1 **An instance of presyncope during magnetic stimulation of the median nerve, and**
2 **instances of presyncope and syncope during evaluation of resting motor**
3 **threshold with transcranial magnetic stimulation (TMS)**
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16 To maximise participant safety, Van Dam and Goldsworthy (2020) called for
17 greater reporting of adverse transcranial magnetic stimulation-related (TMS-related)
18 events (see also Vallence et al. 2020). We report the following magnetic stimulation-
19 related (MS-related) events that occurred at the Centre for Integrative Neuroscience
20 and Neurodynamics, University of Reading, Reading (UoR), and the School of
21 Psychology, University of Nottingham, Nottingham (UoN), both in the UK.

22

23 **1. Case reports**

24 **1.1. Participants 1 and 2**

25 The first participant, at UoR, was a healthy 21 year old man with a
26 transannular patch on their pulmonary heart valve (following complete repair of
27 Tetralogy of Fallot as a child), but no reported risk factors. On the day of the event,
28 the participant had no additional risk factors (change in sleep pattern, sleep
29 deprivation, change in medication, occult drug use, high doses of caffeine, etc) (Rossi
30 *et al.*, 2009). MS was presented with a Mag&More PowerMag Research 100
31 stimulator via a 100mm diameter, flat, figure eight coil. The setting was a research
32 lab. In this case we were stimulating the median nerve (MN, target) and the Extensor
33 Digitorum Communis muscle (EDC, as a control site). Coil orientation was with the
34 handle parallel to the long axis of the arm. A biphasic MS pulse, double pulse
35 stimulation with inter pulse interval of 50ms was used. In each trial of an experiment,
36 there were a total of 4 pulses, as follows: pulse 1 - 50ms - pulse 2 - approx. 3s - pulse
37 3 - 50ms - pulse 4. We had two blocks per MS site (target and control), each with 48
38 trials, with two intervals per trial, each with 2 MS pulses (total=192 pulses). Intensity
39 of the TMS pulse was set at 30% of machine output.

40

41 The event happened in the second block of MS over the MN. The participant
42 was comfortably sitting on a chair with his arm on the table. The participant was
43 sweating, and experienced dizziness. The session was therefore terminated and the
44 operator accompanied the participant out of the laboratory testing room and made him
45 lie down with legs raised. The presyncope self-terminated or stopped 30 minutes after
46 the intervention. LT and NPH were the investigators in this instance.

47

48 The second participant, at UoR, was a healthy 20 year old woman with no
49 reported risk factors. She was taking Microgynon 30 contraceptive medication. On the
50 day of the event, the participant had no additional risk factors. The setting was a
51 research lab. The event occurred during the participant's first session of a multi-
52 session experiment, whilst we were searching for the RMT using Rossini *et al.*'s
53 (1994) method. BrainSight 2.2.6 frameless stereotaxy (Rogue Research Inc.,
54 Montreal, QC) was used for neuronavigation. A 100mm diameter, flat, figure eight
55 coil was used, with output from a Powermag Research 100 stimulator. 125
56 monophasic pulses had been applied, up to approximately 75% of machine intensity.
57 The participant was sitting upright.

58

59 The participant stated that she felt faint, and stimulation was stopped. Shortly
60 after, she vomited. Following this, the participant was placed on the floor with legs
61 raised to prevent syncope. She recovered within 10 minutes and reported no further
62 illness (immediately following the event or later in the day). ATR and NPH were the
63 investigators in this instance.

64

65 The clinical diagnosis for Participant 1 and Participant 2 was MS-related
66 presyncope. The specific reasons for favouring this choice among the possible
67 differential diagnoses were that the participants did not completely lose consciousness
68 and muscle strength. In both instances, it was the first MS experience for the
69 participants. Additionally, the ambient temperature of the lab was above normal room
70 temperature (despite the use of a fan). We suspect that emotional components are
71 quite a strong factor in these effects, or at least are involved. Neither participant was
72 retreated with TMS. The events were reported to the University of Reading TMS
73 committee and relevant Health and Safety bodies.

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75 **1.2. Participant 3**

76 We also report an event that occurred at UoN. The participant was a healthy
77 20 year old woman with no reported risk factors. Whilst she reported previously
78 fainting several years ago after a blood test, it had not happened since, and she
79 expressed that she was happy to continue with the experiment. On the day of the
80 event, the participant had no additional risk factors. The setting was a research lab.
81 The event occurred during the participant's first session of a multi-session
82 experiment, whilst we were searching for the RMT using Rossini *et al.*'s (1994)
83 method. A 70mm diameter, flat, figure eight coil was used, with output from a
84 Magstim Rapid² stimulator. The participant was sitting upright.

85

86 Fewer than 100 biphasic pulses were applied. The participant stated that she
87 felt dizzy, and so we stopped stimulation. Shortly after she lost consciousness and

88 muscle strength, and an experimenter held her to prevent her from falling from the
89 chair. Consciousness returned after approximately 10 seconds. She was laid onto a
90 mat with her legs raised for 10 minutes. When asked later if she had felt anxious
91 about the experiment, she responded that she had not. ATR, SZ, and NPH were the
92 investigators in this instance.

93

94 The clinical diagnosis for this event was MS-related syncope. As in the other
95 cases reported above, it was the first MS experience for the participant, and we
96 suspect that emotional components were a factor. The participant was not retreated
97 with TMS. The event was reported to the University of Nottingham research ethics
98 committee and relevant Health and Safety bodies.

99

100 **2. Conclusion**

101 We present three cases of presyncope or syncope associated with MS, which
102 may have been related to emotional factors. In contrast to previous reports of MS-
103 related syncope and presyncope (e.g., Pellegrini *et al.*, 2019; Van Dam &
104 Goldsworthy, 2020), in Participant 1 we stimulated the MN rather than the brain. This
105 supports the notion that such effects may sometimes arise from participant
106 susceptibility to stress and anxiety, rather than from a direct influence of MS on the
107 cerebral cortex. Based on the number of individuals who have provided motor
108 thresholds during our research, (pre)syncope as a result of TMS may occur in as many
109 as 1 in 83 participants. We agree with recent suggestions that experimenters should
110 endeavour to report similar events, and that screening for stress and anxiety may help
111 reduce the risk of syncope (Van Dam & Goldsworthy, 2020).

Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

Acknowledgements

ATR and NPH were supported by the Economic and Social Research Council (ES/J500148/1). LT was supported by a Marie Curie Individual Fellowship (COFUND) grant, European Commission/Provincia Autonoma di Trento (nr. 40101908). The authors had sole responsibility for designing and performing the research and for reporting any findings.

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