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A possible effect of methylphenidate on state anxiety: A single dose, placebo controlled, crossover study in a control group

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ABSTRACT

Methylphenidate affects state-anxiety in ADHD patients. The current study examines the effect of Methylphenidate on state-anxiety in healthy subjects. In a cross-over, randomized, controlled, double-blind study, 36 healthy subjects received either Methylphenidate or placebo. As a group, no change in state-anxiety was detected with Methylphenidate. However, participants reporting higher anxiety levels experienced a significant and specific state-anxiety reduction following Methylphenidate. Moreover, a strong negative correlation was found between the initial-level of anxiety and net-change in state-anxiety. These changes were unrelated to self-perceived attention levels. Our results point to the state-dependent effects of Methylphenidate on anxiety.

1. Introduction

Methylphenidate (MPH) is a widely used medication for attention deficit/hyperactivity Disorder (ADHD). Though ethically controversial, it is also used for cognitive-enhancement in healthy populations (McCabe et al., 2005; Outram, 2010). This type of use raised the need to study the efficacy of such a therapy. To date, studies and public attention focused on the different cognitive functions and the increment of improvement achieved by MPH and stimulants (Caviola and Faber, 2015). Since a common use of MPH as a "cognitive-enhancer" is aimed at anxiety-saturated conditions (e.g. exams), it seems that the effects of MPH on anxiety in controls should be evaluated (Liakoni et al., 2015).

Anxiety, like attention, is attributed at least partially to catecholamines, and the interplay between them is extremely convergent. MPH is related, at times, to aggravating anxiety (Epstein et al., 2014). This was especially stressed in studies with animal models of ADHD (Vendruscolo et al., 2008). Conversely, a recent meta-analysis of clinical studies using MPH points to the opposite effect, in which MPH reduces anxiety in ADHD patients (Coughlin et al., 2015). In a previous study, our group had shown that state-anxiety reduction following the administration of MPH was specific to ADHD patients, and was not observed in controls. Although the MPH effect on continuous performance test execution was more pronounced in ADHD patients, controls improved as well. However, the effect on anxiety was discriminative and was observed only in ADHD subjects. In that study, ADHD patients were more anxious than controls, and there was no blind use of a placebo (Bloch et al., 2013).

With the rising use of MPH as a cognitive enhancer, studying the effect of MPH on anxiety in healthy subjects can contribute to the understanding of its use in this population and in better typifying its effect on ADHD patients.

2. Methods

2.1. Participants

All subjects were recruited through advertisements within the University and in the community.

Inclusion criteria were age 21–40, right handed, Hebrew as mother-tongue and a high-school diploma. Exclusion criteria were (a) any neurological or psychiatric illness; (b) any medical conditions contra-indicated when receiving MPH; (c) any learning disability; (d) drug or alcohol abuse; (e) score 60 or higher on the Connor's Adult ADHD Rating Scale.

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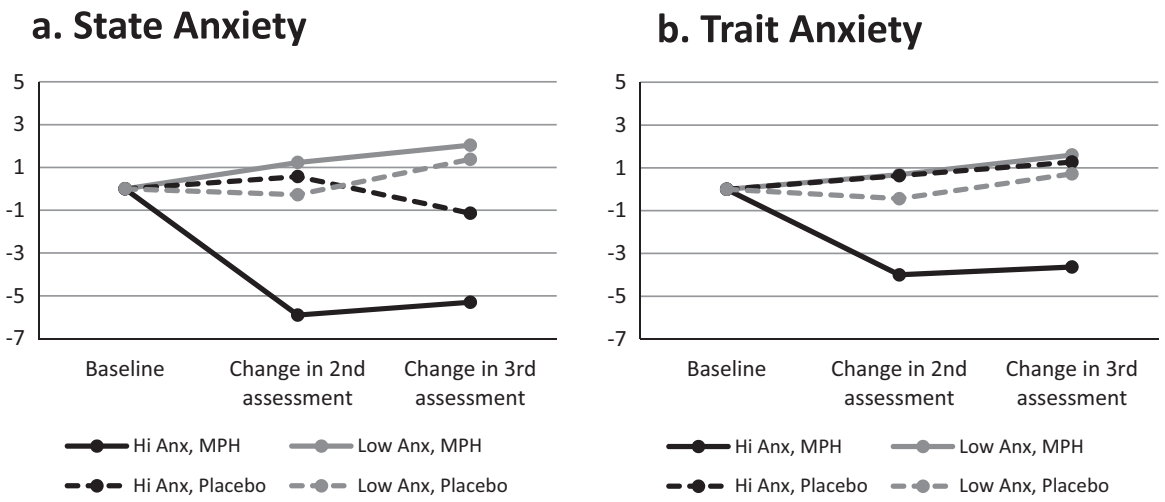

Fig. 1. Net changes in state anxiety, as groups are defined in graph (a) according to initial levels of state-anxiety; and in graph (b) according to trait-anxiety. ANX – anxiety, MPH – methylphenidate.

2.2. Tools

Several assessment tools were used:

1) The Spielberger State-Trait-anxiety Inventory (STAI), a measure of both transient (state) and enduring levels (trait) of anxiety; 2) Conners' Adult ADHD Rating Scales (CAARS) (Conners et al., 1999), which measures ADHD symptoms; 3) on a Visual Analog Scale (VAS) (Revill et al., 1976) subjects reported how attentive they were feeling at present; 4) the Structured Clinical Interview for DSM-IV (SCID) - a diagnostic tool for mental disorders, used as a screen tool to verify suitability for the study.

2.3. Study design

This was a randomized, double-blind placebo-controlled, random block order crossover trial.

Eligible individuals were scheduled for two assessment visits 2 weeks apart which began at the same time of day. The study was approved by the local IRB. All participants went through an informed consent procedure and then underwent a physical screening (including a medical history interview performed by a physician, a physical examination and an ECG test) as well as a psychiatric screening (based on the SCID semi-structured interview conducted by a psychiatrist and the CAARS for further reassurance of ruling out ADHD).

In both sessions, subjects completed VAS and full STAI prior to any intervention. They were randomly assigned to receive MPH 20 mg immediate-release or inert ingredients (placebo). Forty-five minutes after drug administration (during which the participants filled out several questionnaires required for the study), subjects completed VAS and STAI-State questionnaire again and then performed several tasks related to creativity (described elsewhere, unrelated to anxiety and attention). 1.5 h later subjects completed a VAS and STAI-State for a third time. In the second session, medication (MPH/placebo) was crossed-over.

2.4. Statistical analysis

We have applied a repeated measure analysis of variance using state-anxiety levels and drug administered as within-subject factors. In order to examine the differential effect of MPH based upon baseline levels of anxiety, we have used a group variable – low vs. high anxiety level, as a between-subject factor. Determination of a baseline level of anxiety could rely on two measures: either by first state-anxiety assessment or level of trait-anxiety. The cutoff defining low vs. high anxiety was a STAI score of 30 – halfway between the minimal score (20) and clinical cutoff (40).

Baseline level of anxiety was correlated to the net change in state-anxiety levels during the session using a Pearson test, in order to enable a dimensional perspective.

A similar method was performed in order to examine a possible confounding role of gender, order effect and MPH effect on attention level.

3. Results

3.1. General

The 36 Participants were mostly single (92.6%), full-time students (69.0%), young (M=25.36 years, SD=3.88; range=21–39) and gender balanced (50% males).

None of them was a regular user of stimulants. Subjects' weight range was 47–87 kg. Mean CAARS score was 46.7 (SD 7.3, range 32–58), and mean STAI-Trait was 28.0 (SD 6.4, range 20–49).

3.2. Examining the effect of MPH on state-anxiety

A repeated measure analysis of variance with drug (Placebo, MPH) and time (STAI-state assessments 1, 2 & 3) found non-significant interaction ($F(2,34)=0.261$, $p>0.1$). Levels of state-anxiety in the MPH session were 27.06, 26.31 and 27.06, respectively; and 25.42, 25.31 and 26.31 in the placebo session. Follow-up independent *t*-tests for each assessment point yielded non-significant difference at any time.

3.3. Examining the effect of MPH on state-anxiety in low vs. high anxiety subgroups

This was measured by either initial-state or trait-anxiety score. Correlation between those measures was moderate ($r=0.43$. $p<0.01$), reflecting that although linked, there is a discrepancy between anxiety as a long-lasting characteristic (trait) to the transient situational anxiety exhibited in the morning of the first session (state).

Two repeated measure analyses were performed: one with drug and time (as explained), using a between-subject factor of state-anxiety group (low vs. high initial state-anxiety); and a