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Letter to the Editor

Heart rate and blood pressure responses to corticomotor stimulation in young, healthy adults

Single-pulse transcranial magnetic stimulation (sp-TMS) is used to measure cortical excitability (Chen et al., 2016). Serious adverse events of syncope have occurred with sp-TMS (Gillick et al., 2015; Keller-Ross et al., 2018). One such event is neurocardiogenic syncope (Gillick et al., 2015), which occurs from transient blood pressure (BP) changes in response to precipitating factors such as anxiety in combination with a mild noxious, novel stimulus (Grubb, 2005). Previous work investigating the effect of sp-TMS on cardiovascular function has demonstrated equivocal findings. For example, it has been demonstrated that sp-TMS does not alter heart rate (HR) and BP (Keller-Ross et al., 2018; Macefield et al., 1998), yet sympathetic inhibition has been reported, which could reduce BP. However, most prior reports were not designed primarily to measure direct influences of sp-TMS on BP. Thus, it is currently unclear whether sp-TMS reduces BP to subsequently result in neurocardiogenic syncope. The purpose of this study was to directly assess the influence of sp-TMS on BP in healthy adults. Based on previous findings, we hypothesized that sp-TMS would not directly reduce BP to precede neurocardiogenic syncope.

Twenty healthy adults (28 ± 8 yrs, 10 women) attended one experimental visit. Participants gave written, informed consent before participating. Exclusion criteria were pregnancy, taking cardiovascular or psychiatric medication(s), or a history of seizure or syncope. The protocol was approved by the University of Minnesota's Institutional Review Board and was performed in accordance with the Declaration of Helsinki.

Participants were semi-recumbent for the 120-minute experiment and rested for 5 min before commencing the study. HR was recorded using a 3-lead ECG (ADInstruments, Colorado Springs, CO) and beat-by-beat BP was measured using finger photoplethysmography (NIBP, ccNEXFIN, Edwards Lifesciences, Irvine, CI, n = 17, or Human NIBP, ADInstruments, n = 3) of the middle or annular finger on the non-dominant hand and was calibrated via manual brachial sphygmomanometer. These non-invasive blood pressure monitoring systems have previously been validated (Eeftinck Schattenkerk et al., 2009; Imholz et al., 1988).

Stimulation location was identified via resting motor threshold (RMT) determination. A 70 mm figure-of-eight TMS coil connected to a Magstim 200^2 stimulator (Magstim, Whitland, UK) delivered sp-TMS to the primary motor cortex (M1) guided by a neural navigation system (Brainsight, Montreal, QC, Canada). RMT was identified when sp-TMS elicited motor evoked potentials (MEPs) of ≥50 μV peak-to-peak from the first dorsal interosseous of the dominant hand, identified via the Edinburgh handedness inventory, in ≥3 of 5 stimulations (Chen et al., 2016).

To counter-balance this cross-over study, 10 participants received active sp-TMS (TMS_A) to M1 first while 10 received sham sp-TMS (TMS_S) first. During both sessions, 30 stimulations, each separated by 25 s, were delivered at 130% of RMT intensity. Stimulation was delivered 200 ms after R-wave occurrence (Macefield et al., 1998). During TMS_S, the same coil used during TMS_A was oriented 90° relative to RMT location. MEP absence during TMS_S confirmed that M1 was not stimulated. Primary outcome measures were systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP) and HR. A linear mixed model (SPSS, v22 or greater, IBM, Armonk, NY) assessed whether TMS_A vs. TMS_S (condition effect) influenced HR or BP during the beat-by-beat cardiovascular response (20 heartbeats, cardiac beat effect) following each stimulation. Data is reported as average ± SD.

Increases in BP above baseline were observed in SBP, DBP and MAP during specific cardiac beats (SBP: 4th-8th, DBP: 3rd-5th, and MAP: 4th-7th, $p < 0.05$) following either TMS_S or TMS_A (cardiac beat effect, $p < 0.001$; Fig. 1**A–C**). Increases above baseline were greater during TMS_A for SBP, DBP, and MAP (condition effect, $p < 0.001$), but beat-by-beat responses were similar between conditions (condition*cardiac beat interaction, $p > 0.05$ for all). HR increased from baseline during beats 10 through 13 (cardiac beat effect, $p < 0.001$; Fig. 1**D**) similarly (condition*cardiac beat interaction, p = 0.30) following TMS_S and TMS_A (condition effect, $p = 0.15$).

A near-syncopal event occurred following RMT determination (initial exposure to sp-TMS) in one male. Notably, this was his first exposure to sp-TMS. Within 30 s following the final stimulation for RMT determination delivered at an intensity of 100% RMT, his MAP declined by 26 mmHg (Supplemental Fig. 1). A risk mitigation protocol was immediately initiated, which included reclining the participant, elevating his legs and arousal through conversation. The participant's MAP returned to baseline values approximately four minutes after the near-syncopal event and he completed the protocol with no further symptoms. Importantly, his MAP was comparable to group averages, respectively, throughout TMS_A (96 ± 1 vs. 90 ± 7 mmHg) and TMS_S (94 ± 1 vs. 91 ± 7 mmHg) with a similar response profile to the group average during TMS_A and TMS_S.

Important findings of this study include: 1) TMS_A and TMS_S increased HR and BP in a similar pattern, but was greater during TMS_A and 2) during initial TMS exposure, a near-syncopal event occurred in a male participant. Based on previous reports of syncope from sp-TMS (Gillick et al., 2015), it may appear that active sp-TMS

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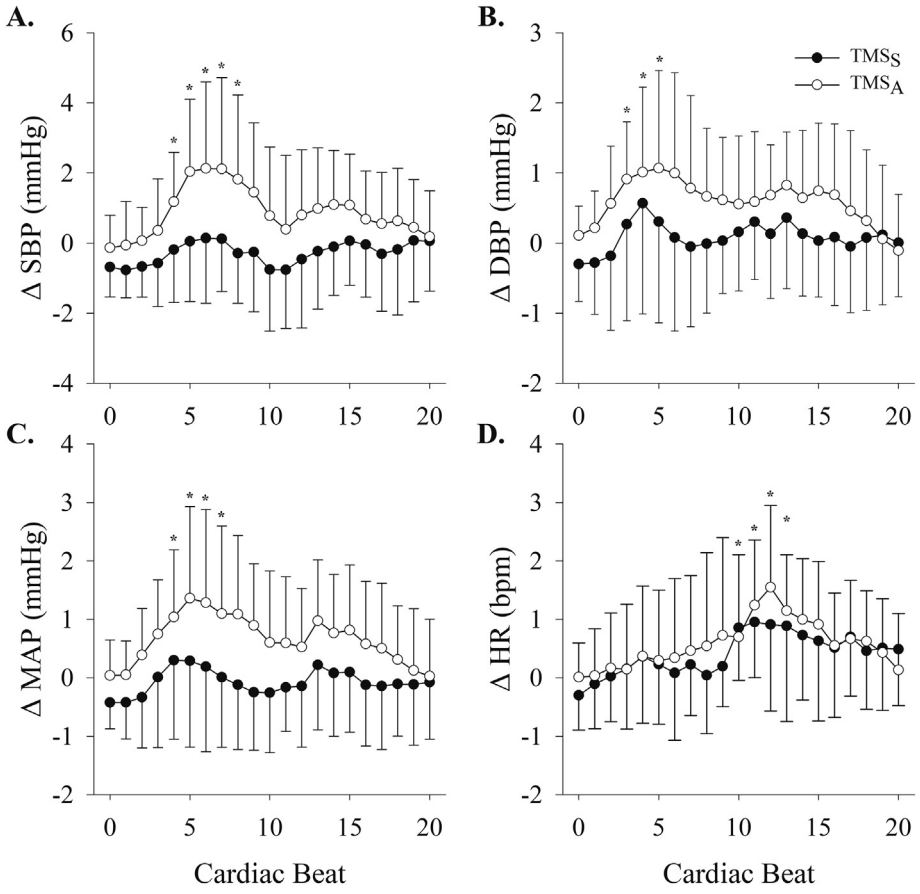

Fig. 1. Change (Δ) in cardiovascular variables from baseline (BL) following active single-pulse transcranial magnetic stimulation (TMS_A) or sham single-pulse transcranial magnetic stimulation (TMS_S) stimulation. Cardiovascular responses from BL to TMS_A and TMS_S of 20 healthy adults of (A) systolic blood pressure (SBP), (B) diastolic blood pressure (DBP), (C) mean arterial pressure (MAP), and (D) heart rate (HR). Reported beats are 0, the beat of stimulation, to beat 20 after stimulation. The change in SBP, DBP, and MAP during TMS_A were overall greater from baseline than TMS_S (condition effect, $p < 0.05$). $^*p < 0.05$ as compared to beat 0 during both TMS_A and TMS_S (cardiac beat effect).

decreases BP. The lack of reductions in BP and HR with sp-TMS in our study is consistent with our previous work in children with cerebral palsy (Keller-Ross et al., 2018). Although, sp-TMS has been shown to inhibit sympathetic activity (Macefield et al., 1998), which would likely decrease BP, Macefield et al. (1998) observed nonsignificant increases in diastolic BP. The similar increases in BP and HR during TMS_A and TMS_S indicates that the acoustic startle reflex may play a role in the cardiovascular response to sp-TMS (Macefield et al., 1998), suggesting an indirect effect of TMS. Further, greater increases in BP with TMS_A could be related to activating M1, directly influencing autonomic function through corticomotor stimulation (Basnayake et al., 2011). Further, although more invasive with direct stimulation of nerve axons, deep brain stimulation of several brain areas (including the cortex, diencephalon and brainstem), can restore autonomic function by either increasing or decreasing blood pressure in clinical populations (Hyam et al., 2012). Collectively, this suggests that brain stimulation (invasively or noninvasively) has the potential to modulate autonomic function.

We recently reported that sp-TMS caused a near-syncopal event in a child with cerebral palsy (Keller-Ross et al., 2018). In both the previous study and the current study, these individuals had relatively stable vitals during experimental sessions indicating that the near-syncopal event was not due to direct physiological responses to cortical stimulation. Although the novel stimulus was less likely the case in our previous report (Keller-Ross et al., 2018), it may be a likely cause in the current study as it occurred during initial TMS testing.

In conclusion, our findings suggest that both sham and active cortical stimulation caused increases in BP and HR within 20 cardiac beats of stimulation, which could be due to an acoustic startle reflex with the greater rise in BP during TMS_A related to direct M1 activation. Importantly, this study was performed in a nonclinical population of healthy, young adults, and extrapolation of our findings to patient populations should be made with caution. Additionally, stimulation was only delivered to M1; thus, sp-TMS to other cortical areas may cause differential cardiovascular responses. Regardless of the increases in BP and HR noted in this study, our studies and others have found that syncope remains a risk with sp-TMS. Thus, it is critical that individuals be monitored closely with a recommendation that BP and HR be measured and reported in future studies with the goal of mitigating risk of syncope during sp-TMS.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cnp.2021.06.004.

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