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Stability of the cardiovascular response during single-pulse TMS in perinatal stroke

To the Editor

Serious adverse events of syncope have been reported with single pulse transcranial magnetic stimulation (sp-TMS) in both healthy adults and adolescents post stroke [3,5,7–9]. Despite these reports, the physiological mechanisms leading to syncope during sp-TMS administration are not clearly understood. A syncopal event is classically identified by a sudden, large reduction in blood supply to neural tissue, cerebral hypoperfusion, to ultimately cause a loss of consciousness [2]. Common symptoms preceding syncope include lightheadedness, nausea, diaphoresis, and/or visual changes. Syncopal events may occur via an irregular autonomic nervous system (ANS) response to emotional or administered stimuli, which is commonly known as neurocardiogenic syncope [2,4]. Neurocardiogenic syncope can result from transient mean arterial pressure (MAP) and heart rate (HR) changes in response to precipitating factors such as anxiety in combination with a mildly noxious, novel stimulus [4]. Although literature is sparse, children with perinatal stroke appear to be at an additional increased risk for autonomic dysfunction [1] and autonomic immaturity in typically-developing pediatric populations increases the risk for neurocardiogenic syncope [4]. We aimed to determine if sp-TMS caused immediate cardiovascular changes in children and adolescents with congenital hemiparesis due to perinatal stroke.

Seven males (12 ± 4 yrs, average ± sd) and eight females (14 ± 5 yrs) completed an experimental session as part of a larger clinical trial (NCT002250092). A 70-mm-diameter Magstim figure-of-eight coil (Magstim, Whitland, U.K.) with a Magstim 200^2 unit delivered stimulation for sp-TMS assessment to determine resting motor threshold of the primary motor cortex (M1) ($59 \pm 13\%$ of maximum stimulator output, range: 35–75%). Continuous MAP (NIBP, AD Instruments, Colorado Springs, CO) and HR (3-lead electrocardiogram) were measured during pre-stimulation rest and throughout sp-TMS administration.

Average MAP ($p = 0.48$, Fig. 1A) and HR ($p = 0.10$, Fig. 1B) did not change from baseline during the initial five or last five pulses of sp-TMS. Analysis of the 6 s following each sp-TMS to M1 indicated that MAP increased during the initial five stimulations, ($p = 0.03$, Fig. 1C), but not during the final five stimulations ($p = 0.86$, Fig. 1D). HR increased during the 6 s following the initial five sp-TMS stimulations ($p = 0.01$, Fig. 1E) and final five stimulations ($p < 0.01$, Fig. 1F). Five of the fifteen participants had been previously exposed to sp-TMS; however, previous exposure did not influence MAP or HR responses ($p > 0.05$).

Adverse events were monitored during and following sp-TMS. There were two reports of headache and one report of dizziness immediately following sp-TMS, which resolved within one hour. The investigator determined that these reports of symptoms were possibly related to TMS. In addition, at completion of the study, one male, who was previously exposed to sp-TMS, reported sleepiness and experienced a near syncopal event. Because this was at the completion of his study, equipment used for continuous monitoring of MAP and HR had been removed. We therefore measured his blood pressure (BP) and HR manually during the event (BP: 80/50 mmHg; HR: 80 bpm). As a component of adverse event management, the study team reclined the participant, elevated his legs, and aroused the participant by engaging him in conversation. After ~3 minutes, his manual BP was 100/70 mmHg, and symptoms had resolved. Throughout sp-TMS administration, we observed minimal alterations in MAP or HR. In fact, he did not demonstrate a fluctuation of MAP greater than 10 mmHg from baseline and his average BP was 114/62 mmHg and HR was 75 bpm throughout sp-TMS testing. The medical monitor for this study reviewed all participant responses, including the responses from this participant, approved of the management, and declared no safety concerns or need for further medical management.

The findings from this study suggest that sp-TMS likely does not disrupt autonomic nervous system function to alter MAP and HR and increase risk of syncope in a pediatric cohort with perinatal stroke. There was an increase in both HR and MAP during the 6 s following each TMS stimuli, but as these changes were small, on average −1 to +3 bpm, the clinical relevance of this is unclear. The delivery of sp-TMS to M1 has the potential to alter the autonomic nervous system through connections to the anterior hypothalamus and the nucleus tractus solitarius of the pons/medulla [6]. Indeed, if sp-TMS directly altered autonomic function to cause syncope, we might expect large reductions in MAP and/or HR immediately following TMS pulses. The male participant who experienced a near syncopal event had stable MAP/HR throughout the duration of the sp-TMS testing. We therefore feel confident that sp-TMS did not directly influence his autonomic nervous system, altering MAP or HR to lead to his near syncopal event. As this participant was previously exposed to sp-TMS it lessens the likelihood of a novel stimulus/environment to be the cause of his symptoms. Therefore, the etiology of the near syncopal event in this participant is unclear. However, evidence suggests that autonomic immaturity may place adolescents at a greater risk for neurocardiogenic syncope and a sex difference in cerebral autoregulation may pose an additional risk for young males [10]. As such, two previously reported syncopal events with TMS were in male children with chronic stroke. Therefore, it is possible that the combination of being an adolescent post-stroke and male increased this

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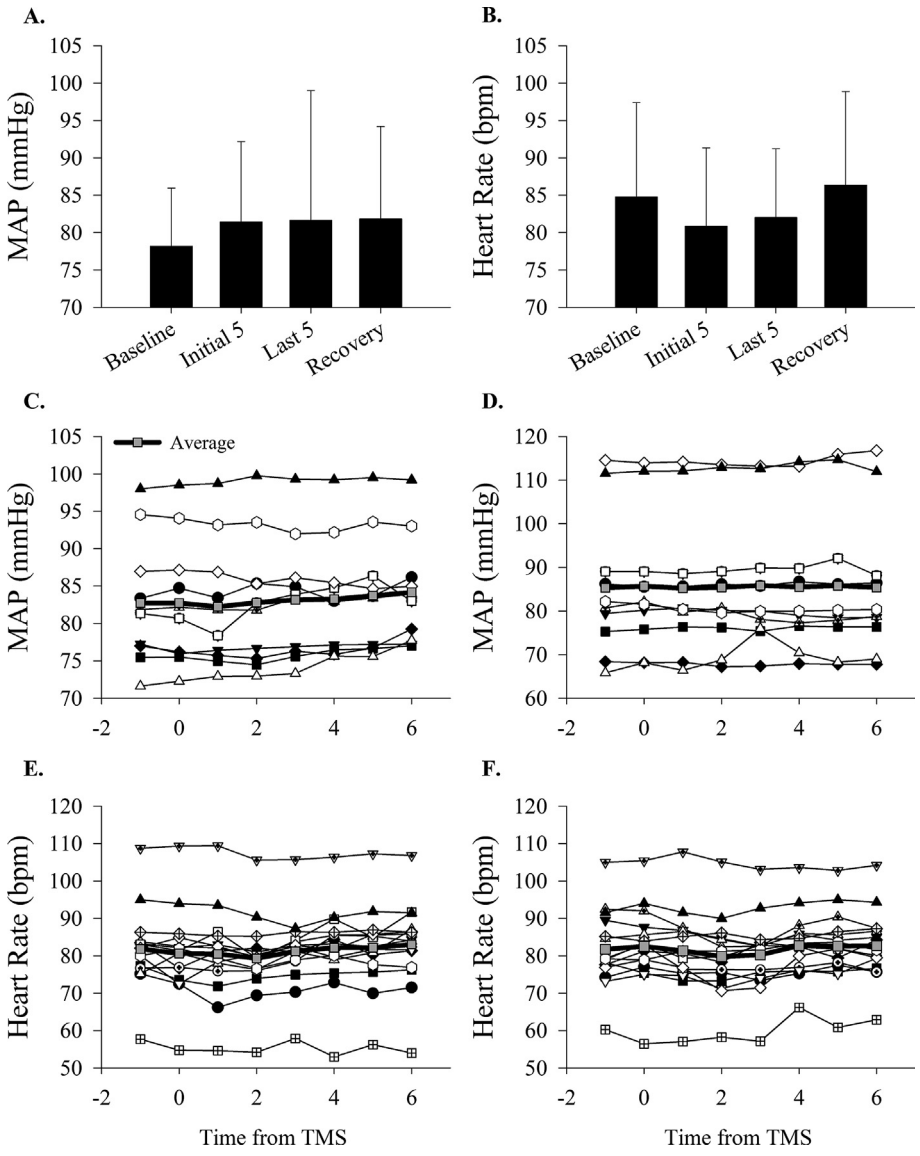

Fig. 1. Averaged mean arterial pressure (MAP) **(A)** and heart rate **(B)** during baseline, the initial five and last five stimulations of sp-TMS during RMT determination, and recovery. Second-by-second averages of MAP and heart rate during the initial (**C&E**, respectively) and last five stimulations (**D&F**, respectively). An average of second-by-second response is indicated by the grey symbols and all other symbols indicate individual responses to sp-TMS. Closed symbols indicate individuals that had previously been exposed to TMS (n = 5).

participant's risk for neurocardiogenic syncope leading to a near syncopal event.

In conclusion, results from this study indicate that MAP and HR were stable during sp-TMS administration in this cohort of children and adolescents with perinatal stroke. To ensure safety in participants during TMS administration, future studies should monitor and report cardiovascular responses.

Conflict of interest

There are no conflicts of interest to disclose.

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