CALIFORNIA STATE UNIVERSITY, NORTHRIDGE

A Pilot Study Investigation of Methylphenidate as a Potential Treatment for Depersonalization/Derealization Disorder

A thesis submitted in partial fulfillment of the requirements

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General-Experimental

By

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Abstract

A Pilot Study Investigation of Methylphenidate as a Potential Treatment for Depersonalization/Derealization Disorder

By

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Master of Science in General-Experimental Psychology

The present quasi-experimental study investigated the potential efficacy of stimulant medication methylphenidate (trade name: Ritalin) in reducing depersonalization/derealization disorder (DPDR) symptoms among a pilot sample of adult individuals (84.6% white, 7.7% black, 3.8% Hispanic, and 3.8% Asian; 50% female) recruited from TurkPrime, a crowdsourcing Internet marketplace. A sample of 26 participants (8 = "treatment" and 18 = controls) were recruited on the basis of either taking methylphenidate as prescribed for attention-deficit hyperactivity disorder (ADHD) or their endorsement of ADHD while not taking methylphenidate or any other central nervous system stimulant medication. Participants in the treatment condition completed questionnaires assessing DPDR, anxiety, and ADHD symptoms prior to taking methylphenidate and approximately two hours post-ingestion, at peak medication

concentration. Participants in the control condition took surveys at the same times. Results revealed marginally significant associations between methylphenidate and DPDR symptom changes over time at high levels of elapsed time between T1 and T2, and significant associations when trait anxiety and ADHD were included as moderators. In the treatment condition, DPDR scores increased if more time had elapsed between T1 and T2 whereas in the control condition, DPDR scores decreased if more time had elapsed. Control participants saw marginal decreases in DPDR symptoms from baseline to two hours later, suggesting a non-significant decrease in symptoms possibly due to diurnal rhythms. There was a significant three-way interaction between STAI-T scores, CDS scores, and methylphenidate ingestion, such that for control participants, DPDR symptoms decreased slightly over time regardless of trait anxiety, whereas for treatment participants, DPDR symptoms increased much more over time the higher the level of trait anxiety the participant reported. There was also a significant three-way interaction between ADHD scores, DPDR scores, and methylphenidate ingestion, such that for control participants, DPDR symptoms decreased slightly over time regardless of ADHD symptom severity, whereas for treatment participants, DPDR symptoms increased much more over time the higher the level of ADHD symptoms the participant endorsed. These results highlight the potentially distinct subtypes of individuals with DPDR symptoms, and how they may respond differently to stimulant medication. This pilot investigation lends baseline insight as to methylphenidate's potential in both reducing and exacerbating DPDR symptomatology for a subset of individuals, and underscores the need to examine its potential utility in treating DPDR in a larger and more controlled setting.

Chapter 1: Introduction

Depersonalization/derealization disorder (DPDR) is a type of dissociative disorder, a classification of psychological disorder based on a disintegration of consciousness, memory, identity, emotion, perception, body representation, motor control, and behavior (American Psychiatric Association, 2013). Specifically, depersonalization represents a detachment from one's own thoughts, feelings, sensations, body, or actions (APA, 2013). In many cases, the sufferer reports feeling as if (s)he is observing him/herself from behind. Derealization is a feeling of detachment from one's surroundings, in which individuals or objects appear "unreal," "dreamlike," or "foggy". To meet the criteria for diagnosis, an individual must experience either recurrent depersonalization, derealization, or both (APA, 2013). The etiology of DPDR is strongly linked to prolonged interpersonal trauma, often in childhood (Simeon, Guralnik, Schmeidler, Sirof, & Knutelska, 2001; Van der Kolk, 2017), though a minority of DPDR cases have been found to result from other factors such as illicit drug use (Simeon, Kozin, Segal, & Lerch, 2009; Simeon, Knutelska, Nelson, & Guralnik, 2003) or combat trauma later in life (Zerach, Greene, Ginzburg, & Solomon, 2014).

DPDR is known to share high diagnostic co-morbidity with attention-deficit/hyperactivity disorder (ADHD), a condition characterized by persistent inattention, hyperactivity, and/or impulsivity (APA, 2013), due to overlapping clinical features (Siegfried & Blakshear, 2016). Both conditions share in common inhibition, concentration, and emotion regulation issues, as well as irritability and disorganization (Cromer, Stevens, DePrince, & Pears, 2006; Szymanski, Sapanski, & Conway, 2011; Siegfried & Blackshear, 2016). One of the most widely utilized questionnaires assessing

dissociative experiences, Bernstein and Putnam's (1986) Dissociative Experiences Scale (DES), features items such as "Some people find that when they are watching television or a movie they become so absorbed in the story that they are unaware of other events happening around them. Select a number to show what percentage of the time this happens to you" (DES). This dissociative experience bears striking similarity to the individual with ADHD's occasional experience of hyper-focus. One study found that cognitive failures are a significant correlate of dissociative experiences (Merckelbach, Muris, & Rassin, 1999). Participants were administered the Dissociative Experiences Scale (DES) as well as Cognitive Failures Questionnaire (CFQ), which features questions such as "Do you fail to notice signposts on the road?" and "Do you forget appointments?" Merckelbach, Muris, and Rassin (1999) found a significant correlation between reports of dissociative experiences and everyday cognitive failures. The CFQ's examples of cognitive failures are highly similar to the inattentive and forgetful experiences commonly reported by individuals with ADHD. Prevalence estimates of ADHD among children and adults across cultures is approximately 5% and 2.5%, respectively (APA, 2013). Dissociative disorders are estimated to affect approximately 2% of individuals worldwide (APA, 2013), though some studies estimate a 10% prevalence within the general population (Loewenstein, 1994). Notably, childhood trauma has been strongly linked to ADHD diagnoses (Szymanski, Sapanski, & Conway, 2011; Rucklidge, Brown, Crawford, & Kaplan, 2006); one study found that 56% of men and women diagnosed with ADHD endorsed childhood experiences of moderate to severe abuse and/or neglect (Rucklidge, Brown, Crawford, & Kaplan, 2006). Additionally, children with reported maltreatment are commonly diagnosed with both

ADHD and post-traumatic stress disorder (PTSD; McLeer, Callaghan, Henry, & Wallen, 1994; Martin, Cromer, & Filgas-Heck, 2005). This relationship between childhood trauma and ADHD-like symptoms has led researchers to question the extent to which ADHD has become over-diagnosed in recent years, and whether ADHD-like symptoms may be better accounted for by PTSD-induced dissociation (Siegfried & Blackshear, 2016).

ADHD and DPDR are distinct in several ways. Fundamentally, DPDR is a disorder characterized by disintegration of oneself from oneself and/or one's surroundings and ADHD is a disorder characterized by impaired attention, disorganization, hyperactivity, and impulsivity (APA, 2013). The etiology of ADHD has been linked to maltreatment, but it is also associated with genetic heritability, prenatal drug and alcohol use, exposure to neurotoxins, perinatal complications, and poor nutrition (Thapar, Cooper, Jefferies, & Stergiakouli, 2011). DPDR often has etiological roots in childhood interpersonal trauma (Simeon, Guralnik, Schmeidler, Sirof, & Knutelska, 2001; Van der Kolk, 2017). ADHD originates in childhood with an often life-long morbidity for those who do not outgrow it by adulthood, whereas DPDR, while also often first seen in childhood or adolescence, may abate following certain drug regimens or psychotherapy (APA, 2013; Kooij et al., 2010; Brand & Loewenstein, 2010).

Neural and neuroendocrine correlates of DPDR and ADHD

fMRI has revealed different patterns of neural activation among the disorders. Decreased regional homogeneity in the frontal-striatal-cerebellar circuits and increased regional homogeneity in the occipital cortex (Cao et al., 2006); reduced brain surface in

the prefrontal cortex and anterior temporal cortices (Sowell et al., 2003); decreased blood flow in the orbitofrontal cortex (Lee et al., 2005); and hypoactivation of the frontoparietal network as well as hyperactivation in visual, attentional, and default networks (Cortese et al., 2012), have all been observed among ADHD participants as compared with controls. These findings highlight the role of frontoparietal dysfunction in ADHD. In DPDR, fMRI has revealed reduced activation in the left insula and increased activation in the right ventral prefrontal cortex among individuals with depersonalization as compared with controls, after viewing aversive stimuli (Phillips et al., 2001); increased activation of the ACC during dissociative responses when compared with hyperaroused re-experiencing responses (Lanius et al., 2005); increased mPFC, superior and middle temporal gyri, inferior frontal gyrus, occipital lobe, parietal lobe, medial frontal gyrus, medial cortex, and ACC activity following trauma imagery in individuals with dissociative PTSD (Lanius et al., 2002); and increased amygdalar connectivity to prefrontal regions and regions implicated in consciousness, awareness, and proprioception as compared to individuals with non-dissociative PTSD (Nicholson et al., 2016). Additionally, the temporal-parietal junction, a region found to be implicated in out-of-body experiences (Blanke & Arzy, 2005), has generated much scientific interest as a potential locus of depersonalization experience.

These neural correlates of ADHD suggest that a considerable amount of the disorder's characteristics may be localized to the prefrontal-striatal-cerebellar network (Wang et al., 2016), though research suggesting other associated networks is modestly accumulating (see Castellanos & Proal, 2012, for a review; see Cortese et al, 2012, for a review). The neural correlates of DPDR, however, reveal a more complex known

interrelationship between numerous structures in distinct regions of the brain, including but not limited to the temporal, occipital, parietal, and frontal lobes, as well as the amygdala and insula. An impairment in one or several of these interconnected structures may lead to a disconnection from the otherwise "normal integration of consciousness, memory, identity, emotion, perception, body representation, motor control, and behavior" (APA, 2013). These findings shed light upon the multitudinous contributions of both cortical and subcortical regions to dissociative experiences, and distinguish their structural impairments and associated symptoms from those of ADHD.

In addition to structural differences, the neuroendocrine responses to dissociative experiences differ somewhat from the neuroendocrine responses of ADHD. DPDR involves the dopaminergic and opioid systems, and increases catecholamine levels but also vagal tone, so the "dissociator" experiences a lowered blood pressure and lowered heart rate but higher levels of circulating epinephrine (Perry, Pollard, Blakley, Baker, & Vigilante, 1995). Supporting theories of autonomic blunting among individuals with DPDR, Simeon, Guralnik, Knutelska, Yehuda, and Schmeidler (2003) observed increased urinary norepinephrine among individuals with depersonalization, but an inverse correlation between basal norepinephrine and depersonalization severity. Hallucinogens, including LSD, psilocybin, and DMT have all been shown to induce depersonalization, with a mechanism of action believed to possibly be attributable to these hallucinogens' actions as serotonin 5HT2A and 5HT2C agonists (Simeon et al., 2003; Simeon, 2009). Other neurotransmitters that have been found to mediate depersonalization experiences include serotonin, glutamate, and endogenous opioids (Nuller, Morozova, Kushnir, & Hamper, 2001; Simeon, 2004). Conversely, research investigating the neurobiology of

ADHD has found dopamine to be a key neurotransmitter implicated in ADHD; individuals with ADHD show reduced size of the caudate nucleus and globus pallidus, two structures rich in dopamine receptors (Swanson, 2007; see Tripp & Wickens, 2009, for a review), as well as possible dopamine transporter binding abnormalities in various structures of the brain (Swanson, 2007; Dougherty et al., 1999; see Tripp & Wickens, 2009, for a review). Norepinephrine transporter abnormalities may play a role in the pathogenesis of ADHD, and research has shown that methylphenidate may exert its therapeutic effect by occupying these transporters, increasing norepinephrine levels in the brain (Kim et al., 2006; Sigurdardottir et al., 2016; see Pliszka, 2005, for a review; Hannestad, 2010). Whereas ADHD pathophysiology appears to predominantly involve catecholamines dopamine and norepinephrine, DPDR again appears more complex with catecholamines, serotonin, glutamate, and endogenous opioids implicated in its pathogenesis.

Despite these structural and neuroendocrine differences, the two conditions appear to share some common neural underpinnings, with increased brain activation in the medial frontal gyrus (Brodmann area 10) and ACC (Brodmann area 24) seen in both conditions (Lanius et al, 2002; Yu-Feng et al., 2007; Dickstein, Bannon, Xaxiver Castellanos, & Milham, 2006). Brodmann area 10 is thought to be responsible for alertness to one's environment, concentration, memory, and multitasking (Burgess, Dumontheil, & Gilbert, 2007). Brodmann area 24 is thought to be an autonomic effector and cortisol suppressor region (Ward, 1948) as well as responsible for attention skills and theory of mind task performance (Frith & Frith, 2001). Additionally, ADHD and childhood maltreatment (the antecedent of a large number of DPDR cases) have both

been shown to impair some of the same brain structures involved in emotion regulation and processing, executive functioning, and impulsivity (Teicher, 2000). In one study of children diagnosed with ADHD, it was found that an overwhelming 71% had co-morbid dissociative disorder (Endo, Sugiyama, & Someya, 2006). For the adult survivor of childhood relational trauma, ADHD may persist into adulthood and DPDR is likely to persist as well, especially in the absence of proper diagnosis and therapeutic intervention.

Previous pharmacological DPDR research

Although there exist numerous neurobiological differences between the two conditions, the one known research study to date that has investigated a stimulant's role in the treatment of DPDR found an almost complete abatement of DPDR after four months (Foguet, Alvarez, Castells & Arrufat, 2011). Foguet et al. (2011) note that the patient improved first on affective measures including anxiety and suicidality, and after four months' time the DPDR lifted for the first time and did not return. Stimulant medication remains the pharmacological gold-standard treatment for ADHD (see Reeves & Schweitzer, 2004, for a review). At present, there exists no gold-standard pharmacologic treatment option for DPDR, and the small number of clinical trials investigating various drugs' efficaciousness in mitigating DPDR symptoms have yielded mixed results. In Hollander et al.'s (1990) study, SSRIs were given to eight participants with DPDR. Participants with co-morbid anxiety and/or obsessive-compulsive disorder (OCD) reported the DPDR as less distressing yet still present following treatment (Hollander et al., 1990). Simeon, Guralnik, Schmeidler, and Knutelska (2004) also found no significant overall improvement in DPDR symptoms following fluoxetine therapy, but

found clinically significant improvement in DPDR-related distress among participants whose co-morbid anxiety and/or depression improved following treatment. Anticonvulsant medication lamotrigine, which inhibits glutamate release, has also been found to not significantly improve DPDR symptoms when compared with placebo (Sierra, Phillips, Ivin, Krystal, & David, 2003). Opioid antagonists naloxone and naltrexone have shown the greatest therapeutic promise to date; in a study of 14 patients, 3 experienced complete abatement of DPDR and 7 experienced significant improvement following naloxone therapy (Nuller et al., 2001), and in a trial of naltrexone, 3 of 14 patients experienced "very much" improvement and 1 patient experienced "much" improvement following treatment (Simeon & Knutelska, 2005). Finally, in a trial (n = 7) investigating tricyclic antidepressant clomipramine's efficaciousness in reducing DPDR symptoms, 2 subjects experienced significant improvement in DPDR, while 3 dropped out due to intolerable side effects (Simeon, Stein, & Hollander, 1998). The scientific literature investigating potential pharmacological treatments for DPDR remains scant, especially in comparison with research investigating pharmacological treatments for other psychiatric conditions. Of the few studies that have been conducted, the majority of findings have either been largely unpromising, somewhat promising but with significant attrition due to adverse medication effects, or considerably promising only among those whose anxiety, depression, and/or OCD appear(s) to moderate the severity of DPDR. These highly varied results both among studies and within-treatment subject pools elucidate the exigent need for further investigation into possible pharmacological treatments for DPDR. At present, the one investigation (a case study) of the effect of methylphenidate in reducing DPDR symptomatology has revealed a complete abatement

of DPDR in four months. Thus, further investigation into methylphenidate's potential usefulness in treating DPDR is warranted. The aim of this study is to investigate that role.

Methylphenidate

Stimulant drug methylphenidate is the most often prescribed medication for ADHD treatment (Volkow, Fowler, Wang, Ding, & Gatley, 2002). It is ingested orally and exerts its effects by blocking dopamine and norepinephrine transporters, thus inhibiting their reuptake (Volkow et al., 2002). Peak serum concentration occurs at approximately 2 hours, and effects of immediate-release forms typically last between 1 and 4 hours (Kimko, Cross, & Abernethy, 1999). There is a wide range of variability in interindividual methylphenidate response, though this variable potency is poorly understood (Volkow et al., 2002). 20mg/day per day is a common recommendation for adults (Novartis Pharmaceuticals Corporation, 2013).

As stated earlier, elevated catecholamine levels have been linked to DPDR. However, the inverse relationship observed between basal norepinephrine and depersonalization severity may make it worthwhile to consider methylphenidate as a potential treatment option for individuals endorsing DPDR experiences. Individuals with both DPDR and true ADHD may experience the greatest benefit, as studies investigating DPDR alleviation in individuals with co-morbid anxiety found that upon reducing levels of anxiety, DPDR is alleviated as well. As previously mentioned, frontal lobe impairments are thought to primarily underlie ADHD symptoms and DPDR is thought to arise from a complex network of disruptions in the frontal, parietal, temporal, and occipital lobes. It is plausible that increasing activity in the hypoactive frontal lobe

among DPDR sufferers with co-morbid ADHD may normalize activity in the overactive parietal and occipital lobes, thus reducing DPDR. This study investigated whether and to what extent prescribed methylphenidate use alleviates symptoms of DPDR among individuals with co-morbid or misdiagnosed ADHD.

Chapter 2: Specific Aims

<u>Aim 1:</u> To examine DPDR reduction following prescribed methylphenidate use.

Participants will take methylphenidate as prescribed and report levels of dissociation using the Cambridge Depersonalisation Scale (CDS) before administration, at peak action, and 6 hours post-administration.

Hypothesis 1a. In the treatment group, DPDR symptoms will be reduced at peak action compared to pre-test.

Hypothesis 1b. In the control group, DPDR symptoms will not change.

<u>Aim 2:</u> To examine the impact of self-reported anxiety on DPDR amelioration.

Hypothesis 2. In the treatment group only, anxiety will moderate the association between methylphenidate and DPDR symptom reduction. Individuals with higher anxiety will report less efficacy, as methylphenidate's mechanism of action involves inhibiting reuptake of dopamine and norepinephrine (Kuczenski & Segal, 1997) and may exacerbate DPDR symptoms among anxious individuals.

<u>Aim 3:</u> To examine the impact of co-morbid ADHD on DPDR amelioration.

Hypothesis 3. In the treatment group only, ADHD will moderate the association between methylphenidate and DPDR symptom reduction. Individuals with higher ADHD symptoms will report greater efficacy, as methylphenidate activates impaired frontal circuits, and may potentially dampen overactive activity in the parietal lobe.

Chapter 3: Design

Participants

This project is a mixed between/within subjects pilot study in which individuals were recruited from TurkPrime. The "treatment" group (n=8) are currently taking methylphenidate as prescribed, and the control group (n=18) endorsed ADHD but were not taking stimulant medication at the time of the study. The inclusion of a control group was intended to demonstrate that symptom changes observed with medication activity were not better accounted for by natural diurnal rhythms.

The 26-participant sample (8 treatment, 18 control) was 50% female and 50% male, with 75% of treatment participants and 39% of control participants being female. The overall sample was 84.6% white, 7.7% black, 3.8% Hispanic, and 3.8% Asian, and all treatment group individuals were white. Time having taken methylphenidate ranged from 1 year to 29 years (M = 6.75, SD = 10.15). Among the 8 treatment individuals, 5 (62.5%) took immediate-release methylphenidate and 3 (37.5%) took extended-release methylphenidate.

Time between moment of methylphenidate ingestion and second questionnaire administration (targeting peak serum concentration) ranged from 1hr 21min to 6hr 21min (this larger span is due to one participant taking an extended release methylphenidate formulation; M = 2hr 29min, SD = 1hr 36min). A question assessing ingestion of caffeine, a known central nervous system stimulant (Nehlig, Daval, & Debry, 1992), was administered. 81% of the overall sample reported using caffeine; of this sample, 75% (n = 6) of treatment individuals and 83% (n = 15) reported ingesting caffeine. These

individuals were not excluded as they comprised the vast majority of the sample and because an abundance of literature has revealed caffeine to be significantly inferior to methylphenidate and other amphetamines in reducing ADHD symptomatology (see Leon, 2000 for a review). Finally, one individual was excluded from the originally recruited treatment group (n = 10) for not having taken the pre-screen questionnaire and another was excluded from the treatment group for having taken methylphenidate before time point 1 (baseline).

Procedure

Participants were pre-screened for the period of time having taken methylphenidate, number of times per day an individual ingested methylphenidate, and time(s) of day taken. To distract from the true purpose, participants were informed that the purpose of the study was to "assess the effectiveness of ADHD medication". Participants took the CDS, State Trait Anxiety Inventory (STAI), and (Adult ADHD Self-Report Scale) ASRS at two time points: baseline (prior to ingestion) and at peak medication action (2 hours post ingestion).

At peak concentration (based on participants' responses about time of ingestion), participants were prompted by email to re-take these three questionnaires and reminded to answer them based on their experience at that moment. There was a one hour window of time during which the questionnaires were available. Participants received compensation through TurkPrime at the rate of .20 per minute.

Measures

Cambridge Depersonalization Scale (CDS). The CDS, a 29-item questionnaire intended to capture the frequency and chronicity of depersonalization experiences over the most recent six months, is valid, reliable, and well-correlated with the depersonalization subscale of the Dissociative Experiences Scale (DES). Participants reported the frequency which they experience various DPDR events. Frequency is measured with a Likert scale with the following parameters: 0 = never, 1 = rarely, 2 = often, 3 = very often, 4 = all the time. The CDS's questions are more suited to the momentary assessment of symptoms (e.g. "What I see looks 'flat' or 'lifeless', as if I were looking at a picture") than the DES (e.g. "Some people are told that they sometimes do not recognize friends or family members. Select a number to show what percentage of the time this happens to you") and is sufficient for assessing DPDR specifically. For the present study's analyses, the reliability of the CDS for measuring DPDR symptom severity was excellent at both time point 1 ($\alpha = .95$) and time point 2 ($\alpha = .95$).

State-Trait Anxiety Inventory (STAI). Aim 2 seeks to ascertain the impact of self-reported anxiety on DPDR amelioration. To achieve this aim, participants completed the STAI. The STAI is a 20-item self-report screening tool for anxiety, featuring statements relating to calm and anxious experiences, with a 4-option Likert scale with the following range: 1 = not at all, 2 = somewhat, 3 = moderately so, and 4 = very much so. The STAI has acceptable validity and reliability (Marteau & Bekker, 1992). For the present study's analyses, the reliability of the STAI for measuring state anxiety was

excellent at both time point 1 (α = .93) and time point 2 (α = .95). For measuring trait anxiety (only at time point 1), the STAI was excellent (α = .94).

Adult ADHD Self-Report Scale (ASRS). The World Health Organization's ASRS is an acceptably valid and reliable (Adler et al., 2006; Kessler et al., 2006) self-report tool to screen for adult ADHD symptoms over the most recent six months. It contains 18 items to be answered according to a 5-option Likert scale with a range of "never," "rarely," "sometimes," "often," and "very often". For the present study's analyses, the reliability of the ASRS for measuring ADHD symptom severity was excellent at both time point 1 (α = .95) and at time point 2 (α = .96.)

Additional Questions

Participants were additionally asked for demographic information including age, sex, and ethnicity.

Confidentiality of Research Information and Data

All collected data was "de-identified" and participants were assigned worker ID codes to protect anonymity. Information was stored on an encrypted computer that requires a password to access. Participants was informed of confidentiality protocols during the informed consent process. Data were locked and will be protected for approximately ten years, after which it will be destroyed.

Chapter 4: Results

Data Preparation

Data were assessed prior to analysis for missing values, univariate and multivariate outliers, normality, linearity, and homogeneity of regression slopes and variance. There were no missing values. Variables were standardized for z-scores and a test of Mahalanobis distance was used to screen for univariate and multivariate outliers, respectively. There were no univariate or multivariate outliers.

Table 1
Descriptive Statistics

		Treatment group							Control group						
Measure		*n*	Mean T1	SD T1	Mean T2	SD T2	*t*-test	p-value	*n*	Mean T1	SD T1	Mean T2	SD T2	*t*-test	p-value
1.	CDS	8	16.9	14.8	16.9	18.6	.01	.99	18	17.5	14.0	16.6	14.9	.73	.48
2.	STAI-S	8	37.4	11.4	39.5	13.8	-.52	.62	18	40.5	11.4	44.1	13.2	-1.93	.07
3.	STAI-T	8	46.9	10.8					18	51.3	15.3				
4.	ASRS	8	55.3	16.0	41.0	18.6	2.63	.03*	18	49.6	14.5	45.3	17.5	1.81	.09

CDS= Cambridge Depersonalisation Scale; *STAI-S*= State-Trait Anxiety Inventory-State; *STAI-T*= State-Trait Anxiety Inventory-Trait; *ASRS*= Adult ADHD Self-Report Scale
*p <.05.

Table 1. Descriptive Statistics

Table 2
Descriptive Statistics - Treatment and control groups combined

Measure		*n*	Mean T1	SD T1	Mean T2	SD T2	*t*-test	p-value
1.	CDS	26	17.3	14.0	16.7	15.7	.336	.74
2.	STAI-S	26	39.5	11.2	42.7	13.3	-1.79	.09
3.	STAI-T	26	50.0	14.0	50.0	14.0		
4.	ASRS	26	51.3	14.9	43.8	17.6	2.99	.01**

CDS= Cambridge Depersonalisation Scale; *STAI-S*= State-Trait Anxiety Inventory-State; *STAI-T*= State-Trait Anxiety Inventory-Trait; *ASRS*= Adult ADHD Self-Report Scale
**p ≤.01.

Table 2. Descriptive statistics – Treatment and control group combined

Table 3
Bivariate Correlations - time point 1

Measure	1	2	3	4	5	6
1.CDS	1.00					
2. STAI-S	.536**	1.00				
3. STAI-T	.357#	.614**	1.00			
4. ASRS	.636**	.623**	.627**	1.00		
5. Time between T1-T2	-.030	.031	.042	-.293	1.00	
6. CDS difference [T2-T1]	-.139	.269	.068	.021	.368#	1.00

CDS= Cambridge Depersonalisation Scale; *STAI-S*= State-Trait Anxiety Inventory-State; *STAI-T*= State-Trait Anxiety Inventory-Trait; *ASRS*= Adult ADHD Self-Report Scale
**p < .01. #p<.10

Table 3. Bivariate Correlations – time point 1

Preliminary Analyses

Bivariate analyses at time point 1 revealed a positive correlation between CDS scores and STAI-S scores, between CDS scores and ASRS scores, between STAI-S scores and STAI-T scores, and between STAI-S scores and ASRS scores. It revealed a marginally positive correlation between CDS scores and STAI-T scores. The positive relationship between the CDS difference scores and the T1-T2 interval also trended toward significance, and thus, given the size of the sample, T1-T2 interval was controlled for in all CDS score analyses. There was not a significant difference in CDS difference scores (T2 minus T1) between females (M = -1.87, SD = 11.57) and males (M = .62, SD = 7.1); $t(24)$ = -.660, p = .516, or between individuals who ingest caffeine (M = -1.39, SD = 10.17) and individuals who do not ingest caffeine (M = 2.60, SD = 5.32); $t(24)$ = .842, p = .408.

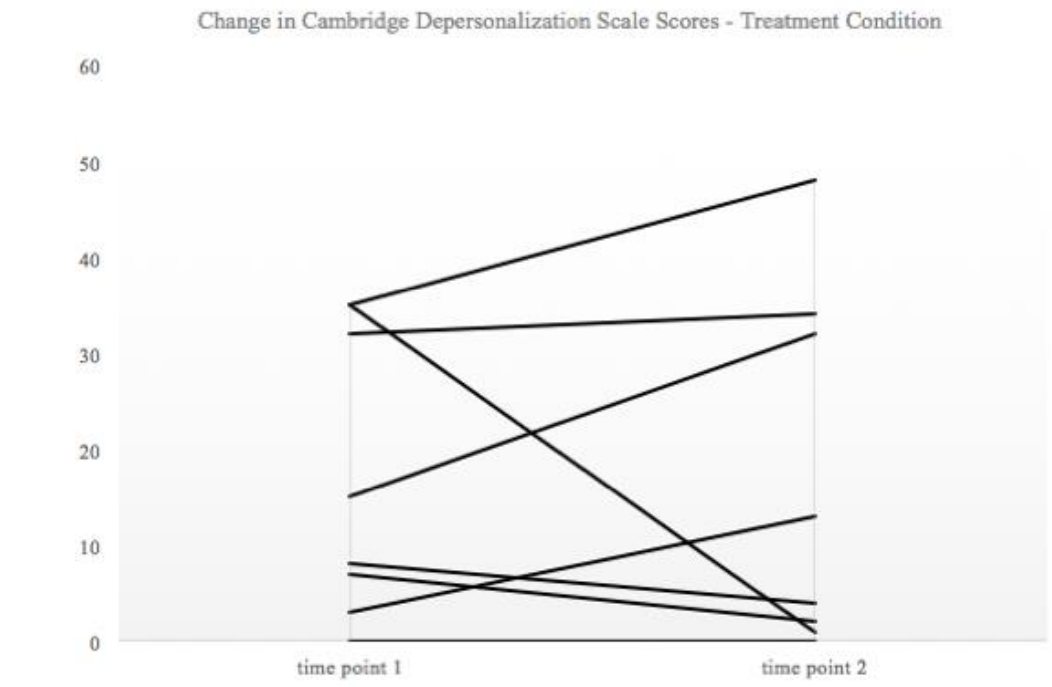

Figure 1. Change in Cambridge Depersonalization Scores – Treatment Condition

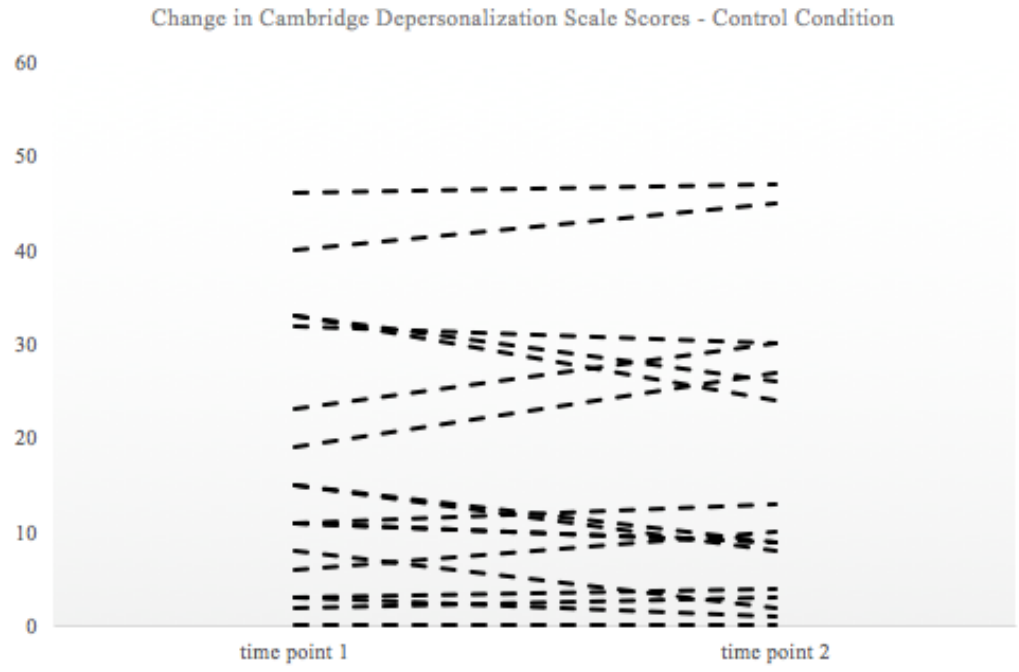

Figure 2. Change in Cambridge Depersonalization Scores – Control Condition

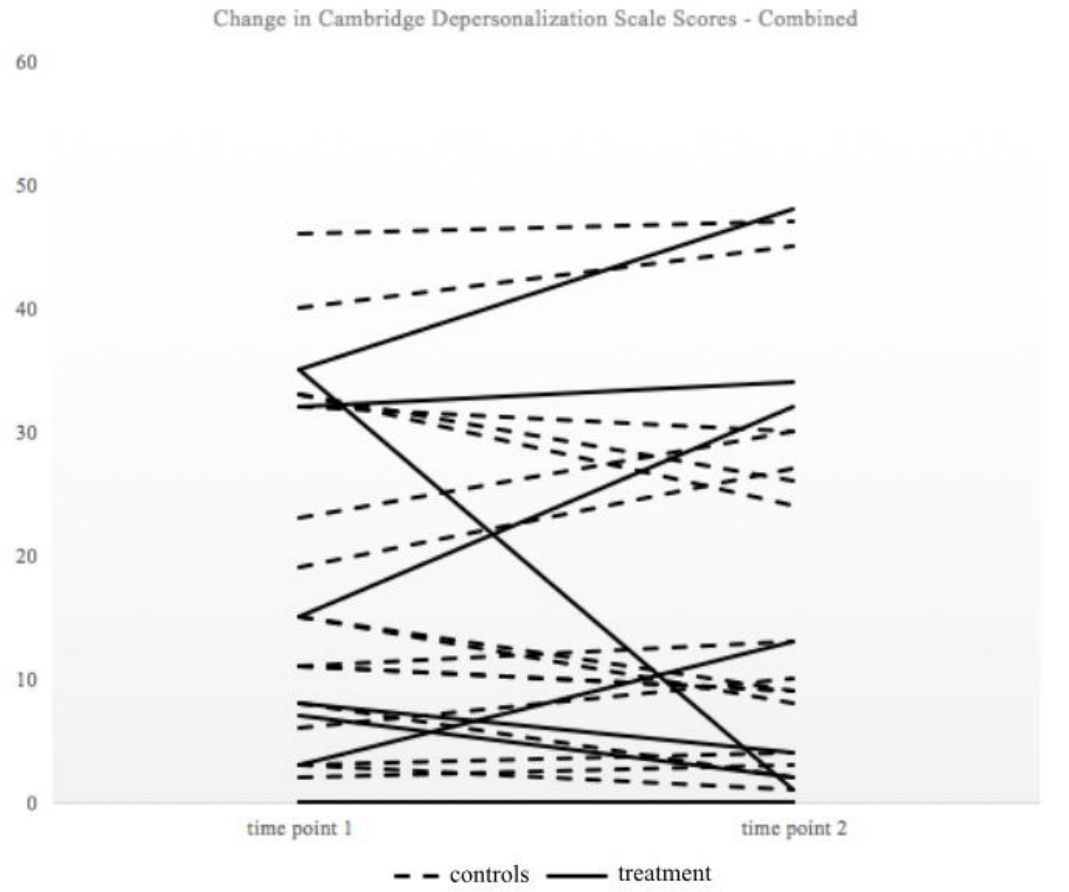

Figure 3. Change in Cambridge Depersonalization Scores – Combined

As a manipulation check, a repeated-measures ANOVA was employed to assess whether ASRS scores were reduced following methylphenidate ingestion. Tests of within-subjects effects revealed a significant main effect of time in reducing ADHD symptoms $F(1, 24) = 13.979$, $p = .001$, as well as a significant interaction between methylphenidate and time $F(1, 24) = 4.304$, $p = .049$, such that the treatment group experienced approximately triple the decrease in ASRS scores than the control group, who did not receive methylphenidate. The main effect of methylphenidate alone was non-significant $F(1,24) = .004$, $p = .948$.

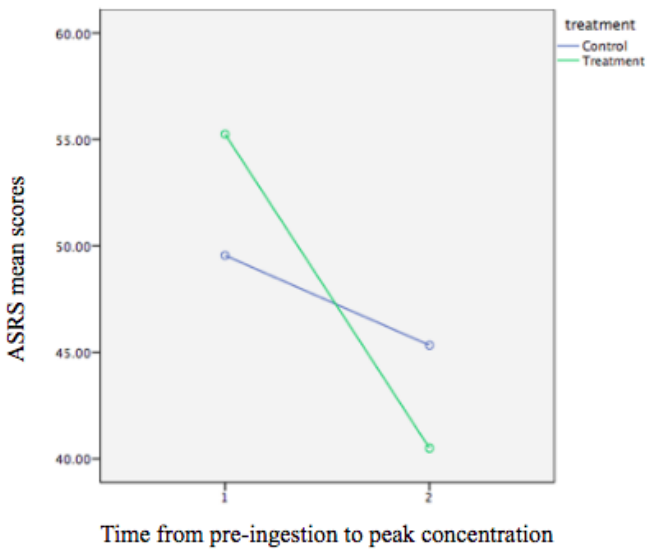

Figure 4. Manipulation Check – Change in ADHD scores

Aim 1 investigated DPDR symptom reduction following prescribed methylphenidate use. To test this aim, mixed factorial ANCOVA was employed to examine the main effect of methylphenidate as well as the main effect of time (pre-test and peak medication concentration), and the interaction between methylphenidate and time, with the T1-T2 interval included as a covariate. Tests of within-subjects effects revealed a significant main effect of time in reducing DPDR symptoms $F(1, 22) = 7.932$, $p = .010$, a non-significant main effect of methylphenidate on DPDR symptoms $F(1, 22) = .053$, $p = .819$, and a non-significant interaction between methylphenidate and time $F(1, 22) = 2.430$, $p = .133$. There was a marginally significant interaction between time, methylphenidate, and T1-T2 interval, $F(1,22) = 3.969$, $p = .059$, such that in the treatment group, CDS scores increased if more time had elapsed whereas in the control condition CDS scores decreased if more time had elapsed. Finally, there was a significant interaction between time and T1-T2 interval $F(1,22) = 8.110$, $p = .009$, such that CDS

scores decreased over time if less time had elapsed, but increased over time if more time had elapsed.

For aim two, mixed factorial ANCOVA was employed to examine the moderating influence of self-reported anxiety on DPDR amelioration. Self-reported anxiety was measured as a continuous covariate, and state and trait anxiety were examined independently. When state anxiety (STAI-S) was examined, there was a non-significant main effect of time $F(1,18) = 1.722$, $p = .206$, a non-significant main effect of methylphenidate $F(1, 18) = .249$, $p = .624$, and a non-significant main effect of the T1-T2 interval $F(1,18) = .299$, $p = .591$, in reducing DPDR symptoms. There was a non-significant interaction effect between CDS scores and methylphenidate $F(1, 18) = 1.926$, $p = .182$. There was a non-significant interaction between CDS scores and STAI-S scores $F(1, 18) = .932$, $p = .347$, as well as between STAI-S scores and methylphenidate $F(1,18) = .250$, $p = .623$. There was a non-significant three-way interaction between STAI-S scores, CDS scores, and methylphenidate $F(1, 18) = 1.516$, $p = .234$.

When trait anxiety was examined, there was a significant main effect of time $F(1,18) = 21.748$, $p < .001$, such that CDS scores increased over time (controlling for trait anxiety), a non-significant main effect of methylphenidate $F(1, 18) = .107$, $p = .748$, and a non-significant effect of the T1-T2 interval $F(1,18) = .190$, $p = .668$, in reducing DPDR symptoms. There was a significant interaction effect between CDS scores and methylphenidate $F(1, 18) = 21.396$, $p < .001$, such that controlling for trait anxiety, treatment individuals experienced increased DPDR symptoms between T1 and T2 whereas control individuals experienced decreased DPDR symptoms between T1 and T2. There was a significant interaction between CDS scores and STAI-T scores $F(1, 18) =$

13.983, p = .002, such that more temperamentally anxious individuals experienced greater increases in DPDR symptoms from T1 to T2, irrespective of treatment status. There was a non-significant interaction between STAI-T scores and methylphenidate $F(1,18)$ = .225, p = .641. There was a significant three-way interaction between STAI-T scores, CDS scores, and methylphenidate ingestion $F(1, 18)$= 16.100, p = .001, such that for control participants, DPDR symptoms decreased slightly over time regardless of trait anxiety, whereas for treatment participants, DPDR symptoms increased much more over time the higher the level of trait anxiety the participant reported (see Figure 4).

There were significant interactions between time and the T1-T2 interval $F(1,18)$ = 14.737, p = .001; time, the T1-T2 interval, and methylphenidate $F(1,18)$ = 14.451, p = .001; time, the T1-T2 interval, and STAI-T scores $F(1,18)$ = 7.173, p = .015; and time, the T1-T2 interval, methylphenidate and STAI-T scores $F(1,18)$ = 8.105, p = .011, such that the above-mentioned significant effects with trait anxiety as a moderator were stronger when longer periods of time had elapsed between T1 and T2.

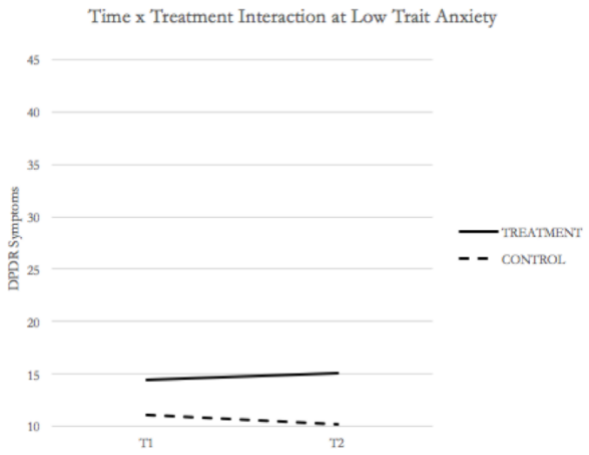

Figure 5a. Time x Treatment Interaction at Low Trait Anxiety

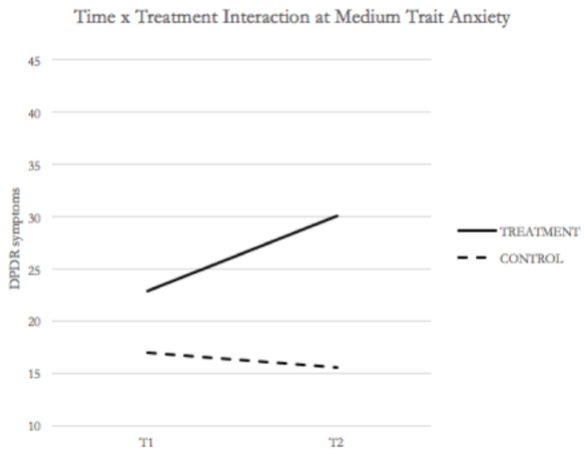

Figure 5b. Time x Treatment Interaction at Medium Trait Anxiety

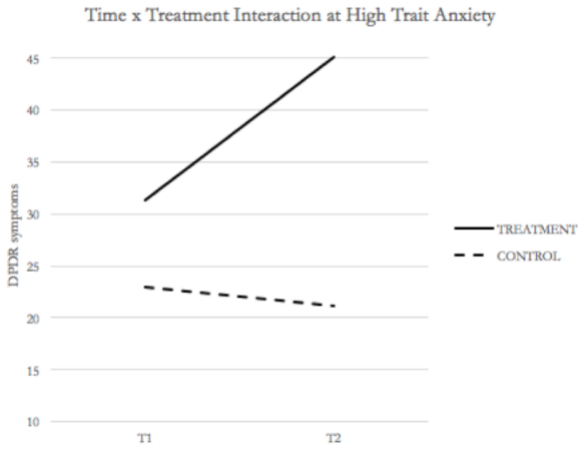

Figure 5c. Time x Treatment Interaction at High Trait Anxiety

For aim three, mixed factorial ANCOVA was employed to examine the moderating influence of co-morbid ADHD symptoms on DPDR amelioration. There was a significant main effect of time $F(1, 18) = 9.215$, $p = .007$, such that symptoms increased over time, controlling for ADHD symptoms, a non-significant main effect of methylphenidate $F(1, 18) = .000$, $p = .983$, and a non-significant main effect of the T1-T2 interval $F(1,18) = .164$, $p = .690$, in reducing DPDR symptoms. There was a significant interaction effect between CDS scores and methylphenidate $F(1, 18) = 6.834$, $p = .018$,

such that controlling for ADHD symptoms, treatment individuals experienced increased DPDR symptoms between T1 and T2 whereas control individuals experienced decreased DPDR symptoms between T1 and T2. There was a significant interaction effect between CDS scores and ASRS scores $F(1, 18) = 5.282$, $p = .034$, such that individuals with higher levels of ADHD experienced greater increases in DPDR symptoms from T1 to T2, irrespective of treatment status. There was a non-significant interaction effect between ASRS scores and methylphenidate $F(1, 18) = .156$, $p = .698$. There was a significant three-way interaction between ASRS scores, CDS scores, and methylphenidate ingestion $F(2, 18) = 4.480$, $p = .048$, such that for control participants, DPDR symptoms decreased slightly over time regardless of ADHD symptom severity, whereas for treatment participants, DPDR symptoms increased much more over time the higher the level of ADHD symptoms the participant endorsed (see Figure 5).

There were significant interactions between time and the T1-T2 interval $F(1,18) = 7.284$, $p = .015$ as well as time, the T1-T2 interval, and methylphenidate $F(1,18) = 5.962$, $p = .025$, such that the above-mentioned significant effects with ADHD as a moderator were stronger when longer periods of time had elapsed between T1 and T2. There were non-significant associations between time, the T1-T2 interval, and ASRS scores $F(1,18) = 3.152$, $p = .093$, and time, the T1-T2 interval, methylphenidate and ASRS scores $F(1,18) = 2.925$, $p = .104$.

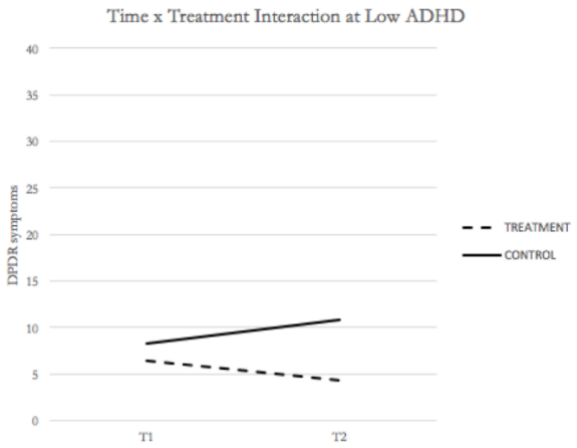

Figure 6a. Time x Treatment Interaction at Low ADHD

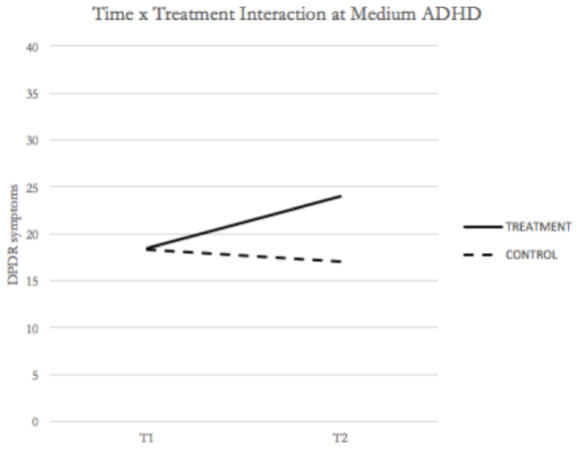

Figure 6b. Time x Treatment Interaction at Medium ADHD

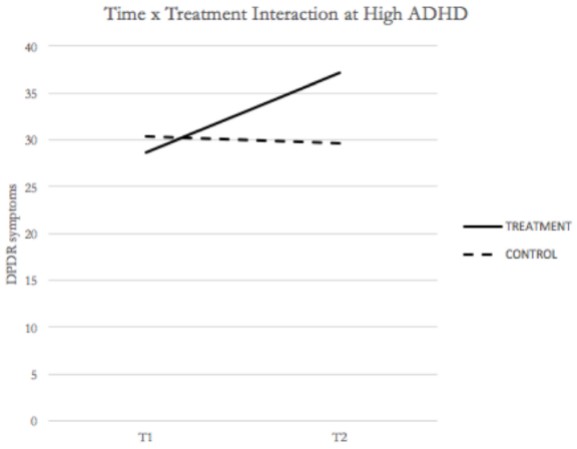

Figure 6c. Time x Treatment Interaction at High ADHD

Chapter 5: Discussion

The present study investigated the potential efficacy of methylphenidate in ameliorating DPDR symptoms. By recruiting 8 individuals to a "treatment" group and 18 individuals to a control group, this quasi-experimental investigation was able to examine DPDR symptom reduction as likely being attributable to methylphenidate rather than natural diurnal variations.

A manipulation check was conducted to assess the credibility of the present study's design. A repeated-measures ANOVA was run to investigate methylphenidate's influence on ADHD symptoms. As a stimulant medication for the treatment of ADHD, it was hypothesized that there would be a significant effect, despite the small treatment sample. This effect was significant in the hypothesized direction, with the treatment group experiencing approximately triple the decrease in ASRS scores than the control group.

Hypothesis 1a

Hypothesis 1a posited that among individuals taking methylphenidate, DPDR symptoms would be reduced at peak action compared to pre-test, as evidenced by reduced scores on the CDS. This hypothesis was unsupported; there was no significant decrease in DPDR symptoms among individuals taking methylphenidate. However, one factor to consider in interpreting these findings is that the majority of "treatment" group participants either saw a sharp increase or decrease from baseline in DPDR symptoms at peak-serum methylphenidate concentration. This effect is illustrated in figures 1-3, and highlights how these non-significant findings should be interpreted with caution. These

sharp increases and decreases likely nullified one another in statistical analyses. They also suggest a significant moderating variable among individuals taking methylphenidate, and that there may potentially be a distinct type of individual with DPDR who may benefit or experience DPDR symptom exacerbation from methylphenidate. It is possible that the sharp DPDR symptom increases among some of the treatment participants could be due to co-morbid diagnoses such as anxiety and ADHD, as well as concomitant use of medications that may interact with methylphenidate to exacerbate DPDR symptoms. In particular, among the two participants whose DPDR symptoms most increased from T1 to T2, one of the individuals endorsed ADHD symptoms at nearly two standard deviations above the mean. The interaction observed in the data between ADHD symptom severity and methylphenidate treatment effects further speak to this potential mechanism.

These participants were also taking either modafinil, an atypical, selective, and weak dopamine reuptake inhibitor, or citalopram, a selective serotonin reuptake inhibitor. No systematic research studies have been carried out on the effects of these medications on DPDR symptoms. However, one isolated case study has reported citalopram's efficacy in reducing DPDR in combination with clonazepam, with positive results (Sachdev, 2002). With scant literature supporting the use of these medications in DPDR, and no published contraindications, it cannot be known whether either has contributed to these sharp rises in DPDR from T1 to T2. However, the significantly elevated ADHD symptoms reported by one of these participants suggests an atypical neurochemistry that may have accounted for increased DPDR symptoms over this interval.

Finally, it is possible that treatment participants who endorsed increased DPDR symptoms from T1 to T2 were experiencing increasing focus on one particular task, to the exclusion of stimuli in the external environment. It is possible that, among individuals taking methylphenidate, this medication-induced "hyperfocus" may mimic the experience of DPDR.

Hypothesis 1b

It was hypothesized that in the control group, DPDR symptoms would not change over time. Although symptoms did not change as substantially as they did in the "treatment" group, there was a marginally significant decrease in DPDR symptoms among individuals in the control group from baseline to two hours post-ingestion of methylphenidate. Control participants saw a negligible decrease (approximately 1.5 points) from baseline to approximately two hours later, whereas treatment participants saw a negligible increase (approximately 2 points) during this timeframe. Unexpectedly, the marginally significant interaction between CDS scores, change over time, and interval suggests that symptom fluctuations may be at least partially attributable to daily rhythms and the simple passage of time that may cause DPDR symptoms to increase or wane more as time passes over the course of a day. In interpreting this finding, consideration must also be given to the study's small sample size and the maximum possible CDS frequency score of 116.

Hypothesis 2

Extending hypothesis one, it was hypothesized that more anxious individuals in the treatment group only would experience less DPDR symptom reduction than their non-anxious counterparts, due to the pharmacodynamic mechanism by which methylphenidate exerts its effect. This hypothesis was formulated on the basis of anxiety being a common adverse effect of methylphenidate (Novartis Pharmaceuticals Corporation, 2013), and knowledge that methylphenidate inhibits the reuptake of excitatory neurotransmitters dopamine and norepinephrine. However, the original hypothesis failed to account for the potentially different structural and neuroendocrine differences between individuals endorsing acute versus chronic anxiety, and the present study's results may have highlighted this distinction.

State and trait anxiety were analyzed independently, and all main and interaction effects with state anxiety as a moderator were non-significant. When analyzing effects of trait anxiety, the original hypothesis was supported; not only did more temperamentally anxious treatment participants experience significantly less symptom reduction, they experienced DPDR symptom *increases* across all levels of trait anxiety, and these increases were most pronounced among individuals with higher levels. More temperamentally anxious control individuals experienced marginally greater decreases in DPDR as compared with their less temperamentally anxious counterparts.

The significance of trait anxiety and non-significance of state anxiety as moderators in DPDR symptom reduction may be attributable, in part, to the differential activation of the noradrenergic and dopaminergic systems, two regulators of the stress response in humans, by acute and chronic stress (see Goddard et al., 2010, for a review;

see Massaly, Morón, & Al-Hasani, 2016, for a review). Compared to individuals low in trait anxiety, individuals with high trait anxiety are significantly more vulnerable to chronic stress (see Weger & Sandi, 2018, for a review), show stronger selective attentional biases toward threatening stimuli, more often interpret neutral expressions as negative, and have more hyper-active fear responses (Sandi & Richter-Levin, 2009). They also exhibit greater amygdalar responsivity when unconsciously processing fear (Etkin et al., 2004). A handful of literature has found that temperamentally anxious individuals have dysregulated neuroendocrine profiles, with higher basal cortisol levels (Takahashi et al., 2005) and abnormal hormone and catecholamine secretion in response to stress (Duncko, Makatsori, Fickova, Selko, & Jezova, 2006; Jezova, Makatsori, Duncko, Moncek, & Jakubek, 2004) having been observed. and one study of children with anxiety disorders found significant psychophysiological similarity to children who have endured chronic stress (Dieleman et al., 2015). Given the potential overlap in physiological response profiles of temperamentally anxious individuals and those who experience chronic stress, the chronic stress literature may provide a window into interpreting these findings.

In an acutely stressful event, activation of the noradrenergic system stimulates the release of glucocorticoids that can lead to increased anxiety in humans. However, a growing body of literature within the past three decades has found that although chronic stress may initially lead to an increase in such glucocorticoids, this increase often drops to normal levels over time and may even eventuate in suppressed glucocorticoid levels (Gunnar, 2001; Miller, Chen, & Zhou, 2007). This allostatic trajectory likely also depends on a multitude of factors such as type(s) of stressor experienced, individual

perceptions of stress, and elapsed time since stress onset (Miller et al., 2007). Despite many different possible profiles of hypothalamic-pituitary-adrenal (HPA) axis-activity following chronic stress, allostatic load has been shown to dysregulate the HPA-axis such that increased norepinephrine may be paradoxically anxiolytic in certain individuals (see Goddard et al., 2010 for a review). Though this may be true, methylphenidate was not associated with DPDR symptom reduction in the present study.

Chronic stress is also known to impair mesolimbic dopaminergic function (Massaly et al., 2016), and methylphenidate is known to activate both the noradrenergic and dopaminergic pathways (see Engert & Pruessner, 2008, for a review; Mueller et al., 2014). In treatment individuals with more chronic anxiety, elevated norepinephrine and dopamine along with structural alterations and alteration in transmission of other unaccounted-for neuroendocrine mediators of anxiety may have manifested in different patterns of anxiety and consequent DPDR symptom amelioration as compared with treatment individuals either only experiencing momentary anxiety at time of data collection or experiencing no anxiety whatsoever.

In summary, the significant association between methylphenidate and increased DPDR symptoms among individuals with more vs. less trait anxiety and no significant association in individuals with state anxiety potentially implicates dysregulated HPA-axis neuroendocrine signaling in the experience of DPDR. Indeed, the literature supports this suggestion. HPA-axis dysregulation has been reported in DPDR. Some studies have reported hypo-secretion of basal cortisol in participants with depersonalization disorder as compared with participants with major depressive disorder (Stanton et al., 2001; Dubinina et al., 2000). One study reported altered plasma cortisol following

dexamethasone administration among participants with depersonalization disorder compared with healthy controls (Simeon, Guralnik, Knutelska, Hollander, & Schmeidler, 2001), and another reported higher basal urinary cortisol than healthy controls, greater resistance to dexamethasone suppression as compared to controls, and a significant inverse relationship between dissociation severity and cortisol reactivity to psychosocial stress (Simeon et al., 2007).

Finally, it is possible that DPDR manifests independently of the anxiolytic or anxiogenic properties of methylphenidate, and that temperamentally anxious treatment individuals saw greater increases in DPDR symptoms because by T2 they became more aware of the study's objective, taking a more hypervigilant and anxious inventory of methylphenidate's influence on DPDR symptoms. Individuals experiencing only transient anxiety may not have taken this stance.

Hypothesis 3

It was hypothesized that individuals with more severe ADHD symptoms would report greater DPDR symptom reduction, as methylphenidate activates impaired frontal circuits, and may potentially dampen overactive activity in the parietal lobe. This hypothesis was not supported; based off of ASRS scores, ADHD did significantly moderate the association between DPDR symptoms and methylphenidate ingestion, but DPDR symptoms increased at higher levels of ADHD endorsed.

The present study's findings may loosely suggest that (1) any possible activation of prefrontal networks by methylphenidate would not by proximity dampen overactive activity in the parietal lobe, leading to a consequent alleviation of DPDR symptoms, (2)

any dampening of parietal hyper-activation would not be sufficient alone to significantly alleviate DPDR symptoms, and/or (3) that frontal and parietal dysfunction seen in DPDR are not due to impaired frontoparietal communication, and that any methylphenidate-induced improvements to communication between these structures would not re-regulate impaired segregated regions associated with DPDR.

Perhaps the most important finding of aim three is that DPDR symptoms worsened among treatment individuals the greater the level of ADHD endorsed. One rationale for this finding may be that methylphenidate activates frontal circuitry (Vaidya et al., 1998), and could worsen DPDR symptoms by means of increasing the corticolimbic disconnection that has been proposed as a mechanism of DPDR experiences. Sierra and Berrios's (1998) theory of corticolimbic disconnection, which partially posited that the emotionally detached experience of DPDR likely results from the overly active left prefrontal cortex's inhibition of the limbic structures, has since been upheld by the neuroscience literature (Phillips et al., 2001; see Lanius et al., 2010, for a review). Any increased activity in the frontal structures implicated in amgydalar suppression may have contributed to increased feelings of detachment among treatment individuals.

Limitations

There were several limitations to the present study. Perhaps most notably, this study included only 8 treatment individuals and only 18 controls. This 26-person sample lacked the statistical power to draw conclusions about non-significant effects, and any effects such as caffeine ingestion that emerged as non-significant may have been

considered significant with a much larger sample pool. Nevertheless, statistically significant associations were found, and support a rationale to conduct this research with a larger sample pool.

Secondly, this study analyzed results from only two time-points: pre-ingestion of methylphenidate and peak medication concentration. Though the study was originally conceptualized as consisting of three time points: (1) pre-ingestion, (2) peak medication concentration, and (3) post-drug metabolism, post-drug metabolism was not examined due to significant attrition after time-point two. Using TurkPrime to engage participants required email prompts inviting them to take second and third time point questionnaires. By time point three, individuals were either not responding to survey invitations or responding after the available time window had closed. Without CDS scores returning to baseline at post-drug metabolism, it cannot be deduced that methylphenidate is the sole or main contributing factor to DPDR symptom alteration.

In addition, TurkPrime as a crowdsourcing Internet platform provides a very loosely controlled quasi-experimental sample pool and setting. CAPTCHAs were appended to the beginning of each questionnaire to counter the possibility of "bots" completing the surveys, an increasingly problematic phenomenon in internet-based research. Despite this intervention, there is high opportunity for users to lie about having taken methylphenidate and to answer questionnaires as if they had. To counter this possibility, a long list of medication options was offered to the survey-taker so that (s)he could select methylphenidate among several options that would preclude his/her participation in the study. Further, the manipulation check provided evidence that treatment group individuals were likely taking ADHD medication during the specified

time interval. Nevertheless, without the ability to administer methylphenidate at scheduled intervals in a controlled setting, it was impossible to control for non-adherence and contextual factors that may have influenced DPDR symptom alteration.

It was also impossible to control the type of environment(s) in which the individuals responded to questionnaires. Because individuals did not come into a laboratory, it was not possible to create an environmental setting that was similar across all survey administrations. It was also not possible to control what activities the participants engaged in prior to taking surveys. For instance, one participant whose DPDR symptoms dropped significantly from T1 to T2 indicated that she was at a social luncheon and took a nap in between the two time points. This lack of control may have influenced results.

Finally, individuals were not barred from participation if they reported ingesting caffeinated products or taking other medications. Beverages such as coffee are central nervous system stimulants and other medications may interfere with methylphenidate's effectiveness. Due to the niche sample and lack of recruitment opportunities, it was not possible to apply such a narrow filter. Although the study's pre-screen questionnaire asked participants to indicate what caffeine-containing products they consumed as well as how much, many participants did not reply with quantities that allowed for control as a covariate. For instance, one individual indicated that he drank "2 per day of coffee," not indicating whether he drank from a small or large cup or mug, or how many milligrams of coffee he had. For this reason, caffeine ingestion was not controlled.

Suggestions for future quasi-experimental studies using TurkPrime include customizing the pre-screen questionnaire in such a way that requires individuals to

answer questions as specifically as possible. For example, in a question about units of caffeine ingested, researchers can include a question in which the participant must indicate the quantity of milligrams of caffeine ingested throughout the day. Additionally, one way to increase the likelihood of obtaining a T3 response would be to inform participants that compensation will be paid as a lump sum at the end of the third administration. Although this option increases the likelihood of attracting fewer participants, those who do respond would more likely answer questionnaires at all three time points. Ideally, a randomized clinical trial would better control for confounding variables that may have influenced results.

Implications

Dissociative disorders, including DPDR, are associated with significant psychological distress as a result of feelings of unreality, emotion dysregulation, relationship difficulties, intrusive traumatic memory, self-harm, and overall diminished quality of life (Myrick et al., 2017; Schielke, Brand, & Marsic, 2017). In addition to their psychological burdens upon the sufferer, dissociative disorders impose a tremendous economic burden upon society as a result of increased hospitalizations, functional impairment and unemployment, and mental healthcare utilization (Mueller-Pfeiffer et al., 2012; Myrick et al., 2017). At present, pharmacotherapy is not a mainstay of dissociative treatment programs, which may be attributable to the scarcity of research and lack of consensus as to what medications might best help particular dissociative patients.

There may exist a subgroup(s) of DPDR sufferers for whom methylphenidate exacerbates DPDR symptoms. A larger and more controlled study that reveals this effect

may add to the literature a potential pharmacological contraindication in certain individuals. There may also be a subgroup(s) of DPDR sufferers for whom methylphenidate alleviates conditions. If methylphenidate proves efficacious on a larger and more controlled scale, it may greatly aid in the stabilization and symptom reduction phase of psychotherapeutic treatment, increasing the likelihood that the patient may successfully progress to subsequent phases of treatment. It would be an optimal medication with which to supplement psychotherapy, as it is highly accessible, affordable, and commonly prescribed. The long-term goal of the proposed study is to contribute to the body of knowledge that seeks to understand the neurobiological mechanisms by which DPDR manifests and the process by which it is alleviated, to improve prognoses among DPDR sufferers, and to further explore whether there are distinct subgroups of DPDR sufferers and whether or not they should be treated with different medications.

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