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The Role of Brain-Derived Neurotrophic Factor in the Link between Physical Activity and Psychosocial Recovery from Alcohol Use Disorder

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My cohort, the students who entered the PhD program in 2014

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My Mum and Dad

My wife Karlyn.

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Abstract

Objective: Alcohol Use Disorder (AUD) is a common, chronically relapsing condition with substantial health and economic costs. United States federal agencies have put out calls in the last decade to expand the scientific evidence base for broad biopsychosocial recovery from AUD and other substance use disorders (SUD). The present study examined the role of physical activity and exercise in early recovery from AUD, with specific attention to changes in brain-derived neurotrophic factor (BDNF) as a marker of neuroplasticity and a potential mechanism for instantiation of recovery-aligned behaviors. *Method*: Individuals in the first year of recovery from AUD were recruited into a 12-week study with exercise sessions and pre/post-exercise blood sample collection performed in a laboratory setting at baseline, 6 weeks, and 12 weeks. Data analyses included BDNF enzyme-linked immunosorbent assays (ELISA) to establish pre/post-exercise BDNF concentrations, estimation of the magnitude of the effect of exercise on BDNF, and prospective associations of exercise-induced BDNF change with coping, craving, consumption and mood outcome measures. *Results*: 26 participants were screened, 22 were

eligible, 7 had entered the study, and 6 had provided at least one set of pre/post-exercise blood samples when student research ceased on March 23rd, 2020 due to COVID-19 precautions. Participants with at least one set of pre/post-exercise blood samples demonstrated a statistically significant (p=.014) increase from baseline in BDNF levels after exercise, with a large effect size (Cohen's d=1.519; Hedges' g=1.019). The impact of this increase from baseline on subsequent measures of coping, craving, mood, and substance use is unclear due to lack of statistical power. *Conclusions*: This study is the first to demonstrate that individuals recovering from AUD can increase serum levels of BDNF from baseline levels via sessions of physical exercise.

Keywords: alcohol use disorder, substance use disorder, recovery, brain-derived neurotrophic factor, physical activity, exercise.

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Introduction

Alcohol use disorders (AUD) are common and carry with them substantial health costs. The estimated lifetime prevalence of AUD in the US general population is 29.1% (Grant et al., 2015), 88,000 American deaths per year are attributable to alcohol misuse (U.S. Department of Health & Human Services, 2016), and total economic costs of alcohol use (including factors such as healthcare costs, law-enforcement costs and loss of productivity) are estimated at more than $234 billion in the United States annually (Rehm et al., 2009).

AUD Treatment and Recovery

In recent decades, a number of psychosocial and pharmacological treatments have been developed and tested for efficacy and effectiveness in reducing or resolving alcohol and other drug use disorders. These include motivational interviewing (Miller & Rollnick, 2012), cognitive behavioral therapies (Magill & Ray, 2009; McCrady, 2000), alcohol-focused behavioral couple therapy (Epstein & McCrady, 1998; McCrady et al., 2016) mindfulness-based relapse prevention (Witkiewitz et al., 2005), community reinforcement approaches (Hunt & Azrin, 1973; Miller et al., 1999), contingency management (cf. Petry, Martin, Cooney, & Kranzler, 2000), twelve-step facilitation (Project MATCH Research Group, 1997), and the medications naltrexone and acamprosate (Anton et al., 2006). Additionally, the positive influence of mutual help organizations has been established (Blonigen, Timko, Finney, Moos, & Moos, 2011; Kelly, Stout, Tonigan, Magill, & Pagano, 2010; Morgenstern, Labouvie, McCrady, Kahler, & Frey, 1997). Despite this progress, AUD treatments tend to perform roughly equally, success rates for any given treatment episode are approximately 30-40%, and AUDs are widely considered to be chronic and relapsing conditions (Miller et al., 2001; Project MATCH Research Group, 1997; U.S. Department of Health & Human Services, 2016).

Policy makers and government agencies including the Office of the Surgeon General and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) recently have advocated for increased research focus on critical elements that may be involved in long term recovery from AUD (“National Institute on Alcohol Abuse and Alcoholism Strategic Plan 2017–2021” ; U.S. Department of Health & Human Services, 2016). Guidance from these oversight and funding agencies includes a call for a conceptually broader definition of recovery and identification of factors that facilitate long-term sustained remission and a return to health. Indeed, a recent (May 15, 2018) NIAAA Director's Report on Institute Activities to the 148th Meeting of the National Advisory Council on Alcohol Abuse and Alcoholism included new program announcements soliciting R01 and R21 grant proposals designed to further the understanding of processes of recovery in the treatment of AUD, focusing specifically on: “1) Defining recovery; 2) Examining new and innovative methods to examine precipitants of relapse; 3) Understanding mechanisms of mutual help and recovery; 4) Evaluating recovery systems of care; and 5) Examining processes of extended treatment for AUD” (NIAAA, 2018).

Research into these factors, and towards a conceptualization of recovery that is broader than a binary abstinence/non-abstinence criterion for success, is not necessarily a new idea. While nominally focused on expanding the scope of AUD treatment evaluation, Moos and Finney (1983) highlighted a number of biopsychosocial, extra-treatment, ‘life context’ factors and client characteristics that may influence the recovery process. These include such areas as family relationships, work settings, life stressors, socioeconomic status, personality, and psychological functioning (Moos & Finney, 1983).

More recently, a panel convened by the National Institute on Drug Abuse (NIDA; Tiffany, Friedman, Greenfield, Hasin, & Jackson, 2012) advocated for the inclusion of

psychosocial functioning, quality of life, social support, self-efficacy and craving as primary outcomes measured in substance use disorder (SUD) treatment research. Subsequent work by Wilson and colleagues (2016) re-analyzed outcomes from Project MATCH and the COMBINE study to take into account many of these proposed non-consumption criteria. Results from latent profile analyses indicated that a substantial number of individuals (approximately 430 in MATCH and 240 in COMBINE), considered to be treatment failures based on consumption outcomes, were functioning as well or better than those deemed treatment successes, across a wide range of biopsychosocial outcomes, one year post-treatment (Wilson et al., 2016). Recent and related work (Witkiewitz et al., 2019) examined a latent construct of recovery derived from both consumption and psychosocial outcomes 3 years post-treatment in the outpatient arm (N=806 in analyses) of Project MATCH. Results indicated four recovery profiles: (a) low functioning, frequent heavy drinking (approximately 15.8% of the sample); (b) low functioning, infrequent heavy drinking (primarily abstinence or light drinking; approximately 16.1% of the sample); (c) high functioning, occasional heavy drinking (approximately 16.9% of the sample); and (d) high functioning, infrequent non-heavy drinking (abstinence or light drinking; approximately 51.2% of the sample). These findings suggest that in half the cases abstinence and/or low risk drinking was, as expected, an integral part of the recovery process. However, the variability in psychosocial outcomes among the other half of cases indicates that recovery may be more heterogenous and nuanced. At three years post-treatment, one-third of this group was drinking infrequently or not at all, but failing to accrue the psychosocial benefits expected with this change. Another one-third was still drinking, and occasionally drinking heavily, while continuing to maintain the psychosocial improvements we associate with recovery. Importantly, the 'bio' component of a biopsychosocial model of recovery went unmeasured (and thus un-

analyzed) in these 3-year data. Though speculative, it seems reasonable to suggest that physical health and physical activity may have influenced or been associated with some of the discordant profiles among the half of participants for whom consumption and psychosocial change did not move in the expected lock-step direction.

Concurrent research around the construct of 'recovery capital' (Cloud & Granfield, 2008) in populations that consist primarily, but not exclusively, of persons with an abstinence goal, is also beginning. Broadly defined as the sum of social, cultural, physical and psychological resources actively utilized or deployed by persons engaged in the recovery process - with or without treatment or mutual support - recovery capital is predictive of sustained remission of substance misuse (Laudet & White, 2008), and has also provided a framework for the development of measures that incorporate a more comprehensive biopsychosocial conceptualization of recovery (Groshkova et al., 2013; Vilsaint et al., 2017).

In summary, consensus is growing among researchers from a variety of theoretical backgrounds, and across a number of policy-making and funding agencies, about the importance of a wider investigation into factors that promote sustained behavior change among those struggling with addictive behaviors. Recent work has identified specific areas worthy of further inquiry. However, gaps remain, and certain areas continue to be overlooked and understudied.

Physical Exercise in AUD, SUD, and Mental Health Treatment and Recovery

AUD Treatment, Recovery, and Physical Exercise

Though physical health is widely acknowledged as a domain worthy of inclusion in a broader conceptualization of recovery, physical activity, physical exercise, sport, and movement are less likely to be considered by addictions researchers as important antecedents to, or positive consequences of, sustained recovery from SUDs. To some degree, this is understandable.

Psychologists and psychiatrists continue to wrestle with the translational and integrational difficulties of a true biopsychosocial model, as well as the research siloes and partisan championing of specific levels of analysis intrinsic to the mind-body problem more generally (cf. Bishop, 1994; Engel, 1982; Gabbard & Kay, 2001; Skinner, 1990). Additionally, researchers face the prevailing opinion (supported, to a certain degree, by data) that although physical activity and exercise show robust benefits across a host of physical and psychological disorders, patient adherence to exercise protocols and lifestyle change is less than ideal. Evidence suggests that patient adherence rates rarely reach above 75% in physical exercise effectiveness research (Bourke et al., 2013; Michie et al., 2009; Zizzi et al., 2006). However, a series of recent meta-analyses and systematic reviews looking at real-world effectiveness of interventions to increase physical activity indicate a modest but significant impact. A 2009 meta-analyses of behavior change interventions targeting obesity found that across 69 experimental or quasi-experimental trials of physical activity interventions (N=18,330) the pooled effect size was 0.32 (95% CI=0.26 to 0.38; Michie et al., 2009).

Despite the aforementioned challenges, over the past 45 years a small but promising literature of approximately 20 randomized (RCT) and non-randomized (CT) controlled trials investigating the impact of physical exercise on AUD- or health-related outcomes (cf. Giesen et al., 2015; Hallgren, Vancampfort, Giesen, Lundin, & Stubbs, 2017) has emerged. As Hallgren and colleagues (2017) point out, the overwhelming majority of these studies were either (a) conducted at an inpatient substance use disorder treatment facility, or (b) measuring the acute biological effects of one single bout of exercise making it difficult to determine conclusively that exercise has a measurable effect on any indices of alcohol consumption, or real world remission, recovery, or relapse. The studies also differed with respect to type, duration, and intensity of

exercise, as well as measured outcomes of interest, but the results are generally suggestive of a positive benefit. Trials reviewed below are generally those in which a program of exercise was studied, rather than a single session, except where acute responses to a single session of exercise are informative in their relation to a broader conceptualization of recovery.

In an early and small (*N*=20) randomized controlled trial, Gary and Guthrie (1972), tested an adjunct jogging intervention versus a treatment as usual (TAU) control condition at an inpatient treatment facility for AUD. Though the inpatient nature of the sample precluded assessment of alcohol consumption in this study (and indeed the majority of studies in this area), the authors found significant benefits to both self-image and body-image (Jourard Self-Cathexis and Body Cathexis Scales; Secord & Jourard, 1953) and an expected significant improvement in physical fitness among the intervention sample. Similar early trials (Luedke, 1978; McKelvy et al., 1980; Piorkowski & Axtell, 1976) investigating physical health and fitness improvements among those hospitalized for AUD might best be viewed as feasibility studies, with outcomes that suggest individuals with AUD can exercise safely and will likely see physical fitness gains, but without measured outcomes related to alcohol consumption, alcohol-related consequences, cravings, or affect.

The earliest controlled trial (*N*=58) to follow inpatients after release from a rehabilitation center (Sinyor et al., 1982) found a difference in abstinence rates between intervention and control groups at the three-month post-treatment follow up. The intervention involved 6 weeks of 5 times-per-week exercise, which in winter was 45 minutes of cross country skiing, and in other seasons consisted of 55 minutes of combined calisthenics, walking, running and resistance training. At three-month follow up, 69.3% of participants in the intervention condition were still abstinent, whereas only 36.9% in the treatment-as-usual (TAU) remained abstinent.

An early randomized controlled trial in Europe (*N*=36; Weber, 1984), conducted at an inpatient alcohol rehabilitation clinic, used an exercise paradigm wherein participants began a progressive running program three times per week for four months with the goal of being able to run for 30 minutes continuously at the end of treatment before discharge. Though there was no follow up post-discharge, and thus no measurements of alcohol consumption, results indicated significant improvements in state anxiety and trait anxiety, as well as perceived stress.

The first RCT (*N*=60) conducted outside the confines of an inpatient rehabilitation facility (Murphy et al., 1986) randomized college students who were "high-volume drinkers" (averaging 45 drinks per month or more) to one of three conditions: (a) 70 minutes of group running three times per week for eight weeks with intensity individually prescribed based on a pretreatment submaximal effort stationary cycling test; (b) 20 minutes of meditation two times per day for eight weeks, with a group meditation sessions offered three evenings per week; or (c) a pre and post assessment-only condition with self-tracking of alcohol consumption behavior. As well as the expected significant improvements in fitness (VO2 max), the exercise condition participants also showed a significant decrease in alcohol consumption at post treatment compared to the assessment-only control group. Interestingly, there were no significant differences at post treatment between the exercise condition participants and the meditation condition participants. Perhaps not surprisingly, given the rigor and time demands of both the exercise and meditation conditions, compliance and drop-out were issues in both these conditions, and thus the results should be interpreted with caution.

Palmer and colleagues (1988) were one of the first groups to apply recommendations from the American College of Sports Medicine with regard to a graded aerobic exercise program (60 minutes per day, three times per week, for four weeks, at 60-80% of participants' age

predicted maximum heart rate). Results from this controlled trial (*N*=53) in a 12-step based inpatient AUD treatment facility showed significant decreases ($p<.01$) in state anxiety and trait anxiety, and significant decreases in depression in the exercise group compared to the TAU control group.

In a U.S. military veteran inpatient AUD sample, Ermalinski and colleagues (1997) conducted a controlled trial (*N*=90) to investigate the impact of a series of body-mind components substituted in place of group psychotherapy five times per week for six weeks. The components included breathing and stretching exercises, 20 minutes of progressive aerobics, a verbally delivered motivational component, and a verbally delivered responsibility for health component. Though there were significant decreases in negative mood and alcohol craving from baseline to post treatment in the body mind condition, there were no significant differences between the intervention group and TAU controls (Ermalinski et al., 1997).

In a comparison of moderate vs. light aerobic exercise in a hospital-based alcohol rehabilitation clinic, Ussher and colleagues (2004) studied the acute effect of a single bout of 10 minutes of indoor cycling (*N*=20). Compared to baseline, there was a significant decrease (p=0.02) in alcohol urges - as measured by the Alcohol Urge Questionnaire - at five minutes into the cycling session, for participants in the moderate exercise condition versus the light exercise condition. No significant differences existed between the groups, however, at assessment time points after the bout of exercise had finished (Ussher, Sampuran, Doshi, West, & Drummond, 2004).

Weinstock and colleagues (2014) randomized hazardous-drinking sedentary college students (*N*=31) into one of two conditions: a single 50 minute session of motivational enhancement therapy (MET) for exercise plus eight weeks of contingency management (CM;

prize bowl with number of draws dependent on number of exercise sessions; $1, $20, $100 gift certificates); or a single 50 minute session of motivational enhancement therapy for exercise. Post treatment assessments indicated a significantly increased frequency of exercise from baseline in the MET + CM condition, but no other indices of exercise, fitness, or alcohol use were significantly different between the conditions over time (Weinstock et al., 2014).

In summary, the majority of these trials were conducted in an inpatient setting, or with non-treatment seeking college students, and as such, most of the evidence in support of adjunct exercise for AUD is limited to positive findings around reductions in craving, reductions in depression and anxiety-related symptomatology, increases from baseline in self-concept and internal locus of control, and various measures of physical health.

To date, only one RCT (Brown et al., 2014) of aerobic exercise with an AUD sample has been conducted in an outpatient setting. Results indicated significantly lower frequency and intensity of alcohol use during, and at the end of, treatment in the exercise condition as compared to the control condition, and a significant inverse relationship between minutes of exercise and heavy drinking days at the 6-month post-baseline follow-up.

SUD Treatment, Recovery, and Physical Exercise

In the broader substance misuse literature, a recent meta-analysis by Wang and colleagues (2014) included 22 RCTs published between 1990 and 2013 examining the effects of physical exercise on SUD outcomes for nicotine (N=11), alcohol (N=3), and heroin, cocaine or polysubstance use (N=8). Results indicated a significant effect on abstinence rates (OR=1.69 [95% CI: 1.44, 1.99] p<.001), reductions in anxiety (SMD=−0.31 [95% CI: −0.45, −0.16], p<.001), reductions in depression (SMD = −0.47 [95% CI: −0.80, −0.14], p<0.01), and reductions in withdrawal symptoms (SMD=−1.24 [95% CI: −2.46, −0.02], p<0.05).

Mental Health Treatment, Recovery, and Physical Exercise

In the general psychopathology literature, there exists a larger, more continuous investigation of the impact of physical exercise on mental health (Asmundson et al., 2013; Bourbeau et al., 2020; Josefsson et al., 2014; R. Rosenbaum et al., 2014; Schuch et al., 2016). Effect sizes are generally in the range of small to medium (0.19-0.55) for positive impacts on anxiety and depression, but newer reviews also point to modest effect sizes for schizophrenia (0.39; Dauwan, Begemann, Heringa, & Sommer, 2016), and PTSD (0.35; Rosenbaum et al., 2015). It is important to note, however, that there is currently no consensus in the field as to what constitutes the optimal 'dose' of exercise. Meta-analyses (Barton & Pretty, 2010; Carayol et al., 2013) indicate that 90-120 minutes of aerobic activity per week are sufficient for an effect, and recent reviews indicate benefits accruing after exercise sessions as short as 20 minutes (Frederiksen et al., 2021; Powers et al., 2015). There is, additionally, evidence across disorders of a dose-response effect (Dauwan et al., 2021).

A number of potential mechanisms of action, including the reductions in anxiety, depression and other psychopathology described above have been proposed as mediating factors in the positive impact of physical activity on SUD outcomes. Additional hypothesized mechanisms include increases in coping repertoire, reductions in acute craving, attenuated stress reactivity, improvements in affective instability, and neurochemical changes related to endogenous opioid, glutamate and dopamine transmission (Moriarty et al., 2020; Zschucke et al., 2012). Although the direct effects of exercise on acute craving for alcohol have been investigated in humans (Ussher et al., 2004), as have some of the direct effects of exercise on neurotransmitter release (Boecker et al., 2008; G.-J. Wang et al., 2000; Yoder et al., 2016), many of the proposed mechanisms have not been targeted in clinical research. One unstudied but

promising mechanism in SUD recovery research is the possible impact of exercise on brain-derived neurotrophic factor (BDNF).

BDNF and Implications for the Neurocircuitry of Addiction Model

BDNF, first isolated and described in 1982 (Barde et al., 1982) is one of a number of proteins in the neurotrophin family of growth factors, which includes nerve growth factor (NGF; Levi-Montalcini & Hamburger, 1951), neurotrophin-3 (NT-3; Maisonpierre et al., 1990), and neurotrophin-4 (NT-4; Ip et al., 1992). Other growth factors involved in neurogenesis/plasticity/protection include glial cell line-derived neurotrophic factor (GDNF; Airaksinen & Saarma, 2002), fibroblast growth factor (FGF), more specifically FGF-1 and FGF-2 (K. D. Beck et al., 1993; Bikfalvi et al., 1997), and insulin-like growth factor-1 (Basta-Kaim et al., 2014; Ozdemir et al., 2012; Szczęsny et al., 2013). Although BDNF is the neurotrophic factor most studied in relation to physical exercise, (Churchill et al., 2002; Huang et al., 2014; Klintsova et al., 2004; Swain et al., 2003; Vaynman et al., 2004), there is evidence to suggest that exercise also drives upregulation of NGF (Neeper et al., 1996), FGF-2 (Gómez-Pinilla et al., 1997), and IGF-1 (Carro et al., 2001)

Preclinical investigations using rodent models of drug-taking behavior have identified BDNF as a mediator of synaptic plasticity associated with reinforcement (M. A. Smith & Lynch, 2012). Similarly, BDNF is implicated in neuroplasticity and cell survival in the hippocampus related to new learned behaviors (Curlik & Shors, 2013; Shors et al., 2014). Chronic heavy alcohol use is associated with both decreases in hippocampal neurogenesis, and lower BDNF expression (Briones & Woods, 2013). Additionally, physical exercise has been found to exert an epigenetic influence on the *Bdnf* gene responsible for expression of the BDNF protein implicated in neuroplasticity, neurogenesis, and cell survival (Gomez-Pinilla et al., 2011). Thus, more

physical exercise over time among individuals with AUD could theoretically be associated with greater increases in BDNF expression over time (Szuhany et al., 2015).

Though much of the research around BDNF has focused on the hippocampus, the protein is expressed throughout the central nervous system and has been implicated in the neural plasticity of a number of brain areas identified by Koob & Volkow's (2009) neurocircuitry of addiction model. These include the hippocampus (Egan et al., 2003), the nucleus accumbens (Berton et al., 2006), the central nucleus of the amygdala (Conner et al., 1997) and the ventral tegmental area (Vargas-Perez et al., 2009).

Early research with a cloned exogenous injectable form of BDNF using human autopsy tissue (Pardridge, Kang, & Buciak, 1994) suggested BDNF is not easily transported through the brain capillary endothelial wall (blood-brain barrier; BBB). However, more recent work (Pan et al., 1998; Poduslo & Curran, 1996) with in vivo rodent models suggests efficient transport of BDNF back and forth across the BBB, making measurement of serum and plasma levels of BDNF a valid proxy for levels of BDNF in the brain. Although there seem to be challenges in measuring blood-serum levels of BDNF in mice, newer work using rats and pigs demonstrates that, across species, BDNF concentrations in blood do reflect BDNF levels in brain tissue (Klein et al., 2011). There remain, however, questions around what quantity, or quantity increase of BDNF in the brain is necessary to support neuroplasticity and the survival of new neural connections. Comparisons of quantity of BDNF in the blood to quantity of BDNF in the brain to quantity of observed neuronal change are rare. The most widely accepted investigation to date, using synapsin 1 mRNA as a proxy for synaptic formation, and GAP-43 mRNA as a proxy for axonal growth and synaptic remodeling, found that, compared to sedentary controls, physical exercise corresponded to a 64% increase in BDNF protein levels from baseline in muscle tissue

after 7 days of voluntary exercise. This increase, in turn, corresponded to a 56% increase from baseline in BDNF protein in the spinal cord, which corresponded to a 47% increase from baseline of synapsin 1 mRNA and a 54% increase from baseline in GAP-43 mRNA (Gómez-Pinilla et al., 2002). Although this is by no means conclusive evidence that all three variables move in lock-step, and while it is important to acknowledge that these data come from a preclinical investigation using animal models of exercise behavior, these results are compelling enough to suggest that commensurate changes may be occurring in humans.

In summary, BDNF is a protein critically implicated in neurogenesis and the sustenance of new neurons and neural connections. Research suggests individuals with AUD have lower circulating levels of BDNF than healthy controls (Joe et al., 2007). Increased BDNF may promote increased neuroplasticity in the neural pathways associated with addictive behaviors, including altered responses to cue-related craving, and learned acquisition of coping and other behavioral skills (Olsen et al., 2015; Shors et al., 2014). This, in turn, may promote sustained improvements in outcomes related to alcohol consumption and biopsychosocial functioning, and strengthen recovery efforts. Although the conceptual basis for this mechanism has been tested and demonstrated in animal models, no extant studies in the literature have directly tested the associations between physical exercise, BDNF, and SUD recovery in humans.

To address this gap in the recovery research literature, the overarching goal of the proposed study was to investigate the relationships among changes in physical exercise, changes in BDNF, and alcohol-related outcomes in a population of individuals in early recovery from AUD. Broadly speaking, this study was designed to test the association between physical exercise and BDNF levels over time, and the association between BDNF levels and AUD-related outcomes. It was also designed to estimate effect sizes for the association between physical

exercise and both consumption and non-consumption variables of interest among individuals in early recovery.

The specific aims of the proposed study were to: (a) examine the relationship between frequency, intensity, and duration of physical exercise and changes in BDNF blood serum levels over time; (b) examine the concurrent and predictive relationships between changes in BDNF blood serum levels, alcohol consumption outcomes, and secondary outcomes such as coping skills acquisition, craving, mood, and stress reactivity; and (c) estimate the effect sizes of different exercise modalities (high intensity interval training vs. low/moderate intensity aerobic training) on BDNF and AUD outcomes.

With regard to the first aim, it was hypothesized that (a) greater frequency of exercise would promote higher levels of BDNF over time; (b) greater intensity of exercise would promote higher levels of BDNF over time; and (c) greater duration of exercise would promote higher levels of BDNF over time.

With regard to the second aim, it was hypothesized that (a) BDNF levels would be negatively associated with alcohol consumption; (b) BDNF levels would be positively associated with coping skills acquisition; and (c) BDNF levels would be negatively associated with craving, symptoms of anxiety and depression, and stress reactivity.

With regard to the third aim, it was hypothesized that individuals involved in community Crossfit and bootcamp-style high intensity interval training (HIIT) workouts would exhibit lower program adherence and long term involvement in the HIIT workouts, but that those who remained involved in the HIIT workouts would exhibit higher effect sizes with respect to BDNF changes and AUD-related variables of interest. It was also hypothesized that individuals involved in a community program that recommends 30 minutes of low to moderate intensity

exercise per day (e.g. walking to the bus-stop) will exhibit higher program adherence but lower effect sizes with respect to BDNF changes and AUD-related variables of interest.

Method

Participants

The study proposed to recruit forty-six adults with AUD (23 per site) into a quasi-experimental two-group observational prospective study to test the association between physical exercise, BDNF expression, and alcohol-related outcomes among those in early recovery (< 1 year). The study began by recruiting participants exclusively from two sites: (a) a transitional living and recovery community facility with a requirement that residents complete 30 minutes of exercise per day (low-to-moderate intensity group); and (b) a recovery community center with an ongoing free crossfit/bootcamp program available 4 times per week (high intensity group). Participants had to be in early recovery from AUD, and also engaged in, or planning to engage in, physical exercise at least 2 times per week. Resources were available to recruit and compensate 46 individuals (23 per site).

The proposed sample size was chosen for a number of reasons: (a) a recent meta-analysis of the effects of exercise on BDNF provided evidence of robust effect sizes (Hedges g=0.46, p<.001 for a single session of exercise; Hedges g=0.58, p=.02 for a program of regular exercise; Szuhany et al., 2015) and a power analysis (G*Power; Faul, Erdfelder, Lang, & Buchner, 2007) determined that using a within-subject repeated measures design (i.e., mixed model) with exercise predicting changes in BDNF over time, 42 participants would be necessary to achieve 0.80 power to detect a significant effect of exercise on BDNF (Aim 1) in the entire sample; (b) power analysis further determined that 40 participants would be necessary to achieve 0.80 power

to detect a significant difference between the two groups (Aim 3); (c) the single extant RCT of the effect of exercise on alcohol use outcomes (Aim 2; Brown et al., 2014) in a non-inpatient setting found significant differences between groups sized *N*=26 (intervention) and *N*=23 (control); and (d) limitations of the BDNF testing apparatus (96-assay trays; each blood sample tested twice at each time point) limited the total *N* tested to 48 at each time point.

Inclusion and Exclusion Criteria

Inclusion criteria were: (a) engagement or planned engagement in physical exercise at least twice per week over the next 3 months; (b) past year history of AUD, as measured by the Structured Clinical Interview for DSM-5 Diagnoses (SCID); (c) availability for a 3 month study; and (d) willingness to have blood drawn pre-post exercise at 3 timepoints, for a total of 6 blood draws over a 3-month period.

Exclusion criteria were: (a) not proficient in English, as some measures were only available in English; (b) substantial damage to veins from a history of prior intravenous drug use, such that blood sample collection would be difficult or dangerous; (c) being unable to complete a 3-month study by virtue of plans to leave Albuquerque, New Mexico in the next 5 months; (d) current amphetamine use, (as this has been shown to temporarily increase BDNF;(Meredith et al., 2002); and (e) having active psychotic symptoms, indicated by endorsing items on a SCID psychosis screening instrument, as this may have affected the accuracy of the information provided.

Protocol and Study Design Adjustments

One participant was recruited and consented in late January 2019 to examine the feasibility and work out the logistics of an initial study protocol that required bringing the blood sampling equipment and centrifuge out to community gyms and exercise sites. This approach

proved logistically challenging and resource intensive, and was additionally viewed by one community site as a barrier to afternoon and evening data collection following HIIT classes.

As a result, the design and protocol were adapted to allow for blood sampling and exercise sessions to occur in the UNM exercise physiology laboratory spaces. Recruitment for this protocol began in April, 2019. Due to lower than expected recruitment at the two established sites, IRB amendments were submitted to collapse the two conditions in the study design, and begin recruiting directly from the community. Following this, in January 2020 resources were allocated toward advertising the study in the local weekly newspaper. This advertisement increased recruitment dramatically. Whereas 11 individuals had expressed interest in the study in all of 2019, the first two months of 2020 saw 24 new individuals contact the study to express interest in participating. In total, 26 participants were screened, 22 were eligible, 7 had entered the study, and 6 had provided at least one set of pre/post-exercise blood samples when student research ceased on March 23rd, 2020 due to COVID-19 precautions.

Procedures

The present study ran as a non-randomized, open trial recruiting participants from April 2019 to March 2020. The study was approved by the University of New Mexico Institutional Review Board. All study participants gave informed consent. Additionally, a Federal Certificate of Confidentiality was obtained to ensure a greater level of protection for research study participant data. Study participants were asked to meet with study staff three times, for approximately 2 hours per occasion, at baseline, week 6, and week 12. Each meeting involved, in order: (a) a battery of self-report and clinician-administered psychosocial measures; (b) an approximately 5 minute wait in the phlebotomy lab; (c) a pre-exercise withdrawal of 10-ml of blood; (d) A 30-60 minute self-directed exercise session, with equipment made available in the

exercise physiology lab, monitored, with cues asking participants for their perceived level of exertion at the midway point; (e) an approximately 5 minute wait in the phlebotomy lab; (f) a post-exercise withdrawal of approximately 10-ml of blood.

Measures

Study testing and assessment materials fell into five categories (a) measures to determine participant eligibility; (b) measures to describe the sample and document participant locator information; (c) measures of alcohol consumption; (d) measures of physiological variables of interest (exercise, BDNF); and (e) measures of psychosocial variables of interest (craving, depression, anxiety, stress, coping skill acquisition, and enjoyment of exercise).

Eligibility Screening

Eligibility screening interviews were conducted by phone and took approximately 20 minutes per screen. The interview was designed to assess all inclusion and exclusion criteria above, and included structured clinical interviews to determine past year AUD diagnosis, and past six-month presence of psychosis.

Demographics and Location

The baseline assessment battery included questions assessing age, gender, ethnicity, marital status, employment status, occupation, family income, and years of education. Additionally, participants were asked to provide an alternate contact, a family member or friend, who could be contacted in the event that the participant was unreachable thru means of supplied personal contact information.

Alcohol Consumption and Related Substance Use Information

The Timeline Follow-Back Interview (TLFB) was administered to assess drinking intensity and frequency in the prior 90 days (Sobell et al., 1996). Number of months in recovery

was assessed via self-report. Number of AUD criteria met prior to entering recovery was assessed with the Structured Clinical Interview for DSM-5 (SCID), Module E, for AUD and other SUDs.

Exercise and BDNF Testing

Exercise intensity and duration were assessed during the in-person exercise sessions at baseline, 6-weeks, and 12-weeks. Exercise frequency, intensity, and duration were assessed between sessions via supplied weekly exercise journals. In both cases, exercise intensity was determined using Borg's Rating of Perceived Exertion (6-20) Scale (Borg, 1982).

Prior to, and again after, each in-person exercise session, trained graduate-level phlebotomists performed 10-ml blood withdrawals from the median cubital vein. Blood samples were labeled with participant ID number, timepoint, pre-exercise or post-exercise, and date. In accordance with recent guidelines on methods for highly reproducible quantification of BDNF (Polacchini et al., 2015), samples were allowed to clot at room temperature. Samples then underwent centrifugation at 2200 rpm for 15 minutes at 22 degrees Celsius. After centrifugation two 1000 microlitre samples of serum were extracted from each blood sample via pipette, and then stored at -80 degrees Celsius until thawed for testing. Testing was performed with R&D Systems Quantikine ELISA for Total BDNF (free BDNF and BDNF bound to TrkB). Testing was carried out at room temperature, with repeated measures of three aliquots of the same sample, diluted 1:50 per recommendation (Moriarty et al., 2019). Assay procedures followed kit instructions. The optical density microplate reader analyzed the plates at wavelengths of 450 nm and 540 nm.

Psychosocial Measures

Measures were selected for their strong psychometric properties and goodness of fit with a streamlined assessment process. The Penn Alcohol Craving Scale (PACS) was administered to assess craving (Flannery et al., 1999). The Beck Depression Inventory (BDI) was administered to assess depressive symptoms (A. T. Beck, Steer, et al., 1988). The Beck Anxiety Inventory (BAI) was administered to assess anxiety symptoms (A. T. Beck, Epstein, et al., 1988). The Perceived Stress Scale (PSS) was administered to assess perceived stress (Cohen et al., 1983). The Process of Change Questionnaire (PCQ) was administered to assess coping skills acquisition and utilization (Prochaska et al., 1988). The Gambling Urge Scale (GUS) was administered to assess urges to gamble (Raylu & Oei, 2004). The Physical Activity Enjoyment Scale (PACES) was administered to assess enjoyment of exercise (Kendzierski & DeCarlo, 1991). Table 1 provides additional information on all measures.

Analysis Plan

Comprehensive preliminary analyses were planned to assess variable distributions and non-normality, as well as patterns of missingness and predictors of attrition. Based on the original study design, preliminary analyses were to include identification of systematic pre-treatment differences in participant characteristics between the groups. Although sample size even in the original design was too small to employ true propensity score matching (Imbens & Rubin, 2015; Rubin, 2006), in the event that confounding looked likely due to differences in baseline characteristics of the two groups, propensity scores were to be created for use in subsequent analyses as a covariate (Holmes & Olsen, 2010). Preliminary analyses were to be conducted on all participants consented (intent to treat). Attrition in the study would be investigated via logistic regressions to assess (a) whether attrition was predicted by baseline characteristics; and (b) whether there was differential attrition from the two groups.

Planned Analyses for Specific Aim Testing

Aim 1: Examine the relationship between frequency, intensity, and duration of exercise and changes in BDNF blood serum levels over time. Generalized linear mixed effects modeling using maximum likelihood estimation in the R package lme4 (Bates, et al., 2007) was planned to examine the impact of cumulative exercise frequency, intensity, and duration on changes in BDNF levels over time.

Aim 2: Examine the association between changes in BDNF blood serum levels and alcohol consumption outcomes, coping skills acquisition, craving, mood, and stress. Bivariate correlations were planned to assess the concurrent association between baseline BDNF levels and (a) past month alcohol use days; (b) past week coping; (c) past week craving; (d) past month anxiety symptoms; (e) past month depression symptoms; and (f) past month stress. Generalized linear mixed models for normally distributed outcomes (e.g., coping, craving, mood, stress) and generalized linear mixed models using a negative binomial hurdle distribution for zero inflated count outcomes (e.g., alcohol use) were identified as appropriate methods to assess the predictive utility of changes in BDNF levels on each of the five dependent variables of interest listed above. As such, individual BDNF change would be included in all models as a covariate along with sex and site.

Aim 3: To estimate the effect sizes of different exercise modalities (via two different recovery community organizations that offered different exercise programs) on BDNF and AUD outcomes. Aims 1 and 2 of this study represent what would traditionally be considered, in a mediation analysis framework, investigations of the ‘a-path’ and ‘b-path’. Based on prior research by Fritz & MacKinnon (2007) the proposed study would have required a sample size of approximately 115 participants to detect a mediated effect. However, mediation analyses could

still provide estimates and effect sizes for the indirect and direct effects, and these might prove useful for future research endeavors. As such, we intended to investigate a mediation model in which change in BDNF level was a mediator and physiological mechanism by which different physical exercise programs might impact alcohol consumption and/or AUD-related outcomes including coping, craving, anxiety, depression, and stress.

In the event that hypotheses from Aims 1 and 2 were not supported, i.e., that exercise did not drive changes in BDNF levels, and/or changes in BDNF levels did not predict changes in AUD-related variables of interest, the study was originally designed to test a range of alternate exploratory hypotheses. The inclusion of psychosocial assessments of craving, stress, mood, and coping skills at all three time points made possible analyses to investigate the impact of exercise on psychosocial outcomes across time, and the impact of psychosocial outcomes on consumption behavior. Though the study was never powered to detect a mediation effect, individual pathways from, for example, exercise to stress reduction, and stress reduction to alcohol consumption or changes in mood, could have been tested, along with estimates of effect sizes for the relevant direct and indirect effects. These additional analyses, specifically of the simple direct effect of exercise on consumption behavior, could, in the absence of effects on mood and craving, lend support to the alternative explanation that physical activity may simply establish competing (and reinforcing) lifestyle activities to drinking.

Revised Analysis Plan and Analyses performed

By necessity, most analyses conducted with data from the present investigation are descriptive in nature. One exception to this is the availability of pre- and post-exercise BDNF levels for six participants from their first exercise session with a pre-post blood draw.

As such, data from the BDNF assays completed at UNM in November, 2020 were cleaned, BDNF concentrations were calculated, and coefficients of variation were established. These estimates of precision of the assay technique (Reed et al., 2002) are calculated by finding the mean value concentration for each sample (each sample is tested in three wells per plate) and dividing the mean value by the standard deviation of the three wells.

Assumptions of normally distributed estimates of exercise-induced BDNF change were examined, followed by tests of statistical significance, and estimation of the magnitude of the effect of exercise on BDNF levels. Finally, concurrent and predictive associations between exercise-induced BDNF upregulation, baseline characteristics, and future coping, craving, consumption and mood outcomes were investigated.

Results

Due to the cessation of student research in March, 2020, there were 15 individuals who screened into the study but were ultimately unable to begin. Seven participants had begun the study; six of them completed pre/post-exercise blood sample collection. Three participants reached the 6-week timepoint, with two of them completing pre/post-exercise blood sample collection. Only one participant in the study reached the 12-week timepoint, and only psychosocial measures were collected at this participant's 12-week contact, as the university laboratories had shut down to research and no pre/post-exercise blood sample collection was possible. Table 4 provides further information about sample size and data collected at each of the three timepoints.

Demographics

Table 2 provides complete information on the demographics of the participant sample. The mean age of the sample was 36.7 years. In line with typical AUD treatment sample

characteristics, participants were majority male (71%). The sample was relatively diverse (43% white, 29% Hispanic/Latinx, 14% Black/African American, 14% American Indian/Alaska Native). Six participants identified as single, one as widowed. All participants were employed, 3 full time, and 4 part time. Occupations listed were: account executive, actor, bartender, educator, groundskeeper, mixed martial arts trainer, restaurant server. Mean years of education was 15, ranging from 11-18. Average family income was $32,333.

Baseline Substance Use Characteristics

Table 3 provides information characterizing participant alcohol and substance use prior to entering the study. All participants screening into the study endorsed being in their first year of recovery from an AUD. Though not a requirement for the study, all participants endorsed a long term goal of becoming and remaining abstinent from alcohol. Six participants extended this abstinence goal to include all addictive substances, one participant reported interest in returning to benzodiazepine use as prescribed. Mean months in recovery was 5.9, with a range from 1.0 to 11.0. Past year AUD symptom/criteria count, as measured by the SCID Module E for DSM-5, ranged from 3-11, with a mean of 8.3. Three participants had consumed alcohol in the previous 90 days; average count of drinking days for these three participants was 29.33. Average count for the entire sample was 14.7. Of the three participants with drinking days in the previous 90, average drinks per drinking day (DDD) was 4.2, with a range from 1.5 to 12.9. Four participants also met criteria for a SUD diagnosis in the prior year. These substances included opioids, cocaine, sedatives/hypnotics/anxiolytics, and cannabis.

Descriptive Statistics

Table 4 provides complete descriptive statistics for all study variables at all study timepoints. Participant BDNF levels pre/post the in-person exercise sessions were largely in line

with established levels of serum BDNF in humans, with an range of 14.27 ng/ml to 65.17 ng/ml, across all tests at all sessions. The study protocol was designed to measure changes in BDNF resulting from self-prescribed exercise sessions and regimens. As such there was some variability in frequency, duration, and intensity. Most participants were exercising between 40 minutes and 1 hour, averaging 6.33 days per week. Average home exercise intensity was 11.82 (light to moderate, suggestive of a workload that would raise heart-rate to 118 bpm). Average exercise intensity during the experimental sessions was higher: 15.67.

On average, participants endorsed mild-to-moderate levels of anxiety and depression, moderate-to-high levels of perceived stress, low levels of alcohol craving, very low levels of gambling craving, high levels of physical activity enjoyment, and moderate-to-high acquisition and utilization of coping skills.

BDNF Analyses

Each serum sample was assayed in triplicate and coefficients of variation (CVs) were calculate to estimate assay technique precision. The CVs ranged from 0.45% to 9.60%, with a mean of 3.94%. Although there is no hard and fast rule, CVs below 15% for this type of assay are suggested (Lim et al., 2015). A standard curve was created, plotting BDNF concentration against optical densities for the prepared standard comparison samples (range: 15.6 pg/ml to 1000 pg/ml). Participant sample concentrations were derived from comparison to these standards, and then multiplied by 50 to take into account the initial 1:50 dilution.

Difference in BDNF Levels Pre- to Post- Exercise

Assumptions of normality in the BDNF data were checked by creating difference scores for each case, and submitting these difference scores to Shapiro-Wilk (W=0.958, df=6, p=.807)

and Kolmogorov-Smirnov (K=0.211, df=6, p=.20) tests. Non-significance in both tests and visual inspection of the plotted data indicated normally distributed data.

Due to participant availability and scheduling challenges, not all participants completed the exercise session and pre-post blood draw on the same day as they completed the baseline psychosocial and substance use assessments. In an attempt to maximize statistical power to detect a difference, an *a priori* decision was made to include the first complete pre/post exercise BDNF data from each participant, regardless of whether that session occurred before, on, or after the baseline psychosocial assessment date. Paired sample t-test results for the change in serum BDNF levels from pre to post exercise (n=6, t=3.72, df=5, p=.014, Cohen's d=1.519, Hedges' g=1.018) are depicted in Figure 1. Auxiliary analyses employing the same paired sample t-test on only those BDNF data collected on the same day as psychosocial data were run as a check, but returned substantively similar results (n=4, t=4.83, df=3, p=.017, Cohen's d= 2.415, Hedges' g=1.015). The n=6 test showed slightly more stability than the n=4 test in terms of the 95% confidence interval around the difference from pre to post (95% CI 4.95-27.09 vs 95% CI 7.21-35.03).

Exercise Intensity and Duration as Predictors of Serum BDNF level changes

The impact of exercise characteristics on changes in serum BDNF levels was modeled by means of a linear regression equation with change in serum BDNF level regressed on exercise intensity and exercise duration. Because, as above, the analyses are not reliant on comparisons with psychosocial data, all first successful exercise sessions with pre/post blood draws were used in the analyses (n=6).

Unstandardized beta-coefficients, 95% confidence intervals, Pearson's r, and R^2 are presented in Table 5. All findings were non-significant at the p<.05 level and should be

considered informative but preliminary. Exercise intensity was correlated r=.761 with serum BDNF level change, and explained approximately 58% of the variance in BNDF changes pre to post exercise. An unstandardized beta coefficient of 2.85 indicates that for every one unit increase in exercise intensity (as measured by Borg's 6-20 scale of perceived exertion) there is a corollary 2.85 ng/ml increase in serum BDNF levels. Exercise duration had a weak negative correlation (r=-0.125), very little explanatory power with respect to variance (0.2%), and an unstandardized beta coefficient indicating that for every additional minute of exercise performed BDNF levels decreased by 0.014 ng/ml.

Concurrent associations between exercise-induced serum BDNF changes and baseline demographic and substance use characteristics rely to some degree on assumptions of data being collected in a certain order. Similarly, any predictive associations that BDNF changes may have with future coping, craving, consumption and mood outcomes are also based on assumptions of when and in what order data were collected. As such, the remaining analyses are based on data from the 4 participants who completed, on the same day, the psychosocial assessment battery first, followed by successful blood sample collection pre and post exercise. Predictive associations were reliant on participants having data at the 6-week timepoint. Three discrete correlation matrices were planned and analyzed. Regardless of p-value, all following results should be considered informative but preliminary. Scatterplots for each of the three planned matrices are included in the supplemental materials section. These plots indicate that due to the small sample size certain correlations are heavily influenced by one participant. See, for example, the vertical column 'Age' in Figure S1, which provides visual evidence that across a number of associations, one older participant responded quite differently than three substantially younger participants who responded similarly.

The first correlation matrix investigated the associations between baseline demographics, baseline substance use characteristics, and baseline exercise intensity, duration, and BDNF level change (9 variables). Notably strong correlations of interest included: (a) exercise intensity with change in BDNF level (r=.91, p=.090); (b) months in recovery with change in BDNF level (r=.952, p=.048); and (c) age with exercise duration (r= -.993, p=.007).

The second correlation matrix investigated associations between baseline measures of craving, coping, stress, mood, enjoyment of exercise, exercise intensity, exercise duration, and BDNF level change (10 variables). Statistically significant and non-significant correlations of interest included: (a) baseline scores on the physical activity enjoyment scale with baseline exercise intensity (r=.969, p=.031); (b) baseline scores on the physical activity enjoyment scale with baseline exercise duration (r=.924, p=.076); (c) anxiety symptom severity with alcohol craving (r=.948, p=.052); and (d) anxiety symptom severity with depression symptom severity (r=.980, p=.020).

The third correlation matrix investigated associations between weeks 1-6 home exercise frequency, intensity and duration, week-6 in-person exercise intensity, exercise duration, and BDNF level change, and week-6 psychosocial measures of craving, coping, stress, mood, and enjoyment of exercise (11 variables). This was planned as an attempt to replicate part of the original study design using lagged mediation across three time points to investigate the impact of exercise on BDNF levels, and BDNF levels on coping, craving, and consumption. All rows and columns in the produced correlation matrix had a maximum three cases (N=3) given the week-6 timepoint, and as such, the matrix was largely uninformative.

Discussion

The present investigation is the first to demonstrate that individuals recovering from AUD can increase serum levels of BDNF from baseline with sessions of physical exercise. Participants with at least one set of pre/post-exercise blood samples demonstrated a statistically significant (p=.014) increase in BDNF levels from baseline following exercise, with a large effect size (Cohen's d=1.519; Hedges' g= 1.019). This finding is in line with evidence from investigations of exercise-induced changes in BDNF among patients with Major Depressive Disorder (MDD) and Panic Disorder (Szuhany et al., 2015).

Strengths & Limitations

Encouraging in this investigation was the precision with which the BDNF assays were performed, and the general concordance between BDNF ng/ml levels established in this study, and those established for humans in other studies. The range of BDNF levels in the present study was approximately 14 ng/ml to 65 ng/ml. This is reasonably in line with the range established in an investigation of best practices and best performing BDNF ELISA kits, which measured 40 participants at rest and recorded values from 8.7 ng/ml - 58.5 ng/ml (Polacchini et al., 2015).

COVID-19 and the consequences of a global pandemic had a marked impact on sample size, and sample size had a marked impact on the statistical significance of certain findings. That said, the preliminary observations and the direction of effects are supported by the literature. For example, the impact of exercise intensity on change in BDNF levels noted in the present study has corollary support in an investigation by Saucedo and colleagues (2015), which found HIIT exercise sessions with short hard intervals to have more of an effect on serum BDNF levels than constant, steady state aerobic exercise (Saucedo Marquez et al., 2015).

The main findings of this study are all the more encouraging for the fact that, unlike MDD and Panic Disorder, AUD incorporates the added damage that comes from chronic administration of a cytotoxic substance. Sakai and colleagues (2005) found evidence that ethanol-induced human neuronal cell damage involved downregulation of BDNF secretion (Sakai et al., 2005). Joe and colleagues (2007) found evidence that that 71 individuals with an AUD diagnosis had mean BDNF levels less than half those of 75 gender matched healthy controls (Joe et al., 2007). A number of studies, using animal models of addiction and chronic ethanol exposure, have identified diminished BDNF secretion in the cortex, striatum, hippocampus and amygdala, as well the adaptive and neuroprotective roles BDNF exhibits in suppressing alcohol intake after moderate consumption (Kyzar & Pandey, 2015; Logrip et al., 2015; McGough, 2004; Pandey, 2016). Taken together, these studies indicate that people in early recovery from AUD may be particularly vulnerable to dysregulated BDNF pathways. Findings from the present investigation are particularly encouraging in that they show, at the very least, the acute capability for upregulation of circulating BDNF after physical exercise.

Findings in Context

Although the large effect size associated with this investigation is higher than the averaged Hedges' g reported by recent meta-analyses, the study effect size is in line with a number of individual studies reporting Hedges' *g* effect sizes for exercise induced changes in BDNF slightly above or below 1.0 (Baker et al., 2010; Seifert et al., 2010; Zoladz et al., 2008). One of the two extant meta-analysis of the effects of exercise on BDNF levels, comprised of 29 studies (N=1,111; Szuhany et al., 2015), showed moderate effect sizes (Hedges' g) for increases in BDNF from baseline following one single session of exercise (g=0.46), following one session

of exercise embedded in a larger/longer exercise regime (g=0.58), and in resting participants engaged in a regular exercise regime (g=0.28).

The second, more recent meta-analysis, looked specifically at exercise-induced changes to resting BDNF levels (Dinoff et al., 2016), and included 29 studies in the analysis by virtue of each containing exercise interventions lasting two weeks or longer. Overall effect sizes were nonsignificant and small for resistance/strength training (SMD= 0.07, 95% CI: -0.15±0.30, p=.52), but substantially more robust for aerobic training (SMD= 0.66, 95% CI: 0.33±0.99, p< .001). Additionally, a meta-analysis of exercise-induced increases in BDNF among patients with Parkinson's disease reported an effect size (SMD) of 2.06, (95% CI 1.36-2.76; Hirsch, van Wegen, Newman, & Heyn, 2018).

To broaden the context of the current findings still more, Polyakova and colleagues (2015) found that in 21 studies (N=735) of treatment response in patients with major depressive disorder, antidepressant treatment led to increases from baseline in serum BDNF levels in treatment responders (d=1.27, p<.001), and in those diagnosed as having moved into remission (d=0.89, p=0.01), but not in those described as treatment non-responders (d=0.11, p=0.69). Though at first glance this might indicate that people in early recovery from AUD may be better served by antidepressant pharmacotherapy than by physical exercise, it is important to consider that these increases in BDNF levels are as likely to be an effect of improvements in MDD symptoms, as they are a cause. And in fact, the authors of this study stop short of the causal language and enthusiasm of many in the field, and suggest only that serum levels of BDNF might best be considered as a biomarker for successful antidepressant treatment response among those suffering from MDD.

Of course, in the same way that BDNF might be an effect rather than a cause of recovery from MDD (i.e. SSRI→ recovery from MDD → BDNF), BDNF might also turn out to be an effect rather than a cause of AUD recovery, invalidating our hypothesized physical exercise→BDNF→recovery from AUD model in favor of an updated physical exercise→recovery from AUD→BDNF conceptualization. As already mentioned, exercise is associated with a number of other improvements in mental health that are associated with recovery from AUD, and this association may exert an influence on a range of behaviors that could lead to an upregulation BDNF.

Proposed Alternative and Future Study Designs

There may be ways of testing the above competing hypotheses. The val66met single nucleotide polymorphism (SNP) results in a substitution of methionine for valine in the gene encoding BDNF (i.e., a Val/Met phenotype instead the more common Val/Val phenotype). It is found in roughly 30% of the Caucasian population world-wide, and has important characteristics that could lead to studies that might be able to disentangle cause from effect in the competing models described above. Although evidence is mixed and the number of high quality studies in this area is small, results to date seem to indicate that exercise might drive upregulation of BDNF and certain specific cognitive improvements, only in Val/Val carriers, and not in Val/Met carriers (Canivet et al., 2015; Colle et al., 2015; Dinoff et al., 2016; Egan et al., 2003; Kleim et al., 2006; Martinowich, Manji, & Lu, 2007; Molendijk et al., 2012; Nascimento et al., 2015). If this turns out to be true, then the opportunity exists to design a study wherein the same exercise regime is prescribed and monitored with participants of both phenotypes. If results indicate that, in fact, exercise only drove increases in BDNF in the Val/Val group, and only the Val/Val group achieved significant remission of, for example MDD or AUD, then this would lend credence to

the hypothesis that BDNF expression is, or is at least one of, the causal mechanisms in the link between exercise and remission of psychopathology. If, on the other hand, exercise was prescribed and only the Val/Val group showed increases in BDNF, yet both groups achieved remittance of symptoms, then this might indicate that BDNF is less a causal mechanism and more of corollary effect. Were this second scenario to play out in a study involving an AUD population, it might lead to decreased focus on BDNF, and new focus on potential mediators involving stress and the HPA axis, or neurochemical changes related to endogenous opioid, cannabinoid, glutamate, or dopamine transmission.

No extant studies could be found in the psychopathology literature that capitalize on the val66met polymorphism in a design framework as outlined above, and this is likely indicative of the fact that in no research area implicated in a study like this have findings coalesced to the point that interpretation of results would be as cut-and-dry as the above example makes it seems. If, however, findings converge and consensus emerges around the influence of the val66met polymorphism, certain research groups in the AUD area are well positioned to take on such a study (cf. Bryan, Hutchison, Seals, & Allen, 2007).

Although this suggested future research direction is perhaps currently constrained by a number things we do not yet know, there are some things we do know. We know that physical exercise is a reliable and low cost means by which to promote BDNF expression. We know that exercise is associated with a host of benefits to physical and mental health. Further, there is a strong argument to be made that innovative translational approaches to testing animal model findings in a human-model, real-world setting are necessary if the science in this area is to move forward.

The present investigation was designed originally as an inexpensive approach to translational research. It was conceived as a quasi-experimental two-group observational prospective study testing the association between physical exercise, BDNF expression, and alcohol-related outcomes among those in early recovery from AUD who are engaged in, or planning to engage in, some level of physical exercise on a regular basis. BDNF serum assays provided the opportunity to investigate a proxy measure of neural change, and a study like this could serve as a building block and justification for future research employing more intensive designs to better address proximal and distal associations and, importantly, determine whether exercise-induced changes in BDNF expression ultimately influence changes in structure and/or function of specific brain regions implicated in the neurocircuitry of addiction.

In most respects the data collected in the course of this abbreviated investigation should be considered pilot data, and the project might more appropriately be considered a feasibility study. As such, an obvious first step on the path toward future directions would be to run the original study as designed.

More resource intensive - but likely more informative - study designs might include BDNF assays in the context a larger longitudinal clinical trial, randomizing, for example, intensive AUD outpatient program participants into TAU, TAU + placebo activity (e.g., static stretching), and TAU + aerobic exercise conditions. Most resource intensive - but likely most informative as to whether exercise has an impact on the brain regions implicated in models of the neurocircuitry of addiction - would be a similar longitudinal clinical trial design, with the addition of fMRI, or other appropriate brain-imaging techniques.

Epigenetic investigations of the impact of exercise on SUD recovery may also shed light on possible interactions. Already established is the fact that exercise turns on or promotes

expression of the *Bdnf* gene, which in turn leads to increases in levels of the BDNF protein in the central nervous system. Less established is the full range of gene expression that physical exercise promotes, and links between this expression and any outcomes that may have an impact on recovery from alcohol or other drug use disorders.

In summary, there is a vital need for translational research investigating a broader biopsychosocial model of recovery from alcohol and other substance use disorders. Though the proposed research directions above focus only on one small component of this overall model, there is accumulating evidence that BDNF is integral to a range of behavioral changes, and that physical exercise is a reliable and low cost means by which to promote BDNF expression. Further, because physical exercise is linked with such a wide range of physical and mental health improvements, and is protective against a number of chronic and acute illnesses, it would appear that based on face-validity alone, treatment agencies, recovery communities, and rehabilitation centers are beginning to expand their own definitions of treatment and recovery to include physical exercise, whether or not the science behind it is conclusive. This is a relatively benign development, as the benefits of exercise more often than not outweigh the risks. It would be useful, however, to move in a direction that bridges this gap between science and practice. As with any mechanisms of behavior change research, there is value added in determining for whom, when, how and why any given intervention exerts its effects. Clinical psychology sits at a remarkably interesting intersection of a number disparate scientific disciplines, and its capacity to move the needle and reduce suffering is enhanced when it functions more as a hub and less like a spoke. Clinical researchers in the addictive behaviors space may be uniquely positioned to, for example, research and implement strategies to improve exercise adherence, due to their deeper familiarity and facility with motivational interviewing techniques. There has been, of

course, broad dissemination and uptake of motivational enhancement techniques across the health professions, and with it a number of studies investigating the impact of motivational interviewing on physical activity and exercise behavior change (Ang, Kesavalu, Lydon, Lane, & Bigatti, 2007; Brodie & Inoue, 2005.; Martins & McNeil, 2009; Smith, Heckemeyer, Kratt, & Mason, 1997). Recently, also, there has been at least one investigation of the effectiveness of an individualized, motivationally-tailored intervention to promote increases in physical exercise, run by a team primarily known for work in the AUD/SUD area (Bryan, Magnan, Hooper, Marcus, & Hutchison, 2013). Similarly, there is a small literature dating back to the 1980s showing promising evidence for a contingency management paradigm applied to exercise adherence (Ellis et al., 2021; L. H. Epstein et al., 1980; Irons et al., 2013; Thyer et al., 1984).

Taken together, these studies across disciplines indicate a growing interest in employing psychotherapeutic techniques developed initially to address addictive behaviors in an effort to address a wider range of health behaviors, including exercise. Collaborative, translational efforts across disciplines and levels of analysis toward broad biopsychosocial behavioral medicine efforts may, in turn, bring fresh viewpoints and ideas into the addictive behaviors research community.

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Tables

Table 1. Study measures and administration

Purpose	Measure	Type of Measure	Time to Administer (minutes)	When Administered			
				Screening	Baseline 0 wks (T1)	6 wks (T2)	12 wks (T3)
Eligibility	SCID-Module E (Alcohol)	Interview	15	X			
	I.V. Drug Use Scr. Quest.	Interview	1	X			
	SCID Psychotic Screener	Interview	5	X			
	Exercise/Plan	Interview	1	X			
Descriptive	CASAA locator form	Self-report	10		X		
	Demographics form	Self-report	10		X		
	SCID-Module E (Primary Drug of Abuse)	Interview	15		X		
Drinking	TLFB (baseline)	Interview	30		X		
	TLFB (follow-up)	Interview	30				X
Physiological	Exercise (frequency, duration & intensity)	Self-report	5		X*	X*	X*
	BDNF level	Blood serum assay	15		X	X	X
Psychological	PACS	Self-report	10		X	X	X
	BDI	Self-report	7		X	X	X
	BAI	Self-report	7		X	X	X
	PSS	Self-report	10		X	X	X
	PCQ	Self-report	10		X	X	X
	GUS	Self-report	3		X	X	X
	PACES	Self-report	7		X	X	X

Note. SCI*D*= Structured Clinical Interview for the DSM-5; CASAA = Center on Alcohol, Substance Use, & Addictions - University of New Mexico; TLFB = Time Line Follow Back; BDNF = Brain-Derived Neurotrophic Factor; PACS = Penn Alcohol Craving Scale; BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory; PSS = Perceived Stress Survey; PCQ = Processes of Change Questionnaire; GUS = Gambling Urge Scale; PACES = Physical Activity Enjoyment Scale. *weekly logs

Table 2. Sample demographic characteristics.

Measure	N*	Minimum	Maximum	Mean (SD) or %
Age	7	22	65	36.7 (14.5)
Sex				
Male	5			71%
Female	2			29%
Ethnicity/Race				
White	3			43%
Hispanic/Latinx	2			29%
Black/African American	1			14%
American Indian/Alaska Native	1			14%
Marital Status				
Single	6			86%
Widowed	1			14%
Employment Status				
Full time (40+ hrs.)	3			43%
Part time (<40 hrs.)	4			57%
Total Family Income ($)	6	11,000	76,000	32,333 (28,261)
Years of Education	6	11	18	15.0 (2.9)

Note. *Seven participants were enrolled in the study, and six participants provided at least one set of pre/post-exercise blood samples. Discrepancies in the sample size reflect this difference, along with psychosocial data collected for these six participants.

Table 3. Baseline substance use characteristics.

Measure	N*	Minimum	Maximum	Mean (SD) or %
Months in recovery	7	1.0	11.0	5.9 (4.6)
Past year AUD symptom criteria ct.	7	3	11	8.3 (2.7)
TLFB Count of Drinking Days	6	0	42	14.7 (17.7)
TLFB Av. Drinks per Drinking Day	6	1.50	12.9	4.2 (6.0)
Other SUD diagnosis				
Opioid	1			14%
Cocaine	1			14%
Sedative/Hypnotic/Anxiolytic	1			14%
Cannabis	1			14%
None	3			43%

Note. Past year AUD symptom criteria ct. = Number of DSM-5 AUD criteria (0-11) endorsed on SCID-Module E based on past year. TLFB = Time Line Follow Back, an accounting of previous 90 days drinking activity. *Seven participants were enrolled in the study, and six participants provided at least one set of pre/post-exercise blood samples. Discrepancies in the sample size reflect this difference, along with psychosocial data collected for these six participants.

Table 4. Descriptive statistics of all study variables at all study timepoints.

Variable	Baseline *N*=6	Week 6 *N*=3	Week 12 *N*=1
	Mean (SD)	Mean (SD)	Mean
Pre-Exer. BDNF level (ng/ml)	24.17 (12.29)	34.10 (1.53)	n/a
Post-Exer. BDNF level (ng/ml)	41.56 (15.09)	37.31 (1.29)	n/a
PrePost Chg.BDNF level (ng/ml)	18.62(9.41)	3.21 (0.24)	n/a
Experimental Exer. Duration	42.50 (11.29)	45.00 (0.00)	n/a
Experimental Exer. Intensity	15.67 (3.14)	16.00 (0.00)	n/a
Avg. Home Exer. Frequency	n/a	6.33 (1.16)	n/a
Avg. Home Exer. Intensity	n/a	11.82 (2.40)	n/a
Avg. Home Exer. Duration	n/a	37.50 (10.61)	n/a
Beck Anxiety Inventory	18.00 (12.07)	8.00 (6.25)	37.00
Beck Depression Inventory	16.17 (13.15)	21.00 (17.52)	40.00
Gambling Urge Scale	7.80 (4.03)	6.50 (0.71)	6.00
Penn Alcohol Craving Scale	9.33 (8.76)	4.67 (4.04)	7.00
Phys. Activity Enjoyment Scale	96.83 (15.36)	87.00 (46.67)	100.00
Processes of Change Quest.	132.5 (10.67)	121.0 (16.46)	159.0
Perceived Stress Scale	22.83 (7.00)	21.33 (8.62)	36.00

Note. Experimental Exercise Intensity and Average Home Exercise Intensity both measured on Borg's Rating of Perceived Exertion Scale with scores ranging from 6-20, corresponding roughly to heart rate divided by 10.

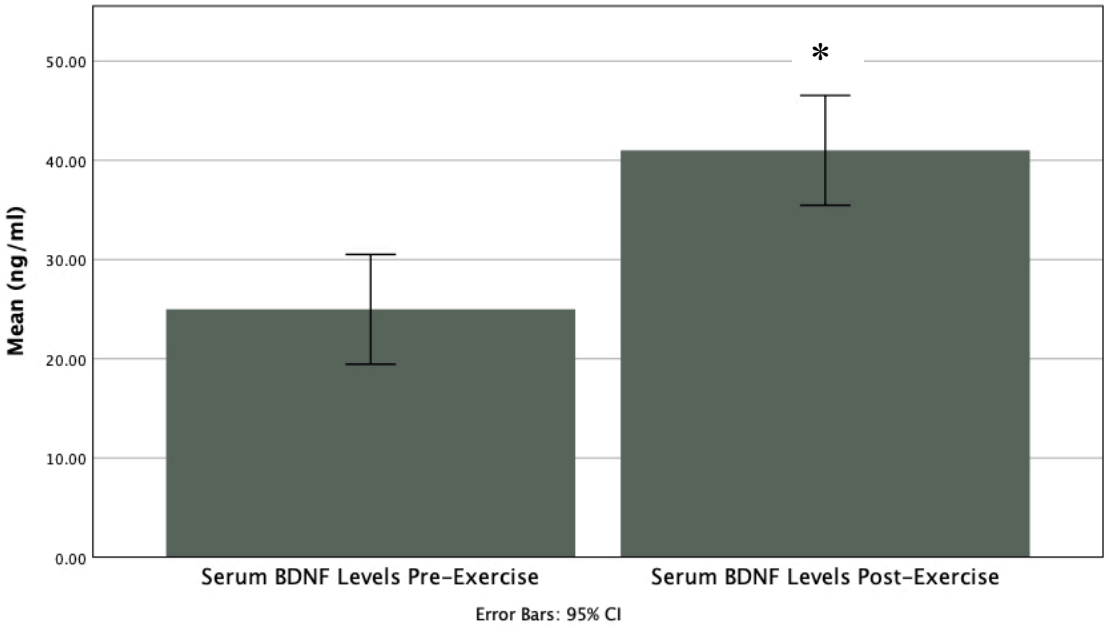
Table 5. Exercise intensity and duration as predictors of one-session change in BDNF levels.

Predictor	ß[a]	95% C.I. for ß	*r*	R^2
Exercise Intensity	2.847	-1.651 – 7.346	0.761	0.580
Exercise Duration	-.014	-1.305 – 1.406	-0.125	0.002

Note. [a] = Unstandardized beta coefficient.

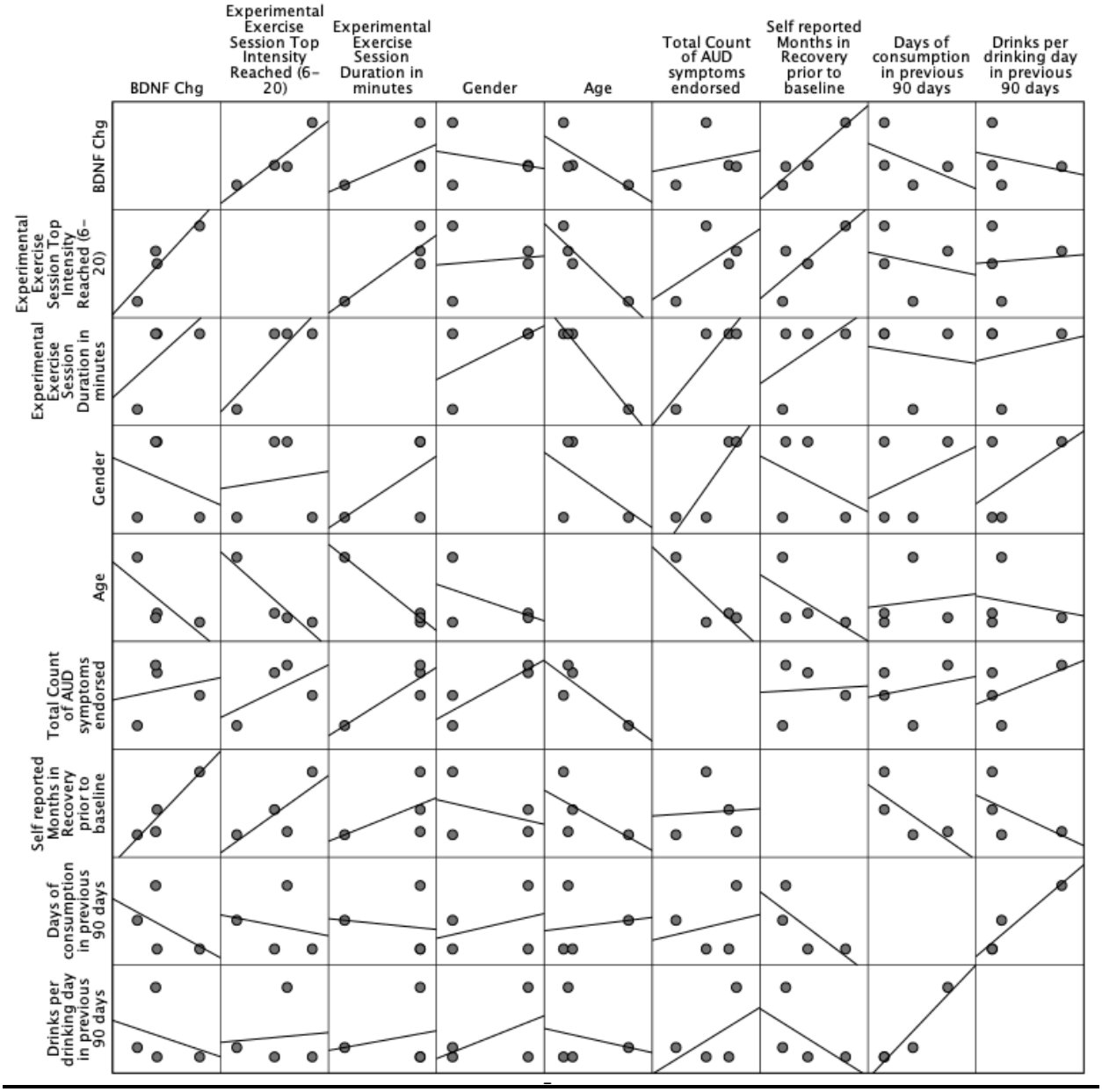
Figures

Figure 1. Mean serum BDNF levels before and after monitored physical exercise session.



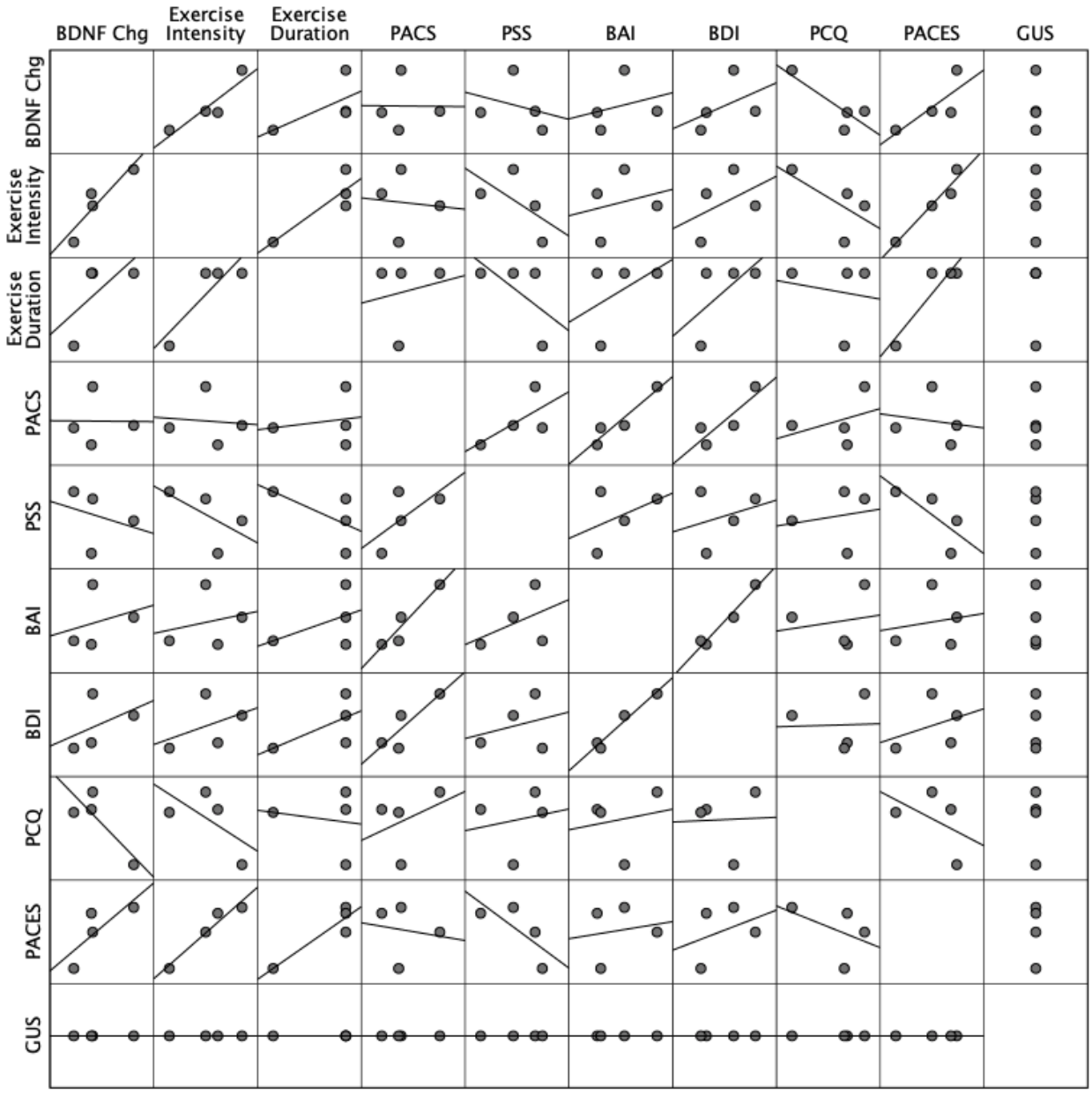
Supplemental Materials

Figure S1. Scatterplot matrix for associations between baseline demographics, baseline substance use characteristics, and baseline exercise intensity, duration, and BDNF level change.



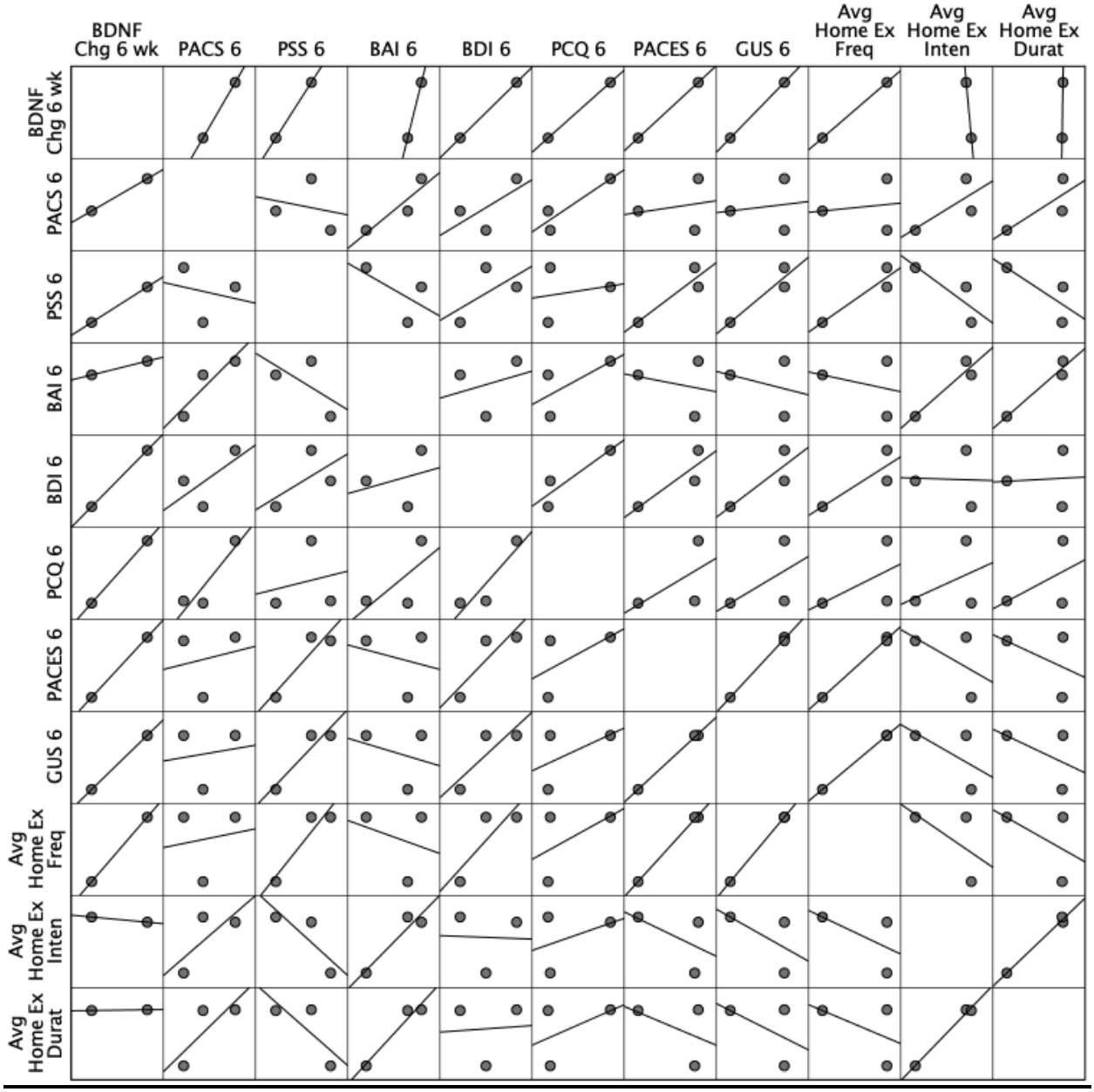
Note. BDNF Chg = Brain-Derived Neurotrophic Factor change from baseline to post-exercise blood draw; Experimental Exercise Intensity was measured on Borg's Rating of Perceived Exertion Scale with scores ranging from 6-20, corresponding roughly to heart rate divided by 10.

Figure S2. Scatterplot matrix for associations between baseline measures of craving, coping, stress, mood, enjoyment of exercise, exercise intensity, exercise duration, and BDNF level change from pre- to post-exercise.



Note. BDNF Chg = Brain-Derived Neurotrophic Factor change from baseline to post-exercise blood draw; Exercise Intensity was measured on Borg's Rating of Perceived Exertion Scale with scores ranging from 6-20, corresponding roughly to heart rate divided by 10; PACS = Penn Alcohol Craving Scale; BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory; PSS = Perceived Stress Survey; PCQ = Processes of Change Questionnaire; GUS = Gambling Urge Scale; PACES = Physical Activity Enjoyment Scale.

Figure S3. correlation matrix investigated associations between weeks 1-6 home exercise frequency, intensity and duration, week-6 in-person exercise intensity, exercise duration, and BDNF level change, and week-6 psychosocial measures of craving, coping, stress, mood, and enjoyment of exercise



Note. BDNF Chg 6 wk = Brain-Derived Neurotrophic Factor change from pre- to post-exercise blood draw at 6 weeks; PACS 6 = Penn Alcohol Craving Scale at 6 weeks; BDI 6 = Beck Depression Inventory at 6 weeks; BAI 6 = Beck Anxiety Inventory at 6 weeks; PSS 6 = Perceived Stress Survey at 6 weeks; PCQ 6 = Processes of Change Questionnaire at 6 weeks; GUS 6 = Gambling Urge Scale at 6 weeks; PACES 6 = Physical Activity Enjoyment Scale at 6 weeks; Avg Home Ex Inten = Average Home Exercise Intensity, self-tracked by participants from week 1 to 6, on Borg's Rating of Perceived Exertion Scale, with scores ranging from 6-20, corresponding roughly to heart rate divided by 10.