

# Cold pressor pain and gambling disorder: implications for the opioid system

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**Objective.** Gambling disorder (GD) is a common, disabling condition that often is exacerbated by stressful life events. Under stress, the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis are activated. The question, therefore, arises as to whether an abnormal sympathetic response can be found in individuals with GD.

**Method.** Adult individuals with GD and no current co-occurring mental disorders were enrolled. Participants completed impulsivity and gambling-related questionnaires and underwent cold pressor evaluation. GD participants were compared with controls on measures of heart rate, blood pressure, and pain.

**Results.** Fifteen people with GD and 18 controls completed the study. Kaplan–Meier analysis indicated that the GD group withdrew their hand from the painful stimulus more rapidly than controls (Wilcoxon chi-square = 3.87,  $p = 0.049$ ), suggestive of lesser pain tolerance. Subjective pain ratings and cardiovascular measurements did not significantly differ between groups.

**Conclusions.** Individuals with GD manifested a relative intolerance to pain on the cold pressor paradigm, even though they physiologically did not seem to experience greater pain. Given the role of the opioid system in pain processing, it would be valuable in future work to examine whether cold pressor measures can predict response to treatments in GD, including with opioid antagonists.

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## Introduction

Gambling disorder (GD) is a significant public health problem affecting 0.4–1% of the US population, also being prevalent in many other countries.<sup>1,2</sup> Psychosocial impairment, financial and family problems, as well as elevated rates of suicide are common among individuals with GD.<sup>3</sup> GD can be conceptualized from a neurobiological perspective in terms of excessive drive from subcortical regions involved in reward processing coupled with diminished top-down control from prefrontal cortical regions.<sup>4</sup> Meta-analyses have confirmed that GD is associated with impulsivity (indicative of loss of top-down control) across a number of domains, compared with controls.<sup>5–7</sup> In a recent Delphi consensus study, impulsivity was

highlighted as an important construct in understanding addictive problems more broadly.<sup>8</sup> Top-down control for many individuals with GD is more difficult under stress.<sup>9</sup> Furthermore, people with disordered gambling commonly report stress both as a trigger to more severe gambling episodes as well as to a relapse when attempting abstinence.<sup>10</sup> Stress and aberrant responses to stress are implicated in etiological models of GD.<sup>11–15</sup> When one is subjected to a stressor, the activation of the sympathetic system and the hypothalamic-pituitary-adrenal (HPA) axis occurs.<sup>16,17</sup> It has been hypothesized that alterations in the HPA axis function may play a role in various stages of addiction, including initiation, maintenance, and relapse.<sup>18,19</sup>

While losing everything on gambling would likely be psychologically painful for healthy individuals, those with GD report gambling episodes lasting several hours, resulting in significant personal and financial ruin,<sup>20</sup>

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which may suggest changes in pain perception, such as loss of pain sensitivity. Conversely, research suggests that in some individuals with GD, the inability to cope with painful or uncomfortable physical sensations may drive the gambling behavior, suggestive of a general inability to cope with discomfort.<sup>21–25</sup> To date, little research has examined whether individuals with GD experience pain differently from healthy controls. Therefore, the question remains as to whether adults with GD have different pain thresholds, pain tolerances, or autonomic responses to painful stimuli, as contrasted to people without this disorder.

One means of understanding pain perception is via the Cold Pressor Test (CPT). The CPT requires a person to immerse their hands in ice-cold water until the task becomes too uncomfortable. Although the role of aberrant pain transmission in GD has not been previously examined, a general understanding of pain suggests that noxious cold cutaneous sensations are recognized primarily by the cold-sensitive ion-channel TRPM8 before sensory signal transduction.<sup>26</sup> Functional neuroimaging data revealed that noxious cold stimulation applied to the upper limbs of healthy subjects activated the amygdala and anterior cingulate cortex, regions classically implicated in aversive emotional processing.<sup>27</sup> Intriguingly, limited imaging data implicate the anterior cingulate cortex and amygdala in the pathophysiology of GD.<sup>28</sup> Using the CPT, and based on the clinical data regarding GD, we hypothesized that adults with GD would exhibit a dampened autonomic response to pain compared with healthy controls. In addition, we hypothesized that adults with GD would subjectively report less discomfort when undergoing the cold pressor task and that pain sensitivity would significantly and negatively correlate with worse gambling symptom severity.

## Materials and Methods

### Participants

Adult men and women with a current primary diagnosis of GD, based on DSM-5 criteria (see later for diagnostic methods), were recruited by media advertisements, referrals, and in person at the University of Chicago. Age- and gender-matched healthy controls were recruited by word-of-mouth and through poster and newspaper advertisements. All control group participants were free of any current psychiatric disorder, as measured using the Mini International Neuropsychiatric Inventory (MINI)<sup>29</sup> and Minnesota Impulse Disorder Inventory (MIDI).<sup>30,31</sup>

Exclusion criteria across all participants included: (1) current psychiatric disorder (other than GD in the GD group); (2) use of any psychotropic medication; (3) history of therapy for GD; (4) current nicotine dependence; (5) history of Raynaud's phenomenon; (6) history of cardiovascular disorder; (7) open cuts or sores on the

hands; (8) history of fainting or seizures; (9) fracture of the limb to be submersed; (10) history of frostbite; and (11) an inability to understand or undertake the procedures or to provide written informed consent.

The Institutional Review Board (IRB) of the University of Chicago approved the study and consent procedures, which followed the Declaration of Helsinki's ethical principles for medical research involving human participants. After a complete description of study procedures, participants were given the opportunity to ask questions and provided voluntary informed consent using the IRB-approved consent form. Subjects were compensated with \$10 cash at the end of the visit.

### Procedures

Demographics and clinical features of GD were assessed with an unpublished semi-structured interview, in both cases and controls (available on request from the authors). The diagnosis of GD was confirmed using the Structured Clinical Interview for Gambling Disorder<sup>32</sup> modified for DSM-5. Psychiatric comorbidity was assessed using the MINI<sup>29</sup> and MIDI.<sup>30,31</sup> Gambling severity measures were the Yale Brown Obsessive Compulsive Scale modified for Pathological Gambling (PG-YBOCS) (a 10-item clinician-administered scale that assesses gambling symptoms during the last 7 days)<sup>33</sup> and the Gambling Symptom Assessment Scale (G-SAS) (a 12-item self-report scale of gambling symptoms over the past 7 days).<sup>34</sup> We also assessed impulsive personality traits in the gambling group using the Barratt Questionnaire.<sup>35</sup>

We examined pain perception using the CPT, a reliable and valid pain induction method<sup>36</sup> that requires participants to submerge their non-dominant hand in a 85-ounce container filled with ice water at a temperature between 0 and 4 °C. Participants were instructed to keep their hand open (rather than in a closed fist position) in the water. Before immersion, participants were told to keep their hand in the water until the pain became intolerable or until the cutoff time of 3 min was reached. During the task, subjects rated their pain at 15-s intervals using an adapted version of the Wong-Baker Faces Pain Rating Scale (0 = not painful at all, 100 = extremely painful, with intermediate ratings marked on the Likert scale: 25 = somewhat painful, 50 = moderately painful, and 75 = very painful).<sup>37,38</sup> Pain ratings were displayed on a large poster in a line from 0 to 100. Latency to pain tolerance (when the hand was voluntarily withdrawn) was measured with a stopwatch in seconds. Heart rate and blood pressure were recorded using an automated digital device: heart rate every 15 s and blood pressure at baseline and at the point of hand withdrawal. Because the CPT may cause physical discomfort or psychological stress, participants were free to discontinue the task at any point.

### Data analysis

Demographic measures were compared between the GD and the control groups using one-way analysis of variance or equivalent non-parametric tests as indicated in the text. Kaplan–Meier curve analysis was used to explore whether the two groups differed in pain tolerance, that is, length of time before withdrawing their hand from cold water (Wilcoxon chi-square test). Kaplan–Meier analysis is ideal for use in situations whereby a period of time is monitored and times-to-event (in this case, withdrawal of the hand) differ between subjects, and cannot always be determined (i.e., here, when subjects reached the study time cap, and had still not withdrawn their hand).<sup>39</sup> Subjective pain ratings and cardiovascular parameters were analyzed using full-factorial mixed modeling (restricted maximum likelihood; effects of time, group, time  $\times$  group) with subject (nested by group) included as a random effect. Where any evidence of effects of group was found, potential relationships with participant age (all subjects), and with symptom severity in the GD group, were explored using Pearson's  $r$ . Statistical significance was defined as  $p < 0.05$  uncorrected. Statistical analyses were conducted using JMP Pro software.

### Results

The mean (SD) age in the GD and control groups, respectively, were 47.5 (13.6) and 31.4 (8.8) years, the GD group being significantly older ( $F = 16.92$ ,  $p < 0.001$ ). Groups did not differ significantly in terms of gender (GD: 7F, 7M; controls: 14F, 4M; likelihood ratio chi-square = 3.465,  $p = 0.063$ ). The mean PG-YBOCS and G-SAS scores for the GD participants were 20.6 (5.9) and 26.9 (10.7), respectively, which equates to an average moderate severity of symptoms. The mean age at onset for those with GD was 20.9 (6.4) years.

#### Cold Pressor Test

The key findings are summarized for convenience in Table 1 and are outlined in further detail below.

#### Pain tolerance

Kaplan–Meier analysis (Figure 1) indicated that the GD group withdrew their hand from the painful stimulus more readily than controls (Wilcoxon chi-square = 3.87,  $p = 0.049$ ). Survival time did not relate significantly to age across subjects ( $p = 0.2663$ ), nor to symptom severity (PG-YBOCS total scores) in the GD group ( $p = 0.371$ ), nor to Barratt impulsivity scores in the GD group ( $p = 0.13$ ).

**TABLE 1.** Summary of key findings of CPT challenge in gambling disorder subjects versus controls

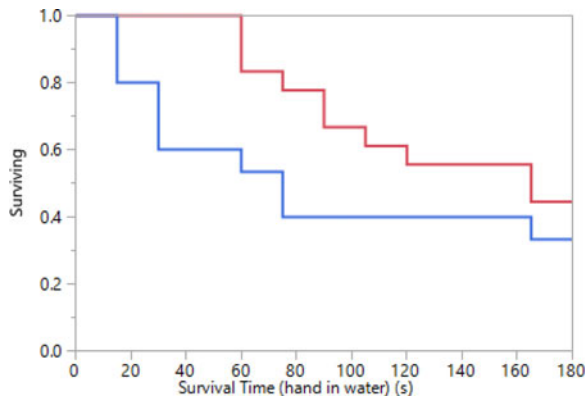
CPT-related measure	Description	Key finding
Pain tolerance	Kaplan–Meier analysis of time to hand withdrawal	Significantly earlier hand withdrawal in GD versus controls
Subjective pain ratings	Serial visual analogue assessment of subjective pain, analyzed using mixed model	No significant group differences (or group $\times$ time interactions)
Pulse rate	Serial pulse rate recordings, analyzed using mixed model	No significant group differences (or group $\times$ time interactions)
Blood pressure	Serial systolic and diastolic blood pressure recordings, analyzed using mixed model	No significant group differences (or group $\times$ time interactions)

#### Subjective pain ratings

Mixed modeling indicated that there was a significant effect of time on subjective pain ratings ( $F = 42.78$ ,  $p < 0.001$ ; see Figure 2). There was no significant effect of group ( $F < 0.01$ ,  $p > 0.99$ ), nor was there a significant group  $\times$  time interaction ( $F = 0.878$ ,  $p = 0.570$ ). The effect of time was mainly due to subjective pain ratings increasing between baseline and +15 s ( $t = 9.87$ ,  $p < 0.001$ ), then again between +15 and +30 s ( $t = 2.74$ ,  $p = 0.007$ ), whereas changes between other sequential time points were non-significant (all  $p > 0.10$ ) except for a significant increase between +45 and +60 s ( $t = 2.22$ ,  $p = 0.03$ ).

#### Cardiovascular parameters

For pulse rate (Figure 3), mixed modeling indicated a significant effect of time ( $F = 5.781$ ,  $p < 0.001$ ). There was no significant effect of group ( $F = 1.184$ ,  $p = 0.283$ ), nor was there a significant group  $\times$  time interaction ( $F = 1.117$ ,  $p = 0.347$ ). The main effect of time was mainly due to pulse increasing significantly from baseline to +15 s in the pooled sample ( $t = 6.08$ ,  $p < 0.001$ ), whereas other step-by-step changes over time were generally insignificant (all  $p > 0.10$ ). Mixed modeling indicated that there was a significant effect of time on systolic blood pressure ( $F = 10.03$ ,  $p < 0.001$ ; see Figure 4, top panel). There was no main effect of group ( $F = 0.285$ ,  $p = 0.600$ ), nor was there a significant group  $\times$  time interaction ( $F = 1.03$ ,  $p = 0.385$ ). Overall,



**FIGURE 1.** (Color online) Kaplan–Meier curve showing the proportion of subjects (Y-axis) keeping hand in cold water over time (X-axis). Top line (red in color version): controls; bottom line (blue in color version): gambling disorder.

systolic blood pressure increased significantly between baseline and 30 s of pain challenge ( $t = 2.70, p = 0.009$ ), then was similar to +30 s at hand withdrawal ( $t = 0.48, p = 0.636$ ), and then significantly reduced again after pain had resolved ( $t = -0.472, p < 0.001$ ). For diastolic blood pressure, there was a significant main effect of time ( $F = 21.36, p < 0.001$ ; see Figure 4, bottom panel). There was no significant main effect of group ( $F = 0.712, p = 0.402$ ), nor was there a significant group  $\times$  time interaction ( $F = 1.451, p = 0.234$ ). Overall, diastolic blood pressure increased significantly between baseline and 30 s of pain challenge ( $t = 5.96, p < 0.001$ ), then remained similar from 30 s through to hand withdrawal ( $t = -1.28, p = 0.203$ ), then decreased significantly again after pain had resolved ( $t = -5.38, p < 0.001$ ).

## Discussion

In this study, and contrary to our hypothesis, adults with GD failed to exhibit a different autonomic response to pain during the CPT compared with control participants. GD participants, however, pulled their hands out of the water quicker and thereby exhibited an inability to tolerate the CPT, as indicated by the Kaplan–Meier analysis. Taken together, these findings suggest that GD may be associated with greater difficulty to tolerate discomfort. This biological finding is in keeping with clinical observations that have reported stress as a trigger to gambling behavior in individuals with GD.<sup>21–25</sup> Gambling itself may serve a function of allowing the person to escape unpleasant or stressful events, ironically though resulting in possibly more stress due to the financial and personal problems associated with gambling. These findings may suggest a need to include stress-coping skill modules in the psychotherapy used in the treatment of GD.

These findings are also potentially interesting when seen in light of the pharmacological treatment for GD.

Opioid antagonists have generally produced positive results in GD and may even be considered as first-line pharmacotherapy for the disorder,<sup>39–43</sup> but many individuals fail to respond to opioid antagonists. Opioid receptors influence the sensation of pleasure and pain. Given their ability to block opioid receptors, opioid antagonists have been used to dampen painful stimuli. Studies examining the stress response in GD may thereby lay the groundwork for future studies to see if stress response could be a useful biomarker for subsequent treatment response to an opioid antagonist.

This study has several limitations. First, because a small sample was used, it is unclear how generalizable our results are to the larger population of individuals with GD. Second, groups differed by age; however, we found no evidence that age correlated with the cardinal measure of pain tolerance on the CPT; hence we feel it less likely contributed to the key finding. Third, we used a well-respected model of pain perception (the CPT), but other methods of assessing the response to painful stimuli could theoretically yield different results, such as if the model utilized a different pain modality. Despite these limitations, the study inclusion/exclusion was fairly broad, and the study used objective measures of both heart rate and blood pressure. Lastly, statistical power to detect more subtle differences between groups, or correlations between cold pressor measures and symptom severity in patients, might have been limited.

## Conclusion

Our results suggest that adults with GD may have decreased ability to cope with painful stimuli, as indexed by an objective pain challenge task (cold pressor). Future research should be directed at understanding the mechanisms of pain regulation in GD, and whether these mechanisms can be targeted with novel interventions to help patients reduce the frequency of gambling behavior. In light of these findings, it would also be interesting to examine whether baseline cold pressor measures are predictive of who does or does not experience symptomatic improvement following treatments, such as with opioid antagonists.

## Disclosures

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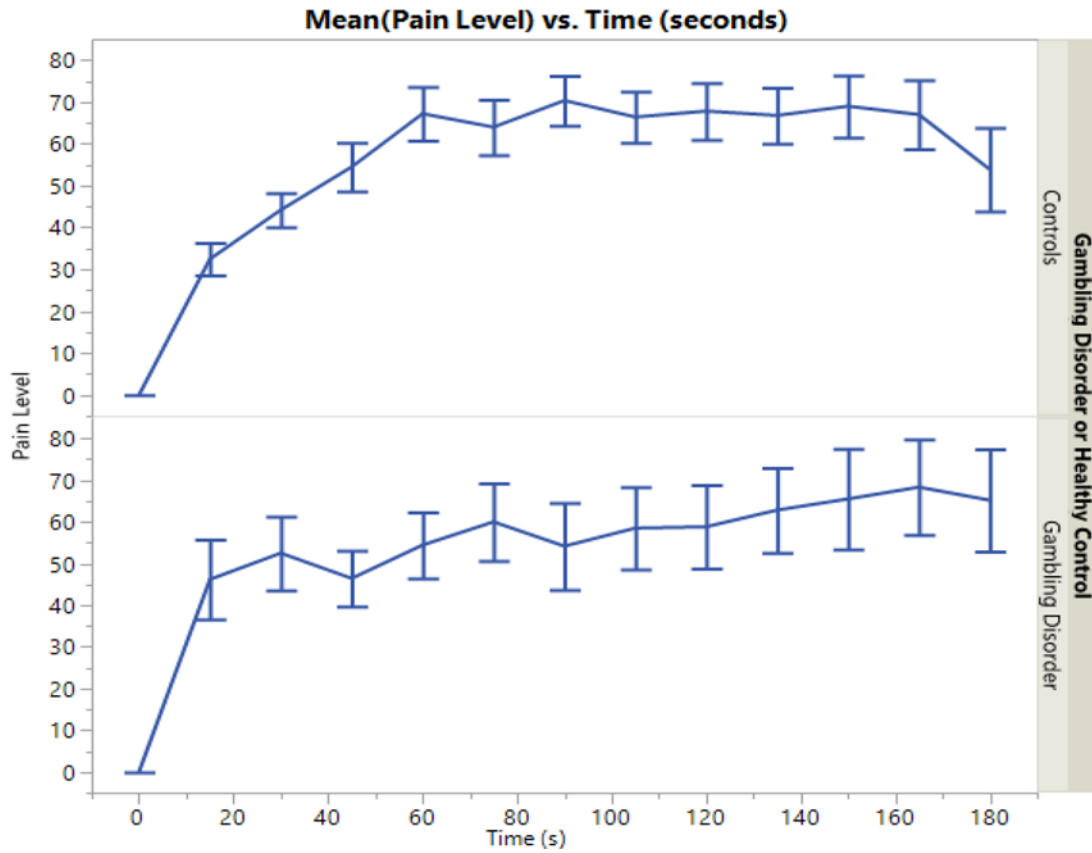


FIGURE 2. Mean (SEM) subjective pain ratings (range 0–100) over time in controls (top) and gambling disorder subjects (bottom).

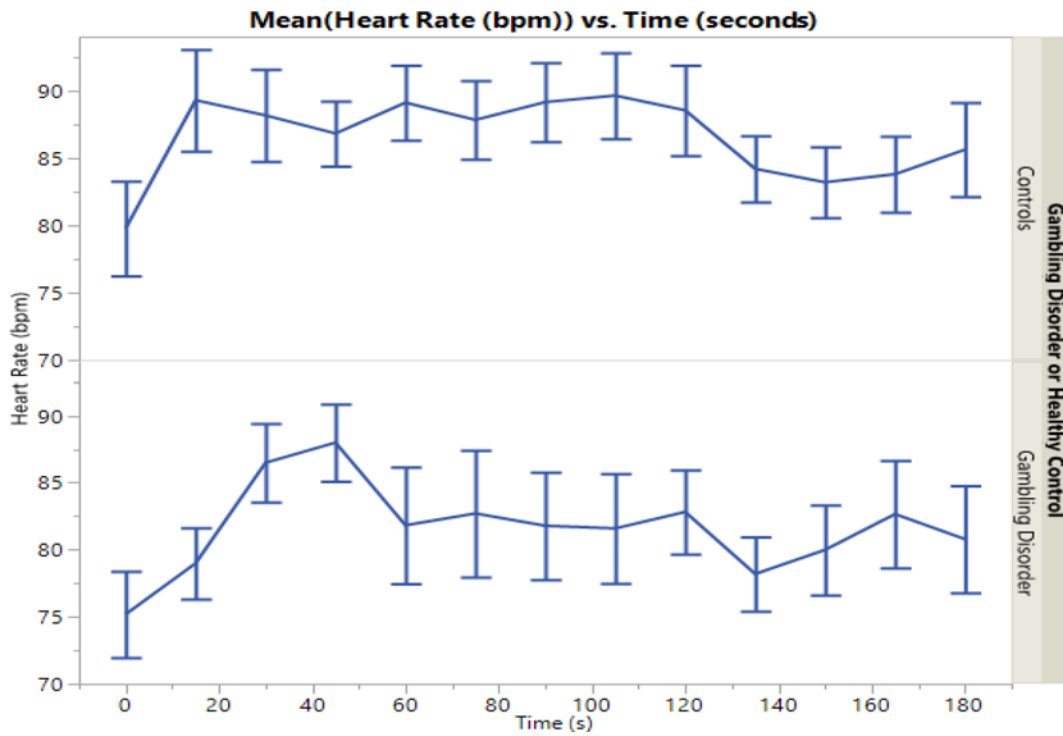
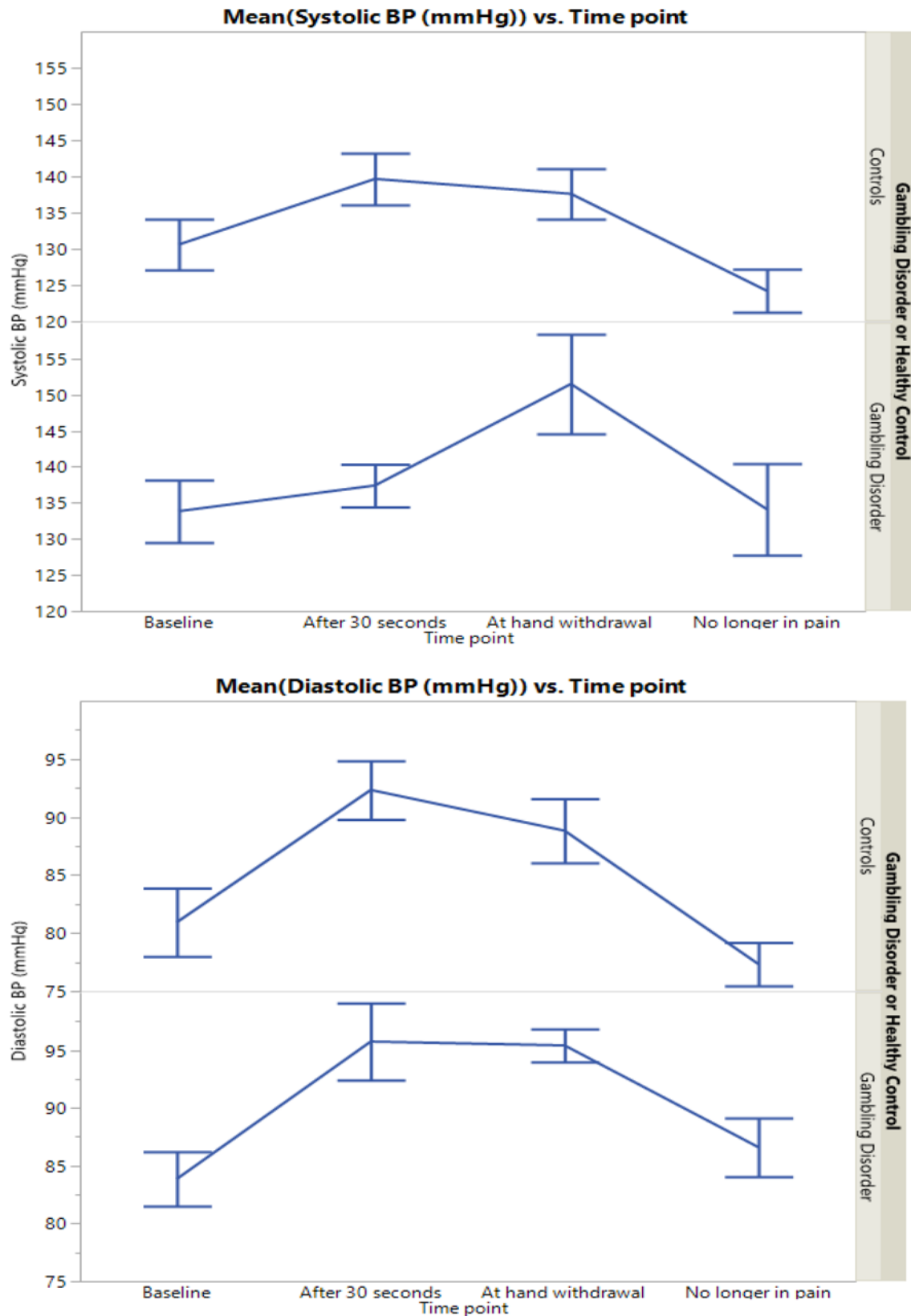


FIGURE 3. Mean (SEM) pulse rates (in beats per minute, bpm) at each recorded time point in controls (top graph) and gambling disorder subjects (bottom).



**FIGURE 4.** Top panel: Mean (SEM) systolic blood pressures at each recorded time point in controls (top) and gambling disorder subjects (bottom). Bottom panel: Mean (SEM) diastolic blood pressures at each recorded time point in controls (top) and gambling disorder subjects (bottom).

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