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Short communication

Propranolol's impact on cognitive performance in post-traumatic stress disorder

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ABSTRACT

Background: Propranolol has effectively diminished fear-based emotional memories in posttraumatic stress disorder (PTSD) and this effect has been attributed to traumatic memory reconsolidation blockade. However, propranolol may also exert cognitive effects by modulating stress and arousal.
Method: Within a randomized double-blind placebo controlled trial, propranolol's impact on cognitive functioning was examined in individuals who were diagnosed with chronic PTSD. Participants received a single dose of 1 mg/kg of propranolol ($n=20$) or placebo ($n=21$), and completed subtests of the Wechsler Adult Intelligence Scale third edition (WAIS-III). PTSD symptoms were assessed 1 week before and after treatment by the Impact of Event Scale Revised (IES-R).
Results: The propranolol group performed significantly better on the Processing Speed composite measure compared to the placebo group. Furthermore, greater heart rate decreases were associated with higher Perceptual Organization performance, within the propranolol group.
Limitations: The generalizability of results may have been reduced as participants were treatment seeking; the sample size was small and included a greater proportion of females.This study could not assess whether pre-existing psychological function influenced cognitive performance, post-trauma. Future studies might consider including a non-PTSD control group to determine if our findings are specific to propranolol's effect on PTSD associated cognitive impairment.
Conclusions: Our preliminary results demonstrated that cognitive functioning improved following propranolol administration in PTSD patients. The implications are discussed with regards to the processing of traumatic events.

1. Background

Cognitive dysfunction has been identified in posttraumatic stress disorder (PTSD); and associated with impaired traumatic memory processing (Brandes et al., 2002), increased psychiatric symptom severity, and functional disability (Geuze et al., 2009). Executive function deficits notably in working memory (Aupperle et al., 2012b), sustained attention (Vasterling et al., 1998), and response inhibition (Stein et al., 2002) are among the neurocognitive abnormalities reported, post-trauma. Presented before memory recall, trauma relative to neutral sentences significantly disturbed working memory performance in individuals with current and lifetime PTSD (Schweizer and Dalgleish, 2011). Moreover, frequent intrusions during verbal and visual memory recall (Vasterling et al., 1998), may reflect difficulty inhibiting internal trauma representations (Twamley et al., 2009). As attentional processes become allocated to managing distress, limited cognitive resources remain to facilitate PTSD recovery (Twamley et al., 2009). The inability to disengage from perceived environmental threat, and disinhibited emotional arousal (Aupperle et al., 2012b) strain cognitive and attentional control networks, impairing information processing and maintaining PTSD (Shin et al., 2001).

Despite the negative neuropsychological impact of prolonged traumatic stress, few studies have examined cognitive outcomes following pharmacotherapies for PTSD. In an uncontrolled trial, PTSD participants' verbal memory performance increased after paroxetine treatment (Vermetten et al., 2003). Fani et al. (2009), reported that although paroxetine improved verbal declarative memory in PTSD, this effect was not significant compared to placebo.

The β-adrenergic receptor antagonist, propranolol has also

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shown promise for the treatment of chronic PTSD. It is postulated that traumatic memory consolidation is enhanced by strong stress and arousal responses, partly mediated by heightened noradrenaline (NA) release, at the time of a distressing event (Southwick et al., 1999). In PTSD, propranolol's therapeutic mechanism has been attributed to reconsolidation blockade, which has attenuated the emotional strength of traumatic memories (Pitman and Delahanty, 2005). Compared to placebo, propranolol significantly reduced psychophysiological responses during script-driven traumatic imagery (SDI) in PTSD patients (Brunet et al., 2008), though other studies failed to replicate these findings with a variety of memory destabilizing agents (Wood et al., 2015).

During stressful experiences, augmented NA has inhibited prefrontal cortex (PFC) function (Arnsten, 2009; Ramos and Arnsten, 2007), and this may diminish the cognitive control of emotional processing. It is possible that central β-adrenergic modulation of neurocognitive functions may also influence treatment responses. For example, in healthy men, relative to placebo, propranolol significantly increased working memory performance by reducing attention for emotionally negative distracters during high cognitive load (Oei et al., 2010).

In the following study, we examined the cognitive functions regulated by propranolol in PTSD patients; and whether improved cognitive performance might be important to facilitate trauma imagery processing, presented through reactivation. Across studies of neuropsychological performance in PTSD, executive function impairments and increased responsiveness to emotional stimuli have been associated with frontal–subcortical circuit disturbances (Aupperle et al., 2012a; Morey et al., 2009, 2008; Stein et al., 2002; Vasterling et al., 1998). As clinical studies have shown that chronic traumatic stress responses negatively affected working memory, sustained attention and processing speed (Beers and De Bellis, 2002; Cohen et al., 2013; Twamley et al., 2009; Vasterling et al., 1998, 2002), we hypothesized that propranolol would improve performance on tests associated with these cognitive functions.

2. Method

2.1. Participants

Forty-one individuals (30 female) who experienced traumatic events were recruited through advertisements and invited to the PTSD Clinic at the Douglas Hospital (Montreal, QC, Canada). Informed consent was obtained for participation in a randomized, double-blind, placebo controlled trial (RCT), which was part of a larger study investigating pre-retrieval propranolol effects on traumatic memory reconsolidation. During the RCT, PTSD participants received an oral dose of propranolol ($n=20$) or placebo ($n=21$), and completed a cognitive assessment, followed by SDI. The Douglas Hospital REB and Health Canada approved study procedures (www.clinicaltrials.gov identifier: NCT01349439).

Groups were similar in age (mean ± SD): 45.2 ± 10.7 [Propranolol] vs. 41.7 ± 12.5 [Placebo] years; $t_{37}=.93$, $p=.36$) and sex distribution ($\chi^2=.93$, $p=.34$). PTSD duration ranged from 3 to 12 years. Traumatic experiences included accidents ($n=8$), physical and sexual assaults ($n=27$), combat exposure ($n=1$), violent or unexpected deaths of close ones ($n=4$) and other stressors ($n=1$).

2.2. Clinical assessments

At the initial assessment (Time 0) the Clinician Administered PTSD Scale (CAPS) (Blake et al., 1995) evaluated PTSD symptom severity corresponding to the past month, directly preceding study enrollment. Candidates with a CAPS score ≥ 50 points were considered for participation in the trial. Additionally, participants self-reported PTSD symptom severity within the past 7 days, using the Impact of Event Scale-Revised (IES-R) (Weiss and Marmar, 1997). Treatment groups did not differ in symptom severity, at study entry (mean ± SD): CAPS = 80.4 ± 23.3 [Propranolol] vs. 78.3 ± 17.1 [Placebo]; $t_{39}=.31$, $p=.75$); and IES-R = 87.8 ± 16.6 [Propranolol] vs. 83.7 ± 11.4 [Placebo]; $t_{39}=.91$, $p=.36$). The Mini Neuropsychiatric Inventory (MINI) (Sheehan et al., 1998) evaluated the presence of co-morbid Major Depressive Disorder: $n=7$ [Propranolol] and $n=5$ [Placebo]; and other anxiety disorders: $n=9$ [Propranolol] and $n=12$ [Placebo].

Urinalyses confirmed that participants were free of illicit substances. Individuals prescribed stable doses of anxiolytics ($n=4$ [Propranolol], $n=6$ [Placebo]), anti-depressants ($n=13$ [Propranolol], $n=11$ [Placebo]), or antipsychotics ($n=4$ [Propranolol], $n=5$ [Placebo]) at least 1 month before screening, continued these medications during the trial. Participants skipped their morning doses of Selective Serotonin or Norepinephrine Re-uptake Inhibitors on the treatment day to minimize potential drug interactions with propranolol. Electrocardiograms verified that participants > 40 years old were not at risk for cardiac complications. Pregnancy, bipolar disorder, head injury, and medical conditions contraindicating propranolol use were exclusionary.

2.3. Cognitive testing

One week after the assessment session, under medical supervision, participants ingested a single, oral dose of 1 mg/kg of short-acting propranolol or placebo in a double-blinded manner (Time 1). Heart rate (HR) and blood pressure (BP) were monitored at baseline and every 30 min for a 2 h period to measure systemic propranolol exposure. Thirty minutes post-drug, a trained assessor began administering the Wechsler Adult Intelligence Scale third edition (WAIS-III) (Wechsler, 1997) to participants. The WAIS evaluates several cognitive domains in a single session. As psychiatric samples often require longer WAIS completion times than healthy controls (Axelrod, 2001), testing continued to 2 hour post-treatment. Subsequently, a sub-group of participants underwent SDI, once during the visit (Brunet et al., 2011, 2014). PTSD symptom severity changes were assessed by the IES-R 7 days, post-treatment (Time 2).

2.4. Statistical analysis

Analyses were conducted using SPSS 20.0 (Armonk, NY, 2011). Difference scores computed between the baseline and 2 hour post-treatment points reflected the mean change in HR, diastolic and systolic BP. *T*-tests compared vital sign changes between groups. To assess symptom severity, IES-R total scores were computed for participants at baseline and 1 week post-treatment. Difference scores were computed between these time-points, and *t*-tests compared symptom change between groups.

To evaluate cognitive performance, a composite score was computed for each WAIS-III Index based on the age normed (scaled) scores for the: Verbal Comprehension (VC) Index = Vocabulary + Information test scores; Perceptual Organization (PO) Index = Blocks + Matrix Reasoning test scores; Working Memory (WM) Index = Digit Span (Forward and Backward) + Arithmetic scores; and Processing Speed (PS) Index = Digit Symbol Coding + Symbol Search scores. First, we only examined differences for Index composite scores using independent sample *t*-tests. Post-hoc analyses of subtests were conducted, only if the Index composite scores were significant between groups. Pearson correlation tests assessed relationships between vital sign changes, symptom severity changes (IES-R scores), and cognitive performance.