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Exercise is an effective treatment for positive valence symptoms in major depression

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ABSTRACT

Introduction: Measurement of symptoms domains and their response to treatment in relative isolation from diagnosed mental disorders has gained new urgency, as reflected by the National Institute of Mental Health's introduction of the Research Domain Criteria (RDoC). The Snaith Hamilton Pleasure Scale (SHAPS) and the Motivation and Energy Inventory (MEI) are two scales measuring positive valence symptoms. We evaluated the effect of exercise on positive valence symptoms of Major Depressive Disorder (MDD).

Methods: Subjects in the Treatment with Exercise Augmentation for Depression (TREAD) study completed self-reported SHAPS and MEI during 12 weeks of exercise augmentation for depression. We evaluated the effect of exercise on SHAPS and MEI scores, and whether the changes were related to overall MDD severity measured with the Quick Inventory of Depression Symptomatology (QIDS).

Results: SHAPS and MEI scores significantly improved with exercise. MEI score change had larger effect size and greater correlation with change in QIDS score. MEI also showed significant moderator and mediator effects of exercise in MDD.

Limitations: Generalizability to other treatments is limited. This study lacked other bio-behavioral markers that would enhance understanding of the relationship of RDoC and the measures used.

Conclusions: Positive valence symptoms improve with exercise treatment for depression, and this change correlates well with overall outcome. Motivation and energy may be more clinically relevant to outcome of exercise treatment than anhedonia.

1. Introduction

Given the high prevalence and associated morbidity of depression (Ustun et al., 2004), much effort has been made to meaningfully subtype patients for targeted therapy (Goldberg, 2011). However, this strategy has failed to improve our understanding of mental disorders or to direct treatment for patients in practice. Most recently the National Institute of Mental Health tried to address this issue through the introduction of the Research Domain Criteria (RDoC) model (Insel et al., 2010). RDoC is designed to examine biological correlates of behavior and to define meaningful groups and subgroups. This means examining the relationships among brain circuits, cells, intracellular components and particular behaviors – relationships that are understood best currently in animal models – rather than on how symptoms are experienced *subjectively* in human beings (Cuthbert and Insel, 2013). There is an increasing recognition that no single global clinical or bio-behavioral marker is likely to universally explain the variable presentations of Mood Disorders or assist with treatment selection (Trivedi, 2013; Trivedi et al., 2016). The need to evaluate patient presentations according to a more precise bio-behavioral model necessarily requires evaluation of specific symptoms in addition to overall severity.

Although patients with depression present with symptoms clearly mapping onto specific RDoC domains, these are rarely assessed routinely with focused measurement tools. While there is a need to develop new assessments based on RDoC, there are standardized rating instruments already available that bear face validity with RDoC domains and constructs. Routine measurement with these tools is needed to clarify the relationships between the core Major Depressive Disorder (MDD) symptoms as defined by the Diagnostic and Statistical

Abbreviations: MDD, Major Depressive Disorder; RDoC, Research Domain Criteria; TREAD, Treatment with Exercise Augmentation for Depression; SHAPS, Snaith Hamilton Pleasure Scale; MEI, Motivation and Energy Inventory; QIDS, Quick Inventory of Depression Symptomatology; SSRI, Selective Serotonin Reuptake Inhibitor

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Manual of Mental Disorders (upon which current diagnoses are based) and RDoC constructs. This will link bio-behavioral results to more traditional outcomes and serve as a basis for the development of RDoC based trials. For example, differential effect of treatment modality (e.g. medication, psychotherapy, exercise) on symptom constructs cannot be determined without a measurement that parses individual constructs from the overall picture of depression. With this in mind we examined symptoms associated with the RDoC Positive Valence Domain using the Snaith Hamilton Pleasure Scale (SHAPS) and Motivation and Energy Inventory (MEI) - two scales that were used in the Treatment with Exercise Augmentation of Depression (TREAD) study.

The positive valence domain contains five constructs: 1) approach motivation, 2) initial reward responsiveness, 3) sustained reward responsiveness, 4) reward learning, and 5) habit (National Institutes of Mental Health, 2011). While all positive valence constructs may conceivably be impaired in depression, approach motivation may be one of the most relevant. Approach motivation is a complex construct that itself includes four sub-constructs – reward valuation, effort valuation, reward expectation, and preference. Anhedonia, a core positive valence symptom of depression, is often parsed in animal studies as a state in which preferences are intact but motivation is lacking (Berridge and Kringelbach, 2015; Treadway and Zald, 2013). Following this lead, RDoC, deemphasizes the experience – or lack – of pleasure in positive valence, replacing it with a model in which consummatory behaviors are taken as the outcome of the interplay of underlying constructs. For example, hunger may increase the reward value of food sources in general but prior experience (learning) may direct behavioral responses to particular types of food based on effort required or taste preference. On the other hand, when hunger is low, even though preferences are intact, motivation is decreased and consumption of even preferred foods declines. Other than the emphasis on behavior over experience, the description of anhedonia in the Diagnostic and Statistical Manual for Mental Disorders (DSM) (American Psychiatric Association, 2013), as lack of enjoyment specifically of things for which one has preference, is clearly analogous. However, it is also important to consider that positive valence may apply to other traditional symptoms of depression. For example, fatigue may be viewed as dysfunction in positive valence systems, a conceptualization consistent with literature examining fatigue as a medical, more than psychiatric, symptom (Dantzer et al., 2014). The SHAPS and MEI by measuring specific components of deficits in positive valence are well suited to assessment of this domain in a way that bridges the traditional concept of anhedonia with RDoC.

Trials of exercise therapy for depression are well suited to the application of RDoC principles because they utilize complex bio-behavioral treatment (Schuch et al., 2016). In the Treatment with Exercise Augmentation for Depression (TREAD) study, adults who failed to respond to a Selective Serotonin Reuptake Inhibitor (SSRI) were treated with an augmentation regimen of aerobic exercise for 12 weeks (Trivedi et al., 2011). Half of the subjects were randomized to each of two dose groups while all continued to take the antidepressant prescribed prior to study entry. To assess the effect of exercise on anhedonia, decreased motivation and other positive valence domain symptoms, subjects in TREAD were assessed with domain specific measures including the SHAPS and MEI.

2. Methods

Complete details of the TREAD study have been previously published (Trivedi et al., 2011, 2006). Briefly, this was a 12-week comparison of a public health dose of exercise to a low dose in patients with MDD who were eligible for augmentation treatment due to partial or no response to an SSRI.

2.1. Subjects

TREAD enrolled adults, ages 18–70, with MDD who were taking a stable adequate dose of an approved SSRI for at least 6 weeks (and up to 6 months) at screening. Included subjects reported no more than partial response as defined by a screening Hamilton Depression Rating Scale (HDRS) score of ≥14 and reported being sedentary for at least the last month. Subjects with medical illness contraindicating exercise were excluded, as were those with lifetime history of psychosis. History of two or more failed anti-depressant trials in the current episode was also exclusionary. All subjects provided voluntary informed consent and remained on their prescribed antidepressant throughout the trial.

2.2. Exercise treatment

At baseline, subjects were randomized to receive one of two doses of exercise: a high dose of 16 kcal/kg/week or a low dose of 4 kcal/kg/week. The high dose was chosen based on public health recommendations for weekly exercise requirements and had previously been shown to be effective as an antidepressant treatment (Dunn et al., 2002). Subjects met with trainers at the Cooper Institute in Dallas, TX to develop exercise plans meeting the prescribed dose using aerobic exercise; for example, walking, jogging, or running on a treadmill. Subjects were able to choose the intensity of exercise and received instruction on time needed to meet the prescribed dose. After the first two weeks of the study period in which trainers assisted in the development of the exercise prescription, subjects returned for one supervised session a week (at which weekly assessment occurred) and completed the remaining exercise at home, using a web-based tracker to log exercise completed.

2.3. Assessments

All subjects had inclusionary and exclusionary diagnoses validated using the Structured Clinical Interview for DSM-IV (SCID) at screening. They also received maximal oxygen consumption (VO_2 max) testing to determine baseline level of fitness and confirm medical suitability for exercise.

The primary outcome measure used in TREAD was the Inventory of Depression Symptomatology – Clinician Rated (IDS-C). From each of the 30 item IDS-C and the corresponding self-rated IDS (IDS-SR), item scores for each depression symptom domain were extracted to form a Quick Inventory of Depression Symptomatology – Clinician (QIDS-C) and self-rated (QIDS-SR) score respectively (Rush et al., 2000, 2003). The IDS includes items designed to assess non-core symptoms of depression (such as diurnal variation and mood reactivity) that are associated with subtypes as identified in the DSM. The QIDS measures only the core depression symptoms, and therefore, unlike the IDS, the QIDS is uni-dimensional. For this reason we used extracted QIDS-C and -SR scores as the measures of outcome in this analysis. The self-reported SHAPS and MEI were given at baseline, week 6 and week 12.

2.4. SHAPS

The SHAPS was developed in the mid-1990s to measure 'hedonic tone" (Snaith et al., 1995). At the time, Snaith et al. were concerned that previous assessments were too dependent on personal preferences. The items were created by surveying healthy adults about pleasurable experiences, and the scale was tested on healthy and mentally ill samples to establish norms. A key feature of the scale is the use of the Montgomery Asberg Depression Rating Scale (MADRS) item "inability to feel" (Montgomery and Asberg, 1979) as the index by which presence of anhedonia was established. The SHAPS contains 14 items, which ask subjects to strongly agree, agree, disagree or strongly disagree with statements beginning "I would enjoy…" followed by an activity or experience. Any agreement with the statement is scored zero