Curriculum Vitae

Sarah E. Aronson Fischell

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EDUCATION

2014 – Present **M.D. Candidate**
University of Maryland School of Medicine
Medical Scientist Training Program (MSTP)
Baltimore, MD

2016 – 2020 **Ph.D. Candidate, Neuroscience**
University of Maryland School of Medicine, and the
National Institutes of Health M.D., Ph.D. Partnership Training Program

National Institute on Drug Abuse, Intramural Research Program (NIDA-IRP)
Advisor: Dr. Elliot Stein, Ph.D., Chief, Neuroimaging Research Branch
Baltimore, MD

Program in Neuroscience at the University of Maryland School of Medicine
Advisor: Dr. Asaf Keller, Ph.D., Prof., Department of Anatomy and Neurobiology
Baltimore, MD

2009 – 2013 **Bachelor of Arts, Neuroscience**
Dartmouth College
Honors: Graduated *cum laude* with High Honors in the Neuroscience Major
Hanover, NH

LICENSES & CERTIFICATION

2016 United States Medical Licensing Exam (USMLE), Step 1

2011 – Present Basic Life Support Health Care Provider, American Heart Association

RESEARCH EXPERIENCES

2016 – Present **Pre-Doctoral Fellow, Intramural Research Training Award**
Neuroimaging Research Branch, NIDA-IRP. Baltimore, MD.
Advisor: Dr. Elliot Stein, Ph.D.
Thesis title: Neuroimaging Insights Into Neuromodulation for Addiction: Effects of Transcranial Direct Current Stimulation on Cognitive Circuits Implicated in the Nicotine Withdrawal Syndrome

Summer 2015 **Graduate Research Assistant – Rotation II**
Neuroimaging Research Branch, NIDA-IRP. Baltimore, MD.
Advisors: Dr. Elliot Stein, Ph.D., & Dr. Elise Lesage, Ph.D.
Topic: Reward Processing and Cognitive Flexibility in Nicotine Addiction

Summer 2014 **Graduate Research Assistant – Rotation I**
Neuroimaging Research Program
Maryland Psychiatric Research Center. Catonsville, MD.
Advisor: Dr. L. Elliot Hong, M.D.
Topic: Schizophrenia and Co-occurring Nicotine Addiction

2012 – 2013 **Honors Thesis & Presidential Scholars Assistantship II**
Psychiatry Department
Dartmouth Hitchcock Medical Center. Hanover, NH.
Advisor: Dr. Alan I. Green, M.D.
Topic: Mouse Models for Schizophrenia and Co-occurring Alcoholism

2011 – 2012 **Presidential Scholars Assistantship I**
Psychology and Brain Sciences Department
Dartmouth College. Hanover, NH.
Advisor: Dr. Jay Hull, Ph.D.
Topic: Personality, Risk Behavior, Mindfulness Therapy

Summer 2010 **NSF Research Experience for Undergraduates Scholar**
Wadsworth Center
New York State Department of Health. Albany, NY.
Advisor: Dr. Gary Winslow, Ph.D.
Topic: Splenic Response to Chronic Ehrlichiosis

2010 **Undergraduate Research Assistant**
Poverty and Learning Laboratory
Education Department at Dartmouth College, Hanover, NH.
Advisor: Dr. Michele Tine, Ph.D.
Topic: Exercise and Attention in Adolescents

FUNDING & GRANTS

2020 – 2022 **T32 Individual MSTP Supplement, for M.D. Training Years 3–4**
NIH MD/PhD Partnership Training Program supplement awarded to UMSOM

2017 – 2020 **NIH Pre-Doctoral Intramural Research Training Award Fellowship**
National Institute on Drug Abuse, Intramural Research Program

2018 **F30 Ruth L. Kirschstein National Research Service Award**
NIDA, F30-DA047028, "Transcranial Direct Current Stimulation for the Nicotine Withdrawal Syndrome", $170,987 awarded on July 05, 2018.
Declined in favor of NIH IRTA Fellowship & NIH MD/PhD T32 Supplement

2016 – 2017 **Program in Neuroscience at the University of Maryland, Baltimore**
Graduate Program in Life Sciences

2014 – 2016 **University of Maryland MSTP, for M.D. Training Years 1–2**

HONORS & AWARDS

2018 – Present **Nataro Family Foundation Scholar**
University of Maryland School of Medicine MSTP, Baltimore, MD

2020 **Society of Biological Psychiatry Pre-Doctoral Travel Fellowship Award**
Award applied toward 2021 Annual Meeting due to COVID-19 pandemic.

2011 – 2013 **James O. Freedman Presidential Scholar at Dartmouth College**
Presidential Scholars Senior Thesis/Conference Fund, Hanover, NH
James O. Freedman Presidential Scholarship, Hanover, NH

2012 **William Jewett Tucker Foundation Fellow in International Service**
Dartmouth Center for Service, Hanover, NH
Hand in Hand Center for Jewish-Arab Education in Israel, Jerusalem

2010 **Research Experience for Undergraduates (REU) Scholar at the Wadsworth Center**
National Science Foundation (NSF), REU Program Grant
Wadsworth Center Laboratory, NYS Department of Health, Albany, NY

2009, 2012 **Citations for Academic Excellence at Dartmouth College**
Department of Studio Art, Hanover, NH
Drawing I (2009), Printmaking I (2012)

ADVANCED COURSES & WORKSHOPS

June 25 – 28, 2018 **Transcranial Electrical Stimulation**
Harvard Berenson-Allen Research Center, Beth Israel Deaconess.
Boston, MA.

Feb 13 – 17, 2017 **Analysis of Functional Images (AFNI) Bootcamp**
Scientific and Statistical Computing Core, NIMH-IRP.
Bethesda, MD.

Oct – Nov 2017 **NRSA Grant Writing Workshop, Four-part Course**
Office of Professional Career Development, UMSOM.
Baltimore, MD.

LEADERSHIP & INSTITUTIONAL SERVICE

2019 MSTP Representative. UMSOM Curriculum Renewal *Research & Scholarly Activity* and *Dual-Degree* Working Groups

2018 – 2019 NIDA Board Member. Baltimore Brain Series talks at NIDA, Johns Hopkins, and UMSOM.

2017 – 2018 Committee Member. Pre-Doc/Post-Doc Advisory Board at NIDA

2016 – 2018 Co-Editor in Chief. MD/PhD Dual Decree Newsletter at UMSOM.

2015 – 2016 Co-President: Psychiatry Interest Group at UMSOM.

2017 – 2019 Leader, Women Physician-Scientist Interest Group at UMSOM.

2014 MSTP Stephen Max Lectureship Selection Committee at UMSOM

TEACHING & MENTORING

Summer 2018 Mentor, Research Training for Under-Represented Populations in Science (RTURP) at NIDA-IRP.

2015 – Present Big Sib Mentor at UMSOM MSTP.

June 4, 2019 Contributor, *F30 Workshop* for the UMSOM MSTP.

Summer 2012 Classroom Teacher, Max Rayne Hand in Hand Center for Jewish-Arab Education, Dartmouth Center for Service Tucker Foundation Fellowship. Jerusalem.

2011 – 2012 Study Group Leader and Tutor in Psychology and Chemistry. Academic Skills Center at Dartmouth College. Hanover, NH.

2011 – 2012 Teaching Assistant, Department of Biological Sciences at Dartmouth College. Hanover, NH.

SEMINARS & SPEAKING ENGAGEMENTS

May 13, 2020 *tDCS Modifies Cognitive Circuits Implicated in the Nicotine Withdrawal Syndrome.* Fourth International Network of tES/TMS Trials for Addiction Medicine (INTAM) Webinar. Internationally broadcast web seminar.

Jan 24, 2020 *tDCS for the Nicotine Withdrawal Syndrome: A Simultaneous tDCS-fMRI Study*. Fellows Research Lunch Talks at the National Institute on Drug Abuse, Baltimore, MD.

June 7, 2019 *tDCS for the Nicotine Withdrawal Syndrome*, Friday Faculty Talks at the Maryland Psychiatric Research Center, Catonsville, MD.

Jan 24, 2019 *Brain Stimulation and Neuroimaging for Addiction*. Physician Scientist Seminar, UMSOM MSTP Program. Baltimore, MD.

Dec 6, 2018 *Non-invasive Brain Stimulation as an Intervention to Treat Substance Use Disorders*, Clinical Rounds at the National Institute on Drug Abuse. Baltimore, MD.

June 7, 2017 *How to Succeed in Medical School Panel* at the National Institute on Drug Abuse, Post-bac IRTA program. Baltimore MD.

Aug 5, 2016 *Alumni Careers in Science Panel* at the Wadsworth Center. New York State Department of Health, Research Experience for Undergraduates Program. Albany NY.

May 15, 2013 *Schizophrenia and Co-occurring Alcoholism*. 2nd Student Assembly Undergraduate Research Seminar at Dartmouth College. Hanover NH

Jan 21, 2013 *Empowerment and Resolution Through Art.* 4th Annual Student Forum on Global Learning at Dartmouth College: A Celebration of Martin Luther King Day. Hanover NH.

PROFESSIONAL SOCIETIES

2016 – Present American Psychiatric Association.

2014 – Present American Medical Association.

2010 – Present Scientific Research Society of Sigma Xi.

PUBLICATIONS

- **Aronson Fischell, S.**, Ross, T. J., Deng, Z.D., Salmeron, B. J., & Stein, E. A. (2020). Transcranial Direct Current Stimulation Applied to the Dorsolateral and Ventromedial Prefrontal Cortices in Smokers Modifies Cognitive Circuits Implicated in the Nicotine Withdrawal Syndrome. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 5 (4), 448-460. https://doi.org/10.1016/j.bpsc.2019.12.020.

- Lesage, E., **Aronson, S.**, Sutherland, M.T., Ross, T.J., Salmeron, B.J., Stein, E.A. Neural Signatures of Cognitive Flexibility and Reward Sensitivity Following Nicotinic Receptor Stimulation in Dependent Smokers: A Randomized Trial. JAMA Psychiatry. Published online April 12, 2017. doi:10.1001/jamapsychiatry.2017.0400

ABSTRACTS & CONFERENCE PRESENTATIONS

- **Aronson Fischell**, **S.**, Ross, T., Deng, Z.D., Salmeron, B.J., Stein, E.A. 75th Annual Scientific Conference of the Society of Biological Psychiatry. (2020). Measuring the effect of Transcranial Direct Current Stimulation (tDCS) on Large Scale Brain Networks with Simultaneous Functional Magnetic Resonance Imaging (fMRI). Biological Psychiatry. New York, NY. *Accepted abstract; meeting cancelled due to the COVID-19 pandemic, with Travel Award applied to the 2021 Annual Meeting.*

- **Aronson Fischell, S.**, Ross, T., Deng, Z.D., Salmeron, B.J., Stein, E.A. ACNP 58th Annual Meeting: Poster Session III. (2019). W258: Transcranial Direct Current Stimulation Applied to the Left Dorsolateral Prefrontal Cortex in Smokers Modifies Cognitive Circuits Implicated in the Nicotine Withdrawal Syndrome. Neuropsychopharmacology. doi:10.1038/s41386-019-0547-9. Orlando, FL.

- **Aronson Fischell, S.**, Rose, E., Ross, T., Salmeron, B.J., Stein, E.A. ACNP 57th Annual Meeting: Poster Session II. (2018). T242: Identifying Imaging Biomarkers of Resilience to Drug Use: Interaction Between Childhood Trauma History and Smoking Status on Gray Matter Structure in Adulthood. Neuropsychopharmacology. doi: 10.1038/s41386-018-0267-6. Hollywood, FL.

- **Aronson, S.**, Salmeron, B.J., Ross, T.J., Stein, E.A. Transcranial Direct Current Stimulation (tDCS) for the Nicotine Withdrawal Syndrome. Abstract for Poster Presentation. (2018). 14th Annual NIH Graduate Student Research Symposium. Feb 22, 2017. NIH Natcher Conference Center, Bethesda, MD.

- Lesage, E., **Aronson, S.**, Sutherland, M., Ross, T., Salmeron, B.J., Stein, EA. Nicotinic Receptor Stimulation Affects Reversal Learning in Smokers. (2015). 54th Annual Meeting of the American College of Neuropsychopharmacology. Hollywood, FL. Dec 6-10, 2015. 40, S272-S442. doi:10.1038/npp.2015.326.

- **Aronson, S.** and Hong, L.E. Schizophrenia and High Risk of Smoking: Understanding a Neurobiological Link through Functional Magnetic Resonance Imaging. (2014). 37th Annual Medical Student Research Day, University of Maryland School of Medicine. Baltimore, MD.

- **Aronson, S.**, Gulick, D., MacLeod, J., Khokhar, J., Adams, A., Green, A.I. Schizophrenia & Co-occurring Alcoholism: Post-Natal MK-801 & Alcohol Drinking in C57 Mice. (2013). Abstract for Poster Presentation. 22nd Annual Wetterhahn Undergraduate Science Poster Symposium, Dartmouth College, Hanover, NH.

- **Aronson, S.**, Yates, J. and Winslow, G. Illuminating Immunity: Visualizing B Cells in the Spleen during Chronic Bacterial Infection. (2010). Abstract for Oral Presentation. 1st Annual Research Experience for Undergraduates (REU) Symposium at the Wadsworth Center. July 30, 2010. New York State Department of Health at the Wadsworth Center, Albany, NY.

- Smith, E., Towner, A., Schnieder, J., **Aronson, S.**, & Tine, M. (2010). Acute Bouts of Exercise: A Novel Way to Reduce the Income Achievement Gap. Abstract for Poster Presentation. 19th Annual Wetterhahn Undergraduate Science Poster Symposium. Dartmouth College, Hanover, NH.

Abstract

Title of Dissertation: Neuroimaging Insights Into Neuromodulation for Addiction: Effects of Transcranial Direct Current Stimulation on Cognitive Circuits Implicated in the Nicotine Withdrawal Syndrome

Sarah E. Aronson Fischell, Doctor of Philosophy, 2020

Dissertation Directed by:

Elliot A. Stein, Ph.D., Chief, Neuroimaging Research Branch, National Institute on Drug Abuse, Intramural Research Program, National Institutes of Health.

Asaf Keller, Ph.D., Professor and Interim Chair, Department of Anatomy and Neurobiology, University of Maryland School of Medicine.

Cigarette smoking is the leading cause of preventable death in the United States. The nicotine withdrawal syndrome (NWS) remains a barrier to successful smoking cessation; however, current pharmacological treatments minimally impact sustained abstinence. An emerging class of non-invasive neuromodulation devices, such as transcranial direct current stimulation (tDCS), have been proposed as novel therapeutics for smoking cessation. tDCS has the potential to modulate brain circuits by application of weak currents through the scalp; its use builds upon recent advances in mapping the large-scale network organization of the brain. Functional magnetic resonance imaging (fMRI) functional connectivity (FC) studies have identified three networks as particularly vulnerable to disruption in psychopathology: the Executive Control Network (ECN), Salience Network (SN), and Default Mode Network (DMN). The NWS has been hypothesized to be mediated by reduced FC within the ECN, and between ECN–SN; and increased FC within the DMN, and between DMN–SN.

It is hypothesized that tDCS, applied to cortical nodes of the ECN (e.g. dorsolateral prefrontal cortex) and DMN (e.g. ventromedial prefrontal cortex), may remediate NWS

network dysregulation. Network effects of tDCS were assessed by simultaneous task-based fMRI. 15 smokers (in sated and withdrawal states) and 28 matched nonsmokers participated in a double-blind, randomized crossover design of three tDCS conditions: anodal left-dlPFC/cathodal right-vmPFC *("An-dlPFC"*), polarity reversed ("*An-vmPFC"*), and Sham. Although single-session (25min, 2mA) tDCS did not evoke task behavior changes, *An-dlPFC* tDCS robustly suppressed DMN nodes during a working memory task, and enhanced anterior cingulate activity (SN node) during a conflict monitoring task. DMN suppression within smokers was more pronounced during the sated (vs. withdrawn) state. Given that DMN and SN are hypothesized to be dysregulated in nicotine and other addictions, these data quantitatively support the hypothesis that tDCS may modify large-scale circuits implicated in addictive disease. Additionally, the observation of state-dependent tDCS effects in smokers suggests that tDCS may be most efficacious when combined with standard smoking cessation therapies. This work contributes a translational approach to assessment of tDCS, an emerging intervention at the crossroads of basic neuroscience research and clinical therapeutics in addiction and psychiatric disease.

Neuroimaging Insights Into Neuromodulation for Addiction: Effects of Transcranial Direct Current Stimulation on Cognitive Circuits Implicated in the Nicotine Withdrawal Syndrome

by
Sarah Aronson Fischell

Dissertation submitted to the Faculty of the Graduate School of the
University of Maryland, Baltimore in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
2020

To my family, for your unwavering support and encouragement.

Acknowledgements

I would like to express my sincere thanks and appreciation to all of the individuals who have supported me throughout my graduate studies:

First and foremost, special gratitude to my mentor, Dr. Elliot Stein, for providing me with the opportunity to grow as a medical scientist, and for fostering a vibrant and creative scientific community within the Neuroimaging Research Branch (NRB). Thank you for providing me with an exceptional training experience that enables me to pursue my clinical and research aspirations.

My thesis committee: Drs. Asaf Keller (Chair), Elliot Hong, Mary Kay Lobo, and Geoff Schoenbaum, for providing insightful and thoughtful feedback on my research work. Special thanks to Dr. Keller, for serving as my University of Maryland co-mentor, and to Dr. Hong, for hosting me as a research rotation student.

The University of Maryland School of Medicine MSTP: Dr. Achsah Keegan, Dr. Mary-Claire Roghmann, and Jane Bacon, as well as former director Dr. Michael Donnenberg, for providing me with the opportunity to pursue a dual degree program; and to the Program in Neuroscience, especially Dr. Mary Kay Lobo and Dr. Georgia Rogers, for supporting my cross-institutional research program.

Dr. Thomas Ross and Dr. Betty Jo Salmeron, for scientific and clinical mentorship throughout my training; Dr. Zhi-De Deng, for contributing technical expertise in MR-compatible tDCS and electrical field modeling; and Dr. Elise Lesage, for her mentorship during my summer research rotation.

The many current and former members of the NRB, a talented team of neuroscientists who have been a source of scientific expertise, inspiration, and guidance; I am grateful for having the opportunity to learn from this group every day. Special thanks to the NRB Clinical Team and NIDA-IRP Clinical Core Services, for invaluable clinical, research and technical support.

My undergraduate research mentors at Dartmouth College: Drs. Alan Green, Jay Hull, and Michele Tine, who inspired me to pursue research in neuroscience and human behavior.

Finally, I would like to acknowledge the organizations that have supported my training financially: the UMSOM MSTP; the NIDA-IRP IRTA Fellowship Program; the NIH MD/PhD Partnership Program; and the UMSOM Nataro Family Foundation Scholarship Program.

The work contained herein would not have been possible without the support and encouragement of these many individuals. Thank you!

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List of Abbreviations

ACC	Anterior Cingulate Cortex
An-dlPFC	Anodal electrode applied to dlPFC
BNST	Bed Nucleus of the Stria Terminalis
BOLD	Blood-oxygen-level-dependent
Cat	Cathodal electrode
Cat-vmPFC	Cathodal electrode applied to vmPFC
CBF	Cerebral Blood Flow
CBT	Cognitive-Behavioral Therapy
CON	Cingulo-Opercular Network
CPD	Cigarettes Per Day
CRH	Corticotrophin Releasing Hormone
dACC	Dorsal Anterior Cingulate Cortex
DA	Dopamine
DIY	Do-It-Yourself
dlPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
dmPFC	Dorsomedial Prefrontal Cortex
DTI	Diffusion Tensor Imaging
ECN	Executive Control Network
ECT	Electroconvulsive Therapy
EMA	Electronic-Momentary Assessment
FDA	Food and Drug Administration

fMRI	Functional Magnetic Resonance Imaging
FPN	Fronto-Parietal Network
FTND	Fagerstrom Test for Nicotine Dependence
FWE	Family-Wise Error
GABA	Gamma-aminobutyric Acid
HD-tDCS	High Definition tDCS
ICA	Independent Components Analysis
IFG	Inferior Frontal Gyrus
I-RISA	Impaired Response Inhibition and Salience Attribution
LTD	Long-Term Depression
LTP	Long-Term Potentiation
MCL	Mesocorticolimbic
MDD	Major Depressive Disorder
MEP	Motor Evoked Potential
MFB	Medial Forebrain Bundle
MFG	Middle Frontal Gyrus
mPFC	Medial Prefrontal Cortex
NAcc	Nucleus Accumbens
nAChR	Nicotinic Acetylcholine Receptor
NE	Norepinephrine
NRT	Nicotine Replacement Therapy
NWS	Nicotine Withdrawal Syndrome
PCC	Posterior Cingulate Cortex

PET	Positron Emission Tomography
PHG	Parahippocampal Gyrus
PPC	Posterior Parietal Cortex
QALY	Quality Adjusted Life Year
RAI	Resource Allocation Index
RCT	Randomized Controlled Trial
ROI	Region of Interest
rs-fMRI	Resting-State fMRI
rTMS	Repetitive Transcranial Magnetic Stimulation
SELECT-TDCS	Sertraline vs. Electrical Therapy for Treating Depression Clinical Trial
SN	Salience Network
SUD	Substance Use Disorder
tACS	Transcranial Alternating Current Stimulation
tDCS	Transcranial Direct Current Stimulation
TDE	Temporal Difference Error
TMS	Transcranial Magnetic Stimulation
tRNS	Transcranial Random Noise Stimulation
vmPFC	Ventromedial Prefrontal Cortex
VTA	Ventral Tegmental Area
WM	Working Memory

Chapter 1: Introduction

Overview

Cigarette smoking is a leading cause of preventable death and disease in the United States, resulting in 480,000 deaths each year (U.S. Department of Health and Human Services, 2020). The health risks of smoking are well known, but cessation can be an elusive goal for many smokers. In 2015, approximately 68% of smokers reported desire to quit, and 55.4% made a serious attempt within the previous year; yet, only 7.4% of smokers maintained abstinence at six months (Babb et al., 2017). Encouragingly, public health campaigns have reduced the number of new smokers taking up conventional cigarettes and driven a dramatic reduction in prevalence between 1965 and 2017: from 52% to 15% in men, and from 34% to 12% in women (U.S. Department of Health and Human Services, 2020). By 2017, only 2.7% of high school students reported frequent cigarette use, compared to 36.4% in 1997 (Kann et al., 2018). However, the recent rise in e-cigarette marketing and availability has led to nicotine use resurgence in young adult and youth demographics. In 2019, one in four high school students had used an e-cigarette in the past month, and of those, 34.2% reported using e-cigarettes more than 20 days out of 30 (Cullen et al., 2019). Given the known risks of conventional cigarette smoking (U.S. Department of Health and Human Services, 2020), and new risks of e-cigarette use (Layden et al., 2019), continued development of smoking cessation aids is of essential public health importance.

The common addictive component to both cigarette and e-cigarette consumption is nicotine, first widely accepted as addictive with the publication of the 1988 Surgeon General's Report. Among its sites and mechanisms of action, nicotine acts on the

mesolimbic dopamine system, binding to nicotinic acetylcholine receptors (nAChRs) in the ventral tegmental area (VTA), and initiating release of dopamine (DA) onto the nucleus accumbens (NAcc), a pathway common to the action of most drugs of abuse (Balfour, 2004; Nestler, 2005). Following chronic exposure, nicotine abstinence leads to a cluster of physical and psychological symptoms, collectively described as the Nicotine Withdrawal Syndrome (NWS). NWS peaks within one week of quitting, is alleviated by acute smoking, and contributes to the high rate of smoking relapse observed during the first 1–2 weeks of a quit attempt (Hughes, 1992, 2007; Hughes et al., 2004; Rigotti, 2012).

Pharmacotherapies for smoking cessation primarily manage symptoms of the NWS. First-line therapies include nicotine replacement therapy (NRT), varenicline (partial nicotinic agonist), and bupropion (norepinephrine [NE]/DA reuptake inhibitor), and are recommended in conjunction with counseling (Rigotti, 2012). While these treatments improve cessation rates above non-assisted quit attempts (6-month success rate: 10.6%; (Cahill et al., 2014)), outcomes remain disappointing. The most efficacious, varenicline and combination NRT (patch plus inhaler), have 27.6% and 31.5% 6-month cessation rates, respectively, whereas single NRT and bupropion both remain below 20% (Cahill et al., 2014). Thus, roughly two-thirds of smokers trying to quit will fail, despite motivation-to-quit and use of therapies that have been approved by the Food and Drug Administration (FDA).

Given the inadequate treatment response, searching for approaches beyond pharmacotherapy could provide novel, much needed options for patients. Indeed, outside of addiction, a trend has emerged to look toward a family of noninvasive neuromodulation devices, such as transcranial direct current stimulation (tDCS) or transcranial magnetic

stimulation (TMS), for addressing treatment-resistant psychopathology. These devices apply electrical impulses, either conductively (tDCS) or inductively (TMS), to cortical tissue through the scalp, in order to modulate brain regions considered to be dysregulated in psychiatric disease. This approach has found some success in other neurologic and psychiatric disorders: TMS over the dorsolateral prefrontal cortex (dlPFC) has been FDA-approved for treatment of treatment-resistant major depressive disorder (2008) and obsessive compulsive disorder (2018).

tDCS, which leverages the action of weak applied currents, has been proposed as an adjuvant or alternative treatment for nicotine addiction and dependence, among other substance use disorders (Dunlop et al., 2017; Ekhtiari et al., 2019; Yavari et al., 2016). Early clinical evidence is encouraging (for review, Table 1.1). Mechanistically, use of tDCS for smoking cessation would build upon known cortical plasticity associated with addictive disease broadly (Kalivas & O'Brien, 2008; Koob & LeMoal, 1997; Koob & Volkow, 2010) and recent developments in mapping the neurocircuitry of the NWS specifically ((Fedota & Stein, 2015; Sutherland et al., 2012); elaborated in sections below). *However, direct evidence for tDCS modulation of NWS-related neural circuits remains untested.*

This dissertation aims to identify the acute effects of tDCS on large-scale brain networks dysregulated in the NWS, using a state-of-the-art method to combine tDCS and functional magnetic resonance imaging (fMRI) simultaneously, and a translational design approach. In this chapter, the physiology of nicotine addiction and withdrawal, from synaptic and systems standpoints, is reviewed, with an emphasis on the tripartite network model of NWS and plastic nature of addictive disease (Sutherland et al., 2012). This is

followed by an overview of tDCS physiology and mechanism of action, past applications to addiction and nicotine dependence, and advantages of combining tDCS with fMRI for hypothesis testing. Finally, these elements are combined toward a unifying framework for application of tDCS to nicotine addiction and withdrawal, building to the Specific Aims for the thesis in Chapter 2.

Physiology of Nicotine Addiction and Withdrawal

It is generally accepted that drugs of abuse, including nicotine, alter reward processing pathways, resulting in their dysregulation. Theories of altered mesocorticolimbic (MCL) reward processing can be traced back to intracranial self-stimulation studies by Olds and Milner (1954), in which rats rapidly learned to lever press for self-administration of an electric pulse to regions along the MCL pathway, such as the medial forebrain bundle (MFB). It became known that the MFB contains fibers of DA neurons that project from the VTA to the NAcc, a part of the ventral striatum, and are central to reward processing in animals and humans (Wise & Rompre, 1989). Later, single-cell recordings from DA neurons in the VTA and substantia nigra showed that these cells not only respond to reward, but also provide prediction signals about whether a reward is expected based on cues, with neurons eventually responding to the reward cue itself (Schultz et al., 1997, 1998). Further, mismatched predictions of reward generates a learning signal within this circuit called a temporal difference error (TDE): positive TDEs, i.e. increased dopamine release, result from unexpected or better than expected rewards, while negative TDEs result from lack of, or worse than expected, anticipated reward (Schultz et al., 1997, 1998). Reinforcement learning in this circuit is further modulated by canonical glutamate-mediated plasticity mechanisms, including long-term potentiation (LTP) and

long-term depression (LTD), of glutamatergic synapses onto VTA and NAcc neurons (Kauer & Malenka, 2007).

Thus, neuroplasticity in the MCL circuit is essential to processing first-level reward salience and learning. Appropriately to these functions, the VTA and ventral striatum have diverse afferent and efferent connections with frontal cortical regions responsible for higher cognition (Haber & Knutson, 2010). However, the circuits can be co-opted by drugs of abuse, which act on these pathways (Kauer & Malenka, 2007; Volkow et al., 2019; Wise & Rompre, 1989). In humans, repeated/chronic disruption of these systems results in the pathological behavior characteristic of substance use disorders, in which the user continues to seek, use and crave the drug despite significant impairment to quality of life and desire to quit (American Psychiatric Association, 2013).

It is well known that nicotine is the addictive substance contained in cigarettes and tobacco products (Department of Health and Human Services PHS, 1988), with one cigarette delivering between 0.1–2.6 mg nicotine, with variance attributed to smoking topography and individual cigarette content (Counts et al., 2005; M. V. Djordjevic et al., 2000; Mirjana V. Djordjevic & Doran, 2009). Inhaled nicotine is delivered rapidly to the central nervous system by arterial circulation, reaching the brain within 10-20 seconds following a puff (Benowitz et al., 2009). Once there, nicotine easily passes through the blood-brain barrier and binds to nAChRs, ligand-gated cation channels that are distributed widely throughout the cortex and particularly concentrated within the mesolimbic and nigrostriatal pathways (Changeux, 2010). The fast rate of binding to nAChRs, especially the $\alpha 4\beta 2$ receptor subtypes present on dopamine neurons projecting from the VTA to the NAcc, has been attributed as the primary cause of the addictive properties of cigarette

smoking (Balfour, 2009; Benowitz et al., 2009), in addition to actions on gamma-aminobutyric acid (GABA) and glutamate signaling within this pathway (Changeux, 2010).

Consistent with the above described mechanism of action, initial nicotine exposure in naïve individuals may produce a mild reward sensation, increased alertness, or act as a cognitive enhancer (Heishman, 1998; Heishman et al., 1994). However, because nicotinic receptors are widespread throughout the peripheral nervous system (i.e. neuromuscular junctions and autonomic ganglia), predominant responses to initial nicotine include tachycardia, nausea, dizziness, and vomiting (Benowitz, 1988). Over time, users develop tolerance to both the rewarding and aversive effects of nicotine (Benowitz, 1988).

Given that the reward associated with initial nicotine use is minimal and transitory, compulsive use is considered to be driven primarily by a second element of addictive disease: avoidance of symptoms associated with drug abstinence ("the dark side of addiction"). This previously overlooked aspect of addiction-related neuroplasticity was introduced in 1997, by Koob and LeMoal (1997, 2008) who proposed an Allostatic Model of drug addiction, based on Solomon and Corbit's opponent process theory (1974), in which chronic drug use results in deviation from the normal homeostatic set point for brain reward regulation.

The model posits that brain systems are in place to limit the excessive reward experience produced by drugs of abuse. With continued use, the brain anticipates the excessive drug-induced reward signal, and pre-emptively hyper-engages "anti-reward" systems. Anti-reward systems include "within" & "between" system neuroadaptations. Examples of "within system" neuroadaptations include decreases in dopaminergic

neurotransmission, changes in receptor affinity or number, and changes in transmitter uptake. “Between-system” adaptations include increases in dynorphin and/or corticotrophin releasing hormone (CRH). Over time, these systems dominate the individual’s hedonic state to drive craving, withdrawal and negative affect, resulting in a new “allostatic set point.” Drug taking then occurs primarily to alleviate symptoms of craving, withdrawal, and cognitive/affective dysfunction, further exacerbating the downward spiral away from homeostasis.

For nicotine, chronic exposure significantly affects nAChRs (especially VTA α4β2 receptors), which become less responsive to nicotine (desensitized) and subsequently upregulated in number (Benowitz, 2010; Changeux, 2010; De Biasi & Dani, 2011). Abrupt removal of chronic nicotine initiates a withdrawal syndrome in preclinical models and in humans, due to inadequate activity within the MCL pathway (within-system adaptation), which can be remediated by acute nicotine administration (Balfour, 2009). The NWS is also mediated by mechanisms separate from the VTA-NAcc pathway (between-systems adaptations), including the habenular-interpeduncular pathway (De Biasi & Dani, 2011; Salas et al., 2004, 2009), the hypothalamic-pituitary axis (corticoid stress response) system (Benowitz, 2010; Koob, 2010), and changes in the dopamine, serotonin, glutamate, and neuropeptide systems (for review, K. J. Jackson et al., 2015). Thus, avoidance of aversive sensations associated with nicotine withdrawal, described below, is a significant contributing factor in the continuation of daily smoking in dependent individuals.

Clinical Signs and Symptoms of Nicotine Withdrawal Syndrome

Clinically, nicotine abstinence in a chronic smoker induces both somatic and psychological symptoms. Somatically, withdrawal from nicotine can cause insomnia,

increased appetite, weight gain (4–5 kg average), and bradycardia (De Biasi & Dani, 2011). Coughing, mouth ulcers, dizziness, and some gastrointestinal changes have also been reported (Hughes, 2007). Psychologically, withdrawal precipitates irritability, dysphoria or anhedonia, depressed mood, anxiety, difficulty concentrating, fatigue or drowsiness and general restlessness (Hughes, 2007). Withdrawal can also be accompanied by intense cravings, often triggered by smoking-related environmental cues (Rigotti, 2012). Symptoms of withdrawal peak within the first three days and gradually subside over 3–4 weeks (Hughes, 2007; Rigotti, 2012). In illustration of the impact of NWS on behavior, dependence severity is associated with reduced time to smoke after awakening (for heavy smokers, within five minutes), likely relieving the earliest withdrawal signs that developed overnight (Heatherton et al., 1989, 1991).

Systems Neuroscience Pathophysiology of Addiction and Nicotine Dependence

In addition to the synaptic and neuroplasticity mechanisms of addiction and withdrawal described above, an extensive literature on cognitive systems and large-scale brain networks contributing to nicotine dependence, and drug abuse generally, has been elaborated since the early 2000s, bolstered with advances in neuroimaging technology. In 2002, Goldstein and Volkow proposed the *impaired response inhibition and salience attribution* (I-RISA) model of addiction, combining evidence from early neuroimaging studies of drug abuse (Goldstein & Volkow, 2002). In this framework, altered function of the anterior cingulate and orbitofrontal cortex (i.e. reduced top-down control of striatal and amygdala circuits) leads to hypersensitivity to drug-related cues and drug reward, and devaluation of non-drug reinforcers, contributing to maladaptive behavior (Goldstein & Volkow, 2002, 2011).

This syndrome was further elaborated by Koob and Volkow (2010), who conceptualized addiction as a cycle of binge/intoxication, withdrawal/negative affect and preoccupation/anticipation that results in continued drug use despite negative consequences. Based on both preclinical and human neuroimaging evidence, Koob and Volkow generated a framework that described the circuitry underlying each addiction cycle *state* (i.e. binge, withdrawal, craving). Initial reinforcing effects of drugs and continued drug-taking behaviors (binge/intoxication), are attributed to signaling within ventral and dorsal striatal pathways. For example, Volkow and colleagues observed, through positron emission tomography (PET) in humans, that psychostimulant-induced DA release in the striatum is associated with self-reported reward sensations (Volkow et al., 1996), and that the reward experiences are greater for fast DA changes (Volkow & Swanson, 2003) or with reward expectation (Volkow et al., 2003).

In contrast, the dysphoria associated with drug abstinence (withdrawal/negative affect), is attributed to activity of the bed nucleus of the stria terminalis (BNST) and central nucleus of the amygdala, and various neuroendocrine stress systems. In the case of smoking, abstinence increases cerebral blood flow (CBF) in the extended amygdala (Z. Wang et al., 2007), while acute nicotine nasal spray suppresses withdrawal-induced CBF in the amygdala (Zubieta et al., 2001). Neuroimaging evidence also illustrates the above-described "within system" adaptation to chronic drug use: protracted withdrawal from cocaine is associated with downregulation of D2 receptor expression and DA release, as measured with PET (Volkow et al., 1997).

Finally, craving (preoccupation/anticipation) is attributed to conditioned cues (processed by the insula and basolateral amygdala, among other regions) triggering salient

reward and contextual memories (hippocampus), alongside weakened top-down (prefrontal) control. This complex circuitry is supported by studies showing that drug cues and craving are associated with increased activity in the orbital and medial prefrontal cortices (mPFC), as well as the cingulate gyrus (McClernon et al., 2009; Volkow et al., 2005), hippocampus and amygdala (Childress et al., 1999; Kilts et al., 2001; Volkow et al., 2004). The insula, a region highly involved in interoceptive awareness with representations of homeostatic, environmental, motivational and hedonic conditions and with strong connection to the cingulate cortex (Craig, 2002, 2009), notably became implicated in this circuitry following observations that stroke-related insula lesions in smokers improved ability to quit, and reduced craving and relapse (Naqvi et al., 2007), and that drug urges modulate insula activity in imaging studies (Naqvi & Bechara, 2009).

Large-Scale, Intrinsic Brain Networks

The Volkow and Koob framework was largely pieced together from coinciding experimental evidence in which each element of the circuit was tested individually by task or other targeted experimental design. Concurrently, additional insight into the large-scale functional organization of the brain was being advanced by resting-state functional magnetic resonance imaging (rs-fMRI) methods. Resting-state fMRI uses low-pass filtering of the blood-oxygen-level-dependent (BOLD) signal (generally, 0.01-0.1 Hz) measured while the individual remains in a task-free state (e.g. eyes closed or focused on a fixation cross, absent a cognitive task) to quantify patterns of spontaneous neural activity (Fox & Raichle, 2007). These signals were traditionally considered to be noise during task-induced BOLD acquisition, but evidence of their interpretability and utility dates back to 1995, when it was found that the "noise" signals of left and right motor cortices were more

correlated to each other than to any other part of the brain, while the subject was at rest (Biswal et al., 1995). Over a decade later, in 2009, advanced data-driven methods (e.g. independent components analysis, "ICA") allowed reproducible parcellation of multiple, large-scale "intrinsic" networks within the brain; these included visual, auditory, motor, and higher-order cognitive networks (S. M. Smith et al., 2009). Notably, in support of the functional validity of rs-fMRI parcellation, the networks derived from ICA analyses of resting state data strongly corresponded to task-based methods for evoking the same sub-components; for example, similar patterns of activity are seen in visual , auditory and higher cognitive function brain areas (S. M. Smith et al., 2009). Further, these networks have been observed to be stable within (Chen et al., 2008) and between (Damoiseaux et al., 2006) healthy individuals, although the specific number and sub-components of each network can vary by analytical parcellation methods (Fox et al., 2005; S. M. Smith et al., 2009; Yeo et al., 2011).

Among these networks, three higher-order cortical networks have been the subject of recent focus for their apparent involvement in psychiatric disease: Executive Control Network (ECN), Salience Network (SN), and Default Mode Network (DMN). The Executive Control or Fronto-parietal Network (ECN/FPN) consists most characteristically of parietal attention areas (e.g. lateral posterior parietal cortex; PPC) and dorsolateral prefrontal cortex (dlPFC; (Fox et al., 2005; Habas et al., 2009; Seeley et al., 2007)). The ECN was initially observed as part of a pair of stable anticorrelated networks, and was labeled "task-positive" because its components (including frontal eye fields, supplementary and pre-supplemental motor areas, dlPFC, and PPC) were well defined in the literature as involved in task-based cognition (Fox et al., 2005).

In contrast, the anticorrelated "task-negative" network consisted of the medial prefrontal regions, temporal and parahippocampal regions, posterior cingulate cortex (PCC) and precuneus (Fox et al., 2005), a set of regions understood to be down-regulated during goal-directed performance and activated during self-referential tasks (Greicius et al., 2003; Kelley et al., 2002). This network had been defined as early as 2001 by Raichle and colleagues and labeled a "Default Mode Network", because it appeared to be tonically active at rest (Raichle et al., 2001). The DMN has since been stably replicated (Buckner et al., 2008; Greicius et al., 2009; S. M. Smith et al., 2009), and over time has come to be considered an essential self-referential processing network comprising of sub-systems involved in facilitating self-related decision making, constructions of mental scenes, and social cognition (Andrews-Hanna et al., 2014).

Finally, the Salience or Cingulo-Opercular Network (SN/CON), canonically encompasses the anterior insula and anterior cingulate cortex (ACC), and is sometimes extended to include amygdala and striatum (Menon, 2011; Seeley et al., 2007). The is consistent with task-induced fMRI studies showing concurrent activation of insula and ACC, and evidence that the two regions share a specialized population of neurons known as Van Economo neurons (VENs) that may enable reciprocal communication (Craig, 2009). As mentioned above, the insula processes salient endogenous and exogenous stimuli incoming from hypothalamic, limbic, entorhinal/temporal and prefrontal cortical regions (Craig 2009). The ACC, along with the mPFC, is involved in conflict monitoring, emotional appraisal and top-down control of limbic regions, such as the amygdala (Etkin et al., 2011). The combined function of the subcomponents of this network in attending to

important autonomic, emotional and reward-related events, led to description of this network as the Salience Network (Seeley et al., 2007).

Vinod Menon and colleagues formulated a "Tripartite Network Model" for function within and between these networks in neurotypical behavior and disruption in psychopathology (Bressler & Menon, 2010; Menon & Uddin, 2010; Sridharan et al., 2008). In this model, the SN, in its role as evaluator of homeostatically relevant stimuli, is proposed to coordinate attentional resources between the goal-directed ECN and self-referential DMN, to effect adaptive behavior (Sridharan et al., 2008). Further, disruption in one or all three of the networks forms a functional basis of cognitive dysfunction in neuropsychiatric disease (Menon, 2011). This model has been supported by evidence of network imbalance in a variety of illnesses including Alzheimer's (Greicius et al., 2004), schizophrenia (Garrity et al., 2007), autism (Uddin & Menon, 2009), and depression (Greicius et al., 2007), among others. The model's structure is appealing for application to psychopathology, as it provides a cognitive, large-scale circuit level framework for understanding complex maladaptive behaviors, and unifies the relationship between distinct component regions.

Large-Scale Network Dysfunction in Nicotine Addiction

The Tripartite Networks advanced by Menon share common substrates with the Volkow, Koob and Goldstein addiction neurocircuitry frameworks described above, especially striatal, limbic, insula, and prefrontal regions. Of note, dysregulation of activity within and between nodes of these networks have been consistently observed in nicotine dependence and withdrawal (Fedota & Stein, 2015; Pariyadath et al., 2016; Sutherland et al., 2012; Sutherland & Stein, 2018). The dysregulations further correspond to the

cognitive and affective disturbances of the NWS, and are most notable with changes in nicotine state (i.e. satiety to abstinence), but are also observable as a function of smoking trait.

Cognitive deficits of attention and task performance are characteristic of NWS, primarily a feature of the nicotine withdrawal *state* (Heishman, 1998; Heishman et al., 1994, 2010; Hughes, 2007; McClernon et al., 2015), while acute nicotine administration generally improves attention and cognitive processing (Hahn et al., 2007; Lawrence et al., 2002; Lesage et al., 2017). Further, the severity of deficits in cognitive processing are predictive of smoking relapse (Loughead et al., 2015). The changes in cognitive function related to nicotine state appear to be attributed to a two-fold process, deprivation-induced reduction in function of ECN nodes, and enhanced function of DMN nodes (Sutherland et al., 2012). Several studies have observed that nicotine deprivation reduces activity in ECN-related nodes, such as dlPFC (Beaver et al., 2011; Ettinger et al., 2009; Loughead et al., 2010), along with a corresponding increase in activity of DMN nodes, such as precuneus, PCC, and mPFC (Hahn et al., 2007; Tanabe et al., 2011; Z. Wang et al., 2007). Further, Cole and colleagues (2010) observed that nicotine deprivation reduces the anti-connectivity between DMN and ECN nodes, and the degree of deviation corresponded to withdrawal symptom severity. These observations are consistent with studies demonstrating that inadequate DMN suppression, and corresponding reductions in ECN nodes, during task is associated with poorer task performance (Eichele et al., 2008; Prado & Weissman, 2011). Notably, failure of to suppress DMN, especially, has been widely replicated in both smokers and other drug users and corresponds to clinical outcomes (for review, R. Zhang & Volkow, 2019).

An extensive number of studies have observed alterations in SN nodes, especially insula and cingulate as well as striatum and amygdala, as a function of both smoking trait and state. As these areas are central to emotional and reward/salience processing, affective (irritability, anxiety) and altered incentive salience (heightened sensitivity to smoking cues) are attributed to their disruption. As previously described, interest in the insula was sparked by the observation that insula lesions improve cessation outcomes (Naqvi et al., 2007), possibly due to reduced interoceptive perseveration on feelings of craving or withdrawal. In further support of the role of the insula in smoking, smokers demonstrate altered insula gray matter structure (X. Zhang et al., 2011) and reduced recruitment of the insula during the Flanker conflict-monitoring task (Fedota et al., 2016), and connectivity with the amygdala (Sutherland, Carroll, Salmeron, Ross, Hong, et al., 2013b) as a function of smoking trait. Nicotine state further alters insula connectivity in smokers: nicotine deprivation enhances insula–amygdala connectivity (Sutherland, Carroll, Salmeron, Ross, Hong, et al., 2013b) and insula–DMN connectivity (Fedota et al., 2018).

Given the function of the amygdala in negative emotional and stress processing, and that these affective states are typical of nicotine withdrawal (Hughes, 2007), it is significant that amygdala reactivity is modulated by nicotine state in smokers. Nicotine abstinence generally results in hyper-excitability of the amygdala (Sutherland, Carroll, Salmeron, Ross, Hong, et al., 2013a; Z. Wang et al., 2007) with reintroduction of nicotine or nicotinic agonists suppressing such activity (Franklin et al., 2011; Zubieta et al., 2001, 2005).

In addition to insula and amygdala, dorsal ACC (dACC) connectivity with the striatum is also altered as a function of smoking trait and dependence severity (Hong et al.,

2009, 2010). The role of these regions in salience attribution to drug-related cues and modulation of craving (Koob & Volkow, 2010) is consistent with their dysfunction in nicotine dependence. Smokers demonstrate altered reactivity of striatal components to non-drug monetary reward compared to nonsmokers (Fedota et al., 2015; Rose et al., 2013); further, enhanced reactivity of insula, dACC, amygdala, and striatum to smoking cues has been correlated with greater likelihood of relapse (Janes et al., 2010). Together, these studies strongly suggest an important role of the SN in affective and reward dysregulation in nicotine dependence and withdrawal.

Tripartite Nicotine Withdrawal Syndrome Model

Integrating the above evidence with Menon's Tripartite Network template, Stein and colleagues generated a working model of large-scale network dysregulation in the NWS (Fedota & Stein, 2015; Pariyadath et al., 2016; Sutherland et al., 2012; Sutherland & Stein, 2018). Specifically, the cognitive and affective disturbances of the NWS are attributed to failure of the SN to appropriately allocate attentional resources away from inward/self-referential processing (i.e. toward DMN, withdrawal-related ruminations and preoccupations) toward outward, goal-directed processing (i.e. toward ECN). This failure results in reduced circuit strength within and between the ECN and SN, increased connectivity strength within the DMN and between SN–DMN, and hyperactivity of the amygdala and disruption of its connectivity with prefrontal aspects of the other networks.

This model was empirically tested in 2014, when Lerman and colleagues quantified the interaction among the three networks using a "Resource Allocation Index" (RAI). The RAI was calculated as a ratio of the resting connectivity strengths between SN–ECN (right and left hemispheres) and SN–DMN, with positive index values corresponding to increased

SN–ECN synchrony, and negative index values to increased SN–DMN synchrony. It was observed that, within smokers, RAI values were reduced following 24-hours abstinence compared to ad-libitum smoking. Further, lower RAI values predicted worse craving severity in the abstinent smokers, and impaired suppression of DMN nodes (vmPFC, PCC) during an N-back working memory task (Lerman et al., 2014). This study, along with those described in the preceding paragraphs, suggests that the imbalance of these three networks is clinically relevant, and modulation of the networks may be a possible mechanism for improving outcomes for smoking cessation. Additionally, given that ECN, SN, and DMN networks are shared across other addictive diseases (for example, the RAI was recently reproduced in gaming addiction, (c.f. J. T. Zhang et al., 2017)), the NWS model may serve as a framework for understanding network dysfunction and remediation in addiction more broadly.

Section Summary: The NWS is a clinically relevant model derived from fundamental addiction neurocircuitry principles.

To summarize, an NWS large-scale network model, proposing dysfunction within and between the SN, DMN and ECN in nicotine addiction, has been defined based on fundamental and emerging principles of addiction neurocircuitry. The model builds from both the synaptic physiology of addiction generally and nicotine addiction specifically, as well as more recent, systems-level circuitry derived from functional neuroimaging analyses. Importantly, the logical consequence of the NWS model is that remediation of SN, DMN, and ECN dysregulated interactions could be a possible means to improve smoking cessation outcomes. Therapeutic modulation of nodes or interactions within and between the networks could alleviate aspects of the NWS, thereby improving the ability to

sustain a quit attempt through the peak withdrawal period, or and/or modulating circuits long-term to resist relapse and craving. Non-invasive brain stimulation technologies such as tDCS are poised to support such circuit-level changes. In the next section, the mechanism of action and physiology of tDCS is discussed, as well as clinical evidence supporting its efficacy in psychiatric disease and addiction. The chapter concludes with a discussion of combination tDCS-fMRI, an emerging technique that can be used to directly quantify the effect of tDCS on network nodes and interactions.

Neuromodulation for Addictive Disease

Neuromodulation is a large family of interventions, which includes both invasive (e.g. deep brain stimulation) and non-invasive (e.g. transcranial magnetic stimulation, transcranial electrical stimulation, electro-convulsive therapy, focused ultrasound) methods. Here, the physiology and clinical applications of tDCS are explored, with focus on application to nicotine addiction and withdrawal, and how efficacy of tDCS might be improved with functional magnetic resonance imaging methods.

Physiology of Transcranial Direct Current Stimulation (tDCS)

Transcranial electrical stimulation has existed in various forms in the 20th century, including electroconvulsive therapy (ECT) beginning in the 1930s (Kalinowsky, 1986), as well as repetitive transcranial magnetic stimulation (rTMS), popularized in the 1980s (Fitzgerald 2013). Both ECT and TMS apply suprathreshold electrical current to the brain. In ECT, ~800 milliamperes of direct current is applied through bilaterally placed electrodes, usually over the temples, dosed individually to 1.5–2 times seizure threshold, inducing a generalized seizure lasting 15–70 seconds (Kellner, 2020; Lisanby, 2007; Peterchev et al., 2010). In rTMS, current passing through a coil placed on the scalp

generates a rapidly alternating magnetic field, which induces a spatially focal electrical current within the cortex. rTMS dosing is based on the threshold to evoke a localized motor response (e.g. contralateral hand muscles) following stimulation of the motor cortex, usually 100–120% of resting motor threshold (Fitzgerald & Daskalakis, 2012; Holtzheimer, 2020; Perera et al., 2016). Both ECT and rTMS have been successfully applied to a variety of psychiatric diseases; however, the adverse effects associated with seizure (or seizure risk, for rTMS), such as memory loss, have generally limited their use beyond treatment-resistant cases. Additionally, ECT and rTMS are both relatively expensive procedures, costing in the range of $35,000 per quality-adjusted life-year (QALY) for TMS treatment of major depression (Simpson et al., 2009), and $54,000 per QALY for ECT (Ross et al., 2018), though these numbers can vary by provider and individual case. ECT in the United States continues to sustain a stigma in public perception (McFarquhar & Thompson, 2008), as well, making it a choice of last resort for patients despite evidence of treatment efficacy (Sackeim, 2017).

Interest has emerged for the delivery of weak currents subthreshold to induce a neuronal action potential (milliampere range, up to 4mA), which provide a more accessible, lower risk method for psychiatric disease treatment (Bikson et al., 2016). This class of stimulation includes transcranial direct current stimulation (tDCS) devices, alternating current (tACS), and random noise stimulation (tRNS). Among these, tDCS has emerged as a prominently applied method (Brunoni et al., 2012; Fregni et al., 2015; Woods et al., 2016).

tDCS has the potential to modify neuronal circuit firing properties following an electrical current applied across the scalp, with current flowing from an anodal to a cathodal

electrode. Placement of the electrodes varies depending on disease state and research hypothesis, in a montage designed to target a particular cortical region. However, because the current must traverse a wide space with a range of tissues providing a variety of possible current paths, tDCS produces a somewhat generalized and diffuse electrical field distribution (although innovations such as "high-definition" tDCS, in which a central anode is surrounded by four or more cathodal electrodes, have increased experimentation with focality parameters, (Alam et al., 2016)). Early evidence that weak transcranial currents modify cortical signals came from studies in which tDCS was used to 'prime' the motor cortex immediately prior to application of a TMS pulse (Nitsche & Paulus, 2000). Anodal current (1 mA, 5 min) applied to the left motor cortex (cathodal electrode placed over contralateral forehead) increased the measured motor evoked potential (MEP) by about 40%, while cathodal stimulation reduced the motor evoked potential by about 30%, with the response returning to baseline level within five minutes.

These results suggested that tDCS may act to modify the resting membrane potential of neuronal cells. It is estimated that 1 mA of applied current produces a peak field of 0.3 V/m in the cortex, and 0.4 V/m for 2 mA, resulting in a maximum somatic polarization of less than 1 mV (Moreno-Duarte et al., 2014; Radman et al., 2009; Rahman et al., 2013). In contrast, TMS applies an electric field of about 100 V/m. Given that the membrane potential of a neuron at rest must depolarize by approximately 15–20 mV (i.e. from approximately -65 to -50 mV, for a typical neuron) to reach action potential threshold, tDCS is considered to modulate spontaneous neuronal activity, increasing or decreasing the likelihood of neuronal firing alongside endogenous signaling. More specifically, it has been hypothesized that tDCS induced current flow affects the polarization of pyramidal

cells oriented perpendicularly to the cortical surface. Under the anode, current flows from dendrite to soma, resulting in depolarization of the soma and increased excitability; under the cathode, current flow reverses direction, resulting in hyperpolarization of the soma and reduced excitability (Moreno-Duarte et al., 2014; Radman et al., 2009). However, given the complexity of cell morphology and individual-specific anatomy, polarity specific effects of tDCS are still an area of active investigation.

In addition to immediate effects on cortical excitability, tDCS is considered to influence long-term plasticity. Plasticity in response to tDCS occurs on two scales, after-effects measurable in the window following stimulation (on the scale of 10s of minutes, depending on duration of stimulation; (Nitsche et al., 2007)), and clinical effects measurable following multiple sessions of tDCS across days or weeks (Boggio et al., 2007). Pharmacological studies of tDCS mechanisms revealed that, while acute effects of tDCS on MEP priming are dependent on sodium and calcium channel signaling (effects are blocked by administration of carbamazepine or flunarizine), the after-effects of tDCS are dependent on NMDA receptor function (effects blocked by dextromethorphan) (Nitsche et al., 2003, 2004), indicating that after-effects involve mechanisms of long-term potentiation. Long term plasticity with tDCS has been observed in clinical trials, in which multi-session tDCS is found to improve recovery of speech following stroke (Fridriksson et al., 2018), motor control in Parkinson's disease (Benninger et al., 2010; Costa-Ribeiro et al., 2016) and even laparoscopic technical skills in surgical residents (M. L. Cox et al., 2018).

There has been some controversy about whether tDCS-generated current density induced over the cortex is strong enough to alter neuronal activity. A 2018 report by

Buzsáki and colleagues (Vöröslakos et al., 2018) reported that up to 75% of transcranial current may be shunted away from the cortex by soft tissues and CSF, and that the remaining current is unlikely to be sufficient to affect neurons, as measured by electrophysiologic activity in a cadaver. While it is correct that tDCS-generated current is attenuated by passage through soft tissue before it reaches the cortex, findings observed in a cadaver may not be directly comparable to living tissue. Neuronal activity is dependent on the dynamics of intracellular and extracellular activity, both of the neuron and surrounding glia and vascular smooth muscle; this is further dependent on oxygen delivery and glucose metabolism, which is absent in a cadaver. The work described previously in this section provide evidence from a diverse series of studies supporting that tDCS has the potential to alter neurophysiology in the living brain. Importantly, imaging studies with tools such as simultaneous tDCS-fMRI provide unique insight into how tDCS may alter neuronal circuits in-vivo.

Clinical Trials and Applications of tDCS in Psychiatric Disease and Addiction

The preceding section described the action of tDCS and its effect on cortical physiology. To review, tDCS is considered to affect neural circuitry over two time scales: acutely, by modulating the likelihood of neuronal membrane potentials to reach action potential threshold; and, in the long term, by synaptic plasticity adaptations to those circuits over time with repeated sessions. Earlier, we discussed evidence supporting models of addiction as a disease of altered neurocircuitry due to chronic drug exposure. Thus, it follows that tDCS may be poised as an appropriate tool for remediating neural circuits implicated in addictive pathology.

Below, evidence is presented that tDCS may affect clinical treatment outcomes in psychiatric disease and substance use disorders. Of note, the majority of the evidence in the literature is clinically or behaviorally based. Only a few studies have taken a mechanistic approach, such as through use of simultaneous tDCS-fMRI. This technique is discussed at the conclusion of the chapter.

Applications to Psychiatric Disease

A handful of randomized, controlled clinical trials for tDCS have been carried out to examine clinical effects, primarily efficacy in depression. In a landmark trial ("SELECT-TDCS") involving 120 patients with Major Depressive Disorder (MDD), Brunoni and colleagues observed greater improvement in depressive symptoms in patients treated with 6-weeks combined sertraline plus tDCS, compared to either alone (Brunoni et al., 2013). An additional trial involving 245 patients with MDD found that, while 10-weeks escitalopram was superior to 10-weeks of tDCS, tDCS treatment was superior to placebo (Brunoni et al., 2017). Other trials have reported that tDCS improves depressive symptoms of bipolar depression, without a concomitant increase in manic symptoms compared to sham (Sampaio-Junior et al., 2018); add-on tDCS also improved negative symptoms of schizophrenia above sham-tDCS (Valiengo et al., 2019). However, not all studies have observed positive outcomes. In an international consortium trial of 130 subjects, active tDCS did not differ from sham in reduction of depressive symptoms (Loo et al., 2018).

Applications to Addiction

Within addiction, a number of sham-controlled studies have investigated effects of tDCS on craving, use, and dependence symptoms in substance use disorders (SUDs), with the majority of trials examining alcohol or tobacco, and a smaller subset examining cocaine

use, methamphetamine, opiates, or cannabis; a number of these studies demonstrate reductions in use or craving (for review, Brunoni & Palm, 2019; Coles et al., 2018). For nicotine specifically, of 14 sham-controlled clinical studies, 11 observed positive findings on at least one outcome measure, suggesting that tDCS may have promise as a smoking cessation tool (for review, **Error! Reference source not found.**). Heterogeneity in methods (electrode placement and size, stimulation intensity, number of sessions, etc.) and outcome variables among research groups may account for some discrepancies in published results (for further discussion, Chapter 4). Overall, the studies to-date suggest potential for tDCS therapeutic use in addictive disease, but have yet to provide definitive evidence or guidance on the parameter space for such a use.

Table 1.1: Sham-Controlled Clinical Studies of Nicotine and tDCS, *next page*

*Included smokers who smoke once per week, 13 subjects with FTND = 0, 12 with FTND 1-7.

Total Sample size reflects final analytical sample.

tDCS Parameters: An = Anode, Cat = Cathode, dlPFC = Dorsolateral Prefrontal Cortex, FPT = Fontal-Parietal Temporal Association Area, OFC = Orbitofrontal Cortex, PCC = Posterior Cingulate Cortex, PHG = Parahippocampal Gyrus, SOR = Supraorbital Ridge.

Outcome Measures: fNIRS = Functional Near-Infrared Spectroscopy, FTND = Fagerstrom Test for Nicotine Dependence, CO = Carbon monoxide, Cig. Intake = Cigarette intake and consumption, HRV = Heart Rate Variability, MCCB = MATRICS Consensus Cognitive Battery for schizophrenia cognitive deficits, PANSS = Positive and Negative Syndrome Scale for Schizophrenia, POMS = Profile of Mood States, UTS = Urge to Smoke Scale, VAS = Visual Analog Scale.

Sample: SCZ = Schizophrenia patient sample, M = Male

Study	Question	Design	tDCS Parameters	Outcome Measures	Total Sample	Result
(Alghamdi et al., 2019)	Does active tDCS reduce number of cigarettes smoked vs. sham stimulation?	Active (n=12) or sham (n=10) tDCS for 3 consecutive days	1.5mA; 20min An-(L) dlPFC / Cat-(R) dlPFC	Cig. intake up to 4-months follow-up	22 Smokers	(–): No effect of tDCS vs. sham
(Behnam et al., 2019)	Is tDCS an alternative to bupropion for smoking cessation?	5 groups: (32-35 subjects per group) 300mg bupropion (8 weeks); tDCS (20 sessions, 4 weeks; i.e. 5 sessions/week for 4 weeks), or sham; tDCS (20 sessions, 12 weeks, i.e. 5 sessions/week for 2 weeks, followed by one/week for 10 weeks), or sham.	2mA; 20min An-(L) dlPFC / Cat-(R) dlPFC	Salivary cotinine, FTND score, and cig. intake up to 6-months follow-up	170 Smokers	(+): 12-week tDCS treatment improved outcomes at 6-months vs. bupropion (abstinence rate, FTND, and cotinine)
(Falcone et al., 2019)	Does active tDCS improve smoking abstinence over 1-week, in a dose-dependent manner?	3 groups: 1mA vs 2mA vs Sham (35-36 participants per group) Three tDCS sessions in one week (days 1, 3, 5) followed by 7-day monitoring period with CO measures on days 6, 8, 10, and 12.	1-2mA; 20 min; An-(L) dlPFC / Cat-(R) SOR	Days abstinent (CO verified), smoking latency, and cig. intake for 7 days	106 Smokers	(–): No effect of tDCS (1mA or 2mA) vs. sham
(Mondino et al., 2018)	Does tDCS change cue reactivity, measured by fMRI, craving, or CPD?	*MRI Study*: 10 sessions: 2 per day for 5 consecutive days; active (n=17) or sham (n=12)	2mA; 20min; An-(R) dlPFC / Cat-(L)Occipital	Pre/Post fMRI: Cue-reactivity task; Craving.	29 Smokers	(+): tDCS reduced smoking craving and increased PCC reactivity to smoking cues. No effect on cig. intake.
(Vitor de Souza Brangioni et al., 2018)	Does tDCS change motivation to quit smoking or CPD?	5 tDCS sessions, one per day for consecutive days (active (n=19) and sham (n=17) groups).	1mA; 20min; An-(L) dlPFC / Cat-(R) dlPFC	Cig. intake and motivation-to-quit VAS; up to 4-weeks follow-up	36 Smokers	(+): tDCS reduced cig. intake; greater response to tDCS associated with greater motivation-to-quit

Table 1.1: Sham-Controlled Clinical Studies of Nicotine and tDCS
Caption on preceding page.

Study	Question	Design	tDCS Parameters	Outcome Measures	Total Sample	Result
(Yang et al., 2017)	Does tDCS affect BOLD fMRI, and/or smoking craving?	*MRI Study*. 1 session each active and sham, 1-week separated (crossover).	1mA; 30min; An-(L) dlPFC / Cat-(R) dlPFC	Post-tDCS fMRI: Resting state, cue-reactivity task, emotion task	32 Smokers (M only)	(+): tDCS increased dlPFC–PHG functional connectivity
(Falcone et al., 2016)	Does tDCS affect latency to smoke or CPD immediately following treatment?	Participants completed active and sham tDCS, separated by 2 weeks (crossover).	1mA; 20min; An-(L) dlPFC / Cat-(R) SOR	Smoking latency and cig. intake following tDCS	25 Smokers	(+): tDCS increased smoking latency and decreased cig. intake.
(Kroczek et al., 2016)	Does tDCS affect smoking cue reactivity or craving?	Active (n=13) and Sham groups (n=12), 1 session. Cue reactivity paradigm and fNIRS of the prefrontal cortex simultaneous tDCS.	2mA; 15min; An-(L) dlPFC / Cat-(R) OFC	Cue reactivity, HRV, craving and fNIRS	25 Smokers*	(+): tDCS increased OFC–dlPFC connectivity, no effect on craving or HRV.
(R. C. Smith et al., 2015)	Does tDCS improve schizophrenia symptoms and comorbid smoking?	5 tDCS sessions on consecutive days. Active or Sham tDCS (15 sham, 14 active completers)	2mA; 20min; An-(L) dlPFC / Cat-(R) SOR	MCCB, PANSS, cig. intake and craving	29 SCZ-Smokers	(−): tDCS improved MCCB score, no effect on PANSS, smoking craving or cig. intake.
(Fecteau et al., 2014)	Does tDCS reduce smoking consumption?	5 tDCS sessions, one per day for consecutive days (crossover active and sham, counter-balanced order within subject, separated by 3 months)	2mA; 30min; An-(R) dlPFC / Cat-(L) dlPFC	Cig. Intake; Pre/post cognitive tasks (ultimatum game, risk task)	25 Smokers	(+): tDCS reduced cig. intake up to 4 days post-stimulation and increased cigarette rejections in ultimatum game. No effect on risk task.
(Z. Meng et al., 2014)	Does FPT tDCS affect smoking cue reactivity or CPD?	3 groups (10 participants/group): bilateral Cat-FPT / bilateral An-Occipital; An-(L) FPT / Cat-(R) FPT, Sham. Single session tDCS with pre/post assessment.	1mA; 20min; Cat-FPT montages	Cue reactivity (eye tracking) and cig. intake	30 Smokers (M only)	(+): tDCS reduced cig. intake 24-hours post-stimulation

Table 1.1 Continued: Sham-Controlled Clinical Studies of Nicotine and tDCS

Study	Question	Design	tDCS Parameters	Outcome Measures	Total Sample	Result
(Xu et al., 2013)	Does tDCS affect cigarette craving and negative affect?	Single-session active or sham tDCS (within subjects), separated by at least 48 hours. Sessions followed overnight abstinence from cigarettes.	2mA; 20min An-(L) dlPFC / Cat-(R) SOR	POMS, UTS, attention task	24 Smokers	(+): tDCS reduced withdrawal-associated negative affect, but not craving or inattention
(Boggio et al., 2009)	Does tDCS affect cigarette craving and cigarettes smoked?	5 tDCS sessions, one per day for consecutive days (Active or Sham groups, 13-14 participants per group)	2mA; 20min; An-(L) dlPFC / Cat-(R) dlPFC	Cue-provoked craving and VAS, cig. intake	27 Smokers	(+): tDCS reduced cue-provoked craving and decreased cig. intake
(Fregni et al., 2008)	Does tDCS affect cigarette craving?	Single session An-(L)dlPFC, An-(R)dlPFC, or Sham tDCS, separated by 48 hours (within-subject design)	2mA; 20min; An-(L) dlPFC / Cat-(R) SOR; or An-(R) dlPFC / Cat-(L) SOR	Cue-provoked craving and VAS	23 Smokers	(+): tDCS reduced craving after stimulation

Table 1.1 Continued: Sham-Controlled Clinical Studies of Nicotine and tDCS

Combining Functional Magnetic Resonance Imaging with tDCS

Application of a mechanistic or conceptual model, with evidenced-based support, would significantly improve the quality of research for tDCS and addiction. Physiological outcome measures, such as functional brain activity, could provide a stepping-stone for investment in large-scale clinical trials, as well as valuable insight into the mechanism of tDCS to guide parameter selection. Functional neuroimaging can make a two-fold contribution to the field: first, there is a profuse literature detailing the circuitry involved in addictive disease (detailed in the Systems Pathophysiology section, above), enabling hypothesis-driven testing for neuromodulatory interventions; second, fMRI provides a method for obtaining intermediate outcomes measures (e.g. BOLD signal response to tDCS within addiction relevant circuits), rather than more distal behavioral or clinical variables that are likely to have a smaller effect size (Rasetti & Weinberger, 2011). Thus, neuroimaging offers a valuable technique for quantifying early brain response to tDCS, lending support for or against any specific set of stimulation parameters prior to investment in a clinical trial.

tDCS-fMRI studies indicate that tDCS can modulate regions targeted by the electrode array, as well as distal regions connected to the targeted network. Observations of changes in BOLD signal and network connectivity have been made either through an 'offline' approach (i.e., fMRI scans taken before and after tDCS stimulation outside the scanner), or, more selectively, an 'online' approach (i.e., tDCS applied inside the scanner, simultaneous with fMRI scanning).

The first evidence that tDCS can induce local BOLD signal changes under the electrodes was observed by Baudewig and colleagues (2001), in a small sample of six

subjects. In this study, cathodal tDCS over the left motor cortex reduced activity in the same area during a finger-tapping task, while anodal stimulation resulted in a non-significant increase. The finding that tDCS can directly alter BOLD signaling in the motor cortex has since been replicated (Antal et al., 2011; Kwon et al., 2008). Anodal stimulation over the visual cortex (1mA, 10min) similarly enhances BOLD response to evoked visual stimuli in occipital cortex (Alekseichuk et al., 2016). Demonstrating that this effect is not limited to sensory and motor processing, higher-order cognitive regions, such as the left inferior frontal gyrus (IFG), involved in language processing and verbal fluency have also been modulated. Specifically, anodal stimulation of the left-IFG has been observed to increase connectivity within the region (Meinzer et al., 2012), as well as enhanced processing efficiency corresponding to improved language task performance (Fiori et al., 2018). The above findings suggests that tDCS can alter cortical processing with relative focality.

As has been observed with TMS stimulation (Fox et al., 2012), there is evidence that tDCS can also modify distal sites that may be related to the stimulation target. Stimulation of motor cortex with cathodal tDCS has been observed to increase both interhemispheric coherence between right and left motor networks, as well as within-network DMN connectivity strength (Amadi et al., 2014), while bilateral stimulation of supplementary motor areas altered connectivity with multiple prefrontal regions, including superior, medial, and inferior frontal gyri, as well as posterior insula (Sehm et al., 2012). Stimulation of the left dlPFC has been observed to alter connectivity of the region with distal areas in the contralateral hemisphere that are considered to be ECN-related nodes (e.g. right medial frontal gyrus; (Park et al., 2013)), as well as within-network connectivity

of the DMN and ECN. Peña-Gómez and colleagues reported that left dlPFC stimulation increased within-network strength of the ECN, and reduced within-network strength of the DMN (2012); however, Keeser and colleagues observed that within-network connectivity of DMN and ECN were both augmented by left-dlPFC stimulation (2011). Of note, dlPFC stimulation has further been reported to increase striatal glutamate and glutamine (as measured by magnetic resonance spectroscopy; (Hone-Blanchet et al., 2015)), and to suppress amygdala reactivity (Ironside et al., 2019), both regions implicated in the addiction neurocircuitry.

Based on the above combined evidence, tDCS appears to have potential to modulate brain networks, including those implicated in psychiatric disease. fMRI offers a quantitative method to evaluate the efficacy of tDCS action, either acutely after a single session, or pre/post clinical treatment. Some researchers have already begun advancing this method in its application to drug addiction, and this work is described below.

tDCS-fMRI Studies of Drug Addiction

Two studies have examined offline tDCS effects on fMRI correlates of smoking addiction ((Mondino et al., 2018; Yang et al., 2017); **Error! Reference source not found.**, for fMRI summary). Mondino and colleagues ((2018); **Error! Reference source not found.** for clinical design) examined the impact of 10 sessions of tDCS on smoking outcomes and circuitry (2mA; 20min; 2x per day for five consecutive days), with anode over right-dlPFC and cathode over left occipital area. 24 participants, assigned to either active (n=14) or sham stimulation (n=10), completed a smoking cue-reactivity fMRI task paradigm before and after tDCS treatment. The group found that active stimulation enhanced PCC reactivity to smoking cues and reduced craving, compared to sham. The

increased PCC was interpreted as related to a strategy to resist craving, as reported in a previous study (Brody et al., 2007).

In a second study, Yang and colleagues (2017) tested the effect of single-session tDCS on smoking-related circuitry (1mA, 30min; active/sham crossover design, 1-week washout), with anode over left-dlPFC and cathode over right-dlPFC in 32 participants. Immediately following stimulation, participants completed a resting state scan, smoking cue-reactivity task, and emotional images task (an MR-compatible tDCS device was used, but no simultaneous data reported). The authors observed that active tDCS suppressed BOLD response to smoking cues in the left superior-frontal and medial-frontal gyri, and strengthened connectivity between left-dlPFC and right parahippocampal gyrus (PHG); further, the strength of the dlPFC-PHG relationship was associated with reduced craving. Given that the parahippocampal gyrus is a core node of the medial-temporal DMN subsystem, involved in autobiographical memories (Andrews-Hanna et al., 2014), and that these memories may be focused on smoking-related experiences or mental scenes during withdrawal (R. Zhang & Volkow, 2019), the increased dlPFC–PHG strength may represent enhanced top-down control over a hyperactive DMN circuit.

Table 1.2: Studies using fMRI and tDCS to examine addictive behavior, *next page*

Outcome Measures: fALFF = fractional amplitude of low-frequency fluctuation; rsfMRI = Resting State Functional MRI; ASL = Arterial Spin Labeling; DTI = Diffusion Tensor Imaging; ADC = Apparent Diffusion Coefficient; FA = Fractional Anisotropy; CBF = Cerebral Blood Flow; BART = Balloon Analog Risk Task; *Sample:* MUD = Methamphetamine Use Disorder; CUD = Cocaine Use Disorder; HC = Healthy Controls.

Table describes only fMRI/tDCS study arms; additional experiments not reflected in this table.
Sample size represents final analytical sample.

Study	Substance or Behavior	tDCS Parameters	MRI Methods & Outcome Measures	Sessions	Sample Size	Result
(Mondino et al., 2018)	Nicotine	2mA; 20min; An-(R) dlPFC / Cat-(L) Occipital	Pre/Post fMRI: Cue-reactivity task. Craving measure.	10 sessions: 2 per day for 5 consecutive days; active or sham	24 Smokers (14 active, 10 sham)	tDCS reduced smoking craving and increased PCC reactivity to smoking cues. No change in CPD.
(Yang et al., 2017)	Nicotine	1mA; 30min; An-(L) dlPFC / Cat-(R) dlPFC	Post-tDCS fMRI: Resting state, cue-reactivity task, and emotion task	1 session each active and sham, 1-week separated	32 Smokers (M only)	tDCS increased dlPFC–PHG functional connectivity
(Shahbabaie et al., 2018)	Methamphetamine	2mA; 20min; An-(R) dlPFC / Cat-(L) dlPFC	Pre/Post fMRI: Resting state. Craving measure.	1 session each active and sham, 1-week separated	15 MUD (M only)	tDCS reduced craving, suppressed DMN and strengthened SN and ECN intra-network connectivity
(Nakamura-Palacios et al., 2016)	Cocaine	2mA; 20min, or 13on, 20off, 13on; An-(R) dlPFC / Cat-(L) dlPFC	Pre-post DTI	5 sessions; 1 per day for 5 consecutive days; active or sham	14 CUD (7 active, 7 sham)	Increased voxels, FA, and ADC between vmPFC and NAcc in active tDCS, and reduced craving and relapses
(Meyer et al., 2019)	Reward Systems (Healthy Controls)	2mA; 15min An-vmPFC / Cat-(R) dlPFC	Pre/Post fMRI: fALFF	1 session either active or inverse polarity	40 HC (20 active, 20 inverse)	An-vmPFC tDCS increased resting-state frequency (0.01-0.08 Hz) signal and increased activity in striatal areas
(Weber et al., 2014)	Reward Systems (Healthy Controls)	1.5mA; 15min; An-(R) dlPFC / Cat-(L) dlPFC	Pre/Post fMRI: ASL, BART task	1 session either active or sham	22 HC (11 active, 11 sham)	tDCS reduced resting CBF in the OFC and caudate, and reduced whole-brain connectivity of right ACC
(Chib et al., 2013)	Reward Systems (Healthy Controls)	2mA; 15min; An-vmPFC / Cat-(R) dlPFC	Pre/Post fMRI: Face rating task	1 session either active or inverse ("active sham")	39 HC (19 active, 20 inverse)	Face ratings more positively correlated with ventral midbrain activity following An-vmPFC tDCS

Table 1.2: Studies using fMRI and tDCS to examine addictive behavior
Caption on preceding page

Two pilot (≤ 15 subjects) studies have explored effects of tDCS on stimulant addiction coupled with fMRI (**Error! Reference source not found.**). Shahbabaie et al. (Shahbabaie et al., 2018) found that single session tDCS (Anode right-dlPFC/Cathode left-dlPFC, 2mA, 20min) reduced acute craving and intra-network DMN connectivity, while increasing ECN and SN intra-network connectivity, in 15 methamphetamine users. Nakamura-Palacios and colleagues (2016) tested the effect of five sessions of tDCS (Anode right-dlPFC/Cathode left-dlPFC, 2mA, 20min) on diffusion tensor imaging (DTI) outcome measures in sample of 14 cocaine users. Active tDCS (n=7) appeared to strengthen the pathway between vmPFC and NAcc, and this change was associated with reduced craving reports, suggesting improved top-down control of craving.

While the above results are promising, the findings are still preliminary, given certain methodological constraints. Mondino et al. (2018) reported effects of active tDCS in a small sample size (n=14) with a generous statistical threshold (voxel-wise p-value equal to 0.005, rather than the more appropriate 0.001, (Woo et al., 2014)) with multiple comparisons correction level not reported for the tDCS effect. For Yang et al. (2017), reporting was unclear as to the duration of each task and how long measurements were taken following stimulation; time to measurement could impact whether the data was collected within the tDCS "after-effects" window. Additionally, Yang et al. did not use recommended MR-tDCS technique (gel over electrodes; (Woods et al., 2016)), but rather used the saline-sponge method. While effective for impedance control in non-MRI studies, the sponges are likely to dry out in the MR environment, especially for long stimulation sessions such as 30 minutes, potentially compromising stimulation quality. Finally, the studies by Shahbabaie et al. and Nakamura-Palacios et al. are encouraging, but constrained

by exploratory sample sizes. Thus, these early results should be considered preliminary, and could be enhanced by improved rigor and reproducibility.

As of time of writing, no other publications have quantified tDCS effects on addicted populations (including gaming/gambling) using fMRI methods[1]. However, three studies assessed tDCS effects on reward-related circuitry in nonsmokers ((Chib et al., 2013; Meyer et al., 2019; Weber et al., 2014); **Error! Reference source not found.**). Meyer et al. and Chib et al. reported that anodal vmPFC stimulation resulted in increased activity of the striatal DA system, including ventral midbrain (encompassing VTA and SN); Weber et al. observed that anodal tDCS to R-dlPFC decreased resting CBF within the orbitofrontal cortex and caudate, and enhanced evoked activity within both right dlPFC and ACC during a risk-taking task. Together, these studies suggest that tDCS, especially targeted to vmPFC or dlPFC, may mediate both local and distal changes to reward processing circuits.

Overall, while there has yet to be a "gold standard" study or set of studies examining tDCS effects on addictive disorders, the handful of pilot fMRI studies and larger cohort clinical trials suggests that the intervention may improve functional circuitry associated with nicotine and other addictions. Contributions to rigorousness of experimental design would greatly improve evidence-based decisions regarding application of tDCS to addictive disease.

Summary and Conclusion

In sum, early evidence suggests that tDCS may be uniquely poised as a non-invasive neurostimulation tool to modulate neural circuits dysregulated in nicotine

[1] Systematic query of PubMed database for MeSH terms related to tDCS, fMRI, and common drugs of abuse (cocaine, methamphetamine, opiates, hallucinogens, cannabis, alcohol), or addiction-related keywords (reward, addiction, substance use disorder); excluded review articles, preclinical studies, and manuscripts not using tDCS combined with functional neuroimaging. Query conducted January 2020.

addiction, used independently or as an add-on to current counseling and pharmacotherapy for smoking cessation. While studies thus far have been encouraging, none have utilized a large-scale network model, or tested the model using simultaneous, 'online' fMRI technique. In addition to clinical trials that could empirically narrow the parameter space, the field would benefit from mechanistically designed tDCS protocol to specifically test hypothesis-based tDCS montage. As the circuits of interest in nicotine dependence (SN, ECN, DMN) are thought to be common across several substance use disorders, as well as other forms of psychopathology, such an experimental design would be generalizable and speak to the efficacy of tDCS to modify clinically relevant cognitive circuits.

The rationale described above forms the basis of the thesis work presented herein. The specific aims of the thesis are described next in Chapter 2, followed by the published manuscript describing the work in full (Chapter 3), and a discussion on its contribution to the field and future directions of the work (Chapter 4).

Chapter 2: Specific Aims

Cigarette smoking remains the leading cause of preventable death and disease in the United States, accounting for about half a million deaths each year. Current smoking cessation aids are highly inadequate, with the most efficacious treatment, varenicline, having only ~27% cessation rate at 6-months post-quit date. Specifically, symptoms of the NWS remain a major impediment for smokers trying to quit; most attempts fail within the 1–2 weeks of abstinence. Resting state functional connectivity studies have revealed that the brain can be divided into multiple large-scale functional networks, which can become dysregulated in psychiatric disease. The cognitive and affective disturbances of the NWS have been hypothesized to be mediated via dysregulation within and between three of these large-scale networks, specifically: reduced connectivity within the ECN, and between the ECN and SN; along with increased connectivity within the DMN, and between the DMN and SN (for review, p. 16). A treatment that acts by modifying one or more of these network alterations may address the underlying pathophysiology of nicotine addiction and improve clinical outcomes.

Transcranial Direct Current Stimulation (tDCS) has the potential to modify neuronal circuits by producing a subthreshold conductive current through the scalp. Two potential targets for tDCS as a smoking cessation aid are the dorsolateral prefrontal cortex (dlPFC), a node of the ECN, and the ventromedial prefrontal cortex (vmPFC), a node of the DMN. The goal of this work is to investigate the acute effects of tDCS on modulating large-scale brain networks dysregulated in nicotine addiction and withdrawal.

The central hypothesis of this dissertation is that connectivity of the ECN, DMN, & SN will be modified by acute application of tDCS to cortical nodes of ECN and DMN

networks in chronic cigarette smokers (Figure 2.1). Cognitive constructs associated with the three networks were individually probed by task-based fMRI, with outcome measures of task-related BOLD signal and behavioral performance. NWS-remediating tDCS was targeted to two regions near the cortical surface: the dorsolateral pre-frontal cortex (dlPFC), a node of the ECN; and the ventromedial prefrontal cortex (vmPFC), a node of the DMN. The experimental Aims examine the effect of tDCS on two separate aspects of nicotine addiction and withdrawal: *Trait-Smoking*, i.e. whether tDCS affects smokers in the nicotine-sated state differently as compared to healthy, nonsmoking controls; and *Nicotine-State*, i.e. whether tDCS affects smokers differently in nicotine deprived (i.e. acute withdrawal) vs. sated conditions.

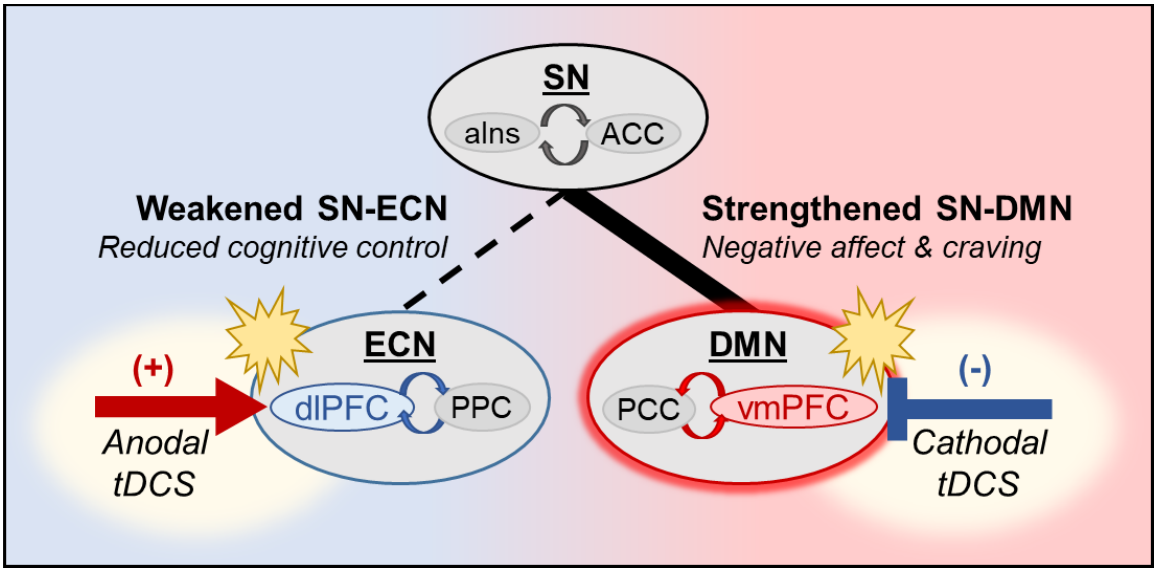


Figure 2.1: Hypothesis.

The Nicotine Withdrawal Syndrome is characterized by poor cognitive control and increased negative affect. Abstinent smokers exhibit reduced functional connectivity within the ECN, and between the ECN & SN; and increased connectivity within the DMN, and between the DMN & SN. tDCS may improve the NWS by applying excitatory (anodal) stimulation to the dlPFC, a node of the ECN; and inhibitory (cathodal) stimulation to the vmPFC, a node of the DMN. *ECN = Executive Control Network, DMN = Default Mode Network, SN = Salience Network, dlPFC = dorsolateral prefrontal cortex, vmPFC = ventromedial prefrontal cortex, aIns = anterior insula, ACC = Anterior cingulate cortex, PPC = posterior parietal cortex, PCC = posterior cingulate cortex, tDCS = transcranial direct current stimulation. Reproduced with publisher permission from (Aronson Fischell et al., 2020).*

Overall Approach: Acute, neurophysiological effects of single-session tDCS on three NWS-related, large-scale brain networks were investigated through cognitive task probes and simultaneous fMRI. Smokers and matched nonsmokers were recruited to participate in a randomized, sham-controlled, double-blind, crossover design with three tDCS (2mA, 25min) conditions: anodal left dlPFC and cathodal right vmPFC (*"An-dlPFC"*, i.e. therapeutic montage); cathodal left dlPFC and anodal right vmPFC (*"An-vmPFC"*, i.e. positive control); and *Sham*. To assess *Trait-Smoking* and *Nicotine-State* comparisons, smokers attended two study visits -- each following 12-hours of overnight abstinence -- wearing a double-blinded, randomized Study Patch containing either nicotine (sated condition) or placebo (withdrawn condition). It was expected that smokers would perform similarly to nonsmokers on task behaviors (accuracy, response speed) and cognitive processing (whole-brain, task-evoked BOLD activity) during the sated condition, but would demonstrate withdrawal-associated deficits during the nicotine deprivation condition.

Each prefrontal NWS network, and downstream amygdala circuitry, was engaged by a specific cognitive task probe. The ECN, and anticorrelated DMN, were engaged using a well-validated working memory task (the N-back task); SN activity (specifically, insula and ACC) was induced through an established conflict monitoring task (the Flanker task); and amygdala reactivity and regulation were probed using an emotional face matching paradigm (the Matching Faces and Shapes task). Outcome measures for each task included reaction time, accuracy, and BOLD signal in both *a-priori*, task-related regions of interest, as well as in whole-brain exploratory analysis.

Aim 1, Trait-Smoking: To evaluate the effects of prefrontal (combined dlPFC and vmPFC) tDCS on ECN, DMN, and SN activity; and determine whether the effects are modified by trait smoking.

PREDICTION 1.1: *An-dlPFC* tDCS will strengthen ECN and SN activation, weaken DMN activity, and improve behavioral performance in the three cognitive tasks, in both smokers and healthy controls.

PREDICTION 1.2: *An-vmPFC* tDCS will mimic an NWS-like effect in both groups.

Aim 2, Nicotine-State: To determine whether a tDCS response in smokers is modulated by the nicotine sated and nicotine deprived states.

PREDICTION 2.1: Smokers will be most sensitive to *An-dlPFC* tDCS effects (enhancement of ECN and SN, suppression of DMN) during the withdrawal state, and *An-vmPFC* tDCS (NWS-like pattern) during the sated state.

Broader Impact: tDCS is an emerging intervention at the crossroads of basic neuroscience research and clinical translation, with the potential to alter the dynamics of brain network connectivity. Through simultaneous tDCS-fMRI in a population of smokers and nonsmokers, this study explored the ability for tDCS to alter cognitive constructs and neuronal activity previously implicated in nicotine dependence, and thus potentially serve as a smoking cessation tool.

Chapter 3: Transcranial Direct Current Stimulation Applied to the Dorsolateral and Ventromedial Prefrontal Cortices in Smokers Modifies Cognitive Circuits Implicated in the Nicotine Withdrawal Syndrome [2, 3]

Introduction

The Nicotine Withdrawal Syndrome (NWS) significantly contributes to the high rate of smoking relapse (Hughes et al., 2004; Shiffman et al., 1996). NWS peaks within one week of quitting, is associated with craving, negative affect (dysphoria, irritability, anxiety), attentional and cognitive impairment (poor concentration, impulsive decision making), and is alleviated by acute smoking (American Psychiatric Association, 2013; Hughes, 1992). Despite the well-known importance (U.S. Department of Health and Human Services, 2014) and challenge (Babb et al., 2017; Centers for Disease Control and Prevention, 2009) of smoking cessation, response rates to current FDA-approved pharmacotherapies remains poor; the most efficacious, varenicline, has ~27% absolute cessation rate (6-months post-quit), while various nicotine replacement therapies (e.g. patch, gum, nasal spray) fare worse (Cahill et al., 2013, 2014). Inadequate therapeutic response may be explained by the neuroplastic nature of the disease; pharmacotherapy relieves withdrawal *state* symptoms, but acts minimally on underlying disease *trait* pathology. Addiction, a chronic, relapsing cycle of binge, intoxication, and withdrawal (Koob & Volkow, 2010), develops from drug-induced neuroplastic and allostatic changes to reward, cognitive and self-referential brain circuits (Goldstein & Volkow, 2011; Kalivas

[2] Aronson Fischell, S., Ross, T. J., Deng, Z.-D., Salmeron, B. J., & Stein, E. A. (2020). Transcranial Direct Current Stimulation Applied to the Dorsolateral and Ventromedial Prefrontal Cortices in Smokers Modifies Cognitive Circuits Implicated in the Nicotine Withdrawal Syndrome. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *5*(4), 448–460. https://doi.org/10.1016/j.bpsc.2019.12.020.

[3] Author's manuscript reproduced with permission from publisher.

& O'Brien, 2008; Koob & LeMoal, 1997; R. Zhang & Volkow, 2019). Thus, a treatment acting directly on these circuits, such as noninvasive neuromodulation, would be of important clinical value. As such, transcranial direct current stimulation (tDCS) has been considered as an adjuvant or alternative treatment for smoking cessation (Dunlop et al., 2017, p. 2016; Ekhtiari et al., 2019; Yavari et al., 2016). Here, we investigated the influence of tDCS on large-scale brain networks associated with smoking dependence and withdrawal.

The brain is intrinsically organized into multiple large-scale functional networks that appear to be stable across healthy individuals (Biswal et al., 1995; Damoiseaux et al., 2006; Fox et al., 2005; S. M. Smith et al., 2009; Yeo et al., 2011). Because networks are functionally (vs. anatomically) defined using data-driven methods, the total number of networks and their components can vary across parcellation methods. However, three networks have consistently emerged that are considered to be especially vulnerable to disruption in neuropsychiatric disorders (Damoiseaux et al., 2006; Garrity et al., 2007; Greicius et al., 2004; Menon, 2011): (1) the Executive Control Network (ECN), a "task-positive" network with core nodes in the dorsolateral prefrontal cortex (dlPFC) and posterior parietal cortex (PPC), which supports goal-directed performance and attentional control (Seeley et al., 2007); (2) the Default Mode Network (DMN), localized within the ventromedial prefrontal cortex (vmPFC), parahippocampal gyrus (PHG) and the posterior cingulate cortex (PCC), which supports many forms of self-referential thought, including planning and rumination (Buckner et al., 2008; Greicius et al., 2003, 2009), and is generally anticorrelated to the ECN (Fox et al., 2005; Raichle et al., 2001); and (3) the Salience Network (SN), thought to guide attention to endogenous or exogenous stimuli based on

homeostatic and environmental context, and includes the anterior insula and dorsal anterior cingulate cortex (dACC) (Sridharan et al., 2008). Aspects of each of these networks downregulate the amygdala and related limbic circuitry (Ochsner et al., 2002).

The cognitive and affective disturbances of the NWS have been attributed to reduced circuit strength of the ECN and SN, increased connectivity strength of the DMN, and hyperactivity of the amygdala (Fedota & Stein, 2015; Sutherland et al., 2012)**.** This model has been supported by functional magnetic resonance imaging (fMRI) studies demonstrating network dysfunction as a trait characteristic of smoking, and a state characteristic of acute nicotine deprivation (Fedota et al., 2015, 2016; Hong et al., 2009; Lerman et al., 2014; Lesage et al., 2017; Sutherland, Carroll, Salmeron, Ross, Hong, et al., 2013a, 2013b). Nicotine deprivation in smokers enhances amygdala reactivity (Sutherland, Carroll, Salmeron, Ross, Hong, et al., 2013a), reduces anti-connectivity between the DMN and ECN (Cole et al., 2010), and enhances insula–DMN connectivity (Fedota et al., 2018).

tDCS has the potential to modify neuronal circuits by applying a subthreshold electrical current through the scalp. tDCS alters resting functional networks (Amadi et al., 2014; Keeser et al., 2011; Krishnamurthy et al., 2015; Meinzer et al., 2012; Park et al., 2013; Peña-Gómez et al., 2012), brain neurochemistry (Hone-Blanchet et al., 2015), and BOLD signal (Antal et al., 2011, 2012; Ironside et al., 2019; Zheng et al., 2011), and has been reported to reduce cigarette craving and consumption (Boggio et al., 2009; Falcone et al., 2016; Fecteau et al., 2014; Fregni et al., 2008; Z. Meng et al., 2014; Mondino et al., 2018). We assessed acute, single-session tDCS modulation of the three large-scale brain networks and their associated cognitive functions in a cohort of healthy controls and nontreatment seeking smokers, in both nicotine sated and deprived states.

We hypothesized that function of the ECN, DMN, and SN would be modified by acute, single-session application of tDCS to cortical nodes of ECN (dlPFC) and DMN (vmPFC) (**Fig. S1**)[4]. We predicted that, compared to sham, excitatory, anodal-dlPFC tDCS paired with inhibitory, cathodal-vmPFC tDCS would enhance ECN and SN nodes, and downregulate DMN and amygdala nodes. Further, we predicted that the direction of network change would be inverted following tDCS polarity reversal.

Methods and Materials

Participants

Healthy, right-handed subjects, 18–60 years, were enrolled from the Baltimore, Maryland area (**Fig. S2** for CONSORT diagram, **Table 3.1** for demographics): an exploratory sample of 15 smokers (smoking ≥ 1 year with NicAlert ≥ 4) and 28 demographically matched nonsmokers (no past-year nicotine use and no lifetime daily nicotine use of >1 month). Exclusion criteria included MRI contraindications, major medical, neurologic or psychiatric conditions, regular medication use that might interfere with BOLD signal, and drug dependence (except nicotine in smokers). Written informed consent was obtained in accordance with the National Institute on Drug Abuse - Intramural Research Program (NIDA-IRP) Institutional Review Board.

[4] Supplemental figures, tables and text can be found in Appendix A

Total Completers (N = 43)	Nonsmokers (N = 28)	Smokers (N = 15)	p-value*
Gender (F:M)	14:14	7:8	1.00
Age (Mean: SD)	39.3 (10.3)	40.1 (12.0)	0.82
Years of Education (Mean: SD)	14.1 (2.1)	13.3 (1.63)	0.19
Highest Degree			0.46
Some H.S.	1	1	
High School	6	4	
Some College	9	8	
A.A. Degree	1	1	
College Graduate	9	1	
Masters	2	0	
WASI Full-4 IQ	101 (9.75)	103 (15.5)	0.59
Race			0.40
Asian	1	0	
White	10	6	
Black/African-American	15	6	
Multiracial	1	3	
American Indian/Alaska Native	1	0	
Ethnicity (Hispanic: Not Hispanic)	2:26	1:14	1.00

Table 3.1: Participant Demographics.
Numbers represent *N* or mean/SD. *Welch's Two-Sample t-test for numerical data (R, *stats::t.test*), Pearson's Chi-squared test for categorical data (R, *stats::chisq.test*, with simulated p-values for Education, Race, and Ethnicity).

Experimental Design

The randomized, double-blind, sham-controlled crossover design (**Fig. 3.1A**) involved three tDCS-fMRI sessions (detailed below). Smokers completed all three tDCS-fMRI sessions twice, across 2 days separated by ≥48h, randomized and blinded between a 24h-release nicotine (NicoDerm-CQ; GlaxoSmithKline) or placebo patch, each following biochemically verified 12h nicotine abstinence. Nicotine patch dose matched cigarettes smoked per day ('cpd'; 10–15cpd, 21mg; 15–20cpd, 28mg; 20–25cpd, 35mg; ≥25cpd, 42mg), and was applied the morning of the appointment, ≥2h prior to scanning (Benowitz et al., 2009). Primary tDCS outcomes were behavioral and neural responses to three cognitive tasks, during tDCS-fMRI sessions.

Figure 3.1: Experimental Design, tDCS Montage and Simulation of tDCS-induced E-field Distribution.

(A) Experimental Design. Double-blinded, randomized, sham-controlled crossover study completed by both smokers ("Smoker timeline") and nonsmokers ("Nonsmoker timeline"). All subjects completed three tDCS-fMRI sessions, randomized between the three tDCS conditions (part B of this figure). Smokers completed each visit following biochemically verified (CO monitor) 12-hours overnight nicotine abstinence, and placed a study patch, containing either nicotine or placebo, in the morning at least 2 hours prior to the first scan of the day. All conditions (study patch, tDCS condition) were randomized and counterbalanced. On the second visit day, the tDCS conditions were re-randomized for smoker participants. Subjects completed multiple simultaneous fMRI scans before, during and after tDCS, in a fixed order ("tDCS-fMRI session: scan order"). tDCS sessions were separated by at least a 90-minute inter-tDCS period (equating to an inter-scan interval – the time spent outside of the scanner between the end of one MRI session and start of another – of at least ~30-45 minutes). Each tDCS-fMRI scan lasted between 60 and 90 minutes. The study visit day (with 3 tDCS-fMRI sessions) lasted ~7-8 hours, including pre-MRI nursing assessments, task training and questionnaires. In some cases of equipment or participant scheduling issues, some tDCS sessions were separated by a number of days. The counterbalance conditions were determined by the NIDA-IRP Pharmacy and kept blinded there, with tDCS setting programmed by the MR-operator according to a key. Note that subjects performed the N-back twice, both during and after stimulation. Here, we report only the N-back online (during). A DTI scan was taken once per participant, at the end of one of the tDCS-fMRI scan sessions. Note: "tDCS-fMRI session: scan order" panel applies to all tDCS-fMRI sessions.

(B) tDCS Montage (2mA, 25 minutes) with three conditions, from left to right: (1) Anodal-(L)dlPFC + Cathodal-(R)vmPFC, "An-dlPFC"; (2) Cathodal-dlPFC + Anodal-vmPFC, "An-vmPFC"; and (3) Sham. tDCS was administered inside the MRI scanner with simultaneous fMRI scanning. The electrodes were 5cm x 7cm (35cm2) and covered evenly with a 3-5mm layer of conductive paste (Ten20, Weaver and Company). The (R)-vmPFC electrode was placed over the R supraorbital ridge parallel to the brow, and the (L)-dlPFC electrode was placed over F3, perpendicular to the brow.

(C) Across all 43 subjects, average normal component of the electric field, |E|normal, for, from left to right: (1) anodal-(L)dlPFC/cathodal-(R)vmPFC stimulation, and (2) cathodal-(L)dlPFC/anodal-(R)vmPFC stimulation. Positive values denote inward current flow and negative values denote outward current flow.

(D) Average of the E-field strengths across the 43 subjects on the cortical surface. The E-field magnitude distributions are the same for anodal and cathodal tDCS; however, the directions of current flow are opposite. L = Left, R = Right, dlPFC = dorsolateral prefrontal cortex, vmPFC = ventromedial prefrontal cortex.

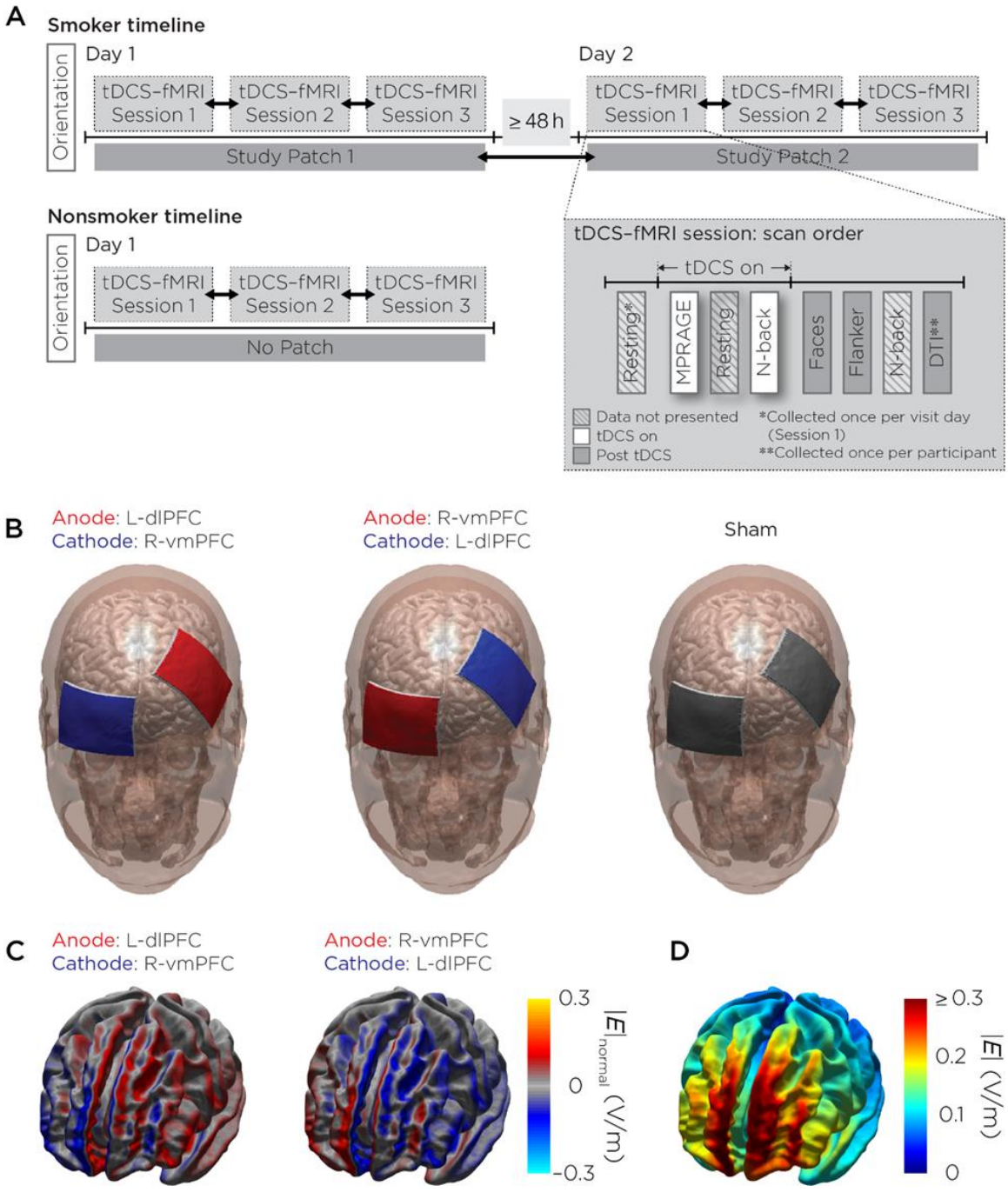


Figure 3.1: Experimental Design, tDCS Montage and Simulation of tDCS-induced E-field Distribution.
Caption on preceding page.

Cognitive Tasks

We used three tasks to test circuitry implicated in the NWS: an N-back (Working Memory, "WM") task, to measure ECN activation (Cohen et al., 1994; Lerman et al., 2014) and DMN suppression (Fox et al., 2005); a modified Parametric Flanker Task (error monitoring task) (Fedota et al., 2016) to measure ACC and insular activity (SN nodes); and a modified Matching Faces and Shapes task (Sutherland, Carroll, Salmeron, Ross, Hong, et al., 2013a) to measure amygdala reactivity, and, indirectly, prefrontal top-down control (Foland-Ross et al., 2010; Hariri et al., 2002; Ochsner & Gross, 2005). Tasks were performed inside the scanner either during (online: N-back, 13m into tDCS) or immediately following stimulation (offline: Faces, 1m post-tDCS; Flanker, 10m post-tDCS). Task details are fully described in the **Supplemental Methods**. Each task has previously detected characteristics of nicotine dependence or withdrawal: N-back performance is predictive of smoking relapse (Loughead et al., 2015); smokers demonstrate difficulty recruiting SN activity during the Flanker (Fedota et al., 2016); and the amygdala is hyperactivated in NWS, whereas connectivity of amygdala, insula and DMN circuits is down-regulated by nicotine agonism (Sutherland, Carroll, Salmeron, Ross, Hong, et al., 2013a, 2013b).

Transcranial Direct Current Stimulation

Subjects completed 3 tDCS sessions (2mA for 25m, 15s ramp; NeuroConn DC-Stimulator Plus-MR; neuroCare, München, Germany) per day within the MRI scanner -- two active, one sham -- separated by ≥90m washout (Dedoncker et al., 2016). The order of tDCS sessions was randomized, counterbalanced, and double-blinded. In "*An-dlPFC*" tDCS, anodal stimulation was applied to L-dlPFC (Beam-F3 method (Beam et al., 2009)),

and cathodal stimulation to R-vmPFC (R-supra-orbital ridge, **Fig. 1B**); polarity was reversed in "*An-vmPFC*" tDCS. For sham, current was briefly ramped on and off at session start, after which brief, minimal pulses were delivered only to provide an impedance reading (Gandiga et al., 2006; Woods et al., 2016). Participants completed a blinding questionnaire following each tDCS session. See the **Supplemental Methods** for additional tDCS details.

Image Acquisition

Whole-brain echo-planar functional images, structural T1-weighted brain images (MPRAGE) and diffusion tensor (DTI) images were acquired on a 3T Siemens Magnetom Prisma scanner at NIDA-IRP (Baltimore, Maryland) with a 20-channel head coil (**Supplemental Methods, Table S1**).

Statistical Analysis

We generated statistical models to test tDCS effects on two aspects of smoking dependence: *Trait-Smoking*, the between-subjects factor of nonsmokers vs. sated-smokers; and *Nicotine-State*, the within-smokers factor of nicotine abstinence vs. satiety. For Faces task only, due to technical issues, data for 1 smoker were lost in *Trait-Smoking* analyses (N_{Smoker}=14); an additional smoker did not respond to this task under the placebo patch, and their data were removed in *Nicotine-State* analyses (N_{Smoker}=13).

Behavioral Measures

We measured response speed (inverse Reaction Time, 1/s) and accuracy on each trial. On the N-back, sufficient hits, false alarms, and errors (commission/omission) occurred to evaluate signal detection theoretic measures (d-prime sensitivity, criterion, and omissions). Modeling was conducted using R Statistical Computing software (with

packages *tidyverse* (Wickham, 2017), *afex* (Singmann et al., 2019), *emmeans* (Lenth et al., 2019), *neuropsychology* (Makowski & Alday, 2016)). Type III Repeated-measures ANOVA (*afex::aov_ez*) modeled three mixed factors for each task: within-subjects factor of tDCS stimulation (*An-dlPFC*, *An-vmPFC*, *Sham*); within-subjects factor of Task Level (i.e. difficulty on N-back and Flanker, Matching type on Faces); and between-subjects factor of Group for the *Trait-Smoking* model (Nonsmoker, Smoker-sated), or within-subjects factor of Patch for the *Nicotine-State* model (Nicotine, Placebo). We evaluated significant interactions ($p<0.05$) with Tukey post-hoc contrasts (*emmeans*).

Imaging Analysis

fMRI scans were pre-processed with the Brain Imaging Data Structure (K. Gorgolewski et al., 2011) application fmriprep (v1.3.1) (Esteban, Markiewicz, et al., 2019)), while EPI brain-masking, first-level and group processing were carried out in AFNI (v.18.1.24) (R. W. Cox, 1996). Statistical tests on region of interest (ROI) data were carried out in R. We simulated the average electrical field (E-field) induced by tDCS across all subjects using MPRAGE and DTI scans, processed with SimNIBS v.3.0 (Thielscher et al., 2015). See **Supplemental Methods** for details.

Region of Interest Analysis

For each task, we pursued a ROI analysis to directly test the associated network-based hypotheses. For N-back, nine ECN-associated regions were derived from the Neurosynth (http://neurosynth.org) "working memory" map: bilateral Inferior Frontal Gyrus, bilateral Inferior Parietal Lobule/Angular Gyrus, bilateral Middle Frontal Gyrus/BA10 (MFG), R-MFG/BA6, and bilateral Cerebellum/Crus 1. For Flanker, three SN nodes were functionally defined (Fedota et al., 2016): right ACC, and bilateral Insula.

For Faces, six bilateral amygdala sub-regions were defined (Caparelli et al., 2017): superficial (corticoid) nuclei, centromedial groups, and laterobasal complexes. First-level (participant-session) models of correct-press trials were generated (*AFNI:3dDeconvolve, 3dREMLfit*), including regressors for six head motion parameters, incorrect and omitted events, and censoring timepoints with head motion >0.5mm Framewise Displacement (Power et al., 2012). For N-back and Faces, first-level contrasts represented high WM-load (3-back minus 0-back) and amygdala reactivity (Faces minus Shapes). To maintain the Flanker's parametric design, we generated first-level processed files for each difficulty level (i.e. number of flankers), which were then used as levels in a within-subjects, task-contrast factor for the second-level ANOVA (below). Next, we extracted BOLD signal from the ROIs for each task (AFNI:*3dROIstats*) across all sessions and subjects. We removed outlier data points (>1.5*Interquartile Ratio beyond 25^{th} or 75^{th} percentiles) for all values measured within the ROI.

We modeled factors of interest using a mixed-model ANOVA (*afex::mixed*). For N-back and Faces, we modeled two factors: (1) the within-subjects factor of tDCS; and (2) a between-subjects factor Group (*Trait-Smoking* model), or a within-subjects factor of Patch (*Nicotine-State* model). For the Flanker, we included a within-subjects factor of task difficulty to generate a parametric task contrast. We applied a Bonferroni-corrected significance threshold of $p<0.05$ for number of ROIs for each task (N-back, nine ROIs, $p_{raw}<0.0057$; Flanker, three ROIs, $p_{raw}<0.0167$; Faces, six ROIs, $p_{raw}<0.0085$).

Whole Brain Analysis

We performed exploratory whole-brain analyses using multifactorial ANOVA (*AFNI:3dMVM*). Main effects and interactions of tDCS, Group or Patch, were corrected

for whole-brain familywise error (FWE) $\alpha<0.01$ and p-voxelwise<0.001, with cluster size determined using *AFNI:3dClustSim* for each task/model dataset. Task maps were generated by assessing the main effect of task difficulty for the Flanker, and a first-level contrast for N-back (3-back minus 0-back) and Faces (Faces minus Shapes). We applied a stringent whole-brain correction of at least $\alpha<0.01$ FWE for all task maps.

Lastly, we explored whether tDCS altered brain-behavior relationships using whole-brain regression (3dRegAna, **Supplemental Methods**).

Results

Results are organized by statistical model: *Trait-Smoking*, the between-subjects comparison of sated-smokers to nonsmokers; and *Nicotine-State*, the within-smokers comparison of sated vs. withdrawal state.

Task Behavior

Overall, the tasks produced expected behavioral outcomes (**Fig. S3, S4**).

Trait-Smoking Model:

Sated smokers performed more accurately, missed fewer responses, and had lower signal criterion than nonsmokers on the N-back ($p<0.05$, **Fig.S3A, S5A**), and performed faster, with an accuracy Group*Task interaction on Faces ($p<0.05$, **Fig.S3C-D**). There were no main effects or interactions of tDCS.

Nicotine-State Model:

Across all three tasks, smokers wearing the placebo (vs. nicotine) patch demonstrated slowed response speed (all $p<0.05$), and reduced accuracy on the N-back ($p=0.003$) and Faces ($p=0.02$) tasks (**Fig. S4**). Moreover, smokers on the placebo patch condition also demonstrated reduced d-prime sensitivity ($p=0.01$), increased criterion

(p=0.01) and omissions (p=0.003) when performing the N-back task (**Fig. S5B**). There were no main effects or interactions of tDCS.

Region of Interest fMRI Analysis

Trait-Smoking Model:

There was a strong trend-level main effect of tDCS ($p_{corrected}$=0.05) that was driven by a tDCS*Group interaction ($p_{corrected}$=0.03) in the right ACC (**Fig. 3.2**), when combined across all task difficulty levels. *An-dlPFC* increased ACC activity above both *An-vmPFC* and *Sham* (post-hoc $p_{\text{An-dlPFC-Sham}} = 0.04$, $p_{\text{An-dlPFC-An-vmPFC}} = 0.04$) across all subjects. This effect was most pronounced in smokers (post-hoc $p_{\text{Smoker[An-dlPFC-Sham]}}$=0.005). There were no significant effects of tDCS or Group within the N-back or Faces ROIs.

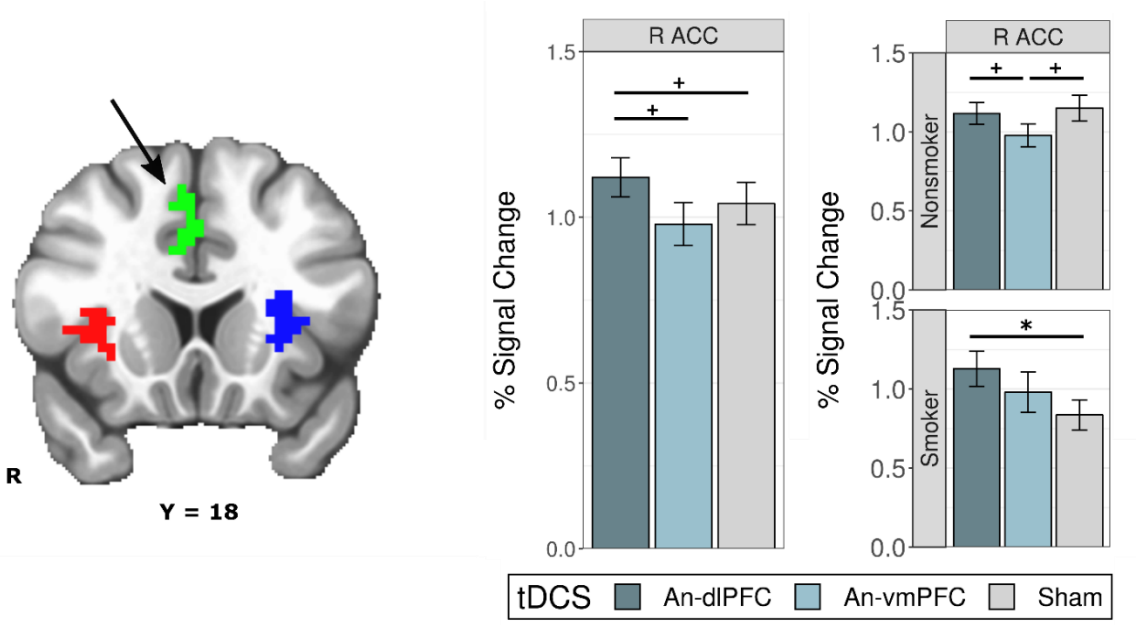


Figure 3.2: Parametric Flanker Task, Trait-Smoking Model (ROI results).

(A) ROI mask of bilateral insula and right dACC (derived from Fedota et al., 2016). Arrow points to right dACC. **(B)** Main effect trend of tDCS in the right dACC (F tDCS (2, 324.07) = 4.08, pcorrected = 0.05). **(C)** tDCS * Group (sated-smokers vs. nonsmokers) interaction on right dACC activation (F tDCS:Group (2, 324.07) = 4.84, pcorrected = 0.03). *Green = dACC, Red = Right Insula, Blue = Left Insula, R = Right, ACC = Anterior Cingulate Cortex, * < 0.05, + < 0.1, Error bars = SE.*

Nicotine-State Model:

There were no tDCS or Patch effects on any task ROI.

Whole-brain Exploratory Analysis

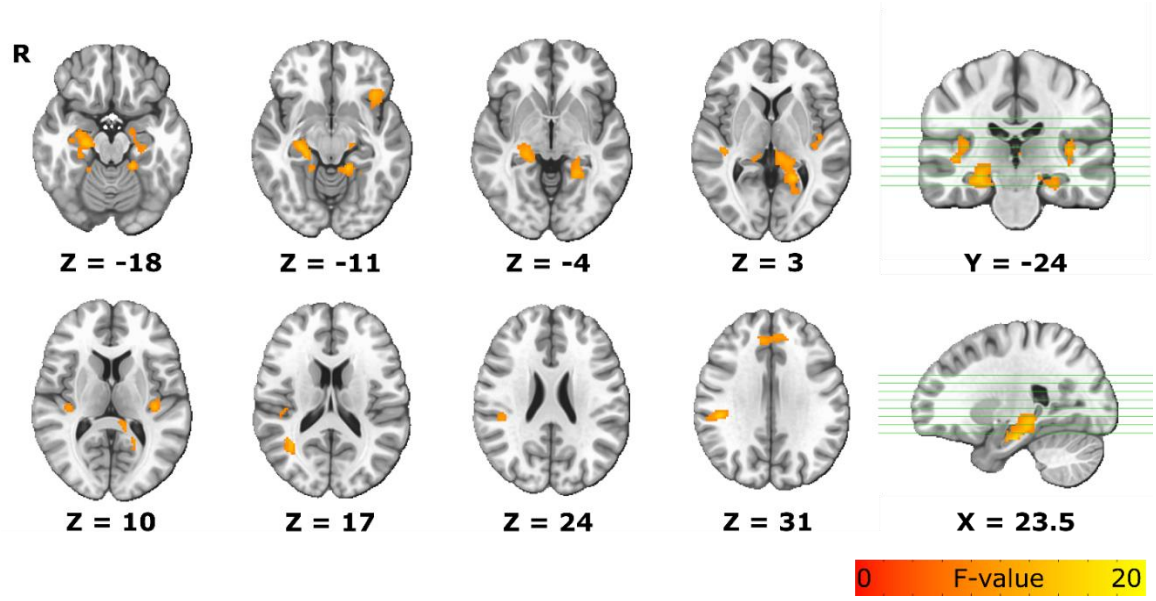
Trait-Smoking Model:

All three tasks produced robust, expected activation maps (**Fig. S6-S8, Tables S2A, S3-S4**), with N-back further producing the expected high WM-load effect for the 3-0 contrast (vs. 1-0, **Fig. S6B**). There was a main effect of tDCS within nine regions associated with the DMN during high WM-load across all 43 subjects (e.g. hippocampus, PHG, superior temporal gyrus, inferior parietal lobule, mid-cingulate gyrus, and precuneus; FWE corrected $\alpha<0.01$; **Fig. 3.3A, Table S2B**). There were no effects of Group. Additionally, *An-dlPFC* tDCS suppressed BOLD signal in the DMN-related regions more than Sham and *An-vmPFC* tDCS (**Fig. 3.3B**). There were no whole-brain effects of tDCS or Group when subjects performed the Flanker or Faces tasks.

Figure 3.3: N-back Task, Trait-Smoking Model (Whole brain results).

(A) 9 regions affected by tDCS during high WM-load (3-0 contrast), whole brain corrected FWE $\alpha < 0.01$ (p-voxel < 0.001, cluster threshold > 85).
(B) Graphical representation of numerical results, by tDCS condition, in each region; for pattern only. *L = Left, R = Right, Ph = Parahippocampal Gyrus, Hip = Hippocampus, Pcn = Precuneus, MCC = Middle Cingulate Cortex, IPL = Inferior Parietal Lobule, SMG = Supramarginal Gyrus, STG = Superior Temporal (Heschl's) Gyrus, pIns = Posterior Insula, MTG = Middle Temporal Gyrus, IFG = Inferior Frontal Gyrus (p. Orbitalis).*

A



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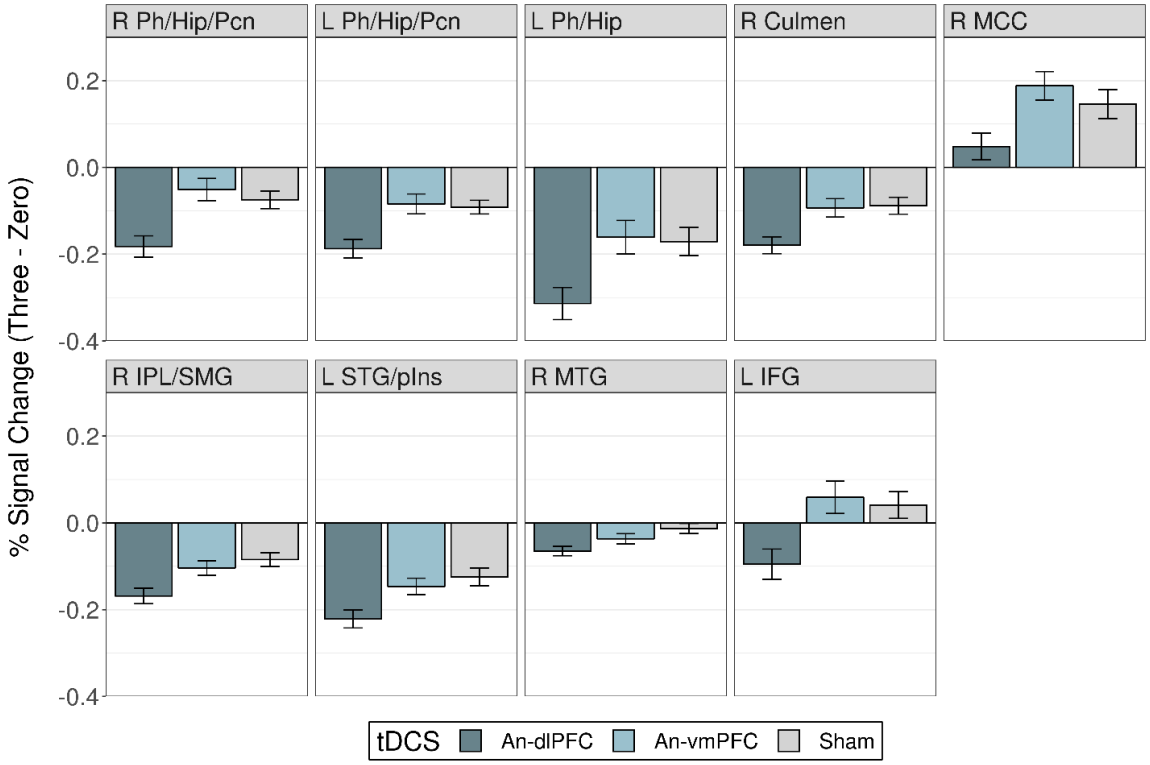


Figure 3.3: N-back Task, Trait-Smoking Model (Whole brain results).

Caption on preceding page.

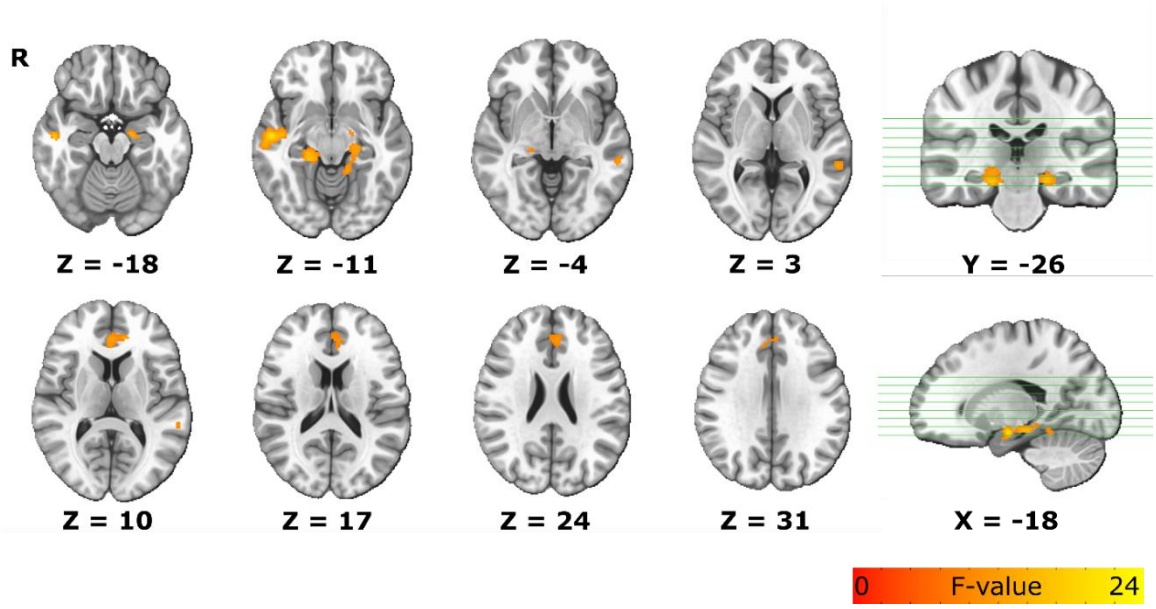
Nicotine-State Model:

There was a tDCS*Patch interaction in six DMN-associated regions during the high WM-load condition, overlapping with the nine regions observed in the *Trait-Smoking* model (e.g. ACC, hippocampus, PHG, and temporal regions, **Fig. 3.4A, Table S5**). *An-dlPFC* tDCS accentuated the downregulation of these regions to a greater extent in the sated (nicotine patch) than in the withdrawal (placebo patch) condition (**Fig. 3.4B**). *An-vmPFC* tDCS again resembled Sham (**Fig. 3.4B**). Finally, the nicotine (vs. placebo) patch appeared to restore diminished DMN suppression, and reduce 'excessive' thalamic and caudate activity, associated with 12h nicotine abstinence. Specifically, during the N-back high WM-load condition, there was accentuated deactivation in the precuneus (posterior DMN node) in the nicotine patch condition following 12h nicotine abstinence, compared to placebo patch (**Fig. S9**). During the Flanker task, under the nicotine patch condition, there was reduced activity in the bilateral thalamus and caudate, compared to the placebo patch condition (**Fig. S10**). There were no tDCS effects in the *Nicotine-State* models of Flanker or Faces, and no effects of Patch on Faces.

Figure 3.4: N-back Task, Nicotine-State Model (Whole brain results).

(A) 6 regions displaying a tDCS * Patch interaction during high WM-load (3-0 contrast), whole brain corrected FWE $\alpha < 0.01$ (p-voxel < 0.001, cluster threshold > 87).
(B) Graphical representation of numerical results by tDCS condition, in each region, separated by patch condition (nicotine patch, top; placebo patch, bottom); representation for pattern only. *L = Left, R = Right, ACC = Anterior Cingulate Cortex, MTG = Medial Temporal Gyrus, Ph = Parahippocampal Gyrus, Hip = Hippocampus, SMG = Supramarginal Gyrus.*

A



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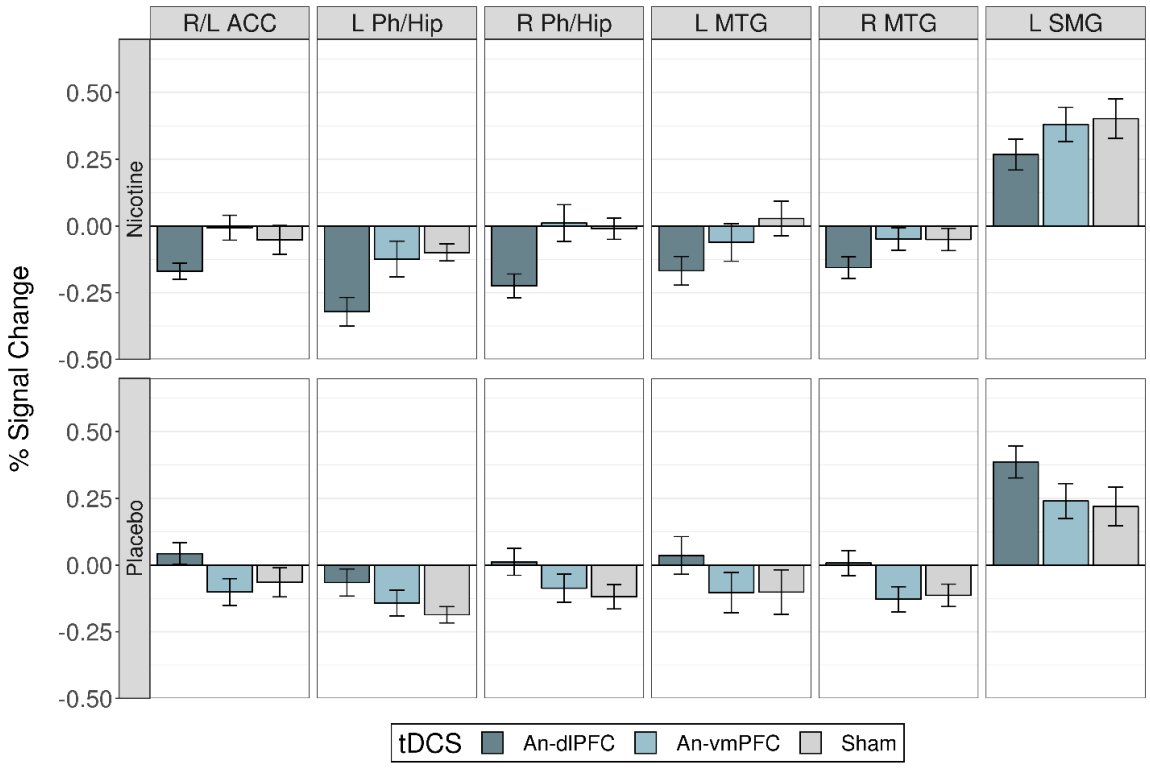


Figure 3.4: N-back Task, Nicotine-State Model (Whole brain results).

Caption on preceding page.

Brain-Behavior Relationships:

tDCS did not modify brain-behavior relationships in the tasks, for either model.

tDCS outcomes

tDCS was well tolerated and effectively blinded (**Fig. S11**). E-field modeling showed that active tDCS produced a generalized, pre-frontal maximum E-field, which extended somewhat along the cortical midline (**Fig. 3.1D**). The normal component of the E-field for *An-dlPFC* tDCS (**Fig. 3.1C, left**) showed an inward field moderately lateralized over L-dlPFC, and an outward field over R-vmPFC; as expected, current flow reversed for *An-vmPFC* (**Fig. 3.1C, right**).

Discussion

We tested whether single-session tDCS of the L-dlPFC/R-vmPFC could acutely modify large-scale brain networks and cognitive task performance implicated in the NWS in a cohort of nontreatment-seeking smokers and matched nonsmokers. *An-dlPFC* tDCS enhanced DMN suppression during a WM task, and SN activation (ACC), during an error monitoring task (**Table 3.2**). Smokers showed a greater effect of tDCS within the ACC than nonsmokers. While both groups were sensitive to the DMN-related tDCS effects, smokers responded to tDCS more in the nicotine sated than the deprived state.

Network/ Region	Predicted *An-dlPFC* tDCS effect	Cognitive Task	Task Contrast	Analysis	Model	*An-dlPFC* tDCS Result	Corrected p-value
Salience Network	Enhance	Flanker	Conflict (None, Med, High)	ROI (Smk-Trait)	Task Difficulty * tDCS * Group	Enhanced dACC activity in smokers more than nonsmokers	0.03
				Whole brain (Smk-Trait)	Task Difficulty * tDCS * Group	No effect observed	-
Executive Control Network	Enhance	N-back	(3-0) back	ROI (Smk-Trait/ Nic-State)	tDCS * Group; tDCS * Patch	No effect observed	-
Default Mode Network	Reduce	N-back	(3-0) back	Whole brain (Smk-Trait)	tDCS * Group	Enhanced reduction of DMN-related activity in response to high WM-load	<0.01
				Whole brain (Nic-State)	tDCS * Patch	In smokers, induced DMN suppression more in sated condition	<0.01
Amygdala (Prefrontal Effector)	Reduce	Amygdala	(Faces – Shapes)	ROI (Smk-Trait/ Nic-State)	tDCS * Group; tDCS * Patch	No effect observed	-

Table 3.2: Summary of Key Findings for *An-dlPFC* tDCS

Given that failed DMN suppression correlates with NWS severity (Cole et al., 2010) and predicts smoking relapse (Loughead et al., 2015), it is salient that tDCS enhanced DMN suppression during high WM-load. Although tDCS did not affect task-related behavioral measures, nicotine satiety alleviated withdrawal-induced impairment in attention (omissions) and consequent task engagement (accuracy, response speed), and enhanced deactivation of the precuneus (a key posterior DMN node) following 12h nicotine abstinence. Together, these data suggest that the NWS circuit dysregulation, partially alleviated by nicotine replacement, may be further improved by "adjuvant" anodal-(L)dlPFC/cathodal-(R)vmPFC tDCS.

An-dlPFC affected widespread DMN and SN regions, including medial-temporal DMN nodes and ACC. Notably, the affected regions were largely distal from the electrode sites, a finding consistent with other tDCS-MRI studies (for review, Wörsching et al., 2016). We consider two possible mechanisms. First, the network organization of the brain, as observed in resting state analysis (Fox et al., 2005; Power et al., 2011; S. M. Smith et al., 2009; Yeo et al., 2011), may explain distal effects. Modulating one node in a network likely alters related nodes within or between networks (Fox et al., 2014). Specific to the anticorrelated ECN–DMN relationship (Fox et al., 2005; Keller et al., 2013), we predicted and observed that anodal-dlPFC stimulation would downregulate the DMN. Our result parallels the literature: excitatory, high-frequency repetitive TMS delivered to the L-dlPFC in depressed patients downregulates the subgenual cingulate and improves depressive symptoms (Fox et al., 2012, 2013), and dlPFC tDCS in methamphetamine abusers downregulates the DMN and reduces craving (Shahbabaie et al., 2014, 2018). Further,

because anodal-dlPFC/cathodal-vmPFC stimulation are paired in our *An-dlPFC* condition, inhibitory vmPFC stimulation may have also directly contributed to DMN suppression.

Distal activations can be further explained by E-field modeling. The L-dlPFC/R-vmPFC montage produced high E-field strengths in prefrontal and anterior midline structures. CSF-mediated current flow (Antal et al., 2014) may have contributed to ACC activation during prefrontal tDCS. Further, the E-field normal component validates that *An-dlPFC* generally produced inward current over L-dlPFC and outward current at R-vmPFC (**Fig. 3.1C, left**), and thus could have accessed the ECN and DMN networks through these nodes. Current over midline dorsal-medial PFC (dorsal-medial DMN sub-system component (Andrews-Hanna et al., 2014; Buckner et al., 2008)) may have additionally modulated DMN. Taken together, our findings support our hypothesis (**Fig. S1**) that tDCS may partially alleviate large-scale network dysfunction associated with the NWS.

It is notable that sated-smokers responded to tDCS in a similar fashion as the nonsmoker group, possibly because tDCS may act through a common physiological mechanism regardless of disease *trait* (i.e. DMN suppression). While *trait* did not affect outcomes in this sample, we observed an influence of nicotine *state* within smokers. *An-dlPFC* most affected DMN in smokers during satiety, compared to during withdrawal. This may be due to reduced cortical flexibility or plasticity during withdrawal, further supported by the impaired behavioral task engagement. Similarly, it has been reported that nicotine deprivation diminishes, and acute nicotine restores, facilitatory plasticity in smokers (Grundey et al., 2012). Withdrawal-related reduced plasticity may be secondary to nicotinic acetylcholine receptor (nAChR) desensitization with chronic smoking (Brody et

al., 2006; H. Wang & Sun, 2005; Wooltorton et al., 2003), necessitating acute nicotine to restore synaptic calcium dynamics (Dani et al., 2001; De Biasi & Dani, 2011), although this is speculative as the current data cannot speak to receptor dynamics. Nevertheless, our data do suggest that tDCS may be most clinically efficacious when combined with nAChR agonism.

We originally predicted that *An-vmPFC* (i.e. cathodal-dlPFC) would have an inverse effect on network outcomes, such that it would exaggerate NWS-related circuit dysregulation; however, in our hands, *An-vmPFC* generally resembled sham, or had inconsistent directionality with weak effect size. While we expected cathodal-dlPFC stimulation would be inhibitory to ECN, consistent with motor cortex findings (Nitsche & Paulus, 2000), the lack of effect corroborates previous MR-tDCS reports in which cathodal and anodal tDCS did not induce opposing BOLD activity (Antal et al., 2011, 2012). tDCS-induced excitability – an area of active research – is affected by neuronal morphology (Radman et al., 2009; Rahman et al., 2013), non-neuronal cellular neighbors (Gellner et al., 2016; Ruohonen & Karhu, 2012), and contemporaneous brain activity (Thirugnanasambandam et al., 2011). The lack of anodal-vmPFC effects may also be attributable to regional anatomy.

DMN modulation by tDCS is physiologically and clinically relevant to the NWS. An NWS circuit model (Fedota & Stein, 2015; Sutherland et al., 2012) describes two components: hyper-excitable, interoceptively-oriented SN-DMN & within-DMN circuits, and under-responsive, exogenously-oriented SN-ECN & within-ECN circuits. Support for DMN and SN-DMN deficits is well documented (Carroll et al., 2015; Fedota et al., 2016, 2018; Hahn et al., 2009; Huang et al., 2014; Lerman et al., 2014; Sutherland, Carroll,

Salmeron, Ross, & Stein, 2013; K. Wang et al., 2014), although ECN and ECN-SN deficits have been somewhat more elusive. One possibility is that attentional deficits (Heishman, 1999; McClernon et al., 2015) are primarily due to exaggerated DMN and SN-DMN activity, promoting a shift of limited attentional capacity toward interoceptive, self-generated, and task-unrelated thoughts (Andrews-Hanna et al., 2014). ECN or cognitive deficits may represent downstream outcomes of shifted attention, as opposed to underlying processing deficits (Petersen & Posner, 2012). Self-generated thoughts drive DMN activity (Kelley et al., 2002), but are not necessarily passive or "task-negative"; they include planning, scene construction, and somatosensory awareness, all of which consume 'executive' resources like other types of internal attention (Chun et al., 2011). Dysfunction in self-generated thought may consist of aberrant content (e.g. negative valence thoughts, rumination, or fixation, such as about smoking) or aberrant context (e.g. thoughts occur intrusively during another task) (Andrews-Hanna et al., 2014). Because self-generated thoughts themselves require attention, fronto-parietal and cingulo-opercular attentional networks may remain active, possibly explaining variable reports of NWS ECN deficits. In support of this interpretation, we found that smokers (deprived and sated) responded appropriately to the N-back WM task with ECN-like activity, but the nicotine-deprived state was associated with hyperactive DMN activity and impaired task performance. An NWS model centered on attentional bias toward DMN activity is also supported by rsFC (Fedota et al., 2018), and parallels findings that DMN hyper-excitability worsens clinically relevant outcomes in addictive disorders (R. Zhang & Volkow, 2019). Given the above, it is notable that *An-dlPFC* tDCS broadly downregulated DMN nodes, evidence that tDCS may support DMN-suppression in NWS.

The present data support further exploration of the use of tDCS as a complementary therapy to other, standard treatments for nicotine dependence, especially the dysregulated attentional and cognitive processes in the NWS. Given that SN, DMN and ECN dysfunction is hypothesized to underly a range of neuropsychiatric diseases (Menon, 2011; Uddin, 2015), our finding has broad mechanistic implications for therapeutic application of tDCS to treatment-resistant psychopathology beyond nicotine dependence. Indeed, tDCS has been successfully tested as a complement to standard therapy in depression, in which tDCS combined with antidepressant medication improved outcomes more than either alone (Brunoni et al., 2013). A similar finding was observed in bipolar disorder, alongside standard mood stabilizers (Sampaio-Junior et al., 2018). Within substance use disorders (SUDs), tDCS shows encouraging clinical effects in stimulant (Batista et al., 2015; Conti et al., 2014; Conti & Nakamura-Palacios, 2014; Shahbabaie et al., 2014), and alcohol (Boggio et al., 2008; da Silva et al., 2013; Klauss et al., 2014; Nakamura-Palacios et al., 2012) dependence. Specific to nicotine, tDCS reduces craving (Boggio et al., 2009; Fregni et al., 2008; Mondino et al., 2018), negative affect (Xu et al., 2013), and cigarette consumption (Falcone et al., 2016; Fecteau et al., 2014; Z. Meng et al., 2014), and improves outcomes in an NWS animal model (Pedron et al., 2014). Our findings suggest that DMN suppression, and SN enhancement, may be important mechanisms by which tDCS exerts these effects. Together with these reports and our finding that tDCS most affects smokers in the nicotine-sated state, we propose that *An-dlPFC* tDCS may be most efficacious as "adjuvant" therapy for nicotine cessation, to support adaptive neurophysiological changes (DMN suppression, SN enhancement) synergistically with standard-of-care (e.g. nicotinic replacement, cognitive behavioral therapy).

Finally, our findings replicated previous *Trait-Smoking* and *Nicotine-State* characteristics of cigarette smoking. Within smokers (*Nicotine-State*), the withdrawal condition (placebo patch) impaired task performance, consistent with literature (Heishman, 1998, 1999; Hendricks et al., 2006; Kozink et al., 2010). Nicotine satiety alleviated both the task deficits, as previously reported (Ashare et al., 2014; Cole et al., 2010; Heishman et al., 1994), and enhanced precuneus suppression (DMN node) during WM. nAChR agonism (e.g. nicotine, varenicline) suppresses DMN nodes (Ettinger et al., 2009; Falcone et al., 2014; Hahn et al., 2007, 2009; Loughead et al., 2010; Tanabe et al., 2011), enhances DMN-ECN anti-connectivity (Cole et al., 2010), and reduces SN-DMN connectivity (Fedota et al., 2018; Lerman et al., 2014). We observed a withdrawal-associated increase in thalamic activity, which was attenuated by nicotine. The reported effects of nicotine in the thalamus are variable (Hahn et al., 2009; Lawrence et al., 2002; Stein et al., 1998; Tanabe et al., 2008). Its high density of nAChRs (Picard et al., 2013), and relationship to SN (Seeley et al., 2007) and attention (Coull, 1998; Halassa & Kastner, 2017), warrant further investigation of its role in NWS. In terms of *Trait-Smoking*, sated-smokers and nonsmokers generally performed equally on the tasks, except for modestly better N-back and Faces performance in sated-smokers. This may reflect minimal cognitive enhancing effects of transdermal nicotine, which, while calibrated to individual cigarettes per day, represented a substantial dosage. While acute nicotine administration can improve task performance (Heishman et al., 2010), chronic exposure results in a new allostatic state (Koob & LeMoal, 1997, 2008) that requires nicotine for normal functioning (Heishman, 1999; Hughes, 2007). Thus, it is expected that a sated smoker will perform approximately equally to a matched nonsmoker, as we found for other task behaviors.

Limitations

Our single-session design naturally constrains generalization regarding either the duration of observed BOLD changes or how outcomes change with multiple sessions, as would likely be applied therapeutically. Multi-session tDCS influences outcomes in mood disorders (Brunoni et al., 2013, 2017; Sampaio-Junior et al., 2018), post-stroke aphasia (Fridriksson et al., 2018) and SUDs (Batista et al., 2015; Boggio et al., 2009; Fecteau et al., 2014; Klauss et al., 2014). The lack of multiple sessions combined with the modest cohort size may have contributed to our null effects on task behavior, which is expected to be less sensitive to stimulation than the underlying neurocircuitry. The acute nature of the intervention (three tDCS conditions within one visit) precluded pre/post-tDCS assessment of NWS clinical correlates (e.g. craving, affect). We further note that the pattern of prefrontal stimulation was somewhat diffuse in this design, a characteristic of the electrode size and configuration. We were unable to assess factors of gender or age in our sample: while both features were frequency-matched across groups, gender was confounded by IQ ($p = 0.04$) across the total sample, and age followed a skewed distribution with uneven representation of age groups. We encourage future studies to directly assess the influence of these factors on tDCS response. Lastly, as the smoker group was relatively small (n=15), these data should be considered exploratory.

Conclusions

tDCS and other noninvasive brain stimulation techniques are emerging interventions at the crossroads of basic neuroscience research and clinical translation, with the potential to alter brain network connectivity dynamics, either as alternative or adjuvant therapies for various neuropsychiatric diseases. Nicotine dependence, and SUDs in

general, are prime examples of the failure of current pharmacotherapies to elicit a satisfactory treatment response (Cahill et al., 2014; Phillips et al., 2014). We present the first evidence that tDCS may have a functional neurophysiological effect on two core large-scale networks implicated in NWS. We show that single-session An-tDCS to L-dlPFC accentuates DMN downregulation and SN upregulation during task performance, and that these effects are accentuated in nicotine-sated smokers. Given the general contribution of SN, DMN, and ECN dysfunction across neuropsychiatric disorders, our results support a mechanistic rationale for therapeutic development of tDCS in psychiatry.

Chapter 4: Discussion

Summary

In this dissertation, I tested the ability of tDCS to modify large-scale brain networks previously hypothesized to be dysregulated in the NWS, a known clinical obstacle to smoking cessation. I utilized a hypothesis-based protocol to test the ability of single-session tDCS to modify cognitive circuits in nontreatment-seeking smokers (in both the nicotine sated and deprived states) and matched nonsmokers, using randomized, crossover, sham-controlled and double-blinded simultaneous tDCS-fMRI. The intervention was based on a well-defined NWS model, in which cognitive and affective symptoms are attributed to reduced ECN, SN, and ECN-SN functional connectivity (FC); and enhanced DMN and DMN-SN FC (Chapter 1). I hypothesized that anodal, excitatory tDCS to an ECN node (L-dlPFC) paired with cathodal, inhibitory tDCS to a DMN node (R-vmPFC) would partially remediate network imbalance, when engaged by several cognitive tasks (Chapter 2). Three tasks (N-back, Flanker and Amygdala Reactivity) were used to probe tDCS effects on the three hypothesis-based networks. Notably, I observed that this tDCS montage robustly suppressed DMN-related nodes during a working memory task (N-back), and enhanced ACC activity during a conflict inducing task (Flanker), when compared to both sham and an active control, across both groups of subjects (Chapter 3). Given that DMN and ACC dysfunction is implicated in the NWS (Sutherland et al., 2012), addictive disease more generally (R. Zhang & Volkow, 2019), and psychiatric disease broadly (Menon, 2011), this finding is of potentially important clinical significance, and suggests a mechanistic rational for pursuing tDCS as a therapeutic tool.

This chapter is organized into two sections: a review and discussion of original Specific Aims and predictions, and a broader discussion of future directions of tDCS research, with a focus on current challenges to the progression of tDCS from a research-grade intervention to a therapeutic tool.

Review of Study Results

Validation of Study Methods

To begin, it is worth noting the experimental validation of methodological approaches utilized by the two Specific Aims: (1) cognitive task probes for each network, (2) the efficacy of blinding of tDCS, and (3) nicotine abstinence and study patch manipulation to reflect *Trait-Smoking* (nonsmokers vs. sated-smokers), or *Nicotine-State* (within smokers, sated vs. deprived condition).

COGNITIVE TASK PARADIGMS

First, the three cognitive tasks (N-back, Parametric Flanker, Amygdala Reactivity/Matching Faces and Shapes) elicited robust activation of brain networks consistent with the extant literature ((Cohen et al., 1994; Eriksen & Eriksen, 1974; Hariri et al., 2002); Figures S6, S7, S8). The N-back task activated ECN network nodes, including inferior and superior parietal lobules, and middle frontal gyrus (i.e. dlPFC; Figure S6, Table S2A), while the Parametric Flanker engaged bilateral ACC and insula (Figure S7, Table S3), and the Matching Faces and Shapes task produced strong bilateral amygdalar activity (Figure S8B), and engaged occipital and fusiform gyri (Figure S8A, Table S4). The tasks also elicited variance in behavioral responses (accuracy, response speed) based on cognitive demand level (Figures S3, S4), such that increasing difficulty or complexity of the task (i.e. number of “backs” or flankers; or matching faces) generally resulted in

reduced response speed and accuracy, across all subjects. These outcomes confirm that the participants were engaged with and appropriately performed the tasks, which evoked brain responses consistent with the literature.

tDCS Blinding Technique

Second, the sham technique for tDCS effectively blinded the experimental conditions. In a post-tDCS blinding questionnaire, participants accurately identified active or sham stimulation at approximately the same rate as if by chance guessing, and the two conditions were indistinguishable by subjective rating of common tDCS-related sensations (e.g. warmth, itching; Figure S11). The research team was also blinded to tDCS condition, such that only the MR operator was aware of the tDCS session code. Thus, both subject response and observer bias were well controlled in this design. Expectancies regarding treatment intervention are well known to influence study response (for review, Colloca & Barsky, 2020); within neuromodulation, poorly controlled tactile and thermal sensory contrast between sham and active stimulation can easily reveal study condition (Woods et al., 2016). Successful blinding in this experiment supports that the findings below are reflective of the tDCS intervention, rather than expectancies related to sensory perception of active stimulation.

Trait-Smoking Manipulation

It was expected that smokers in the sated state would perform similarly to nonsmokers on task behaviors (accuracy, response speed) and cognitive processing (task-evoked BOLD activity), based on evidence that acute nicotine administration relieves cognitive dysfunction in smokers associated with abstinence (Heishman, 1999; Hughes, 2007). While sated-smokers and nonsmokers performed similarly on several task behavioral parameters (Fig. S3, S5A), with no differences in task-evoked BOLD signal

(Fig. S6-8), sated-smokers appeared to have an advantage in certain performance outcomes. On the N-back, sated-smokers demonstrated higher accuracy, fewer omissions, and a more liberal response bias (tendency to respond either correctly or incorrectly, i.e. lower criterion; Fig. S3A-B, S5A); on the Matching task, sated-smokers demonstrated faster response speed, and more stable accuracy rates regardless of block type (faces vs. shapes), compared to nonsmokers (Fig. S3C-D). There were no behavioral differences in the Flanker task performance.

This advantage was likely conferred by transdermal nicotine, which has a mild cognitive enhancing effect, beyond what would be expected from alleviating withdrawal symptoms in smokers (Heishman et al., 2010). This is of significance because, in this study, nicotine was administered at a higher dosage than what is usually prescribed clinically to treat withdrawal (e.g. a 20-25 CPD smoker received 35mg nicotine in this study, whereas clinical dosage would be 21mg; (Lexicomp, 2020)). The rationale for this design is that high dose nicotine patches have been found to better control withdrawal symptoms (Ebbert et al., 2007), possibly by greater availability to bind to upregulated nicotinic receptors (De Biasi & Dani, 2011), and better approaching a true "sated" state. As such, the sated-smoker advantage found in this study likely reflects the relatively large, transdermal delivery of nicotine, as opposed to a trait advantage for sated-smokers vs. nonsmokers. Indeed, trait-smoking differences, when found, tend to indicate subtle deficits of task performance in smokers. For example, sated-smokers have difficulty recruiting the insula when performing a Flanker task (Fedota et al., 2016), and make more perseverative errors performing a reversal learning task (Lesage et al., 2017).

NICOTINE-STATE MANIPULATION

Within smokers, 12-hours overnight nicotine abstinence in the smoker group resulted in impaired task performance (reduced accuracy, response speed) on the three cognitive tasks; the impairment was alleviated by nicotine patch (Fig. S4, S5B). The abstinence period was also associated with increased activity of the precuneus, a core node of the DMN (Andrews-Hanna et al., 2014), during high WM load on the N-back task (Fig. S9), which was reduced by nicotine satiety (Fig. S9). The pattern of enhanced DMN activity during abstinence, and reduction in response to nicotine administration, is consistent with previous literature reports (Ettinger et al., 2009; Falcone et al., 2014; Hahn et al., 2007, 2009; Loughead et al., 2010; Tanabe et al., 2011). Two SN-related regions, thalamus and caudate (Seeley et al., 2007), were also modulated by nicotine state, as observed during performance of the Flanker task (Fig. S10). Both regions have previously been observed to be sensitive to nicotine manipulations (Fedota et al., 2015; Hahn et al., 2009; Lawrence et al., 2002; Rose et al., 2013; Stein et al., 1998; Tanabe et al., 2008).

While DMN and SN regions were modulated by 12-hours nicotine abstinence, amygdala and ECN nodes did not appear sensitive to nicotine-state changes. Evidence of ECN deficits during nicotine withdrawal have been inconsistently observed within the literature; the strongest reports have been of changes to DMN and SN activity (Carroll et al., 2015; Fedota et al., 2016, 2018; Hahn et al., 2009; Huang et al., 2014; Lerman et al., 2014; Sutherland, Carroll, Salmeron, Ross, & Stein, 2013; K. Wang et al., 2014). This trend is suggestive of an alternative NWS hypothesis, in which impairments in task performance may be due to shifted attentional resources, rather than inherent deficits of cognitive function (for complete discussion, see Chapter 3, p. 61). However, it is also possible that ECN deficits were not observed due to the duration of nicotine abstinence used in this study

design. The onset of cognitive and affect symptoms of NWS begins within 2-12 hours of nicotine deprivation, but severity peaks at 2-3 days (Hughes et al., 1994). Although the overnight abstinence manipulation is known to reliably elicit withdrawal signs (Brody et al., 2006; Dawkins et al., 2006, 2007; Mancuso et al., 1999; Z. Wang et al., 2007; Xu et al., 2005), the possibility remains that a longer abstinence period, (e.g. 48-hours) may have more strongly affected ECN function.

Regarding amygdala reactivity, previous reports of hyperactivity in abstinent smokers were observed following division of the group into sub-types: those who consistently improved on behavioral outcomes (e.g. response speed) with nicotinic agonism over multiple sessions, and those who improved inconsistently; only the consistent-improver group demonstrated amygdala hyperactivity (Sutherland, Carroll, Salmeron, Ross, Hong, et al., 2013a). In the present study, smokers' behavioral response to acute nicotine was measured only once (i.e. nicotine patch visit day, Fig. 3.1A). Thus, it was not possible to divide the group into "consistent responders" and "inconsistent responders." A future study may collect behavioral outcomes at multiple timepoints to more closely replicate the amygdala hyperactivity finding, or may better fractionate the phenotype by other methods (e.g. trait or state anxiety ratings, mood profiles, or other characterization).

Overall, the combined outcomes of the primary study methods (cognitive engagement with task, tDCS blinding, and withdrawal and nicotine patch manipulation) were found to be credible, and enable discussion of the experimental findings that follow.

Aim 1: Trait-Smoking.

To evaluate the effects of prefrontal (combined dlPFC and vmPFC) tDCS on ECN, DMN, and SN activity; and determine whether the effects are modified by trait smoking.

EFFECTS OF ANODAL-DLPFC COMBINED WITH CATHODAL-VMPFC TDCS

I predicted that *An-dlPFC* tDCS would strengthen ECN and SN activation during the three cognitive tasks, and that this improvement would be observed in both groups. I observed that *An-dlPFC* tDCS robustly suppressed medial-temporal DMN nodes during the N-back task and enhanced SN activation (ACC) during the Flanker task, but did not enhance activity of ECN nodes or modulate amygdala activity.

The two positive effects – on the Flanker and N-back tasks – are notable because on the relevance of the two task constructs to the NWS. First, the Parametric Flanker Task, a conflict-monitoring task, was chosen to probe the Salience Network, especially bilateral insula and anterior cingulate (Eriksen & Eriksen, 1974). I observed an effect of tDCS on the right dACC (Figure 3.2). The dACC is considered to be a core component of decision-making circuitry, likely involved in resolving conflict between multiple choices, although its specific computational role is debated (Ebitz & Hayden, 2016). Discussion of dACC circuitry has grown around two primary hypotheses: that the dACC may participate in updating behavioral policies based on changing environments, initiating 'switches' away from default, status-quo options (Kolling et al., 2016); or, alternatively, that the dACC may evaluate the cost or benefit of engaging other top-down control circuits during any given decision-making process (Shenhav et al., 2016). Neuroimaging studies have observed robust dACC activity in a variety of selective attention and conflict monitoring tasks, such as the Stroop interference task (Pardo et al., 1990), switching tasks (Liston et al., 2006),

model updating (O'Reilly et al., 2013), and valuation of choices (Kolling et al., 2012), among others.

While the precise computational role of dACC remains an open topic of investigation, it is clear that the region is heavily involved in decision-making behavior, and can be dysregulated in psychiatric disease (Menon, 2011), including nicotine addiction. Abstinent smokers exhibit hypoactivity of the dACC in response to rewards as compared to nonsmokers, and the hypoactivity is more severe with increasing dependence severity (Lesage et al., 2017); and alterations in dACC connectivity have been observed in smokers (Hong et al., 2009, 2010). Based on the above, it is notable that *An-dlPFC* tDCS enhanced ACC activity, especially in the smoker group (Figure 3.2). This finding suggests that that multiple sessions of *An-dlPFC* tDCS may further enhance ACC signaling in smokers, possibly supporting healthy decision-making behaviors in combination with counseling (e.g. to initiate a quit-smoking attempt or refuse offers of cigarettes). Future studies could evaluate how tDCS effects on dACC function effect smoking-related choices.

Second, the N-back Task is a validated working memory paradigm that elicits activity across ECN-associated regions, including dorsolateral prefrontal cortex, parietal and premotor areas (Cohen et al., 1994; Owen et al., 2005); as well as suppression of DMN-associated nodes (Sala-Llonch et al., 2012). I observed that *An-dlPFC* tDCS broadly suppressed medial-temporal DMN regions (Figure 3.3). Previous reports have found that increasing cognitive load parametrically suppresses DMN activity (Fransson, 2006; McKiernan et al., 2003), and that failure to adequately suppress DMN may contribute to impaired task performance (Eichele et al., 2008; Prado & Weissman, 2011; Sonuga-Barke & Castellanos, 2007; Weissman et al., 2006). This may be due to DMN and ECN

competing for limited attentional resources, such that appropriate interaction between the two networks is necessary for optimal goal-directed, task-oriented behavior.

Aberrant DMN activity has been observed in substance use disorders (R. Zhang & Volkow, 2019), and evidence of DMN hyperactivity has been observed in nicotine addiction, specifically (for review, Chapter 1, p. 14; replicated in the present work, Supplemental Figure S9). Appropriate regulation of DMN nodes during cognitive task performance has been associated with improved clinical outcomes in smokers (Cole et al., 2010; Lerman et al., 2014; Loughead et al., 2015). Taken together, the observation that *An-dlPFC* tDCS downregulates the DMN, across all subjects, suggests that the intervention may have the potential to normalize DMN function in smokers if applied clinically, possibly enhancing treatment response to traditional smoking cessation therapies (e.g. counseling, NRT).

Previously, I discussed explanations for *An-dlPFC* tDCS's widespread effects on DMN and ACC (Chapter 3, p. 59), primarily considering the large-scale network organization of the brain (e.g. DMN anti-correlation with ECN, including the dlPFC node; (Fox et al., 2005)) and transmission of current along CSF pathways (Antal et al., 2014). Specifically, CSF within the interhemispheric fissure may have enabled current to access the ACC, while CSF within the lateral ventricles, which border the entorhinal cortex and temporal lobes, may have served as a current pathway to medial-temporal DMN nodes. These physiological mechanisms are agnostic to disease trait, and may explain why sated-smokers and nonsmokers were both similarly affected by *An-dlPFC* tDCS.

Here, I consider reasons for the apparent insensitivity of ECN nodes and amygdala to tDCS intervention. First, ECN modulation may not have been observed due to its unique

functionality, as compared to the DMN or SN. Specifically, the ECN is a 'task-positive network', selectively engaged during goal-oriented behavior (Fox et al., 2005), while the DMN and SN are both considered to be tonically-active, general attention and environmental assessment networks (Andrews-Hanna et al., 2014; Bressler & Menon, 2010; Buckner et al., 2008; Craig, 2009; Seeley et al., 2007). As such, it is possible that the DMN and SN are more receptive to single-session intervention, as applied in this study, whereas the ECN may show evidence of alteration only with multiple tDCS sessions or while actively engaged in task performance.

Regarding insensitivity of the amygdala to tDCS in this study, I consider two possible explanations. First, modulation of the amygdala may require baseline hyper-activity. In two recent reports of amygdala modulation by tDCS, study samples were defined by trait amygdala hyperactivity (i.e. high trait anxiety, Ironside et al 2019; or heightened emotional arousal due to bipolar disorder, Bertocci et al 2020). Because amygdala hyperactivity is not characteristic of either healthy, neurotypical nonsmokers or sated-smokers (Sutherland, Carroll, Salmeron, Ross, Hong, et al., 2013a), the present sample may have been predisposed to a 'basement/floor' effect for tDCS.

A second possible cause of a lack of amygdala response to *An-dlPFC/Cat-vmPFC* tDCS is a mechanistic hypothesis regarding the amygdala's relationship to the two prefrontal electrode targets, vmPFC and dlPFC. The amygdala is not easily accessible by either direct cortical stimulation or CSF-driven current (it lies within the uncus, surrounded by parahippocampal and hippocampal gyrus), so any action of tDCS on the region likely must take place as it relates to 'downstream' synaptic action of the dlPFC/vmPFC targets. It was assumed that anode over dlPFC and cathode over vmPFC would *both* enhance

downregulation of amygdala, because dlPFC activity is generally associated with reduced amygdala activity (Ochsner et al., 2012), and vmPFC is a component of the DMN (Buckner et al., 2008), whose activity is associated with amygdala hyperactivity in smokers (Sutherland et al., 2012). This assumption likely did not fully account for the complex interplay between the vmPFC and limbic, striatal, and prefrontal regions in the regulation and valuation of emotion and reward (Cunningham et al., 2011; Haber & Knutson, 2010; Hiser & Koenigs, 2018; Ochsner et al., 2012; Schoenbaum et al., 2011; Sharpe et al., 2019), and was contradictory to observations that vmPFC activity is associated with amygdala suppression (Johnstone et al., 2007; Urry et al., 2006). Taken together, it is possible that *Cat-vmPFC* stimulation may have actually diminished or reversed vmPFC-related suppression of amygdala reactivity, and perhaps opposed An-dlPFC mediated effects, resulting in overall null outcomes.

Finally, it should be noted that the relatively small sample size in the sated-smoker group (N=14 for the Amygdala Reactivity analysis; N=15 in N-back/Flanker) may have limited power to detect tDCS effects; or, the specific tDCS parameters (electrode location, duration and intensity of stimulation) may not have been optimal for modulation of ECN and amygdala regions.

EFFECTS OF ANODAL-VMPFC COMBINED WITH CATHODAL-DLPFC TDCS

I originally predicted that *An-vmPFC* tDCS would mimic an NWS-like pattern in both the sated-smoker and nonsmoker groups. However, I observed that *An-vmPFC* largely resembled sham effects, or had variable directionality with small effect size as compared to *An-dlPFC*. To disentangle causes of this outcome, it is helpful to break the intervention into two components, cathodal stimulation of the dlPFC and anodal stimulation of the vmPFC. I have previously suggested that the lack of cathodal 'inhibition' of dlPFC may

have been due to a presumption of an equal and opposite relationship between anodal and cathodal stimulation in this region, one that has been challenged in the literature ((Antal et al., 2011, 2012); Chapter 3, p. 61).

Here, I also consider why anodal, 'excitatory' vmPFC stimulation did not enhance DMN activity. Although the vmPFC is a canonical DMN node (Andrews-Hanna et al., 2014; Buckner et al., 2008), its complex integration with limbic and prefrontal regions likely make specific directionality of anodal (or cathodal) current more nuanced than a unilateral "up" or "down" DMN effect. Additionally, if vmPFC and dlPFC generally work in concert with each other (rather than in opposition), anodal current over one region, simultaneous with cathodal current over the other, could "cancel out" combined stimulation effects.

A future study could focus on disentangling the separate modulatory effects of tDCS over vmPFC and dlPFC nodes, though this is methodologically challenging using a two-electrode montage. One approach could be to use a third, 'unrelated' control region for the return electrode (i.e. vertex or occipital cortex, (Woods et al., 2016)), to test the 'isolated' effect of anodal or cathodal stimulation over a single region at a time. However, these 'return electrode' placements would probably result in increased current along the midline, perhaps engaging PCC (c.f. Mondino et al., 2018), a core node of the DMN. Even 'extra-cephalic' return electrode placements, such as the shoulder, have been hypothesized to shunt current through the brainstem or vagus nerve, such that the placement is not truly 'inactive', though evidence of this is limited (Parazzini et al., 2013; Vandermeeren et al., 2010). The most promising approach to individually engage the vmPFC and dlPFC may be through a high-definition tDCS (HD-tDCS) method, in which a central anode or cathode

is proximally surrounded by four electrodes of opposite polarity, to produce a relatively focal electrical field distribution over the target region (Alam et al., 2016).

Lastly, it may have been overly simplistic to predict that An-vmPFC/Cat-dlPFC tDCS would result in an NWS-like state. A withdrawal state, by definition, requires acute deprivation of a drug following chronic exposure. This state results in diverse somatic and psychological symptoms, produced and perceived by many interconnected structures (striatum, insula, limbic circuits, hypothalamus, among others; (Koob & LeMoal, 2008)). While alterations within DMN and ECN may be reflective of withdrawal in nicotine addiction, the simple manipulation of one node within each of these networks is unlikely to fully replicate a withdrawal syndrome, as a small deviation from set-point would likely be opposed by many compensatory circuits.

Aim 2: Nicotine-State.

To determine how tDCS response in smokers is modulated by the nicotine sated and nicotine deprived states.

I predicted that smokers would be most sensitive to *An-dlPFC* tDCS effects (improvement of ECN and SN, suppression of DMN) during the withdrawal state, and An-vmPFC tDCS (NWS-like pattern) during the sated state. However, it was observed that smokers were more sensitive to *An-dlPFC* tDCS during the sated state, and *An-vmPFC* largely resembled sham effects (as above). *An-dlPFC* may have been most efficacious in sated-smokers due to enhanced cortical plasticity in smokers during the sated state, compared to withdrawal ((Grundey et al., 2012); for complete discussion, see Chapter 3, p. 60). This finding supports that tDCS effects are likely to be dependent on participant

state; in this case, an acute, pharmacological deprivation state from a drug of chronic exposure.

This outcome corresponds to other reports that also point to the importance of participant *state* during tDCS stimulation. For example, voluntary isometric muscle contraction during or immediately following tDCS to the primary motor cortex (M1) alters the amplitude of MEPs in response to subsequent M1-TMS pulses (Antal et al., 2007; Thirugnanasambandam et al., 2011). The state-dependent effects of tDCS are not limited to motor cortex. In a study of dlPFC tDCS in patients with major depressive disorder, it was observed that tDCS applied simultaneously with 'cognitive control training' (specifically, tasks that engage the dlPFC) over five consecutive days reduced depressive symptoms at 3-weeks follow-up more than either approach alone (Segrave et al., 2014).

The state-dependent nature of tDCS application is especially relevant to addiction therapy, given the importance of environment and drug-related cues to relapse outcomes (Epstein et al., 2009; Jasinska et al., 2014), and of the changing disease *state* of the patient preceding and following relapse episodes (Koob & Volkow, 2010). Specifically, the observation that tDCS better modulates NWS-related circuitry during the sated state, suggests that tDCS may be best applied clinically in conjunction with nicotinic agonists (e.g. NRT, varenicline).

While the present study provides insight into tDCS effects based on *pharmacological state* (nicotine sated vs. deprived), it remains unknown how *environmental state* (such as presence or absence of drug cues) affects tDCS outcomes in addiction therapy. Home use of tDCS has been suggested as a future direction of clinical use (Knotkova et al., 2019). However, the home environment of an addicted patient likely

contains many cues for drug use and craving that are absent in a clinical setting, and these cues may modulate tDCS effects in unexpected ways. Future studies could compare effect of tDCS on neural circuits (such as by tDCS-EEG devices) between at-home sessions (a naturalistic context, with known drug-related stimuli) or in the clinic (fewer naturalistic drug-related stimuli, additional expectancies based on clinical setting), and measure long-term outcomes associated with each setting.

Limitations

There are some limitations of this work, beyond those described in the manuscript (p. 65), that are worth noting. First, it is possible that alternative brain stimulation techniques may have induced stronger, or different, behavioral and network responses. For example, several studies of rTMS for nicotine addiction have shown reduction in nicotine craving or cigarette consumption following treatment (for review, Coles et al., 2018). However, an rTMS approach has certain disadvantages compared to tDCS. An important aim of this study was to examine acute neurophysiological effects of tDCS using simultaneous fMRI. Given that the duration of effects from single-session brain stimulation remain unknown, it is advantageous to perform stimulation inside the scanner and collect time points seamlessly, during and after stimulation. While this is easily accomplished with MR-compatible tDCS devices, it is technically challenging for TMS: simultaneous TMS-fMRI techniques constrain both the rTMS pulse frequency and BOLD acquisition parameters, because fMRI and TMS pulses must be interleaved. In addition to methodological advantages, tDCS has some clinical advantages compared to rTMS. High-frequency TMS pulses are associated with more severe head pain during stimulation, and carry higher seizure risk; these concerns could affect patient compliance and study

completion. While these factors contributed to the choice to select tDCS as the brain stimulation method in this present study, future investigations could assess clinical and neurophysiological outcomes of TMS in nicotine addiction, such as by advanced fMRI methods, pre/post study designs, or other measurement tools (e.g. EEG).

Second, in this study, outcome measures were focused specifically on cognitive constructs and circuits related to the NWS, as reduction of NWS severity may improve smoking cessation outcomes. Acute neurophysiologic and cognitive task behavior outcomes reflective of NWS were chosen to align with the rigorous experimental design, in which three experimental tDCS conditions were tested within a day-long study visit. While this design enabled investigation of multiple tDCS montages (a unique feature within the extant literature), it precluded testing other, clinically-oriented end-points such as craving, withdrawal symptoms, number of abstinent days, latency to smoke, or cigarette consumption following stimulation. While assessments of withdrawal symptoms were completed at the beginning of each study day, these were used to verify the 12-hour abstinence period (along with exhaled carbon monoxide), but not to measure the outcome of tDCS intervention. Future studies may incorporate such measures into a long-term clinical trial of multi-session tDCS for smoking cessation.

Primary Themes and Contributions

To summarize, two central findings of this dissertation were that Anodal-dlPFC + Cathodal-vmPFC tDCS primarily acts to suppress medial-temporal DMN nodes, and enhance ACC activity, in both smoking and nonsmoking subjects. Further, the smoker group was most sensitive to tDCS during the nicotine-sated, vs. deprived, state. These effects are notable, given the important role of the DMN and SN in the neurocircuitry of

NWS specifically (Sutherland et al., 2012), and addiction broadly (R. Zhang & Volkow, 2019). Taken together, the findings suggest that tDCS may be most efficacious for treatment of nicotine addiction when used in combination with other, existing therapies, especially nicotinic receptor agonists such as NRT or varenicline. Add-on tDCS therapy has improved outcomes in depression (Brunoni et al., 2013), bipolar disorder (Sampaio-Junior et al., 2018) and schizophrenia (Valiengo et al., 2019); the present work provides support for such a multi-modal approach to addiction treatment.

The Future of tDCS for Addictive Disease

There remain a number of intermediate steps between the state of current tDCS research and its clinical use. Practically, no clinical process for applied tDCS has yet been approved by the FDA, and large-scale clinical trials have focused on depression treatment (e.g. Brunoni et al., 2013, 2017). Within addiction, exploratory and preliminary experimental designs predominate (**Error! Reference source not found.**, for specific review of nicotine studies). One impediment to pursuing trials of tDCS for addiction is the wide variability in experimental design and outcomes within the present literature, possibly deterring investment in and consensus around any one particular treatment approach. This variability itself is likely to be compounded by a lack of a foundational framework – especially one based on neurobiology, disease course, and interaction with existing treatments -- for how to apply tDCS therapeutically to substance use disorders.

While large, randomized control trials (RCTs) of tDCS for SUDs are sparse, consumer demand for neuromodulatory devices for addressing a broad array of neuropsychiatric issues is escalating. Market reports have estimated the value of 'consumer neurotechnology' products (e.g. tDCS, TMS, EEG, among others) to reach $3 billion

dollars in 2020 (Wexler & Reiner, 2019). A community of "do-it-yourself" (DIY) users of tDCS on the website Reddit has reached 13,000 subscribers (*R/tDCS*, 2020, Accessed 2/19/2020). In a survey of a sample of ~350 such DIY tDCS users, 42% of participants reported self-treatment with tDCS to address disorders ranging from depression, anxiety, and addiction, to migraine and chronic pain (Wexler, 2018). Products that are used to apply tDCS are not research-grade, and include self-built devices based on online videos, modified iontophoresis devices, and a number of direct-to-consumer tDCS-like devices (Wexler, 2016). Users of these non-regulated products are more likely to report side effects: 16.9% reported "burning" in this sample (Wexler, 2018), vs. 8.7% of active tDCS studies in the literature reporting one or more episodes of burning (Brunoni et al., 2011). While only a small subset of the DIY user sample reported using the device to treat addiction (Wexler, 2018), the combined evidence suggests a demand for tDCS therapy that outpaces evidence-based research, placing additional responsibility on the scientific community to confirm or negate the safety and efficacy of these devices.

Review of the literature of tDCS for SUDs suggests that heterogeneity in study design and outcomes contributes to the slow pace of investment in large-scale RCTs. Studies of tDCS on nicotine addiction illustrate the variability that pervades multiple experimental design domains, including tDCS parameters (e.g. intensity, duration, montage), inclusion/exclusion criteria of participants (i.e. definition of a smoker), and clinical outcomes (e.g. craving, reduced use or abstinence, among others).

Specifically, criteria for defining a smoker in these studies varies between smoking once per week with a Fagerstrom Test for Nicotine Dependence (FTND) score of zero (Kroczek et al., 2016) to DSM-5 criteria for tobacco use disorder (Behnam et al., 2019).

Outcome measures vary between cigarette consumption, cue reactivity or craving scores, mood ratings, latency to smoke a first cigarette, motivation to quit and FTND score (**Error! Reference source not found.**). tDCS parameters are highly variable: intensity ranges from 1-2mA, stimulation duration from 15-30min, and number of active sessions varying between 1 and 20 sessions. Within these reports, only 4 studies were designed for dose-response testing, examining stimulation intensity (Falcone et al., 2019), montage (Fregni et al., 2008; Z. Meng et al., 2014), or session spacing (Behnam et al., 2019). Finally, sample size of the active stimulation group has also been variable, with 5 studies containing less than 15 subjects, 6 studies between 16-25 subjects, and only 3 testing active tDCS in 32-36 subjects. However, there is some consensus in targeting the left dlPFC with anodal stimulation (11/14 studies).

Questions regarding the tDCS parameter space are of scientific importance and contribute to neurobiological understanding of tDCS action; however, exhaustive testing of all possible parameter conditions is likely unfeasible, if not impossible, to pursue in clinical research designs. Even meta-analytic assessments are disadvantaged by the extensive parameter space, as only a select subset of tDCS studies share sufficiently comparable research designs to warrant aggregation of outcome data (Chase et al., 2020).

Preclinical designs and computational approaches may be well-suited to constrain the parameter space of tDCS (or other neuromodulatory) devices. The number of neuromodulation studies in rodents has increased in recent years, including development of focal TMS coils for rodent models (Q. Meng et al., 2018); in the tDCS literature, electrodes may be applied over the skull or directly to the cortex (Bindman et al., 1964; for review, M. P. Jackson et al., 2016). Such techniques may provide insight into how weak

electrical fields affect animal behavior and neuronal physiology, and provide an intermediate step to testing new montages or multi-session designs; for example, these models could be used to more quickly optimize tDCS protocols to modify resting state brain networks, which have replicated in the rodent brain (Lu et al., 2012).

Computational modeling and simulation of current distribution may also improve targeting of tDCS-produced E-fields to specific brain regions or circuits. These methods account for current passage through skin, skull, CSF and other tissues, based on either a generic head model or subject-specific anatomical imaging data (Bikson et al., 2018). Computational modeling may be especially helpful to individualize neuromodulation parameters; it has been demonstrated that individual gray matter volume and white matter integrity affect responsivity to rTMS (Hanlon et al., 2019), and anatomic variability alters simulated E-field distributions in ECT (Deng et al., 2015). An approach in which each patient has a preliminary structural MRI scan, to generate an individual E-field model and personalized tDCS montage, would improve rigor and reproducibility in clinical studies (Bikson et al., 2018).

In addition to the above approaches to standardize tDCS parameters, a framework accounting for tDCS evidence to-date along with currently available addiction therapies (e.g. pharmacotherapy, counseling), and grounded in the known neurocircuitry and life-course of addictive pathology, would further improve progress toward a systematic RCT.

Framework for tDCS Neuromodulation in Addiction

Addiction is a chronic, relapsing brain disease characterized by episodes of uncontrolled drug use (American Psychiatric Association, 2013), that has been proposed to cycle through three phases: binge and intoxication (initiation or relapse to uncontrolled

use), withdrawal and negative affect, and preoccupation and craving, ultimately leading to relapse (Koob & Volkow, 2010). SUDs are complex, chronic diseases (Leshner, 1997) that necessitate an approach reflective of that status: namely, through a multi-factorial, individualized approach that accounts for the disease *state* of the patient.

Within the United States, patients tend to receive brief intervals of outpatient or inpatient care during acute episodes of drug use, often with a single modality of care, with little to no follow up (McKay 2009, McKay 2005). In contrast, a multi-factorial treatment approach, with specific interventions targeted to acute exacerbation and long-term maintenance, is characteristic of management of complex, lifelong diseases. Indeed, corollaries between addiction and other chronic diseases have been recognized since as early as 1996 (Leshner, 1997; McLellan et al., 2000; O'Brien & McLellan, 1996), including conditions of asthma, diabetes, cardiovascular disease, and cancer. Management of these conditions requires a combinatorial approach to reduce disease impact and symptomatology from multiple angles and routes of pathophysiology, and treatment applied according to a chronic care model. This model incorporates continuing contact between patients and providers over time, empowerment of the patient to self-manage their condition, and continuous evaluation of chosen disease management strategies (Wagner et al., 2001).[5]

[5] For example, in asthma, medications are prescribed based on disease severity, with interventions for relief of acute exacerbation (e.g. inhaled corticosteroid, fast-acting β2 agonist) and for long-term management to reduce likelihood of an attack (e.g. leukotriene antagonist, long-acting β2 agonist). Patients are counseled to avoid and control triggers, and supplied with an "Asthma Action Plan" to empower self-management. The provider evaluates and adjusts treatment until episodes are controlled (Global Initiative for Asthma, 2019; National Asthma Education and Prevention Program, 2007). A similar approach is taken for diabetes, with insulin formulations targeted to manage blood glucose over different time-courses (e.g. 24 hours vs mealtime), alongside other aids acting through independent physiology (e.g. metformin); management of myocardial infarction ranges from prevention (e.g. statins, anti-hypertensive therapy), to acute relief (e.g. fibrinolytic therapy, cardiac catheterization), and post-event management. In cancer therapy, approaches range between surgical, immunotherapy, or radiation therapy, tailored based on disease profile and stage.

Among all of these cases, no single approach is an exclusive approach, patients are empowered to recognize exacerbations of their condition and supplied with tools to address acute episodes, and patients and providers engage in ongoing discussion of treatment strategies. Addiction, too, necessitates such an approach, with the goal not necessarily being lifelong abstinence or sobriety, but rather for improved quality of life, through increased interval spacing between relapses, shorter duration of relapse, and faster transition to a sober state or controlled use (Dennis & Scott, 2007; Leshner, 1997; McKay, 2005, 2009, 2011; O'Brien & McLellan, 1996). Given recent developments in modeling the addiction cycle (Koob & Volkow, 2010), and enhanced understanding of the neurocircuitry and pathophysiology underlying each stage (Koob & Volkow, 2016; Volkow et al., 2019), it may now be beneficial to adapt interventions to dynamically address the patient with changing *state*. Among treatment options, tDCS may contribute uniquely to improve outcomes and response at specific stages addiction cycle. While specific tDCS parameters may not need to differ among addiction phases, (e.g. dlPFC tDCS, 20-30 min, 2mA sessions), it may act as an amplifier at specific phases for already existing therapies.

Binge/Intoxication

The approach assumes that the patient is a chronic drug user, who has engaged in quit attempts and experienced several relapses. The binge/intoxication phase, in this context, does not refer to drug-use initiation (in which case, the goal would be *primary prevention*, outside the scope of this dissertation). Rather, binge/intoxication here refers to phases of relapse into uncontrolled use (Koob & Volkow, 2010). Because cigarette smoking is more commonly associated with abatement of withdrawal, rather than

intoxication, relevance of this phase is limited to how acute smoking may affect subsequent withdrawal symptoms; in contrast, the reward-related features of this phase are more likely to apply to other drug addictions such as alcohol or stimulants.

Proposed substrates of this phase include dopaminergic and other transmitter signaling (e.g. glutamate, GABA) within the ventral (NAcc) and dorsal striatum (caudate, putamen) (Koob & Volkow, 2016). Because a primary concern in this phase of the cycle is a sensitized, positive-affective deviation from the hedonic set-point due to drug stimulus -- in turn engaging a negative-affective "after-reaction" following drug metabolism ("anti-reward process", (Koob & LeMoal, 1997)) -- the therapeutic target would be to constrain peak-to-peak contrast between the high and low opponent-process states, in turn reducing the duration of the drug taking episode. This is likely best accomplished pharmacologically, with long-term partial agonist/antagonist treatment, which increases baseline striatal activity when the drug of abuse is absent (preventative action), while opposing the drug's action when present (acute action). Examples of these drugs include varenicline (nicotinic receptor partial agonist) and buprenorphine (μ-opioid receptor partial agonist), sometimes in combination with agonists (e.g. NRT) or antagonists (e.g. naloxone) to refine treatment effects.

Stabilization of peak-to-peak opponent processing may enable responsivity to learned cognitive control tactics based in emotion regulation (Ochsner et al., 2012). These include situation selection, situational modification, and attentional deployment, and can be taught and potentially reinforced with simultaneous tDCS sessions. Because tDCS is unlikely to access the striatum directly (too deep within brain tissue, as tDCS effects are considered to be constrained to the pyramidal cells of the superficial cortex; (Bikson et al.,

2019; Radman et al., 2009)), it is more likely to act as an enhancer for improving top-down prefrontal regulation (e.g. by dorsomedial prefrontal cortex [dmPFC], dACC, dlPFC, vmPFC, superior and medial temporal gyri) of striatal areas over the long term, rather than as an acute intervention during a binge episode. Enactment of these strategies can be supported by technologies such as electronic-momentary assessment (EMA; (Bertz et al., 2018)), in which wearable devices can be used to identify when a patient is at risk of relapse, and subsequently to intervene with appropriate support (e.g. counselor reach-out; (Gustafson et al., 2014)).

Withdrawal/Negative Affect

During the withdrawal phase, the primary concerns are distressing psychological and somatic symptoms of acute drug abstinence. These symptoms vary as a function of the specific substance (e.g. the nicotine withdrawal syndrome is distinct from that of opiate withdrawal), but commonly result in hyperactivity of limbic (Koob & Volkow, 2010), DMN (R. Zhang & Volkow, 2019), and stress-response systems (Koob, 2010; Koob & LeMoal, 2008). Thus, the overarching therapeutic goals are to constrain the severity of withdrawal symptoms (e.g. with replacement therapy), and the secondary response to these symptoms (e.g. over-attending to withdrawal experience, negative/aversive appraisals of withdrawal experience, in the form of Ochsner's model of the cognitive control of emotion, (Ochsner et al., 2012)). Pharmacological interventions targeted to this phase oppose the anti-reward process (e.g. norepinephrine-dopamine reuptake inhibitor/bupropion for NWS, or various replacement therapies) or somatic withdrawal signs (e.g. benzodiazepine to prevent seizures in acute alcohol withdrawal, antiemetics to control nausea and vomiting in opiate withdrawal).

Management of secondary, internal responses to distressing withdrawal symptoms may be accomplished through cognitive-behavioral therapy (CBT), or combined tDCS-CBT, approaches. Emotional regulation strategies have been hypothesized to engage prefrontal circuits (such as dlPFC, dmPFC, ACC, and vmPFC, among other regions) to suppress or modify systems involved in emotional appraisal (Ochsner et al., 2012). These latter systems, which include ventral striatal, amygdalar, and insular signaling, have also been modeled as substrates involved in withdrawal circuitry (Koob & Volkow, 2010). tDCS has been found to modulate activity of prefrontal nodes (Keeser et al., 2011; Park et al., 2013; Peña-Gómez et al., 2012; Sehm et al., 2012), amygdala and striatal activity (Bertocci et al., 2019; Hone-Blanchet et al., 2015; Ironside et al., 2019), and through the present work, cingulate and DMN activity (Aronson Fischell et al., 2020). Based on these findings, it is possible that tDCS may amplify adaptive modification of emotion regulation circuits, if applied simultaneously with CBT training.

Because withdrawal symptoms can be pervasive, and addicted subjects may have deficits of executive processing (i.e. ECN dysfunction; (for review, Sutherland et al., 2012)), an approach that does not require cognitive control of emotion/distressing experience, such as mindful-acceptance (Fruzzetti & Erikson, 2010; Kober et al., 2020), may of additional utility. Mindful-acceptance strategies advocate simply noting, observing, or describing intrusive thoughts, in a non-judgmental manner that does not necessitate taking action to change the thought, feeling, or condition (Kabat-Zinn, 2003); the strategy of acceptance is generally employed when the distressing stimulus is unlikely or impossible to change (Fruzzetti & Erikson, 2010), a feature that may characterize the withdrawal experience for some patients. Mindful-acceptance strategies appear to act directly on

regions responsible for emotion generation, such as amygdala (Kober et al., 2020), possibly accessible to tDCS modulation. Thus, tDCS may be used to enhance learning of either emotion-regulation strategies, or mindful-acceptance strategies, for addressing secondary emotional appraisals of withdrawal symptoms.

Studies of combined tDCS-CBT are beginning to emerge (depression treatment: (Bajbouj et al., 2018; Welch et al., 2019)), as are studies of tDCS combined with mindfulness training ((Ahn et al., 2019; Hunter et al., 2018; Witkiewitz et al., 2019); two active trials "Mindfulness-Based Stress Reduction and tDCS," NCT03680665; and "Mindful Breathing and tDCS for Depression," NCT03897699). Further research in this area will provide important insight into the efficacy of tDCS for enhancing cognitive-behavioral training.

Preoccupation/Craving

During the preoccupation/craving phase, concern surrounds aberrant salience to drug cues, due to alteration of prefrontal valuation circuits (e.g. vmPFC, insula, ACC), and excessive rumination and preoccupation with drug memories or thoughts, possibly attributable to altered function of medial-temporal DMN regions such as the hippocampus or temporal poles (Geng et al., 2017; Koob & Volkow, 2016; R. Zhang & Volkow, 2019). As such, the goal is to enhance resistance to drug cue-induced drive states that could lead to a relapse episode, as well as to reduce the secondary negative appraisal of drug craving/preoccupation. As this is the stage potentially preceding a relapse, effective therapy could extend time between relapse significantly. Cognitive strategies in this phase are similar to the tactics described above (withdrawal phase), with the target being unwanted drug craving or rumination (Ryan, 2013; Westbrook et al., 2013). Further, because the set

of regions involved (vmPFC, ACC, DMN) are highly accessibly by tDCS ((Mondino et al., 2018; Nakamura-Palacios et al., 2016; Shahbabaie et al., 2018; Yang et al., 2017); reviewed in Chapter 1; as well as evidence from Chapter 3), support for tDCS as an amplifying learning tool in this phase is strong. Similarly, modulators of glutamate signaling (the predominant neurotransmitter in this phase; (Koob & Volkow, 2016)), such as NMDA agonists or partial agonists, may further enhance plasticity in this stage to enhance learning of adaptive cognitive strategies, though so far trials with these agents have not succeeded (Tomek et al., 2013). Thus, it is possible that at this stage, the best method for enhancing cognitive circuit remediation may be through neuromodulatory tDCS, rather than pharmacological tools.

Multifactorial Approaches & Suggested Directions

Based on the above, one can imagine a multifactorial approach to addiction treatment that dynamically addresses the patient's disease *state*, in which tDCS addresses underlying alterations of large-scale circuits and enhances learning of adaptive cognitive coping skills; pharmacotherapy remedies biochemical adaptations to chronic drug use; and counseling interventions supporting adaptive choices throughout (**Error! Reference source not found.**). This framework may be further supported by advancement of tele-psychiatry, improving reach and affordability of an integrated treatment program. In this system, a patient may have an at-home tDCS device, which is applied 1-5x/week (similar to physical therapy) alongside online cognitive-behavioral training sessions (for review of possible strategies, (Knotkova et al., 2019)), with provider support to manage tDCS, CBT and pharmacological dosing, and acute intervention based on relapse frequency.

Taken together, while many open questions remain regarding neurobiological mechanisms of tDCS, trials for addiction may focus on use of tDCS as an additional player in an integrated, multifactorial ecosystem to manage a chronic, complex disease.

Phase	Goals	Substrate	Pharmacological Target	Cognitive-Behavioral Target	tDCS Target
Binge/ Intoxication (Phase 1)	1. Reduce duration of relapse episode 2. Reduce deviation from hedonic allostatic set-point during the episode	Striatal, dopaminergic systems (VS, DS)	(Acute) Suppress deviation from striatal allostatic set-point by increasing baseline striatal activity in absence of drug, and reducing responsivity to presence of drug (e.g. partial agonist/ antagonist treatment)	(Acute) Electronic-Momentary Assessment and intervention (e.g. counselor reach-out) (Preventive) Problem-solving tactics (situation selection/modification; attentional deployment)	(Preventive) During Phase 3, enhance down-regulation of striatal pathways by prefrontal cortex, through combined tDCS-CBT practice
Withdrawal/ Negative Affect (Phase 2)	1. Reduce withdrawal (anti-reward) severity 2. Reduce duration of withdrawal period	Amygdala, BNST, NAcc Shell, Habenula; ↑ DMN, HPA axis	NDRI (e.g. bupropion), Replacement therapy, Pharmacological opposition to specific withdrawal syndromes	Emotional regulation tactics (reappraisal, response suppression); Mindful-acceptance (noting, allowing, observing) of internal sensations of distress	Enhance learning of emotion regulation/ mindful strategies to down-regulate limbic and HPA systems
Preoccupation / Craving (Phase 3)	1. Increase time between relapse episodes (potentially indefinite) 2. Reduce influence/ experience of drug craving or obsession	Prefrontal cortex (mPFC, OFC, hippocampus, insula, BLA, ACC, temporal poles)	Possibly act on learning and plasticity mechanisms via NMDA modulators (e.g. memantine, D-cycloserine, others)	Challenging cognitive errors/schemas (e.g. 'I can't handle this without a cigarette') Mindful-acceptance of intrusive drug-related thoughts/cravings	Enhance learning of cognitive-behavioral/ mindful tactics to retrain DMN/SN circuits, reducing aberrant salience of drug cues

Table 4.1: Targeted Treatments for Each Addiction Cycle Phase and Role of tDCS

Conclusions

Despite clear epidemiological need for effective addiction treatments (U.S. Department of Health and Human Services, 2016), addiction remains relatively resistant to pharmacotherapy (Cahill et al., 2014; Phillips et al., 2014). Interest has turned toward novel, non-invasive neuromodulatory approaches, such as tDCS, that may directly modulate underlying circuit pathophysiology (Dunlop et al., 2017; Ekhtiari et al., 2019; Yavari et al., 2016). However, few studies have directly measured tDCS effects on addiction-related neurophysiology (**Error! Reference source not found.**). In this dissertation, I applied specialized tDCS-fMRI technology to test the impact of single-session tDCS on a well-published and defined hypothesized model of the Nicotine Withdrawal Syndrome. I observed that tDCS alters nodes of the DMN and SN networks, and that the effects are dependent on smoking disease state. Given that DMN and SN have been hypothesized to be dysregulated in nicotine and other addictions (Sutherland et al., 2012; R. Zhang & Volkow, 2019), these data quantitatively support the hypothesis that tDCS may modify large-scale circuits dysregulated in addictive disease. In consideration of these findings within the extant tDCS literature, and models of addiction neuropathology (Koob & Volkow, 2010), I further proposed a framework for how tDCS could be integrated into a chronic care model for addiction treatment. While many open questions remain regarding mechanisms of action of tDCS, and the applied science remains in nascency, this dissertation work importantly contributes a translational approach to an innovative field of addiction medicine, bridging pathophysiology derived from neuroimaging methods with a novel clinical intervention.

Appendix A: Supplemental Material

Supplemental materials for: Aronson Fischell, S., Ross, T. J., Deng, Z.-D., Salmeron, B. J., & Stein, E. A. (2020). Transcranial Direct Current Stimulation Applied to the Dorsolateral and Ventromedial Prefrontal Cortices in Smokers Modifies Cognitive Circuits Implicated in the Nicotine Withdrawal Syndrome. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 0 (0). https://doi.org/10.1016/j.bpsc.2019.12.020. In Press.

Supplemental Methods: Cognitive Tasks

N-Back Working Memory (WM) Task

This block-design task parametrically manipulates WM and reliably activates ECN nodes(1,2), while deactivating DMN nodes(3). A series of letters were presented to the participant one at a time (for 500ms each, followed by a fixation '+' for 1500ms), and participants needed to identify, by button press, the target letter that matched a stimulus presented either in the previous trial ("1-back"), or three trials previously ("3-back"). To control for attentional mechanisms, participants completed "0-back" trials, in which they simply respond to letters "d" or "D". A total of 18 blocks (6 blocks for each 0-back, 1-back and 3-back levels), consisting of 15 letter stimuli (i.e. 30s per block), were presented across two runs (5 min each, ~10 min total). The task was given simultaneously with tDCS (~13 min after onset) to assess the online effects of stimulation on WM.

Parametric Flanker Task

The Parametric Flanker Task (Flanker) is a cognitive interference task designed to elicit activity in the SN, particularly the ACC and anterior insula, and the ECN. A string of 7 letters is presented on each trial, and the participant must identify the middle letter (either an 'S' or 'H') by button press. Each trial began with the flanker stimuli displayed for 100ms, followed by the target and flankers for 750ms and a jittered inter-trial interval (ITI; 500-7000ms range). Response conflict increases with increasing number of different-letter flankers surrounding the middle letter. We modified the task from the version used in Ref. (4) Levels for this version of the task were: no-conflict, "Congruent" ('SSSSSSS'); medium-conflict, "Incongruent-2", ('HHSSSHH'); and high-conflict, "Incongruent-3" ('HHHSHHH'). 144 randomly ordered trials were presented, grouped into three 5-min runs (15 min total), and split 50/50 between no-conflict and demand trials (72 no-conflict, and 36 each of medium and high response conflict trials). The task started ~10 min after tDCS offset.

Matching Faces and Shapes Task

This block-design task produces robust bilateral amygdala activity and top-down prefrontal regulation by components of the other three networks (5–7). We replicated the block-design Amygdala Reactivity Task described in Sutherland et al 2013 (8), a variant of the Hariri et al 2002 (6) paradigm, designed to elicit activity from the bilateral amygdala. Participants are presented with a target and two item choices, one of which matches the target, and must select the correct choice by button press. In "Match-Faces" blocks, the subject selects between two emotional faces to match a target face; in "Match-Shapes", the items presented are geometric shapes. The task lasted 8 minutes with 54 total trials completed in one run (4 blocks of Match-Faces trials alternating between 5 blocks of Match-Shapes trials). The Match-Shapes block consisted of 6 trials, each trial lasting 4000ms with a 2000ms ITI, for a block duration of 36s. The Match-Faces block consisted of 6 trials, each trial lasting 4000ms with a jittered ITI (2000-6000ms range), for a block duration of 48s. The task started ~1 min post-tDCS.

Supplemental Methods: tDCS

Washout: We chose a within-day washout for three primary reasons. First, evidence suggests that a within-day washout is unlikely to affect outcomes of dlPFC tDCS. A recent meta-analysis (9) evaluated the impact of interval between sessions for dlPFC tDCS. The report found that inter-tDCS interval (ranging from less than one hour to one week, for cathodal; or two weeks, for anodal) had no influence on outcomes for either cathodal-dlPFC or anodal-dlPFC stimulation across ~60 studies. Second, a design in which each tDCS-fMRI session takes place on a separate day would mean that smokers participants would need attend 6 study days (including 6 overnight abstinence sessions and 6 study patches), which could introduce additional noise to the data due to participant state differences across many visits, increase likelihood of study patch unblinding through experience, and place additional burden on the participant. Lastly, the within-day study design allowed modification of several parameters that otherwise would not have been feasible to test, including both between-subjects factors (smokers, nonsmokers), and within-subjects factors (on/off nicotine in smokers; multiple tDCS conditions). We included both a negative (Sham) and positive (An-vmPFC) control in addition to the active condition (An-dlPFC). A longer washout period may have made direct testing of these important design elements impractical, and potentially resulted in participant drop-out from the study.

Noninvasive brain stimulation has many open-ended questions, including the effect of repeated sessions, inter-session interval, and many other within-session, temporal and spatial stimulation parameters. We designed our study to specifically examine a hypothesis-driven electrode montage on networks involved in smoking addiction. A future pursuit of the tDCS field would be to continue to narrow the parameter space, including washout period.

Sham: The Sham condition was randomized between sham versions of An-dlPFC and An-vmPFC conditions. Sham stimulation was conducted according to the DC Stimulator Plus standard procedure: stimulation ramped up over 15 seconds, remained on for 50 seconds, and ramped down over 15 seconds, followed by continuous impedance checking for the remaining ~24 minutes. For impedance checking, a small current pulse was applied every 550ms (average current over time not more than 2 μA) to display a readout of electrode contact on the device in the MR suite. This sham mimics the fading cutaneous perception of active tDCS following initial ramping of current (10,11). tDCS setting was programmed by the MR-operator according to a key maintained by NIDA Pharmacy.

Supplemental Methods: MRI Scanning

Table S1: Scan Parameters

Scan Type	Parameter Values
Echo-planar functional images (EPI)	2s TR; 27ms TE; 64x64 matrix; 220 FOV; 78° FA; 39, 4mm oblique axial slices ~30° from the AC-PC line
Structural T1-weighted brain images (MPRAGE)	1.9s TR; 3.42ms TE; 900ms TI; 9° FA; 1mm^3 isotropic
Diffusion Tensor Imaging (DTI)	1000 s/mm^2 b-value; 128 directions; 5.4s TR; 64ms TE; 90° FA; 88x88 matrix; 220 FOV; 56, 2.5mm slices

Supplemental Methods: fmriprep v1.3.1

Results included in this manuscript come from preprocessing performed using FMRIPREP version latest ((12,13), RRID:SCR_016216), a Nipype ((14,15), RRID:SCR_002502) based tool. Each T1w (T1-weighted) volume was corrected for INU (intensity non-uniformity) using N4BiasFieldCorrection v2.1.0 (16) and skull-stripped using antsBrainExtraction.sh v2.1.0 (using the OASIS template). Spatial normalization to the ICBM 152 Nonlinear Asymmetrical template version 2009c ((17), RRID:SCR_008796) was performed through nonlinear registration with the antsRegistration tool of ANTs v2.1.0 ((18) RRID:SCR_004757), using brain-extracted versions of both T1w volume and template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using fast (19) (FSL v5.0.9, RRID:SCR_002823).

Functional data was slice time corrected using 3dTshift from AFNI v16.2.07 (20), RRID:SCR_005927) and motion corrected using mcflirt (FSL v5.0.9 (21)). This was followed by co-registration to the corresponding T1w using boundary-based registration (22) with 9 degrees of freedom, using flirt (FSL). Motion correcting transformations, BOLD-to-T1w transformation and T1w-to-template (MNI) warp were concatenated and applied in a single step using antsApplyTransforms (ANTs v2.1.0) using Lanczos interpolation.

Physiological noise regressors were extracted applying CompCor (23). Principal components were estimated for the two CompCor variants: temporal (tCompCor) and anatomical (aCompCor). A mask to exclude signal with cortical origin was obtained by eroding the brain mask, ensuring it only contained subcortical structures. Six tCompCor components were then calculated including only the top 5% variable voxels within that subcortical mask. For aCompCor, six components were calculated within the intersection of the subcortical mask and the union of CSF and WM masks calculated in T1w space, after their projection to the native space of each functional run. Frame-wise displacement (24) was calculated for each functional run using the implementation of Nipype.

Many internal operations of FMRIPREP use Nilearn (25), RRID:SCR_001362), principally within the BOLD-processing workflow. For more details of the pipeline see https://fmriprep.readthedocs.io/en/latest/workflows.html.

Supplemental Methods: Electric Field (E-field) Modeling

We simulated tDCS induced E-field with SimNIBS v3.0 (26). Since subjects wore the tDCS electrodes during the anatomical scan, we manually preprocessed the T1 images using ImageJ (27) to remove traces of the electrodes, conductive paste, and wires. Resultant images were segmented and meshed using SimNIBS:headreco, and DTI data converted to anisotropic conductivity data using SimNIBS:dwi2cond. We assigned standard conductivity values: white matter, 0.126 S/m; gray matter, 0.275 S/m; cerebrospinal fluid, 1.654 S/m; bone, 0.01 S/m; scalp, 0.465 S/m; eyes, 0.5 S/m; electrodes, 29.4 S/m; and paste, 1 S/m. We used the volume normalized anisotropic conductivity with a maximum eigenvalue-ratio of 10 and maximum eigenvalue of 2.

Supplemental Methods: tDCS Effect on Brain-Behavior Relationships

We pursued an investigation to determine whether tDCS changes brain-behavior relationships for each task (Faces, N-back, Flanker), using whole-brain regression to assess the interaction effect of *tDCS condition* and *task behavior*. For each of the three tasks, we selected the behavioral outcome measure with the greatest overall variance to provide an optimal dataset for exploring brain-behavior relationships. This behavior was response speed (1/RT) for all three tasks. We applied the analysis to both the Trait-Smoking (Nonsmoker v. Smoker-Sated) and Nicotine-State (Smoker-Sated v. Smoker-Withdrawn) models, a total of 6 assessments.

We used AFNI's 3dRegAna to test whether the interaction between response and tDCS condition (An-dlPFC, An-vmPFC, Sham) explained more variance than a model including factors for main effects of Group (or Patch), tDCS condition, and Behavior, and the Group (or Patch) x tDCS interaction. We centered response speed to account for testing for interaction effects with the quantitative variable. To correct for multiple comparisons, we applied AFNI's 3dClustSim to each task dataset (both Trait-Smoking and Nicotine-State models) to generate whole-brain cluster thresholds, and constrained voxelwise p-values to 0.001 and whole-brain FWE correction to the $\alpha < 0.05$ level

We did not observe any tDCS modifications of brain-behavior relationships on any of the three tasks, for either the Nicotine-State or Trait-Smoking analyses.

Supplemental Figures

Figure S1: Hypothesis. The Nicotine Withdrawal Syndrome (NWS) is associated with increased strength of the DMN, hyperactivity of the amygdala, and reduced strength of the SN and ECN. tDCS may help remediate NWS by excitatory (anodal) stimulation to the dlPFC (ECN node) and inhibitory (cathodal) stimulation to the vmPFC (DMN node). We predicted *An-dlPFC* tDCS would enhance the SN and ECN, and suppress the DMN and amygdala. *tDCS = Transcranial direct current stimulation, ECN = Executive Control Network, DMN = Default Mode Network, SN = Salience Network, dlPFC = dorsolateral prefrontal cortex, vmPFC = ventromedial prefrontal cortex, PPC = posterior parietal cortex, PCC = posterior cingulate cortex, aIns = anterior insula, ACC = anterior cingulate cortex.*

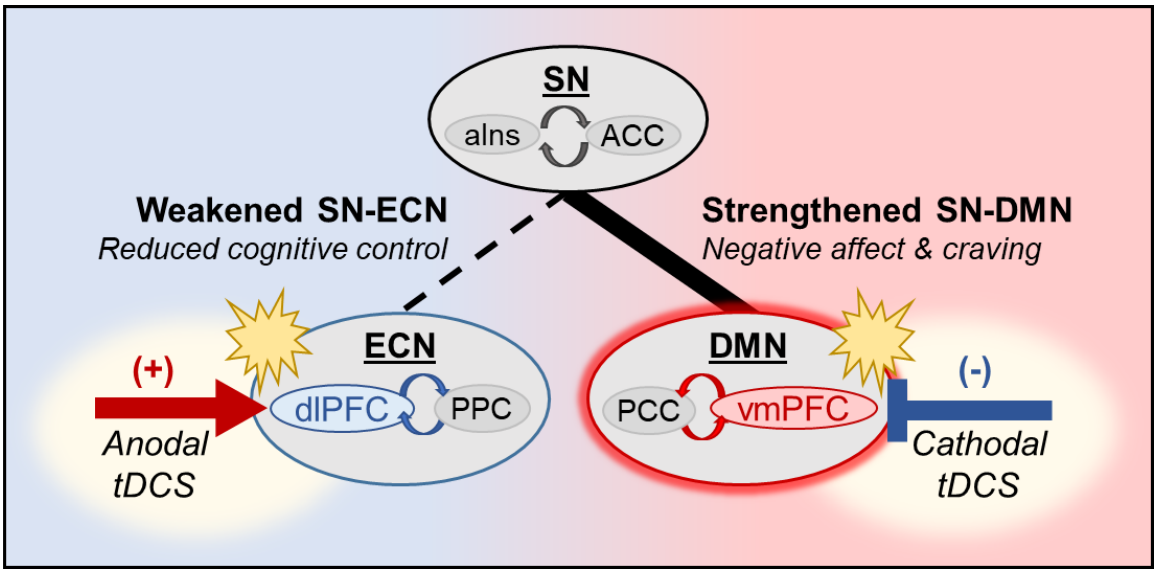


Figure S2: CONSORT Diagram.

Visits took place at the National Institute on Drug Abuse, Intramural Research Program (NIDA-IRP; Baltimore, MD) between December 20, 2017 and June 17, 2019.

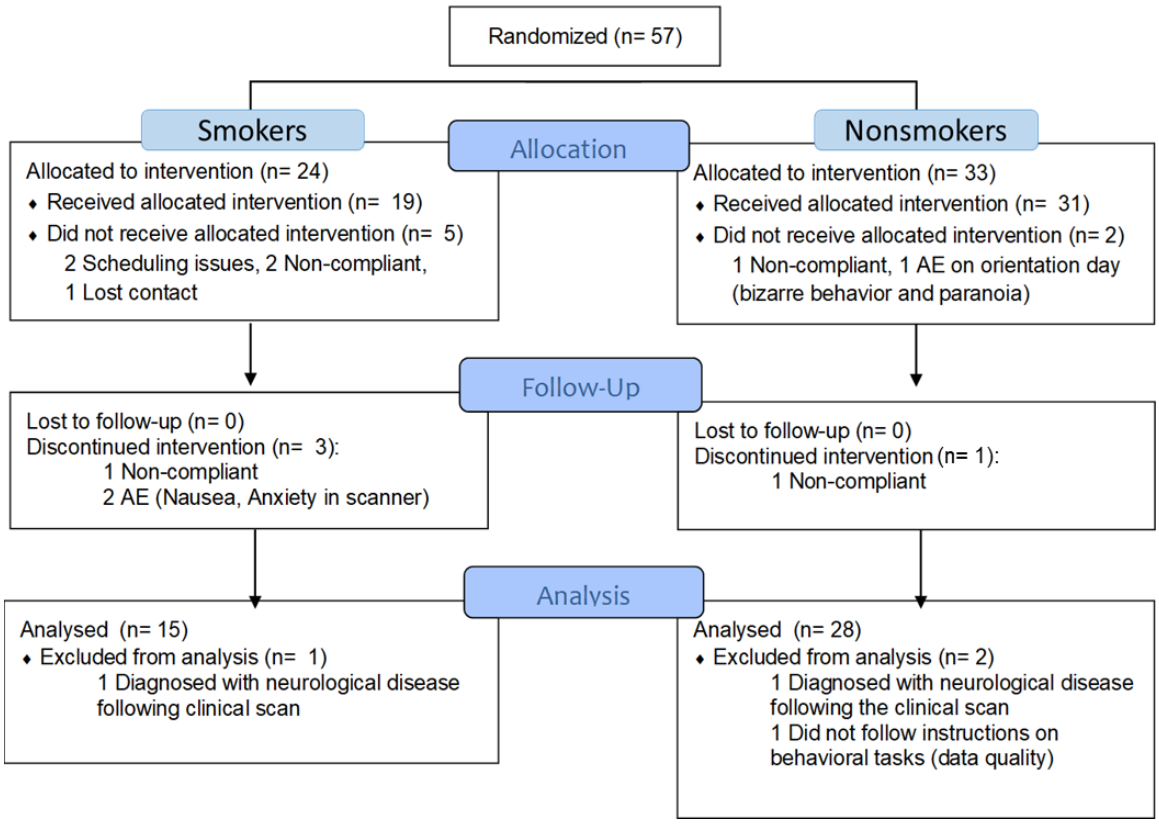


Figure S3: *Trait-Smoking* Model Task Behavior (Nonsmokers and Sated Smokers): Accuracy (% correct trials) and Response speed (1/Reaction Time, 1/s). We observed expected main effects of task difficulty for all three tasks on response speed, and on accuracy for N-back and Flanker. Only results describing trait differences between sated-smokers and nonsmokers are detailed in this legend (A, B) N-back, $N_{Nonsmoker} = 28$, $N_{Smoker} = 15$, main effect of Group for accuracy ($Smk_{Mean\ (SD)}$ = 86.3% [± 0.07%], $Nsmk_{Mean\ (SD)}$ = 80.3% [± 0.09%], $p = 0.03$). (C, D) Matching, $N_{Nonsmoker} = 28$, $N_{Smoker} = 14$. There was a main effect of Group for response speed ($Smk_{Mean\ (SD)}$ = 1.10 [± 0.24] (1/s), $Nsmk_{Mean\ (SD)}$ = 0.97 [± 0.14] (1/s), $p = 0.03$), and a Group*Task Level interaction for accuracy in which nonsmokers were less accurate on Match Shapes than Match Faces (Faces $_{Mean\ (SD)}$ = 97.9% [± 2.1%], Shapes $_{Mean\ (SD)}$ = 96.7% [± 2.6%], *post-hoc* $p = 0.03$), while there was no difference between blocks for smokers (Faces $_{Mean\ (SD)}$ = 97.1% [± 3.4%], Shapes $_{Mean\ (SD)}$ = 97.9% [± 2.2 %], *post-hoc* $p = 0.32$; $F_{Group*Task}(1,40) = 4.4$, $p = 0.04$). (E, F) Flanker, $N_{Nonsmoker} = 28$, $N_{Smoker} = 15$. * = $p < 0.05$, error bars represent standard error.

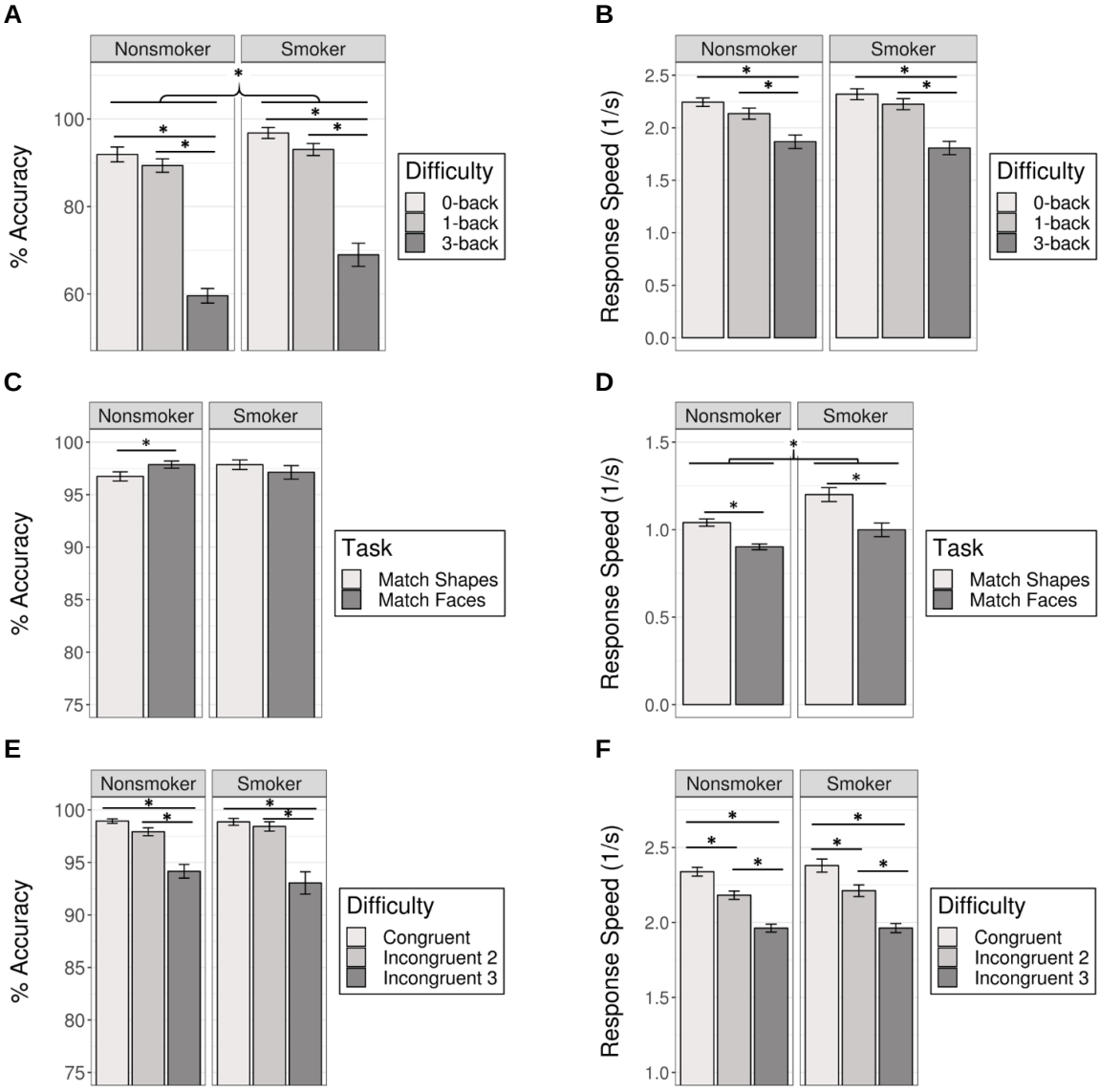


Figure S4: *Nicotine-State* Model Task Behavior (Sated Smokers vs Smokers in Withdrawal), accuracy (% correct trials) and response speed (1/Reaction Time, 1/s). We observed expected main effects of task difficulty for all three tasks on response speed, and on accuracy for N-back and Flanker. (A, B) N-back, $N_{Smoker} = 15$, (C, D) Matching, $N_{Smoker} = 13$, (E, F) Flanker, $N_{Smoker} = 15$. *Nicotine-State* differences (Nicotine vs. Placebo) present in all response speed measures (all $p < 0.05$); as well as N-back accuracy ($p = 0.003$) and Faces accuracy ($p = 0.02$); but not in Flanker accuracy. * = $p < 0.05$, error bars represent standard error.

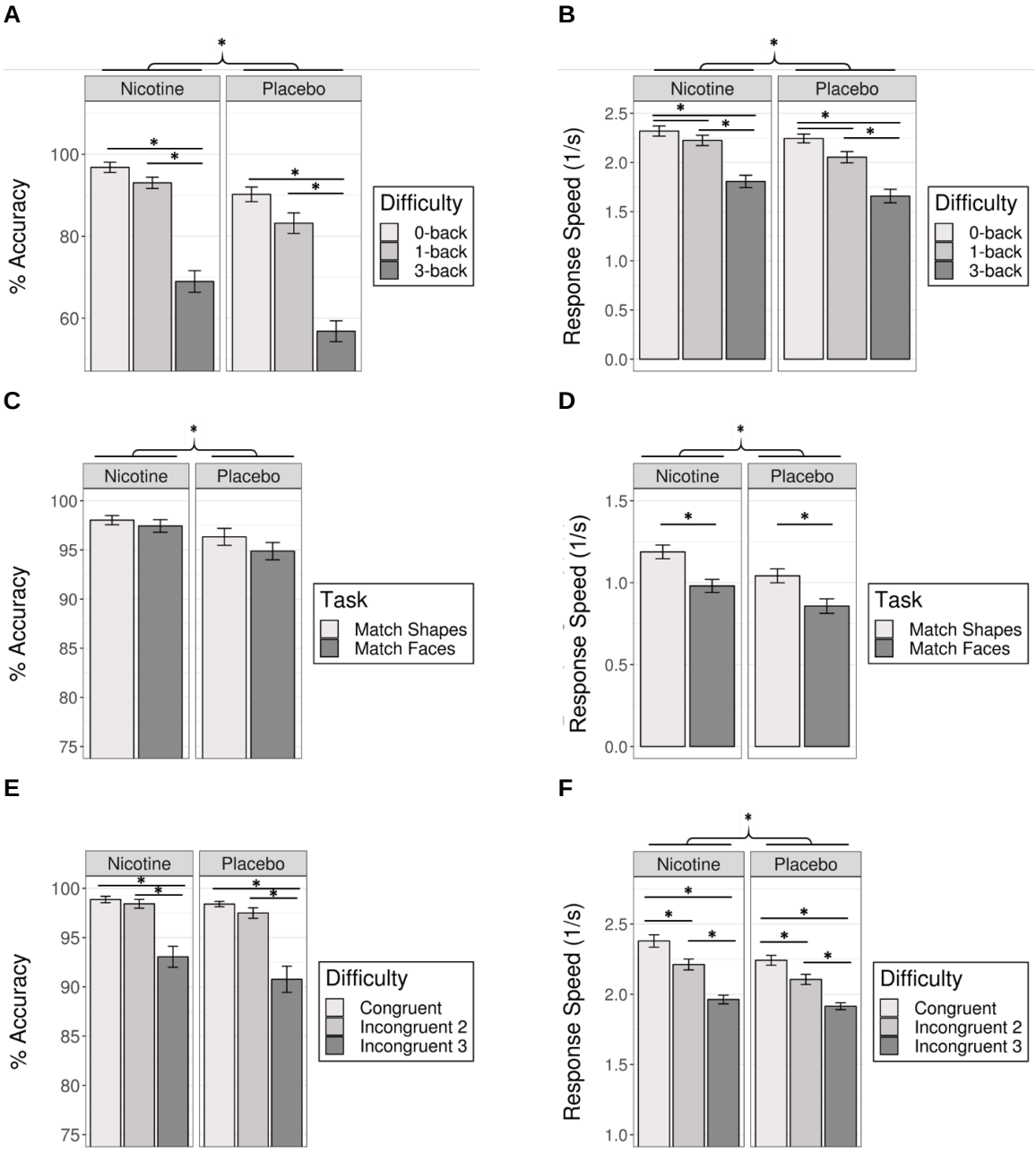
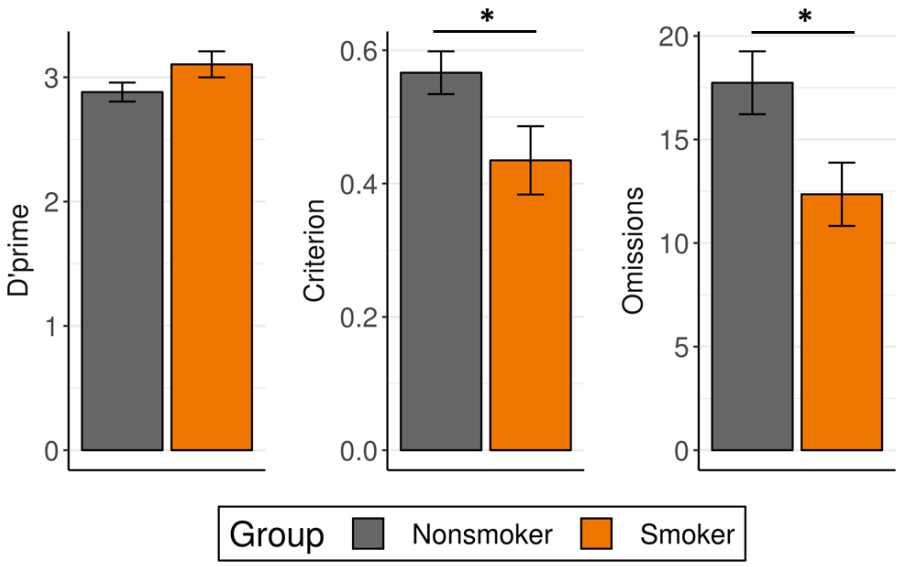


Figure S5: N-back Behavioral Sensitivity Outcomes: D-prime (d'), Criterion, and Number of Omissions. (A) Trait-Smoking Model, $N_{Nonsmoker} = 28$, $N_{Smoker, Sated} = 15$, main effect of Group for Criterion ($p = 0.03$) and Omissions ($p = 0.03$), (B) Nicotine-State Model, $N_{Smoker} = 15$, main effect of Patch for D-prime ($p = 0.01$), Criterion ($p = 0.01$), and Omissions ($p = 0.003$). * = $p < 0.05$, error bars represent standard error.

A



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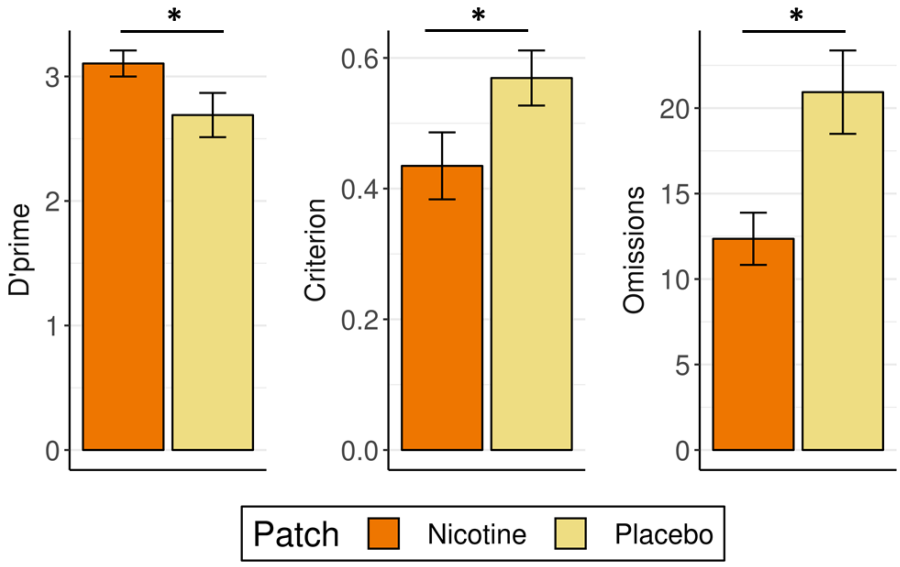


Figure S6: N-back WM Task Map. The N-back strongly activated ECN-related regions. WM load is higher for the 3-0 back contrast (A) than the 1-0 back contrast (B). Whole brain correction (FWE $\alpha << 0.01$, p-voxel $< 1 \times 10^{-5}$, cluster size > 85) was applied equally to both first-level contrasts. We chose an arbitrarily stringent threshold at greater than $\alpha < 0.01$ due to the robust activation produced by the task.

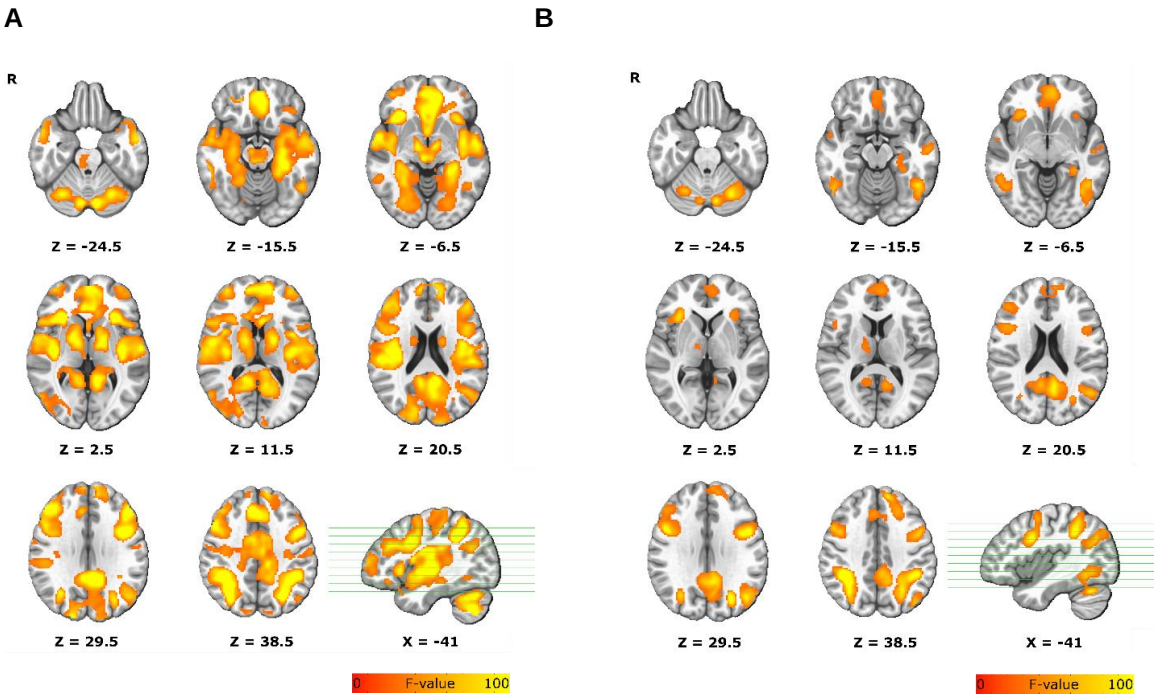


Table S2A: N-back WM Task Map (3-0 contrast), *Trait-Smoking* Model (43 subjects: 28 nonsmokers, 15 sated-smokers). Whole-brain corrected FWE $\alpha << 0.01$ (p-voxel < 1×10^{-5}, cluster threshold > 85). Coordinates represent peak cluster activation in LPI orientation and MNI space (MNI152NLin2009cAsym template); 1 voxel ≈ 8 mL.

Contrast	Anatomical Region	Cluster size (voxels)	X	Y	Z
WM Load (3-back - 0-back)	Bilateral Cingulate / Precentral & Postcentral Gyri / Lingual Gyrus / Insula	38409	55.5	3.5	-10.5
	Bilateral Middle Frontal Gyrus / Inferior Frontal Gyrus / Superior Frontal Gyrus / Striatum / Thalamus	18635	3.5	-24.5	-8.5
	Bilateral Middle & Occipital Gyri / Inferior & Superior Parietal Lobules / Angular Gyrus	7114	-30.5	-72.5	31.5
	Bilateral Medial Frontal Gyrus & Anterior Cingulate	6926	-2.5	35.5	-14.5
	Bilateral Cerebellum	4303	31.5	-68.5	-52.5
	L Inferior Temporal Gyrus	293	-50.5	-56.5	-12.5
	R Middle Temporal Gyrus	288	57.5	-34.5	-12.5
	R Cerebellum (Crus I)	165	27.5	-80.5	-32.5

Table S2B: N-back Working Memory Task, tDCS Main effect on WM load (3-back minus 0-back). *Trait-Smoking* Model (43 subjects: 28 nonsmokers, 15 sated-smokers). Whole-brain corrected FWE $\alpha < 0.01$ (p-voxel < 0.001, cluster threshold > 85). Coordinates represent peak cluster activation in LPI orientation and MNI space (MNI152NLin2009cAsym template); 1 voxel ≈ 8 mL.

Effect	Anatomical Region	Cluster size (voxels)	X	Y	Z
tDCS Main Effect on WM Load (3-back - 0-back)	R Parahippocampal Gyrus / Hippocampus / Precuneus	698	23.5	-16.5	-22.5
	L Parahippocampal Gyrus / Hippocampus / Precuneus / Posterior Cingulate Gyrus	676	-14.5	-42.5	-12.5
	R Supramarginal Gyrus / Inferior Parietal Lobule / Superior Temporal (Heschl's) Gyrus	270	43.5	-30.5	29.5
	R Middle Cingulate Gyrus / L Anterior Cingulate / L Superior Medial Gyrus	205	7.5	37.5	31.5
	L Superior Temporal (Heschl's) Gyrus / Post. Insula	161	-38.5	-22.5	9.5
	L Inferior Frontal Gyrus (p. Orbitalis)	140	-38.5	19.5	-12.5
	L Parahippocampal Gyrus / Hippocampus	117	-28.5	-24.5	-16.5
	R Culmen	91	17.5	-42.5	-14.5
	R Middle Temporal Gyrus	85	35.5	-56.5	15.5

Figure S7: Parametric Flanker Task Map. Main Effect of Difficulty (Number of Flankers). The Flanker strongly activated SN regions, including bilateral insula and anterior cingulate cortex. Whole-brain corrected FWE $\alpha < 0.01$ (p-voxel < 0.001, cluster threshold > 88). *Trait-Smoking* Model (43 subjects: 28 nonsmokers, 15 sated-smokers).

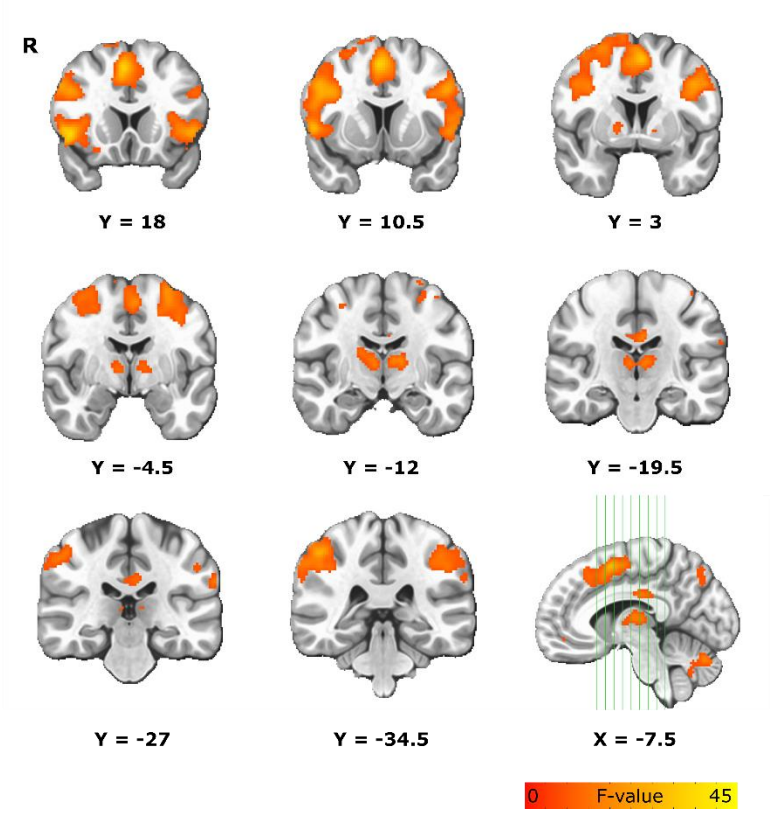


Table S3: Parametric Flanker Task Map. Main Effect of Difficulty (Number of Flankers). Whole-brain corrected FWE $\alpha < 0.01$ (p-voxel < 0.001, cluster threshold > 88). *Trait-Smoking* Model (43 subjects: 28 nonsmokers, 15 sated-smokers). Coordinates represent peak cluster activation in LPI orientation and MNI space (MNI152NLin2009cAsym template); 1 voxel ≈ 8 mL.

Effect	Anatomical Region	Cluster size (voxels)	X	Y	Z
Task Difficulty (Number of Flankers)	**R Insula / Bilateral Anterior Cingulate Cortex** / Bilateral Mid-Cingulate Cortex / Bilateral Supplementary Motor Area / R Precentral Gyrus / R Inferior, Middle, and Superior Frontal Gyri	6776	45.5	19.5	-4.5
	R Inferior Parietal Lobule / Middle Occipital Gyrus / Superior Occipital Gyrus / Supramarginal Gyrus / Angular Gyrus	4268	43.5	-46.5	49.5
	L Inferior Parietal Lobule / Superior Parietal Lobule / Middle Occipital Gyrus / Superior Occipital Gyrus	3797	-44.5	-44.5	45.5
	L Insula / Precentral Gyrus / Inferior Frontal Gyrus (p. Opercularis & p. Triangularis)	2707	-50.5	9.5	33.5
	L Inferior Temporal Gyrus / Cerebellum (Crus 1) / Cerebellar Vermis	1762	-10.5	-76.5	-26.5
	R Inferior Temporal Gyrus / Cerebellum (Crus 1)	987	43.5	-56.5	-12.5
	Bilateral Thalamus	710	-12.5	-12.5	11.5
	L Inferior / Middle Occipital Gyrus	306	-32.5	-92.5	-4.5
	R Inferior / Middle Occipital Gyrus	277	35.5	-88.5	-4.5
	Bilateral Medial Frontal Gyrus / Mid-Orbital Gyrus	204	1.5	53.5	-10.5
	Bilateral Middle Cingulate Cortex	187	-4.5	-20.5	27.5
	L Supramarginal Gyrus	113	-66.5	-26.5	27.5
	R Cerebellum (Crus 1, VI)	95	11.5	-76.5	-24.5

Figure S8: Faces Task, Main Effect of Block Type (Task Map). The task strongly activated bilateral amygdala. Whole-brain corrected FWE $\alpha << 0.01$ (p-voxel < 1 x 10^{-5}, cluster threshold > 93) We chose an arbitrarily stringent threshold at greater than $\alpha < 0.01$ due to the robust activation produced by the task.

(A) All results **(B) Bilateral Amygdala**

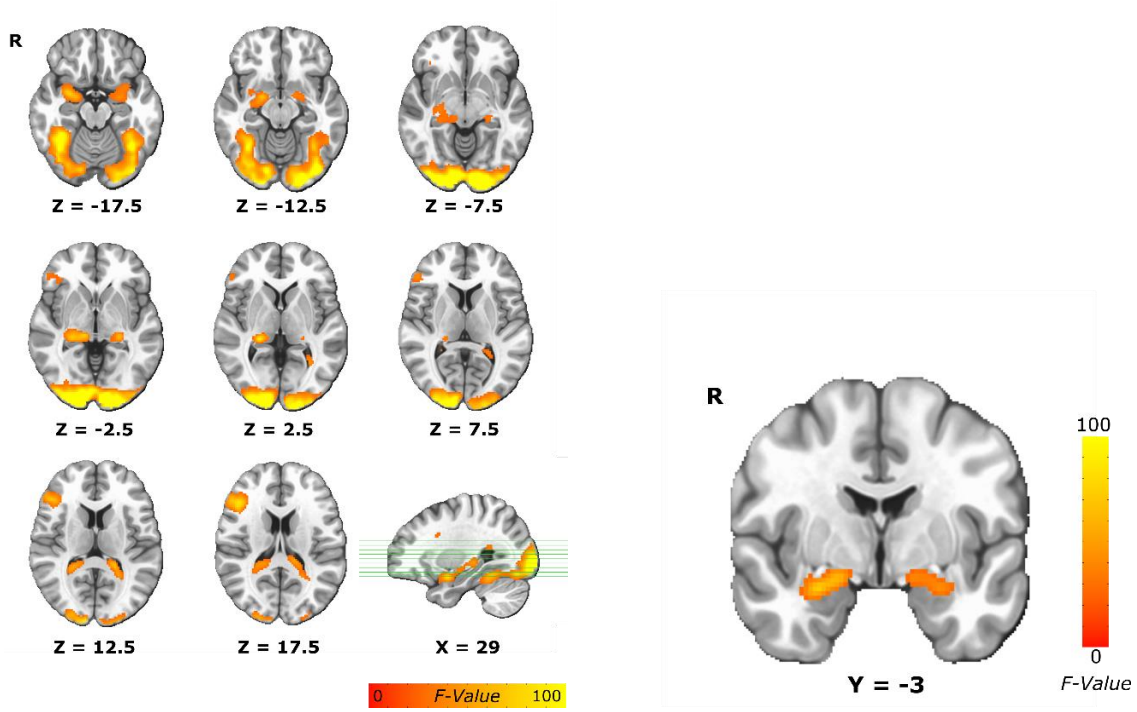


Table S4: Faces Task, Main Effect of Block Type (Task Map). Whole-brain corrected FWE $\alpha << 0.01$ (p-voxel < 0.00001, cluster threshold > 93). Coordinates represent peak cluster activation in LPI orientation and MNI space (MNI152NLin2009cAsym template); 1 voxel ≈ 8 mL.

Contrast	Anatomical Region	Cluster size (voxels)	X	Y	Z
Faces - Shapes	Bilateral Fusiform Gyrus / Middle Occipital Gyrus	7450	-38.5	-54.5	-18.5
	R Inferior Frontal Gyrus / Middle Frontal Gyrus	1244	45.5	27.5	17.5
	R Amygdala / Parahippocampal Gyrus	916	23.5	-30.5	1.5
	L Caudate	326	-20.5	-40.5	13.5
	L Amygdala	259	-26.5	-2.5	-18.5
	R Caudate	178	23.5	-42.5	13.5
	L Inferior Parietal Lobule	141	-56.5	-32.5	47.5
	L Inferior Parietal Lobule II	123	-40.5	-42.5	51.5
	L Hippocampus / Thalamus	120	-24.5	-28.5	-0.5

Table S5: N-back WM Task, tDCS * Patch Interaction Effect during high WM load (3-0 contrast). *Nicotine-State* Model (15 smokers). Whole-brain corrected FWE $\alpha < 0.01$ (p-voxel < 0.001, cluster threshold > 87). LPI coordinates.

Effect	Anatomical Region	Cluster size (voxels)	X	Y	Z
tDCS * Patch interaction, during high WM Load (3-0 back)	Bilateral Anterior Cingulate Cortex	356	-12.5	39.5	11.5
	Right Middle Temporal Gyrus	305	53.5	-12.5	-12.5
	Left Parahippocampal Gyrus / Hippocampus	268	-18.5	-10.5	-14.5
	Right Parahippocampal Gyrus	183	21.5	-30.5	-12.5
	Left Superior Medial Gyrus	128	-4.5	29.5	43.5
	Left Middle Temporal Gyrus	126	-58.5	-38.5	5.5

Figure S9: Main effect of Patch during high WM load (N-back 3-0 contrast). Nicotine patch affected one cluster in the L Precuneus (99 voxels, XYZ = -2.5, -52.5, 19.5). *Nicotine-State* model (15 smokers), whole brain FWE $\alpha < 0.01$ (p-voxel < 0.001, cluster threshold > 87). LPI coordinates. Graphical representations of numerical results, by Patch in each region, for pattern only. *L = Left.*

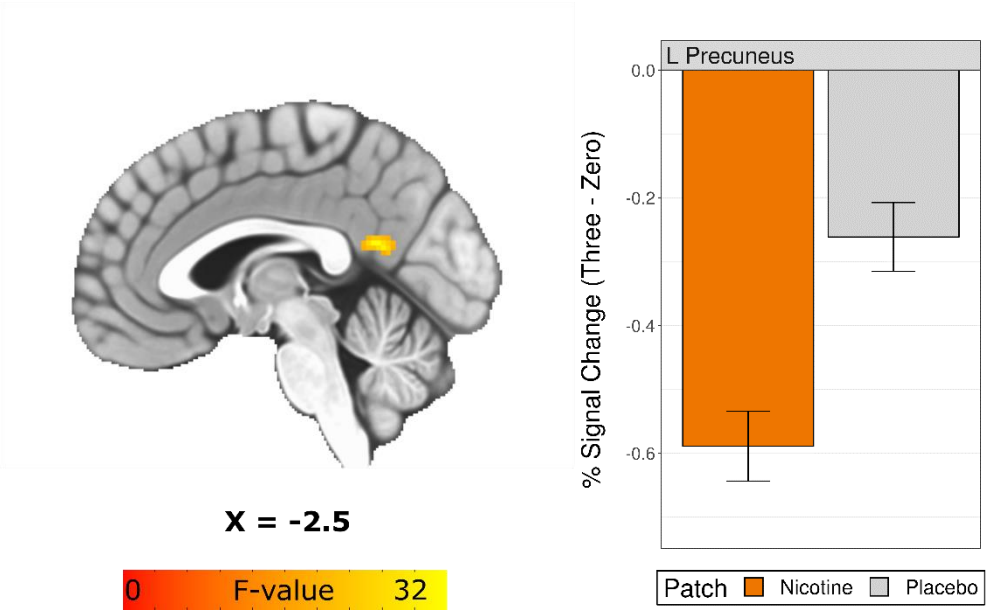


Figure S10: Main effect of Patch during the Parametric Flanker Task. Nicotine patch affected a large cluster in the bilateral thalamus (1146 voxels, XYZ = 1.5, -14.5, 1.5) that extended to bilateral caudate body, as well as clusters in the left caudate nucleus (118 voxels, XYZ = -10.5, 11.5, 21.5) and visual area BA17 (147 voxels, XYZ = 21.5, -100.5, -6.5). *Nicotine-State* model (15 smokers), whole brain FWE $\alpha < 0.01$ (p-voxel < 0.001, cluster threshold > 89). LPI coordinates. Graphical representations of numerical results, by Group in each region, for pattern only.

L = Left, R = Right, Calc/BA17 = Calcarine Sulcus.

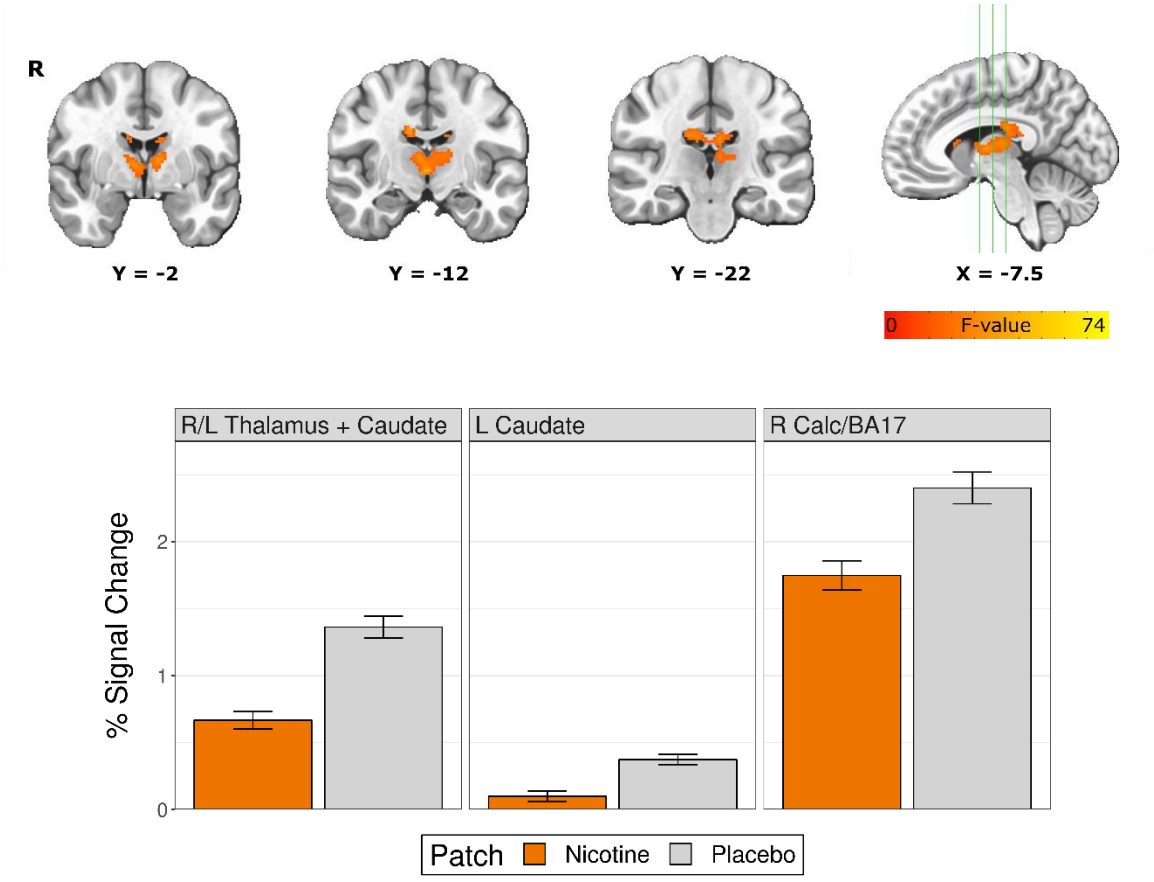
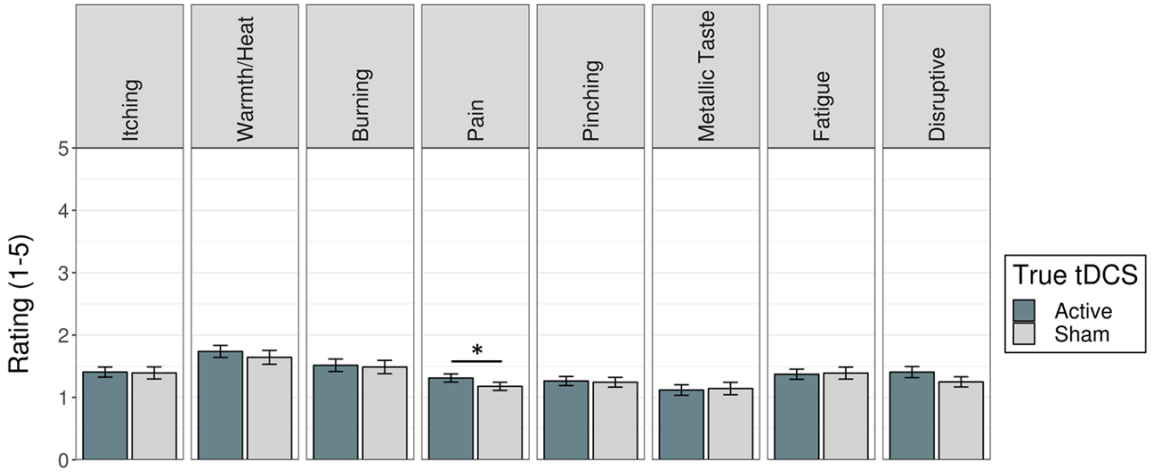


Figure S11: tDCS Toleration and Blinding. Across 161 randomized, counterbalanced tDCS sessions (43 subjects), participants guessed stimulation type (active/sham) at approximately chance rate (active, 62.3% correct; sham, 43.6% correct; chance being 66.7%:33.3%). Guess confidence did not differ between active and sham (active, 6.4/10 ± 2.6 $_{SD}$; sham, 6.1/10 ± 2.8 $_{SD}$). (A) Blinding questionnaire responses on tDCS sensation ratings. Sensations did not differ between active/sham except for one scale ("pain", active = 1.33 ± 0.51$_{SD}$, sham = 1.16 ± 0.42$_{SD}$, p = 0.03). Subjects were additionally asked "How much did these sensations affect your performance?" ("Disruptive", below) and to rate by: "not at all-1", "slightly-2", "considerably-3", "much-4", "very much-5". Only 4.3% of sessions were reported as "considerably" affected or higher. Adverse events were rare with one incident each of nausea and anxiety.

A



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