

## Primary visual cortex excitability is not atypical in acquired synaesthesia



Synaesthesia is a condition wherein stimulation of one modality automatically and consistently triggers activation of a secondary concurrent experience in a separate modality [1]. Although it is typically viewed as a healthy neurodevelopmental condition with idiosyncratic inducer-concurrent associations that manifest in childhood, recent evidence suggests that synaesthesia-like experiences can be temporarily induced via consumption of recreational drugs, particularly serotonin receptor agonists (e.g., LSD, psilocybin) [2]. Nevertheless, whether such experiences constitute a genuine form of synaesthesia remains controversial since drug-induced synaesthetics do not meet behavioural diagnostic criteria for developmental synaesthesia [3].

One interpretation of these phenomenological-behavioural discrepancies is that drug-induced synaesthetics do not meet such criteria because inducer-concurrent associations must undergo a process of consolidation before they achieve the level of automaticity and consistency characteristic of developmental synaesthesia [4]. We recently reported evidence in support of this hypothesis with a case of acquired synaesthesia (LW) following use of the recreational partial serotonin receptor agonist 2,5-dimethoxy-4-bromophenethylamine (2C-B; [3]). LW has reported multiple forms of synaesthesia for over 9 years since ingesting 70–150mg of 2C-B, which is approximately 3–12 times the normal dosage [5]. Using standardized measures, we corroborated that one or more of LW's multiple forms of synaesthesia exhibited either consistency or automaticity, thereby meeting diagnostic criteria for this condition [1]. Despite these results, it remains unclear whether acquired synaesthesia shares overlapping neural mechanisms with developmental synaesthesia.

It was recently proposed that drug-induced synaesthesia results from serotonin cascades triggering elevated cortical excitability in layer V pyramidal neurons, resulting in anomalous perceptual states that are mapped onto inducers, yielding synaesthetic experiences [6]. This hypothesis is consistent with research showing selective hyperexcitability in primary visual cortex, as measured by transcranial magnetic stimulation (TMS) phosphene thresholds, but not motor (control) thresholds, in developmental synaesthesia [7] and after synaesthesia training in controls [8]. If cortical hyperexcitability plays a role in induced synaesthetics, individuals with acquired synaesthesia will display selectively lower phosphene thresholds similar to developmental synaesthetes. The present study sought to test this prediction in LW using a double-blind design and standardized TMS protocols.

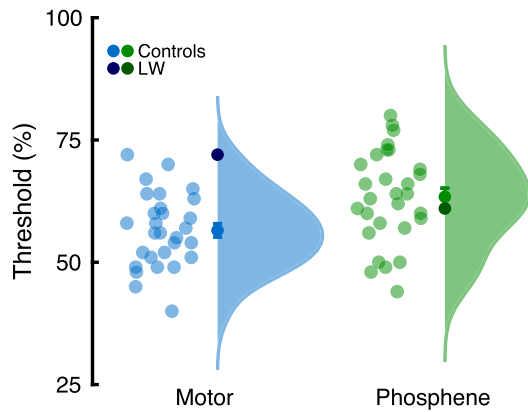
LW (31 years old, male) and 29 non-synaesthete controls (17 females, 12 males,  $M_{Age} = 25.32$ ,  $SD = 4.45$ ) provided informed

written consent to participate in this study in accordance with local ethical approval. LW did not significantly differ in age from controls,  $t = 1.25$ ,  $p = .11$ ,  $Z_{cc} = 1.28$  [0.83, 1.57] with a probability of occurrence in the general population of  $p_{gp} = 11\%$  [7, 21]. None of the participants displayed contraindications for non-invasive brain stimulation and there were no adverse events.

Phosphene and motor threshold estimation followed established TMS protocols [9,10] (see Supplementary Materials). After identification of suitable stimulation sites, single-pulse TMS was applied to left primary motor cortex (motor thresholds) and midline primary visual cortex (phosphene thresholds) in counter-balanced order. For motor threshold estimation, participants rested their right hand on a table, with their forefinger and thumb touching and attended to the interosseous muscle. After stimulation to primary motor cortex with the coil positioned at a 45° postero-lateral angle, they reported whether they observed a visible twitch of the interosseous muscle during the stimulation. For phosphene threshold estimation, participants were first dark-adjusted and then sat with their eyes open at a 1 m distance from a large, non-reflective black curtain (3 × 3 m). After each stimulation with the TMS handle and coil in the vertical position, participants reported whether they had experienced a phosphene. Stimulation intensity varied on a trial-by-trial basis according to individual participants' reports, as determined by a Bayesian adaptive staircase procedure with 30 trials run on each site in order to estimate 60% thresholds for both motor and phosphene thresholds [9].

As can be seen in Fig. 1, in contrast to our central prediction, LW did not display a significantly lower TMS phosphene threshold (61) than controls,  $M = 63.38$ ,  $SD = 9.49$ ,  $t = 0.25$ ,  $p = .60$ ,  $Z_{cc} = 0.25$  [0.13, 0.58], with a probability of occurrence in the general population of  $p_{gp} = 60\%$  [45, 72]. LW displayed a marginally higher motor threshold, 72 (corresponding to the highest threshold in controls), than controls,  $M = 56.52$ ,  $SD = 7.51$ ,  $t = 2.03$ ,  $p = .026$ ,  $Z_{cc} = 2.06$  [1.70, 2.41],  $p_{gp} = 3\%$  [1, 5], and a marginally greater threshold difference (motor-phosphene), 11, relative to the controls,  $-6.86$ ,  $SD = 10.28$ ,  $t = 1.71$ ,  $p = .049$ ,  $Z_{cc} = 1.74$  [1.37, 2.09] with a probability of occurrence of 5% [2, 9].

We tested the prediction that a case of acquired synaesthesia would be characterized by selective hyperexcitability in primary visual cortex, as observed in developmental synaesthesia [7] and induced synaesthesia [8]. In contrast with this prediction, we found that LW, an acquired synaesthete with previously-demonstrated inducer-concurrent automaticity and consistency [3], displayed typical TMS phosphene thresholds that were within 25% of a  $SD$  of the mean phosphene threshold in controls. We did observe a



**Fig. 1.** TMS motor and phosphene thresholds in controls and LW (acquired synaesthete). Error bars reflect standard error of the mean and marginal plots reflect kernel density plots.

tendency for LW to display marginally greater motor thresholds than controls, but this effect was unpredicted and should be interpreted with caution. These results suggest that LW does not exhibit primary visual cortex hyperexcitability and are at odds with the broader hypothesis of a role for cortical excitability in drug-induced synaesthesia [6]. One interpretation of these results is that atypical cortical hyperexcitability will only be observed in acquired synaesthesia further downstream in visual cortex, such as V4.

### Contributors

LL: study concept and design, analysis and interpretation of data, drafting/revising the manuscript. RS: study concept and design, data acquisition, revising the manuscript. DPL: study concept and design, data interpretation, revising the manuscript. DBT: study concept and design, analysis and interpretation of data, drafting/revising the manuscript.

### Compliance with ethical standards

The authors report no conflicts of interests.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2019.10.021>.

### References

- [1] Ward J. Synesthesia. *Annu Rev Psychol* 2013;64:49–75.
- [2] Luke D, Terhune DB. The induction of synaesthesia with chemical agents: a systematic review. *Front Psychol* 2013;4.
- [3] Yanakieva S, Luke PD, Jansari A, Terhune DB. Acquired synaesthesia following 2C-B use. *Psychopharmacology* 2019;236(7):2287–9.
- [4] Terhune DB, Luke DP, Kaelen M, Bolstridge M, Feilding A, Nutt D, et al. A placebo-controlled investigation of synaesthesia-like experiences under LSD. *Neuropsychologia* 2016;88:28–34.
- [5] Johnson MP, Mathis CA, Shulgin AT, Hoffman AJ, Nichols DE. [125I]-2-(2,5-dimethoxy-4-iodophenyl)aminoethane ([125I]-2C-I) as a label for the 5-HT<sub>2</sub> receptor in rat frontal cortex. *Pharmacol Biochem Behav* 1990;35(1):211–7.
- [6] Brogaard B. Serotonergic hyperactivity as a potential factor in developmental, Acquired and drug-induced synesthesia. *Front Hum Neurosci* 2013;7.
- [7] Terhune DB, Murray E, Near J, Stagg CJ, Cowey A, Cohen Kadosh R. Phosphene perception relates to visual cortex glutamate levels and covaries with atypical visuospatial awareness. *Cerebr Cortex* 2015;25(11):4341–50.
- [8] Rothen N, Schwartzman DJ, Bor D, Seth AK. Coordinated neural, behavioral, and phenomenological changes in perceptual plasticity through overtraining of synesthetic associations. *Neuropsychologia* 2018;111:151–62.
- [9] Abrahamyan A, Clifford CWG, Ruzzoli M, Phillips D, Arabzadeh E, Harris JA. Accurate and rapid estimation of phosphene thresholds (REPT). *PLoS One* 2011;6.
- [10] Badran BW, DeVries WH, Glusman CE, Willis A, Pridmore S, et al. Are EMG and visual observation comparable in determining resting motor threshold? A reexamination after twenty years. *Brain Stimulation* 2019;12(2):364–6.

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