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Prismatic adaptation therapy in visual neglect: the importance of connectional anatomy

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We read with great interest the recent meta-analysis published by (Székely et al., 2023) on prism adaptation (PA) therapy in neglect patients. At present, PA is listed as treatment to consider in the 2016 AHA guidelines for adult stroke rehabilitation (Winstein et al., 2016) and in the French guidelines for best practices in spatial neglect rehabilitation (<https://tinyurl.com/3w9axu62>) based on evaluations of existing non-pharmacological treatments. PA is of great interest to clinicians as it is non-invasive, bypasses the neglect patients' lack of awareness, and does not require extensive training. However, (Székely et al., 2023) concluded for a lack of beneficial effects of prism adaptation (PA) in neglect patients. The authors conducted two analyses, one using the conventional Behavioural Inattention Test (BIT) combined with cancellation task as the outcome measure, and the other employing the Catherine Bergego Scale (CBS) as the outcome measure. In comparison to previous meta-analyses, the authors included a greater number of studies, which led to a larger patient sample size. They achieved this by incorporating controlled trials irrespective of the randomization procedure. Furthermore, the authors employed statistical analysis models that considered the differences in baseline symptoms between treatment and control groups, yielding estimates of treatment effect sizes. The meta-analysis offers valuable methodological recommendations that are of great interest for future studies.

In this commentary, we would like to suggest that the effectiveness of PA in neglect patients may actually depend on the connectional anatomy of their lesion, in addition to other potential factors such as demographics, clinical characteristics, or delay post onset

(Scheffels et al., 2022). Regrettably, there have been only a limited number of studies that have analyzed the relationship between lesional patterns and PA outcomes, frequently with sample sizes of fewer than 20 patients. Most of these studies were not included in the (Székely et al., 2023) meta-analysis, because they were not randomized clinical trials, and did not include a sham group. Evidence indicates that patients with lesions in the parietal or occipital cortex were less likely to benefit from PA (Luauté et al., 2006; Saj et al., 2013; Sarri et al., 2008; Serino et al., 2006); in other studies, patients with frontal cortex damage were paradoxically better responders to PA than patients with more posterior damage (Chen et al., 2014; Goedert et al., 2020). However this latter finding was not supported by the study conducted by (Serino et al., 2006), which revealed a negative association between frontal lobe lesions and the extent of change in the BIT scores following PA. The observed discrepancies in these studies can, in part, be attributed to methodological and statistical factors. For instance, variations in neglect severity at baseline between responders and non-responders were not consistently equivalent (Chen et al., 2014; Luauté et al., 2006). Studies conducted during the subacute phase (<2 months) have problems in distinguishing potential effects of PA from spontaneous recovery (Chen et al., 2014). Furthermore, it can be challenging to draw conclusions from studies that involve an extremely small number of patients in experimental and control groups (<5) and have missing data during the follow-up period (Goedert et al., 2020).

However, neglect is not resulting from localized cortical dysfunction, but from dysfunction of large-scale fronto-parietal networks (Bartolomeo, 2021; Lunven and Bartolomeo, 2017), as well as from dysfunctional inter-hemispheric interactions (Bartolomeo, 2021; Kinsbourne, 1970; Lunven et al., 2015). Some of the discrepancies found in the cited studies might thus result from their focusing on cortical sites, rather than on large-scale networks connected by long-range white matter bundles. It thus makes sense to look for possible connectional predictors of neglect evolution in the white matter. For example, we showed in a longitudinal study of 45 right stroke patients that those with splenial inter-hemispheric disconnection continue to exhibit symptoms of neglect in the chronic phase (Lunven et al., 2015). More recently, we assessed in 14 chronic neglect patients the capacity to benefit from a single PA session. All patients had chronic, stable neglect signs and splenial callosal disconnection, consistent with our previous study. We found that patients with splenial disconnection but thicker cortex in the left temporo-

parietal regions and more robust anterior inter-hemispheric connections had a better response to PA, regardless of lesion volume (Lunven et al., 2019). Despite the lack of a sham group, we believe that the inclusion of chronic patients and the use of serial baseline assessments to assess the stability of neglect before the PA session minimized the potential bias of spontaneous recovery of neglect in our study.

The evolution of neglect may follow multiple potential trajectories, which can be either adaptative or maladaptive (Bartolomeo & Thiebaut de Schotten, 2016; Toba et al., 2017, 2020). In this context, PA can rebalance network activity within and across the hemispheres, by acting on the intact nodes of the damaged networks, on their homologs in the undamaged hemisphere, or both (Clarke and Crottaz-Herbette, 2016; Crottaz-Herbette et al., 2017; Saj et al., 2013). If so, then the integrity of white matter pathways between the hemispheres could be a crucial condition for PA to improve neglect signs. In patients with splenial disconnection and chronic left neglect (Lunven et al., 2015, 2014; Tomaiuolo et al., 2010; Umarova et al., 2016), PA might promote neglect compensation by exploiting sensorimotor/prefrontal circuits using more anterior sections of the corpus callosum (Lunven et al., 2019). Thus, the variability in the outcomes of clinical trials assessing the impact of PA on neglect may be due to varying lesional profiles and corresponding variations in the efficiency of the connectivity in the visuomotor circuits involved in PA, as well as differing patterns of interhemispheric communication.

Given the wide variety of clinical manifestations and lesion sites associated with neglect (Kaufmann et al., 2022; Moore et al., 2023; Toba et al., 2022, 2021, 2018), and its negative functional impact (Di Monaco et al., 2011), personalized rehabilitation approaches are desirable. Additional efforts are required to aid clinicians in deciding whether to use PA alone or in combination with other therapies, such as non-invasive brain stimulation (Nyffeler et al., 2019; Stengel et al., 2022; Valero-Cabré et al., 2020). To gain a deeper understanding of the mechanisms behind the effectiveness of PA, it is necessary to conduct research with larger patient series and to thoroughly examine the structural and functional profiles of brain connectivity.

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