from the occipital cortex to the PAG is suppressed while naltrexone is on board; however, given that the occipital cortex has very low opioid receptor site density, naltrexone is most likely effecting the direct pathway from the PAG to the occipital cortex (Herrero, et al., 1991), which may be mediated by modulation of the GABAergic network within the PAG (Behbehani, 1995). Thus, the present results potentially represent diminished processing of the visual methamphetamine cues under naltrexone treatment. Follow-up correlational analyses did not detect a relationship between PAG connectivity and self-reported craving, and as such, further research is needed to evaluate the directionality of the effects of naltrexone on PAG connectivity and to determine whether these effects are clinically meaningful.

Ventral tegmental area (VTA) connectivity. VTA functional connectivity during methamphetamine cue processing was also found to be moderated by naltrexone at the second threshold tested ($Z > 1.96$, cluster corrected). Specifically, naltrexone was associated with stronger VTA functional connectivity to prefrontal (including the ventral PFC and ACC), dorsal

striatal (caudate), and occipitoparietal (including the opercular cortex, angular gyrus, and supramarginal gyrus) regions, as compared to placebo. These results implicate naltrexone-modulated involvement of the mesocortical pathway, which contains direct dopaminergic and GABAergic projections from the VTA to the PFC (Carr & Sesack, 2000) and is thought to serve as a pathway for frontal regulation over midbrain salience attribution (Fields, Hjelmstad, Margolis, & Nicola, 2007; Goldstein & Volkow, 2011; Hare, Camerer, & Rangel, 2009). Preclinical evidence suggests that κ -opioid agonists inhibit cortically projecting VTA dopamine neurons (Margolis, et al., 2006), potentially via interactions with VTA GABAergic interneurons, which synapse locally onto dopaminergic neurons (Creed, Ntamati, & Tan, 2014); thus naltrexone's effects opioid receptors in the VTA could theoretically increase dopaminergic input to the PFC. Further, non-dopaminergic VTA projections, such as the glutamatergic and GABAergic projections to the PFC, have been associated with the establishment of opioid agonist positive reinforcement (Fields, et al., 2007; Sesack & Grace, 2010), advancing dopamine independent VTA-PFC pathways as additional plausible targets for naltrexone-induced modulation.

Given that both the PFC and VTA exhibit high opioid receptor binding potential (Baumgartner et al., 2006), naltrexone could potentially impact local functioning at either (or both) sites. For example, excitatory glutamatergic projections from the PFC to the VTA may also be involved, as these projections have been associated with the capacity of the VTA to detect and signal stimulus salience (Geisler, Derst, Veh, & Zahm, 2007). μ -opioid receptor agonists have been shown to decrease neocortical glutamatergic synaptic transmission via presynaptic inhibition of glutamate release (Ostermeier, Schlosser, Schwender, & Sutor, 2000), thus

advancing the possibility of naltrexone-induced enhancement of glutamatergic activity from the PFC to the VTA as well.

The VTA connectivity results also suggest naltrexone modulates the functional pathway connecting the VTA to the dorsal striatum. In addition to the high density of opioid receptors in the VTA, the medium-spiny neurons within the striatal striosomes express μ -opioid-receptors (White & Hiroi, 1998) and have direct projections to the substantia nigra and VTA, which contain direct dopaminergic and reciprocal GABAergic projections back to the dorsal striatum (McBride & Parker, 2015; Sesack & Grace, 2010; Swanson, 1982; Van Bockstaele & Pickel, 1995). The present findings suggest that naltrexone may be activating the GABAergic and/or dopaminergic pathways between the VTA and dorsal striatum to a greater degree than placebo; however, it remains unclear exactly how naltrexone would be operating within these regions to result in greater connectivity between them.

The greater involvement of the dorsal striatum, as opposed to ventral striatum, within this system is consistent with the hypothesized shift from ventral to dorsal striatum involvement in cues processing at later stages of addiction (Vollstadt-Klein, et al., 2010), as no naltrexone-moderated ventral striatal (NAcc) functional connectivity was observed with the NAcc as a seed region or within the VTA functional connectivity analyses in this sample of moderate to severe methamphetamine dependent individuals. Accumulating evidence suggests that once craving is automatic and well-learned, it can become independent of dopamine release in the NAcc (Barry J. Everitt & Robbins, 2013; McFarland & Kalivas, 2001; See, Elliott, & Feltenstein, 2007) and is instead related to dopaminergic increases of the dorsal striatum (B. J. Everitt & Robbins, 2005; Volkow, et al., 2006). Thus, further research is indicated on the clinical significance of naltrexone's effect on the VTA-dorsal striatal pathway during drug cue-reactivity.

In sum, the pattern of results observed in the present study suggests naltrexone may be enhancing communication between the VTA and PFC, dorsal striatum, and visual processing regions (Takada & Hattori, 1987) through modulatory actions on dopaminergic, GABAergic, and possibly glutamatergic pathways, resulting in greater frontal regulation of salience attribution (Fields, et al., 2007; Goldstein & Volkow, 2011; Hare, et al., 2009) and altered integration of visual information (Seghier, 2013) during methamphetamine cue processing.

Dorsal striatum (caudate) connectivity. Similar to the VTA results, naltrexone was associated with stronger caudate functional connectivity ($Z > 1.96$, cluster corrected) to prefrontal (including the ventromedial PFC, paracingulate gyrus, and ACC) and occipital (including the occipital pole and supracalcarine cortex) regions, as compared to placebo. Furthermore, medication-moderated caudate functional connectivity during methamphetamine cues processing was found to correlate with self-reported methamphetamine craving. Specifically, naltrexone was associated with stronger positive correlations between self-reported craving and caudate connectivity to fronto-parietal regions, as compared to placebo, potentially indicating greater recruitment of frontal involvement with dorsal striatal functioning during the experience of heightened subjective craving under naltrexone treatment.

The caudate-PFC functional connectivity results implicate naltrexone-modulated involvement of the frontal cortico-striatal circuit, which has been shown to become dysregulated by repeated psychostimulant use in preclinical samples (Canales & Graybiel, 2000; Miura, Masuda, & Aosaki, 2008; Saka, Goodrich, Harlan, Madras, & Graybiel, 2004). The frontal cortico-striatal circuit includes excitatory glutamatergic projections from the PFC to the dorsal striatal striosomes (Ferry, Ongur, An, & Price, 2000; McGeorge & Faull, 1989; Mink, 1998). Presynaptic μ -opioid receptors are found on glutamatergic and GABAergic terminals in the PFC,

and postsynaptic μ -opioid receptors are observed on layer V pyramidal cells that project to striatum (Steketee, 2003). Further, the striatal striosomes contain medium-spiny neurons and cholinergic interneurons, both of which express μ -opioid receptors (Jabourian et al., 2005; White & Hiroi, 1998). Thus, naltrexone could be modulating activity at multiple junctions along this pathway, potentially operating to normalize its functioning during methamphetamine cues processing in this sample of individuals with a methamphetamine use disorder.

Combined with the VTA-PFC and dorsal striatum-PFC functional connectivity results (see above), it is possible that naltrexone may be operating within this larger system to result in increased dopaminergic transmission from the VTA to PFC (via interaction with VTA κ -opioid receptors) and decreased inhibition of excitatory output from the PFC to the dorsal striatum, which would appear as enhanced functional connectivity between the VTA, PFC, and dorsal striatum. Given that inputs from the PFC to the dorsal striatum regulate the expression of reward driven decision-making (Apicella, 2002; Delgado, Stenger, & Fiez, 2004; Haber, Kim, Mailly, & Calzavara, 2006; Kitabatake, Hikida, Watanabe, Pastan, & Nakanishi, 2003), and that increased fronto-striatal connectivity is associated with greater frontal regulation over subcortical signals reflecting heightened reward sensitivity (Todd F. Heatherton & Wagner, 2011), these results again implicate greater frontal regulation of salience attribution is occurring during methamphetamine cue processing under naltrexone treatment (Goldstein & Volkow, 2011; Hare, et al., 2009). Further, naltrexone may be modulating the visual corticostriatal loop, which includes connections from the ventromedial occipital cortex to the caudate specifically (Seger, 2013; Yeterian & Pandya, 1995), which may represent altered visual information processing of the methamphetamine cues under naltrexone treatment.

Precuneus connectivity. Naltrexone was also associated with weaker precuneus functional connectivity ($Z > 1.96$, cluster corrected) to sensorimotor regions (superior parietal lobule, precentral gyrus, postcentral gyrus) during methamphetamine cue processing. Interestingly, the precentral and postcentral gyri were also observed to be differentially affected by naltrexone in the main effect mediation contrast, although the peak activation coordinates in the main effects analysis slightly differ from the connectivity results. Furthermore, naltrexone appears to diminish precuneus connectivity to parietal regions and enhance precuneus functional connectivity to frontal regions as craving increases during methamphetamine cue processing, as compared to placebo.

As stated in the introduction, the precuneus has been highlighted by multiple meta-analyses to be reliably involved in cue-reactivity for multiple substances of abuse. Specifically, the precuneus was identified, along with the posterior cingulate cortex (PCC) and superior temporal gyrus, as selectively affected by alcohol-cue presentation in samples of alcohol-dependent individuals (Schacht, Anton, et al., 2013b) and was also implicated in response to smoking cues in samples of daily smokers (Engelmann, et al., 2012). Greater precuneus activation during drug cue processing is associated with greater dependence on the substance (Courtney, et al., 2014), suggestive of the importance of this region in addiction development. The precuneus has strong, presumably GABAergic and glutamatergic, cortical interconnections to the PFC, as well as connections to the PCC, superior parietal lobule, the dorsal premotor area, the supplementary motor area, and the ACC (for a review see Cavanna & Trimble, 2006; Hu, Chen, Gu, & Yang, 2013); however, naltrexone is likely acting on the precuneus in the present study given its relatively greater opioid binding potential, as opposed to the sensorimotor regions (Baumgartner, et al., 2006).

Functionally, the precuneus is putatively involved in self-centered, mental imagery strategies and successful episodic memory retrieval (Cavanna & Trimble, 2006), both of which are likely to have a role in the phenomenology of craving. Thus, reduced functional connectivity between the precuneus and sensorimotor network under naltrexone treatment may reflect a reduced capacity for the integration of drug-cue information (Engelmann, et al., 2012), which appears to be important for the experience of subjective craving (as evinced by the correlational results). Further, naltrexone appears to be facilitating greater frontal involvement with the precuneus as subjective craving increases, again potentially reflecting the engagement of frontal regulatory mechanisms over mental imagery processing during the presentation of methamphetamine cues.

Summary of functional connectivity results. The culmination of results suggest that naltrexone modulates dorsal striatum (caudate), VTA, PAG, and precuneus communication with visual, sensory, and motor-related regions resulting in reduced activation of these regions during methamphetamine cues processing. Naltrexone also enhances dorsal striatum (caudate) and VTA communication with the frontal cortex during presentation of the cues (see **Figure 27** for a simplified pictorial summary of the functional connectivity results). Thus, naltrexone may be functioning to reduce the salience of the methamphetamine cues by reducing sensorimotor processing and integration and by engaging greater frontal regulation of salience attribution via dopaminergic, glutamatergic, and/or GABAergic pathways linking the dorsal striatum, midbrain, and precuneus to frontal, striatal, and sensorimotor regions during methamphetamine cue processing (Goldstein & Volkow, 2011; Hare, et al., 2009). This theory is also consistent with a previous report of naltrexone enhancing frontal engagement during a temporal discounting task in alcohol dependent and control subjects (Boettiger, Kelley, Mitchell, D'Esposito, & Fields,

2009), presumably reflecting greater fronto-striatal control over impulsive behavior (Courtney, Ghahremani, & Ray, 2013; Feil et al., 2010).

Importantly, at least some of these naltrexone-modulated frontal and sensorimotor functional pathways appear to be important for the experience of subjective methamphetamine craving. Naltrexone treatment appears to weaken the association between average subjective craving and precuneus functional connectivity with sensorimotor regions and strengthen the associations between average subjective craving and dorsal striatum and precuneus functional connectivity with frontal regions, as compared to placebo, during methamphetamine cue processing (see **Figure 25** for a simplified pictorial summary of the subjective craving relationships with functional connectivity). Successful self-regulation of craving is thought to be dependent on a balance of prefrontal and subcortical regions involved in reward and reinforcement, such that self-regulatory failures occur whenever the balance tips in favor of subcortical areas (Todd F. Heatherton & Wagner, 2011). Thus, naltrexone appears to be balancing prefrontal, subcortical, and parietal systems during methamphetamine cue processing, possibly via reductions of salience attribution in sensorimotor and reinforcement systems and enhancement of frontal control mechanisms.

Although the present study did not observe overall subjective craving reductions under naltrexone versus placebo treatment, the larger study from which the majority of the present participants were drawn did (Ray, Bujarski, et al., 2015). Trends, however, were observed between naltrexone-induced reductions in subjective methamphetamine craving and the naltrexone-induced enhancement of fronto-dorsal striatal/precuneus functional connectivity and diminished precuneus-parietal functional connectivity. Thus, with a larger sample, and/or the use of a more reliable subjective craving assessment, a direct relationship may be observable

between reduced subjective craving and altered frontal-striatal-parietal connectivity under naltrexone treatment. Further research on the neural changes associated with naltrexone treatment in individuals with methamphetamine use disorders is needed to clarify the roles of these regions and pathways in the instatement and regulation of methamphetamine cue-induced craving.

Clinical Significance and Future Directions

fMRI cue-reactivity paradigms represent an ideal platform to probe the involvement of neurobiological pathways subserving the incentive salience system in addiction (Ray, et al., in press). The novel methamphetamine cues task developed and tested in the present study demonstrated efficacy in this regard with respect to identifying the potential neural systems involved in methamphetamine cue-induced craving in a non-treatment seeking moderate to severe methamphetamine dependent sample. Thus, this paradigm is well-positioned to be applied to investigate other stages of addiction development, such as early problematic use of methamphetamine, or even prior to first exposure (e.g., the Adolescent Brain Cognitive Development Study), in order to gain insight into the neurobiological changes underlying the development of incentive salience and craving (K. C. Berridge & Robinson, 2003; Terry E. Robinson & Kent C. Berridge, 1993; Robinson & Berridge, 2001). Knowledge of these functional pathways may be useful for the classification of individuals who are at high risk for the development of addiction, and could potentially facilitate targeted treatment development by identifying new brain targets involved in craving instatement at the various stages of drug dependence.

In addition, the methamphetamine cues task was shown to be sensitive to naltrexone intervention. This finding highlights the potential utility of the task in medication development

for the treatment of methamphetamine use disorder. Given that BOLD measures of drug cue-reactivity have been shown to predict relapse propensity in treatment seeking patients (e.g., A. Beck et al., 2012; Kosten et al., 2006; Schacht, Anton, Randall, et al., 2013), the investigation of medications that alter BOLD measures of cue-reactivity has the potential to improve real-world clinical outcomes in addiction. For example, groups of individuals dependent on nicotine have been delineated based on BOLD markers of “reward sensitivity” during cue-processing, where the “low reward sensitivity” group, identified by greater cigarette-cue versus pleasant-cue activation in regions such as the precuneus, dorsal striatum, and PFC, were found to be more likely to relapse than the “high reward sensitivity” group at 6 month follow-up (Versace et al., 2013). Thus, BOLD measures of cue-reactivity could prove useful as a platform for testing medications for their ability to target this deficiency in reward sensitivity (or enhanced drug cue-reactivity), which may then facilitate improved outcomes in these “low reward sensitivity” individuals. Similarly, the development of agents that target and rescue deficient processes underlying the drug craving state, such as prefrontal cortical function, has been proposed to be a potentially valuable strategy in treatment development (Sinha, 2013). Lastly, BOLD measures of cue-reactivity could also prove beneficial in the identification of individuals that may respond better to specific medications, thus personalizing treatment based on patient-level characteristics. With respect to naltrexone, the results of the present study suggest that naltrexone alters regional connectivity that is related to the experience of subjective drug craving, and these medication-induced changes may be predictive of treatment outcomes, and thus aid treatment decisions, if tested longitudinally within a treatment seeking sample.

Future directions for the present study data. A number of opportunities remain to be explored with respect to the present study data. For example, all participants in this study also

completed an extended battery of neuropsychological functioning, including measures on executive functioning and various facets of impulsivity (e.g., temporal discounting, response inhibition, and risky-decision making). Correlations between BOLD markers of methamphetamine cue-processing and these neuropsychological assessments may shed light on the cognitive processes involved in methamphetamine cue-reactivity and add to our understanding of the neural correlates of neuropsychological impairments and impulsive behavior in methamphetamine use disorders. Further, subjective responses to intravenous infusions of methamphetamine under naltrexone and placebo conditions are available for a subset of the sample ($n = 16$; Ray, Bujarski, et al., 2015), which could be investigated to elucidate the relationships between acute drug effects and drug craving (Courtney & Ray, 2014), as well as the potential moderating effects of naltrexone on these clinically important relationships.

A number of opportunities for the application of further fMRI data analytic techniques also remain and could be used to address additional important questions. For example, contrast masking could be applied to the BOLD data, which would provide greater specificity on the direction of activation differences observed during methamphetamine versus control cue-processing and when comparing between the medication conditions. These analyses would help to decipher whether the methamphetamine cues and/or naltrexone are effectively “activating” or “deactivating” specific regions, which would add further clarification to the hypothesized neurobiological pathways underling the functional connectivity results. Advanced multi-voxel pattern analysis (MVPA) techniques such as machine learning classifiers could also be used in order to detect and track the state of cue-induced craving in methamphetamine addiction across time, locate where cue-induced craving is represented in the brain (with enhanced sensitivity compared to univariate approaches), and potentially identify an fMRI-based cue-reactivity

biomarker for methamphetamine addiction (L. Zhang, Samaras, Tomasi, Volkow, & Goldstein, 2005), the latter being a principal goal of psychiatric research in general (Fu & Costafreda, 2013).

Future directions of the candidate. The present study facilitated the candidate's development as a clinical psychologist with a focus on the clinical neuroscience of addiction. Through the execution of the dissertation study, the candidate acquired substantial knowledge on: (1) experimental study development and implementation, including acquiring necessary regulatory and institution approvals and abiding by appropriate guidelines, acquiring funding for the implementation of the study (i.e., a National Research Service Award fellowship from the National Institute on Drug Abuse, a pilot grant from the Staglin IMHRO Center for Cognitive Neuroscience, and a grant from the UCLA Clinical & Translational Research Center), administering assessment batteries and neuroimaging protocols, and managing undergraduate research assistants; (2) clinical science of addiction through direct interaction with a patient population, including the administration of structured diagnostic assessments, comprehensive neuropsychological assessments, and brief behavioral interventions to individuals with a methamphetamine use disorder; (3) advanced neuroimaging methods, including functional connectivity analyses and parametric/nonparametric permutation techniques; and (4) behavioral pharmacology through extensive literature research on the pharmacology of naltrexone, as well as the neurochemical systems subserving incentive salience and cue-reactivity.

With this training, the candidate will continue to seek experiences in the clinical science of addiction and experimental clinical neuroscience research through clinical training at the University of California, San Diego/Veterans Affairs San Diego Internship program, a post-doctoral fellowship in neuroimaging measures of addiction, and ultimately a faculty position at a

research-based institution with the goal of establishing an independent clinical neuroscience lab which investigates the neurobiological markers of addiction development and maintenance.

Study Strengths and Limitations

This study must be considered in light of its strengths and limitations. A major strength is the study design. The within-subjects, placebo-controlled design allowed for participants to serve as their own controls, effectively avoiding the issues related to comparing medication effects across participants that may have differential structural brain changes due to varying histories of methamphetamine use (S. Berman, et al., 2008). The investigation of potential naltrexone-induced alterations in cerebral blood flow (CBF) represents another strength of the study. Few pharmacological fMRI studies effectively test medication-related CBF changes despite evidence of an interaction between basal physiologic and metabolic states and task-induced BOLD changes (D. J. Wang, et al., 2011). An additional strength is the well-ascertained and clinically representative sample of individuals with moderate to severe methamphetamine use disorders. It is often difficult to recruit individuals with severe drug addiction for clinical neuroscience research, yet these are precisely the individuals with which addiction science aims to help. Thus, the demographics of the present sample support the generalizability of the study findings to the population of non-treatment seeking individuals with moderate to severe methamphetamine use disorders.

A limitation of the study is the relatively short duration of naltrexone treatment. Thirty or more days of daily naltrexone dosing is associated with improved clinical outcomes in the treatment of alcohol use disorders (Greenstein, Evans, McLellan, & O'Brien, 1983); however, more recent clinical data demonstrate equivalent, or even greater efficacy of acute naltrexone dosing, relative to daily maintenance, in reducing excessive alcohol intake (Hernandez-Avila et

al., 2006). Thus, it is possible that extended treatment of naltrexone could result in differences in medication-related cue-reactivity, as compared to the three-day dosing effects in the present study. An additional, analytic limitation of the present study is the use of anatomically defined regions of interest (ROIs) based on probabilistic atlases and from peak coordinates obtained from a meta-analysis (i.e., the PAG). Greater specificity and sensitivity could have been achieved by segmenting the seed ROIs for each subject individually (e.g., by hand drawing the regions or using an automated anatomical parcellation tool such as FSL's FIRST). However, the use of purely anatomical ROIs is a conservative approach (biasing towards the null hypothesis; Poldrack & Mumford, 2009) and therefore does not detract from the findings that were observed. Furthermore, some of the seed ROIs investigated (i.e., the NAcc and PAG) are quite small in area and as a result are difficult to segment. Lastly, the present study did not investigate medication-related differences in cue-reactivity between participants that expressed high and low levels of cue-reactivity or cue-induced craving. Although the correlational analyses attempted to address this issue, it is possible that a sample selected for high methamphetamine cue-reactivity (and/or cue-induced craving) would have offered greater power to detect subtler differences in naltrexone-induced changes.

Summary and Conclusions

The present study investigated the neurobiological effects of naltrexone on methamphetamine cue-reactivity in a sample of 23 non-treatment seeking individuals with methamphetamine use disorders. The culmination of results suggest that: (1) the novel methamphetamine cues task employed was successful in eliciting cue-induced craving and in activating the expected frontal, parietal, occipital, brain stem, and subcortical regions (e.g., ventral and dorsal striatum) during methamphetamine cues processing, (2) greater subjective

methamphetamine craving is related to enhanced recruitment of prefrontal regions (e.g., IFG, dlPFC) implicated in the regulation of motivational drives, (3) naltrexone moderates methamphetamine cue-reactivity in sensorimotor regions previously implicated to be affected by naltrexone in cue-reactivity studies for other drugs of abuse, (4) these BOLD results are not a reflection of global CBF changes induced by naltrexone, (5) naltrexone modulates dorsal striatum, VTA, PAG, and precuneus functional connectivity with visual, sensory, and motor-related regions resulting in reduced activation of these regions during methamphetamine cues processing, (6) naltrexone enhances dorsal striatum, VTA, and sensorimotor region functional connectivity with the frontal cortex during presentation of the cues, and (7) naltrexone weakens the associations between subjective craving and precuneus functional connectivity with sensorimotor regions, and strengthens the associations between subjective craving and dorsal striatum and precuneus functional connectivity with frontal regions during methamphetamine cue processing, as compared to placebo.

In conclusion, the results of this study provide the first evidence of naltrexone-induced changes in BOLD measures of methamphetamine cue-induced craving and suggest that naltrexone may be functioning to reduce the salience of the methamphetamine cues by reducing sensorimotor processing and integration, and by engaging greater frontal regulation of salience attribution during methamphetamine cue processing. These results also advance multiple neural mechanisms by which methamphetamine cue-induced craving may be instated, the knowledge of which may prove useful in the prediction of clinical outcomes and aid in the development and application of medications such as naltrexone for the treatment of methamphetamine use disorders.

Table 1. Diagnostic and Statistical Manual of Mental Disorders, versions IV and 5, criteria for methamphetamine use disorder.

<i>DSM-IV criteria for methamphetamine abuse</i>	<ol style="list-style-type: none"> 1. Recurrent methamphetamine use resulting in a failure to fulfill major role obligations at work, school, or home. 2. Recurrent methamphetamine use in situations in which it is physically hazardous. 3. Continued methamphetamine use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of methamphetamine. - Recurrent legal problems associated with methamphetamine use (<i>criterion not included in DSM-5</i>)
<i>DSM-IV criteria for methamphetamine dependence</i>	<ol style="list-style-type: none"> 4. Tolerance, the need for greater amounts of the methamphetamine to achieve the same intoxication level or desired effect.* 5. Withdrawal, physiological and cognitive maladaptive symptoms that occur when the blood concentration of methamphetamine declines after prolonged and heavy use of methamphetamine.* 6. Methamphetamine is often taken in larger amounts and/or over longer periods of time as intended. 7. Persistent desire or unsuccessful efforts to stop or cut down methamphetamine use. 8. Increased amount of time is spent consuming, obtaining, or recovering from the effects of methamphetamine. 9. Important occupational, social, or recreational activities are given up or reduced because of methamphetamine use. 10. Methamphetamine consumption continues despite the knowledge of having persistent or recurrent physiological and psychological difficulties (e.g., blackouts, depression, worsening of an ulcer).
<i>New DSM-5 criteria</i>	<ol style="list-style-type: none"> 11. Craving for methamphetamine.
DSM-5 Severity Rating	
Mild = 2 to 3 symptoms met	
Moderate = 4 to 6 symptoms met	
Severe = 7 to 11 symptoms met	

*Not counted as a symptom if prescribed by a physician

Table 2. Sample Characteristics of Study Completers.

Variable	Inpatient Sample (n=16)		Outpatient Sample (n=7)		Full Sample (n=23)	
	Frequency or Mean (SD)	Range	Frequency or Mean (SD)	Range	Frequency or Mean (SD)	Range
Age	36.63 (8.52)	23-48	30.29 (8.90)	20-46	34.70 (8.95)	20-48
Sex - Male/Female	12/4		5/2		17/6	
Ethnicity						
- Latino	6		2		8	
- Caucasian	6		2		8	
- African American	4		3		7	
Age of First MA Use	25.87 (10.51)	14-46	19.14 (5.27)	13-27	23.83 (9.64)	13-46
Years of MA Use	10.75 (8.55)	<1-31	11.14 (9.10)	2-26	10.87 (8.51)	<1-31
Current DSM-IV MA Dependence/Abuse	13/3		7/0		20/3	
Number of MA Use Days (past 30 days)	18.25 (8.74)	1-30	19.00 (7.53)	7-28	18.48 (8.23)	1-30
Education (years)	13.25 (3.71)	7-21	13.86 (2.19)	11-17	13.43 (3.29)	7-21
Shipley IQ (Standard Score)	95.50 (17.24)	56-126	85.86 (18.30)	51-108	92.56 (17.73)	51-126
Working Memory (Digit Span Score)	16.62 (4.51)	9-25	16.71 (3.55)	13-22	16.65 (4.16)	9-25
Current Drug Use						
- Alcohol (>1x month)	2		3		5	
- Marijuana	4		3		7	
- Opiates (Rx)	0		0		0	
- Stimulants (Rx)	0		0		0	
- Cocaine/Crack	0		0		0	
- Ecstasy	0		1		1	
- Heroin	0		0		0	
Cigarettes Per Day (past week)						
- Non-smoker (0)	5		1		6	
- Smoker (≥ 1 daily)	11		6		17	
FTND Score	5.18 (2.53)	1-12	5.60 (2.30)	2-8	5.31 (3.16)	1-12
- <4	5		1		6	
- ≥ 4	7		4		11	
Number of Alcohol Drinking Days (past 30 days)	1.31 (3.86)	0-15	2.00 (2.83)	0-6	1.52 (3.53)	0-15
Alcohol Drinks per Drinking Day (past 30 days)	5.53 (6.52)	1-13	3.33 (1.45)	2-5	4.43 (4.39)	1-13

Note: No differences between study samples were observed on any demographic variables or in medication randomization ($ps > 0.05$). Independent t-tests or Fisher's Exact Tests (due to expected values <5) were used to compare between studies.

Table 3. Locations of Methamphetamine (MA) Cue > Control Cue activation averaged across medication conditions (A), within the placebo (PLAC) condition (B), and within the naltrexone (NTX) condition (C). Analyses were whole-brain cluster-corrected at a raised threshold of $Z > 3.7$ (to enable separation of clusters), $p < 0.05$.

(A) Across Meds: MA Cue > Control Cue						
Cluster/Region	Hemi	Cluster Voxels	Z	x	y	z
Cluster 1: Occipital/Parietal Cortex [Posterior Cingulate Cortex/Precuneus]		38796				
- Superior Lateral Occipital Cortex	R/L		8.26/8.66	38/-36	-76/-82	20/14
- Middle Temporal Gyrus	L		8.01	-50	-62	2
- Inferior Lateral Occipital Cortex	R/L		7.89/7.90	36/-26	-76/-88	8/4
Cluster 2: Right Posterior Frontal Cortex		696				
- Precentral Gyrus/Inferior Frontal Gyrus	R		6.19	48	8	26
Cluster 3: Left Posterior Frontal Cortex		241				
- Precentral Gyrus	L		5.31	-48	2	26
Cluster 4: Prefrontal Cortex		212				
- Dorsolateral Prefrontal Cortex	R		5.24	44	36	10
Cluster 5: Bilateral Subcortical/Brain Stem [Thalamus/Caudate (L)/Anterior Cingulate Cortex/ Hippocampus/Periaqueductal Gray/ Ventral Tegmental Area]		94				
- Amygdala	R		4.53	24	-2	-18
Cluster 6: Right Posterior Frontal Cortex		85				
- Precentral Gyrus	R		5.01	26	-10	50
Cluster 7: Frontal Cortex [Anterior Cingulate Cortex]		45				
- Superior Frontal Gyrus/Middle Frontal Gyrus	L		4.58	-24	4	50
Cluster 8: Cerebellum		45				
- Cerebellum	R/L		4.97	0	-52	-30
Cluster 9: Left Posterior Frontal Cortex		41				
- Precentral Gyrus	R		4.38	-28	-6	46
(B) PLAC: MA Cue > Control Cue						
Cluster/Region	Hemi	Cluster Voxels	Z	x	y	z
Cluster 1: Left Occipital/Posterior Parietal Cortex/Bilateral Subcortical Regions [Hippocampus/Caudate (L)/Thalamus/ Amygdala]		12632				
- Superior Lateral Occipital Cortex	L		7.69	-36	-82	14
- Inferior Lateral Occipital Cortex	L		6.82	-26	-88	2

- Middle Temporal Gyrus	L		6.80	-50	-62	2
- Superior Parietal Lobule	L		6.76	-28	-48	42
Cluster 2: Right Occipital Cortex		10118				
- Superior Lateral Occipital Cortex	R		7.11	24	-68	34
- Inferior Lateral Occipital Cortex	R		6.79	40	-80	8
- Occipital Fusiform Gyrus	R		6.78	38	-62	-12
Cluster 3: Medial Frontal Cortex		790				
- Anterior Cingulate Gyrus	R/L		5.48/5.84	4/-2	42/38	2/4
- Frontal Medial Cortex	L		5.06	-2	54	-14
- Medial Frontopolar Cortex	L		5.03	-2	62	8
- Paracingulate Gyrus	R/L		4.96/4.75	4/-2	54/46	4/-10
Cluster 4: Right Posterior Frontal Cortex (Medial)		529				
- Precentral Gyrus/Inferior Frontal Gyrus	R		5.63	48	8	26
Cluster 5: Anterior Cingulate Cortex (Posterior)		359				
- Anterior Cingulate Cortex	L		6.08	-2	2	26
Cluster 6: Brain Stem Regions		168				
- Periaqueductal Gray	R/L		4.55/4.87	8/-4	-30/-30	-4/-16
- Ventral Tegmental Area	L		4.19	-4	-26	-10
Cluster 7: Left Posterior Frontal Cortex (Dorsal)		158				
- Precentral Gyrus	R		5.58	26	-10	52
- Superior Frontal Gyrus	R		4.05	24	2	50
Cluster 8: Left Posterior Frontal Cortex (Medial)		96				
- Precentral Gyrus	L		4.92	-50	2	26
Cluster 9: Right Posterior Frontal Cortex (Dorsal)		69				
- Middle Frontal Gyrus	L		4.73	-28	32	54
- Superior Frontal Gyrus	L		4.27	-24	22	52
Cluster 10: Anterior Parietal Cortex		61				
- Supramarginal Gyrus	R		4.52	56	-26	36
- Supramarginal Gyrus/Postcentral Gyrus	R		4.15	56	-20	34
- Parietal Operculum Cortex	R		4.03	48	-24	26
Cluster 11: Posterior Cingulate Cortex		56				
- Posterior Cingulate Cortex	R		4.23	14	-38	32
Cluster 12: White Matter/Precentral Gyrus		48				
- White Matter/Precentral Gyrus	L		4.69	-30	-12	40
Cluster 13: Amygdala		42				
- Amygdala	R		4.48	26	-4	-18
Cluster 14: Insula		41				
- Insula	L		4.41	-38	8	-12
- Temporal Pole	L		3.97	-36	2	-20

(C) NTX: MA Cue > Control Cue

Cluster/Region	Hemi	Cluster Voxels	Z	x	y	z
Cluster 1: Right Occipital Cortex		5987				

- Superior Lateral Occipital Cortex	R		6.78	38	-76	20
- Inferior Lateral Occipital Cortex	R		6.24	36	-76	8
Cluster 2: Left Occipital Cortex		4677				
- Superior Lateral Occipital Cortex	L		6.67	-36	-82	14
- Inferior Lateral Occipital Cortex	L		6.42	-48	-64	2
- Occipital Fusiform Gyrus	L		6.11	-40	-66	-10
Cluster 3: Posterior Parietal Cortex		1233				
- Precuneus	L		5.41	-4	-52	10
- Posterior Cingulate Gyrus	L		5.40	-2	-36	32
- Hippocampus	L		4.85	-24	-32	-6
- Lingual Gyrus	L		4.81	-4	-64	2
Cluster 4: Cerebellum		98				
- Cerebellum	L		4.94	-6	-74	-26
- Lingual Gyrus	L		4.12	2	-86	-24
Cluster 5: Dorsal Prefrontal Cortex		78				
- Dorsal Prefrontal Cortex	L		4.51	-18	40	42
Cluster 6: Medial Prefrontal Cortex		75				
- Medial Frontopolar Cortex	L		5.02	-4	64	0
Cluster 7: Thalamus		74				
- Thalamus	L		4.98	0	-8	4
Cluster 8: Dorsal Prefrontal Cortex		73				
- Middle Frontal Gyrus/Superior Frontal Gyrus	L		4.67	-26	24	50
Cluster 9: Anterior Cingulate Cortex		57				
- Anterior Cingulate Cortex	R/L		4.03/4.83	2/-2	44/40	4/4
- Paracingulate Gyrus	L		4.38	-4	46	8
Cluster 10: Dorsal Parietal Lobe		56				
- Anterior Supramarginal Gyrus	R		4.88	62	-20	36
Cluster 11: Anterior Cingulate Cortex (Posterior)		46				
- Anterior Cingulate Cortex	R		3.91	2	-2	32

Note: X, Y, and Z MNI coordinates indicate the location of peak voxel activation (or local maxima for subregions) within each cluster. R, right, L, left.

Table 4. Locations showing a moderation effect of medication (placebo [PLAC] > naltrexone [NTX]) on Methamphetamine (MA) Cue > Control Cue activation. No regions of significant activation were found for NTX > PLAC. Analyses were whole-brain cluster-corrected at $Z > 2.3$, $p < 0.05$.

MA Cue > Control Cue - PLAC > NTX						
Cluster/Region	Hemi	Cluster Voxels	Z	x	y	z
Cluster 1: Right Frontoparietal Regions		1694				
- Postcentral Gyrus	R		4.30	40	-24	60
- Precentral Gyrus	R		4.24	48	-8	56
- Precentral Gyrus/Supplementary Motor Cortex	R		3.77	4	-14	64
- Postcentral Gyrus/Superior Parietal Lobule	L		3.70	-10	-50	70
Cluster 2: Left Frontoparietal Regions		595				
- Postcentral Gyrus	L		4.48	-34	-22	42
- Precentral Gyrus	L		3.47	-26	-20	72
Cluster 3: Occipital Cortex		383				
- Superior Lateral Occipital Cortex	L		4.04	-22	-80	42

Note: X, Y, and Z MNI coordinates indicate the location of peak voxel activation (or local maxima for subregions) within each cluster. R, right, L, left.

Table 5. Locations of significant positive Methamphetamine (MA) Cue > Control Cue activation correlations with average in-scanner self-reported methamphetamine craving averaged across medication condition (A), and within the placebo (PLAC) condition (B). No significant correlations were observed within the naltrexone (NTX) condition, or when contrasting medications (PLAC > NTX, or NTX > PLAC), and no negative correlations were found in any model. Analyses were whole-brain cluster-corrected at $Z > 2.3$, $p < 0.05$.

(A) Across Meds Positive Correlation with Craving: MA Cue > Control Cue						
Cluster/Region	Hemi	Cluster Voxels	Z	x	y	z
Cluster 1: Inferior Occipital Cortex		1121				
- Occipital Cortex/Intracalcarine Cortex	R		3.59	8	-90	4
- Occipital Fusiform Gyrus	L		3.46	-14	-90	-18
- Lingual Gyrus	R		3.42	18	-76	-2
Cluster 2: Superior Occipital Cortex		441				
- Superior Lateral Occipital Cortex	R		3.60	34	-62	40
- Precuneus Cortex	R		3.44	14	-58	46
(B) PLAC Positive Correlation with Craving: MA Cue > Control Cue						
Cluster/Region	Hemi	Cluster Voxels	Z	x	y	z
Cluster 1: Occipital Cortex		1026				
- Intracalcarine Cortex	R		3.83	14	-64	4
- Lingual Gyrus	R		3.43	18	-76	-4
- Occipital Fusiform Gyrus	R		3.31	20	-80	-16
- Occipital Cortex	R		3.21	6	-92	2
Cluster 2: Prefrontal Cortex		352				
- Middle Frontal Gyrus	L		3.96	-48	34	30
- Dorsolateral Prefrontal Cortex	L		3.42	-50	38	20
- Inferior Frontal Gyrus	L		3.19	-48	34	2

Note: X, Y, and Z MNI coordinates indicate the location of peak voxel activation (or local maxima for subregions) within each cluster. R, right, L, left.

Table 6. A priori region of interest (ROI) parameter estimates and significance tests from the Methamphetamine (MA) Cue > Control Cue contrast across medication conditions (A), within the placebo (PLAC) condition (B), and within the naltrexone (NTX) condition (C). No significant differences were observed between medication conditions for any ROI.

(A) Across Meds ROI: MA Cue > Control Cue					
Region	Mean	SD	SE	One Sample <i>t</i>	<i>p</i>
Bilateral Nucleus Accumbens	2.877	8.979	1.872	1.537	0.139
Bilateral Caudate	7.272	6.946	1.448	*	*
Ventral Tegmental Area	6.227	9.812	2.046	3.043	0.006
Periaqueductal Gray	10.621	8.429	1.758	6.043	<0.001
Precuneus	12.989	10.420	2.173	*	*
(B) PLAC ROI: MA Cue > Control Cue					
Bilateral Nucleus Accumbens	5.420	13.620	2.840	1.910	0.069
Bilateral Caudate	9.812	11.736	2.447	4.010	0.001
Ventral Tegmental Area	4.435	12.845	2.678	1.656	0.112
Periaqueductal Gray	10.969	13.981	2.915	3.763	0.001
Precuneus	13.375	18.450	3.847	3.477	0.002
(C) NTX ROI: MA Cue > Control Cue					
Bilateral Nucleus Accumbens	0.333	13.776	2.872	0.116	0.909
Bilateral Caudate	4.731	10.063	2.098	2.255	0.034
Ventral Tegmental Area	8.019	11.538	2.406	3.333	0.003
Periaqueductal Gray	10.273	12.424	2.591	3.966	0.001
Precuneus	12.602	15.414	3.214	3.921	0.001

Note: *Statistics not appropriate for these ROIs given they were functionally constrained by the contrast of interest (MA > Control Cues, averaged across medication conditions).

Table 7. Locations showing a moderation effect of medication (placebo [PLAC] > naltrexone [NTX]) on periaqueductal gray (PAG) functional connectivity within the Methamphetamine (MA) Cue > Control Cue contrast. Results are from the psychophysiological interaction (PPI) analysis using the PAG defined as a 3mm radius sphere around the MNI coordinates: $x = -4$, $y = -29$, $z = -12$ (see methods). Analyses were whole-brain cluster-corrected at $Z > 2.3$, $p < 0.05$. No regions of significant PAG functional connectivity were observed for the reverse contrast (NTX > PLAC).

PAG PPI: MA Cue > Control Cue – PLAC > NTX						
Cluster/Region	Hemi	Cluster Voxels	Z	x	y	z
Cluster 1: Occipital Cortex		827				
- Occipital Fusiform Gyrus	L		3.49	-18	-80	-12
- Intracalcarine Cortex	R/L		2.94/3.12	16/-14	-88/-84	8/4
- Occipital Pole	R/L		2.88/3.10	8/-18	-90/-88	8/10
- Lingual Gyrus	L		3.10	-16	-88	-2

Note: X, Y, and Z MNI coordinates indicate the location of peak voxel activation (or local maxima for subregions) within each cluster. R, right, L, left.

Table 8. Locations showing a moderation effect of medication (placebo [PLAC] > naltrexone [NTX]) on precuneus functional connectivity within the Methamphetamine (MA) Cue > Control Cue contrast. Results are from the psychophysiological interaction (PPI) analysis using the precuneus as a functionally constrained, anatomically defined region of interest (see methods). Analyses were whole-brain cluster-corrected at $Z > 1.96$, $p < 0.05$. No regions of significant precuneus functional connectivity were observed for the reverse contrast (NTX > PLAC).

Precuneus PPI: MA Cue > Control Cue – PLAC > NTX						
Cluster/Region	Hemi	Cluster Voxels	Z	x	y	z
Cluster 1: Frontoparietal Regions		1226				
- Superior Parietal Lobule	L		3.37	-22	-46	48
- Postcentral Gyrus	L		3.26	-24	-28	64
- Precentral Gyrus	L		2.84	-10	-26	46

Note: X, Y, and Z MNI coordinates indicate the location of peak voxel activation (or local maxima for subregions) within each cluster. R, right, L, left.

Table 9. Locations showing a moderation effect of medication (naltrexone [NTX] > placebo [PLAC]) on ventral tegmental area (VTA) functional connectivity within the Methamphetamine (MA) Cue > Control Cue contrast. Results are from the psychophysiological interaction (PPI) analysis using the VTA as an anatomically defined region of interest (see methods). Analyses were whole-brain cluster-corrected at $Z > 1.96$, $p < 0.05$. No regions of significant VTA functional connectivity were observed for the reverse contrast (PLAC > NTX).

VTA PPI: MA Cue > Control Cue – NTX > PLAC

Cluster/Region	Hemi	Cluster Voxels	Z	x	y	z
Cluster 1: Prefrontal Cortex		1679				
- Ventromedial Prefrontal Cortex/Caudate (R)	L		3.21	-8	54	-6
- Paracingulate Gyrus	L		3.18	-12	28	26
- Ventrolateral Prefrontal Cortex	L		3.13	-24	48	2
- Anterior Cingulate Cortex	R		2.94	8	24	22
Cluster 2: Temporoparietal Regions		1111				
- Central Opercular Cortex/Angular Gyrus	R		3.27	42	-14	18
- Planum Temporale	R		3.26	42	-28	16
- Parietal Operculum Cortex	R		2.97	52	-34	26
- Posterior Supramarginal Gyrus	R		2.85	62	-40	26

Note: X, Y, and Z MNI coordinates indicate the location of peak voxel activation (or local maxima for subregions) within each cluster. R, right, L, left.

Table 10. Locations showing a moderation effect of medication (naltrexone [NTX] > placebo [PLAC]) on dorsal striatum functional connectivity within the Methamphetamine (MA) Cue > Control Cue contrast. Results are from the psychophysiological interaction (PPI) analysis using the caudate as a functionally constrained, anatomically defined region of interest (see methods). Analyses were whole-brain cluster-corrected at $Z > 1.96$, $p < 0.05$. No regions of significant caudate functional connectivity were observed for the reverse contrast (PLAC > NTX).

Caudate PPI: MA Cue > Control Cue – NTX > PLAC						
Region	Hemi	Cluster Voxels	Z	x	y	z
Cluster 1: Occipital Cortex		2195				
- Occipital Pole	R		3.52	8	-92	12
- Supracalcarine Cortex	R		3.04	2	-78	18
- Cerebellum	L		3.03	-14	-66	-24
Cluster 2: Prefrontal Cortex		1051				
- Anterior Cingulate Cortex	L		3.58	-8	34	18
- Ventromedial Prefrontal Cortex	R		3.03	10	60	0
- Paracingulate Gyrus	R/L		2.80/2.81	10/-2	32/46	28/16

Note: X, Y, and Z MNI coordinates indicate the location of peak voxel activation (or local maxima for subregions) within each cluster. R, right, L, left.

Table 11. Locations showing a moderation effect of medication (naltrexone [NTX] > placebo [PLAC]) on slope values predicting dorsal striatal functional connectivity within the Methamphetamine (MA) Cue > Control Cue contrast from average self-reported MA craving during the task. Results are from the psychophysiological interaction (PPI) analysis using the caudate as a functionally constrained, anatomically defined region of interest (see methods). Analyses were whole-brain cluster-corrected at $Z > 1.96$, $p < 0.05$. No significant correlations were observed for the reverse contrast (PLAC > NTX).

Caudate PPI and MA Craving: MA Cue > Control Cue – NTX > PLAC						
Region	Hemi	Cluster Voxels	Z	x	y	z
Cluster 1: Frontoparietal Regions		1053				
- Precentral Gyrus	L		3.49	-34	8	30
- Middle Frontal Gyrus	L		3.42	-46	14	32
- Inferior Frontal Gyrus	L		3.28	-38	14	26

Note: X, Y, and Z MNI coordinates indicate the location of peak voxel activation (or local maxima for subregions) within each cluster. R, right, L, left.

Table 12. Locations showing a moderation effect of medication (placebo [PLAC] > naltrexone [NTX], [A]; NTX > PLAC, [B]) on slope values predicting precuneus functional connectivity within the Methamphetamine (MA) Cue > Control Cue contrast from average self-reported MA craving during the task. Results are from the psychophysiological interaction (PPI) analysis using the precuneus as a functionally constrained, anatomically defined region of interest (see methods). Analyses were whole-brain cluster-corrected at $Z > 1.96$, $p < 0.05$.

(A) Precuneus PPI and MA Craving: MA Cue > Control Cue – PLAC > NTX						
Cluster/Region	Hemi	Cluster Voxels	Z	x	y	z
Cluster 1: Parietal Cortex		991				
- Superior Parietal Lobule	R		3.78	36	-40	66
- Postcentral Gyrus	R		3.32	48	-32	58
(B) Precuneus PPI and MA Craving: MA Cue > Control Cue – NTX > PLAC						
Cluster/Region	Hemi	Cluster Voxels	Z	x	y	z
Cluster 1: Frontal Cortex		1617				
- Paracingulate Gyrus/Superior Frontal Gyrus	R		3.51	2	30	44
- Precentral Gyrus	R		3.44	40	6	30
- Middle Frontal Gyrus	R		2.91	32	8	46
- Paracingulate Gyrus	L		2.89	-4	20	48

Note: X, Y, and Z MNI coordinates indicate the location of peak voxel activation (or local maxima for subregions) within each cluster. R, right, L, left.

Figure 1. Study and recruitment flowchart.

Figure 2. Examples of the methamphetamine (MA) and control cue visual stimuli within the three picture subtypes used for the Methamphetamine Cues Task.

MA Cues

Drug

Paraphernalia

Consumption

Control Cues

Figure 3. Schematic of the Methamphetamine Cues Task.

Methamphetamine or Control Cues				Rate Urge
5 sec	5 sec	5 sec	5 sec	Response or 10 sec	10 sec rest + remaining response time

Figure 4. A priori region of interest (ROI) masks. Nucleus accumbens = red; caudate = purple; ventral tegmental area = yellow; periaqueductal gray = green; precuneus = blue.

Figure 5. Line plot of self-reported craving during the Methamphetamine Cues Task within medication conditions. Solid lines represent methamphetamine (MA) cues and dashed lines represent control cues.

Figure 6. Methamphetamine (MA) Cue > Control Cue activation averaged across medication conditions (see Table 3A for list of regions). Z-statistic maps are whole-brain cluster-corrected, $Z > 2.3$, $p = 0.05$. Coordinates are in MNI space, and the brain is displayed in radiological convention (left = right).

Figure 7. Methamphetamine (MA) Cue > Control Cue activation within the placebo (PLAC) condition (see Table 3B for list of regions). Z-statistic maps are whole-brain cluster-corrected, $Z > 2.3$, $p = 0.05$. Coordinates are in MNI space, and the brain is displayed in radiological convention (left = right).

Figure 8. Methamphetamine (MA) Cue > Control Cue activation within the naltrexone (NTX) condition (see Table 3C for list of regions). Z-statistic maps are whole-brain cluster-corrected, $Z > 2.3$, $p = 0.05$. Coordinates are in MNI space, and the brain is displayed in radiological convention (left = right).

Figure 9. Grey matter cerebral blood flow (CBF) estimates within the placebo and naltrexone conditions.

Figure 10. Methamphetamine (MA) Cue > Control Cue activation that is moderated by medication (placebo [PLAC] > naltrexone [NTX]; see Table 4 for list of regions). Z-statistic maps are whole-brain cluster-corrected, $Z > 2.3$, $p = 0.05$. Coordinates are in MNI space, and the brain is displayed in radiological convention (left = right).

Figure 11. Effect size estimates (in Cohen's d) for medication-moderated Methamphetamine (MA) Cue > Control Cue activation.

Regions where placebo (PLAC) > naltrexone (NTX) are represented by hot colors, and regions where NTX > PLAC are represented by cool colors. The brain is displayed in radiological convention (left = right).

Figure 12. Methamphetamine (MA) Cue > Control Cue activation averaged across medication conditions that is positively correlated with average self-reported methamphetamine craving (see Table 5A for list of regions). Z-statistic maps are whole-brain cluster-corrected, $Z > 2.3$, $p = 0.05$. Coordinates are in MNI space, and the brain is displayed in radiological convention (left = right).

Figure 13. Methamphetamine (MA) Cue > Control Cue activation averaged within the placebo (PLAC) condition that is positively correlated with average self-reported methamphetamine craving (see Table 5B for list of regions). Z-statistic maps are whole-brain cluster-corrected, $Z > 2.3$, $p = 0.05$. Coordinates are in MNI space, and the brain is displayed in radiological convention (left = right).

Figure 14. Bar graph of a priori region of interest (ROI) parameter estimates from the Methamphetamine (MA) Cue > Control Cue contrast averaged across medication conditions and within the placebo and naltrexone condition (see Table 6 for means and standard deviations). NAcc = nucleus accumbens, VTA = ventral tegmental area, PAG = periaqueductal gray. # $p < 0.10$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, n/a = statistics not reported given how the caudate and precuneus ROIs were defined (see methods).

Figure 15. Regions of medication moderated (placebo [PLAC] > naltrexone [NTX]) periaqueductal gray (PAG) functional connectivity within the Methamphetamine (MA) Cue > Control Cue contrast (see Table 7 for list of regions). Results are from the psychophysiological interaction (PPI) analysis using the PAG as the seed region of interest, defined as a 3mm radius sphere around the MNI coordinates: $x = -4/4$, $y = -29$, $z = -12$ (see methods). No regions of significant PAG functional connectivity were observed for the reverse contrast (NTX > PLAC). Z-statistic maps are whole-brain cluster-corrected, $Z > 2.3$, $p = 0.05$. Coordinates are in MNI space, and the brain is displayed in radiological convention (left = right).

Figure 16. Regions of medication moderated (placebo [PLAC] > naltrexone [NTX]) precuneus functional connectivity within the Methamphetamine (MA) Cue > Control Cue contrast (see Table 8 for list of regions). Results are from a psychophysiological interaction (PPI) analysis using the precuneus as a functionally constrained, anatomically defined seed region of interest (see methods). No regions of significant precuneus functional connectivity were observed for the reverse contrast (NTX > PLAC). Z-statistic maps are whole-brain cluster-corrected, $Z > 1.96$, $p = 0.05$. Coordinates are in MNI space, and the brain is displayed in radiological convention (left = right).

Figure 17. Regions of medication moderated (naltrexone [NTX] > placebo [PLAC]) ventral tegmental area (VTA) functional connectivity within the Methamphetamine (MA) Cue > Control Cue contrast (see Table 9 for list of regions). Results are from a psychophysiological interaction (PPI) analysis using the VTA as an anatomically defined seed region of interest (see methods). No regions of significant VTA functional connectivity were observed for the reverse contrast (PLAC > NTX). Z-statistic maps are whole-brain cluster-corrected, $Z > 1.96$, $p = 0.05$. Coordinates are in MNI space, and the brain is displayed in radiological convention (left = right).

Figure 18. Regions of medication moderated (naltrexone [NTX] > placebo [PLAC]) dorsal striatum functional connectivity with the Methamphetamine (MA) Cue > Control Cue contrast (see Table 10 for list of regions). Results are from a psychophysiological interaction (PPI) analysis using the caudate as an anatomically defined seed region of interest (see methods). No regions of significant caudate functional connectivity were observed for the reverse contrast (PLAC > NTX). Z-statistic maps are whole-brain cluster-corrected, $Z > 1.96$, $p = 0.05$. Coordinates are in MNI space, and the brain is displayed in radiological convention (left = right).

Figure 19. Regions of dorsal striatum functional connectivity within the Methamphetamine (MA) Cue > Control Cue contrast that correlated with average self-reported methamphetamine craving and differed between medication conditions (see Table 11 for list of regions). Brain regions whose connectivity with the caudate correlated with craving to a greater degree in the naltrexone (NTX) condition as compared to the placebo (PLAC) condition are shown (NTX > PLAC). No significant correlations were observed for the reverse contrast (PLAC > NTX). Results are from a psychophysiological interaction (PPI) analysis using the caudate as a functionally constrained, anatomically defined seed region of interest (see methods). Z-statistic maps are whole-brain cluster-corrected, $Z > 1.96$, $p = 0.05$. Coordinates are in MNI space, and the brain is displayed in radiological convention (left = right).

Figure 20. Scatterplot depicting the relationships between medication-moderated dorsal striatum functional connectivity (naltrexone [NTX] > placebo [PLAC]) and average self-reported methamphetamine craving within the Methamphetamine (MA) Cue > Control Cue contrast. Correlations are depicted for the within-subject differences in functional connectivity parameter estimates between medication conditions (NTX-PLAC). Parameter estimates were extracted for each subject and medication condition from the region that displayed greater NTX versus PLAC correlations with self-reported craving in the psychophysiological interaction (PPI) analysis using the caudate as a seed (see Table 12 and Figure 19). This figure is presented to enable easier visualization of the relationships only (no statistics can be estimated).

Figure 21. Regions of precuneus functional connectivity within the Methamphetamine (MA) Cue > Control Cue contrast that correlated with average self-reported methamphetamine craving and differed between medication conditions (see Table 12 for list of regions). Brain regions whose connectivity with the precuneus correlated with craving to a greater degree in the placebo (PLAC) condition, as compared to the naltrexone (NTX) condition, are shown in hot colors (PLAC > NTX), whereas regions whose connectivity with the precuneus correlated with craving to a greater degree in the NTX condition are shown in cool colors (NTX > PLAC). Results are from a psychophysiological interaction (PPI) analysis using the precuneus as a functionally constrained, anatomically defined seed region of interest (see methods). Z-statistic maps are whole-brain cluster-corrected, $Z > 1.96$, $p = 0.05$. Coordinates are in MNI space, and the brain is displayed in radiological convention (left = right).

Figure 22. Scatterplot depicting the relationships between medication-moderated precuneus functional connectivity (placebo [PLAC] > naltrexone [NTX]) and average self-reported methamphetamine craving within the Methamphetamine (MA) Cue > Control Cue contrast. Correlations are depicted for the within-subject differences in functional connectivity parameter estimates between medication conditions (PLAC-NTX). Parameter estimates were extracted for each subject and medication condition from the region that displayed greater PLAC versus NTX correlations with self-reported craving in the psychophysiological interaction (PPI) analysis using the precuneus as a seed (see Table 12 and Figure 21). This figure is presented to enable easier visualization of the relationships only (no statistics can be estimated).

Figure 23. Scatterplot depicting the relationships between medication-moderated precuneus functional connectivity (naltrexone [NTX] > placebo [PLAC]) and average self-reported methamphetamine craving within the Methamphetamine (MA) Cue > Control Cue contrast. Correlations are depicted for the within-subject differences in functional connectivity parameter estimates between medication conditions (NTX-PLAC). Parameter estimates were extracted for each subject and medication condition from the region that displayed greater NTX versus PLAC correlations with self-reported craving in the psychophysiological interaction (PPI) analysis using the precuneus as a seed (see Table 12 and Figure 21). This figure is presented to enable easier visualization of the relationships only (no statistics can be estimated).

Figure 24. Scatterplot depicting the within-subject trends between differences in dorsal striatum functional connectivity between medication conditions (naltrexone [NTX] - placebo [PLAC]) and differences in self-reported methamphetamine craving between conditions (NTX - PLAC) within the Methamphetamine (MA) Cue > Control Cue contrast. Parameter estimates were extracted for each subject and medication condition from the region that displayed greater NTX versus PLAC correlations with *average* self-reported craving in the psychophysiological interaction (PPI) analysis using the caudate as a seed (see Table 12 and Figure 19). This figure is presented to enable easier visualization of the relationships only (no statistics can be estimated).

Figure 25. Scatterplot depicting the within-subject trends between differences in precuneus functional connectivity between medication conditions (naltrexone [NTX] - placebo [PLAC]) and differences in self-reported methamphetamine craving between conditions (NTX - PLAC) within the Methamphetamine (MA) Cue > Control Cue contrast. Parameter estimates were extracted for each subject and medication condition from the region that displayed greater NTX versus PLAC correlations with *average* self-reported craving in the psychophysiological interaction (PPI) analysis using the precuneus as a seed (see Table 12 and Figure 19). This figure is presented to enable easier visualization of the relationships only (no statistics can be estimated).

Figure 26. Scatterplot depicting the within-subject trends between differences in precuneus functional connectivity between medication conditions (placebo [PLAC] - naltrexone [NTX]) and differences in self-reported methamphetamine craving between conditions (PLAC – NTX) within the Methamphetamine (MA) Cue > Control Cue contrast. Parameter estimates were extracted for each subject and medication condition from the region that displayed greater NTX versus PLAC correlations with *average* self-reported craving in the psychophysiological interaction (PPI) analysis using the precuneus as a seed (see Table 12 and Figure 19). This figure is presented to enable easier visualization of the relationships only (no statistics can be estimated).

Figure 27. Simplified depiction of the functional connectivity results. Yellow-orange blotches represent the areas where the naltrexone (NTX) condition was associated with reduced activation compared to the placebo (PLAC) condition (PLAC > NTX) within the Methamphetamine (MA) Cue > Control Cue contrast (results of Aim 1). Solid lines depict greater regional functional connectivity in the naltrexone (NTX), as compared to placebo (PLAC), condition (NTX > PLAC), and dashed lines greater regional functional connectivity in the PLAC, as compared to NTX, condition (PLAC > NTX). No directionality of the connections is implied.

Figure 28. Simplified depiction of the correlated relationships between self-reported, subjective methamphetamine craving and functional connectivity results. Yellow-orange blotches represent the areas where the naltrexone (NTX) condition was associated with reduced activation compared to the placebo (PLAC) condition ($PLAC > NTX$) within the Methamphetamine (MA) Cue > Control Cue contrast (results of Aim 1). Solid lines depict stronger positive correlations between subjective craving and regional functional connectivity in the naltrexone (NTX), as compared to placebo (PLAC), condition ($NTX > PLAC$). Dashed lines depict weaker correlations between subjective craving and regional functional connectivity in the NTX, as compared to PLAC, condition ($PLAC > NTX$). No directionality of the connections is implied.

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