Editorial for Special Issue on Neglect Rehabilitation

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Introduction

When the editorial team for this special issue on neglect rehabilitation first got together in early in 2019 the world was a different place. Great strides had been made in the treatment of stroke, largely due to refined thrombolysis and new thrombectomy protocols. Patients who received thrombolytic treatment within 4.5 hours after ischemic stroke onset could expect a favourable 3-month clinical outcome, and it had been shown that thrombolysis could predict absence of neglect independently (Kettunen, Nurmi, Koivisto, Dastidar, & Jehkonen, 2012). When COVID-19 hit in early 2020 it was first thought to affect the respiratory system, but early clinical reports soon linked it to an increased risk of stroke. In fact, the first international webinar on the impact of COVID-19 on Neurorehabilitative Care and Research, organized by the World Federation of Neurorehabilitation and held on the 26th of May 2020 (http://wfnr.co.uk/education-and-research/webinars/) was an attempt to quantify these findings. Since then the public and organisational interest and concern has been immense, and many charities and funding agencies have launched calls that aim to understand the potential causal links and mechanisms between COVID-19 and stroke (e.g., https://www.stroke.org.uk/research/our-funding-schemes/covid-19-and-stroke-grant). Even though there is no data on this yet, we can be fairly certain that the incidence of neglect will rise also as a result of COVID-19 and that current and foreseeable future social distancing guidelines will further impact on neglect rehabilitation approaches. This special issue is most timely and, even though conceived before COVID-19, will address this new context where appropriate.

Definition

Spatial neglect is a syndrome caused by damaged neural networks that are critical to spatial processing and attention control, and related cognitive and motor functions (Corbetta & Shulman, 2011; Mesulam, 1999). It typically presents as a failure in responding to stimuli presented in the contralesional side of space; a failure of initiating or completing movement in or toward the contralesional side of space; lack of reporting, manipulating, or producing information stored in the contralesional mental space; or a failure of keeping the gaze or body posture from deviating toward the ipsilesional side (Heilman, Watson, & Valenstein, 2012; Rode, Pagliari, Huchon, Rossetti, & Pisella, 2017; Salvato, Sedda, & Bottini, 2014). Unsurprisingly, the clinical impact is dramatic, with the presence of spatial neglect disrupting basic self-

care activities (e.g., dressing, grooming) (Azouvi et al., 1996; Chen, Hreha, Fortis, Goedert, & Barrett, 2012), impairing postural balance (Nijboer, Ten Brink, van der Stoep, & Visser-Meily, 2014; van Nes et al., 2009), interfering with reading ability (Boukrina, Chen, Budinoska, & Barrett, 2020; Galletta, Campanelli, Maul, & Barrett, 2014; Vallar, Burani, & Arduino, 2010), and impeding navigation such as avoiding furniture or walls when walking or using a wheelchair (Aravind & Lamontagne, 2014; Berti et al., 2002; Tromp, Dinkla, & Mulder, 1995). Spatial neglect also increases the risk of falls (Chen, Hreha, Kong, & Barrett, 2015) and body injuries (Wee & Hopman, 2008) and risks individuals being struck by vehicles when crossing the street (Kim et al., 2007; Navarro, Llorens, Noe, Ferri, & Alcaniz, 2013).

Diagnosis and Prevalence

Given that spatial neglect is not a unitary disorder, no single test can specifically or sensitively detect its presence nor measure its severity, and despite multiple standardised tests being available, at present there is no gold standard for neglect screening nor diagnosis. As a result, depending on the particular assessment methods, brain lesion locations and time post-stroke (Bowen, McKenna, & Tallis, 1999; Chen et al., 2012), its detection rate varies from 20% to 80% (Denes, Semenza, Stoppa, & Lis, 1982; Fullerton, McSherry, & Stout, 1986; Gainotti, Messerli, & Tissot, 1972; Kalra, Perez, Gupta, & Wittink, 1997; McGlone, Losier, & Black, 1997; Ringman, Saver, Woolson, Clarke, & Adams, 2004; Stone, Halligan, & Greenwood, 1993; Ten Brink, Verwer, Biesbroek, Visser-Meily, & Nijboer, 2017). On average, its prevalence is approximately 40% after right and 20% after left hemisphere stroke (Esposito, Shekhtman, & Chen, 2020), which is consistent with ***Yoshida et al.'s*** observations in a rehabilitation hospital setting as well as ***Evald et al.'s*** survey data (both this issue).

Yoshida et al. (this issue) refine our insight here as they screened medical records of inpatients retrospectively and performed multiple regression analysis in patients with both left and right hemisphere damage. The Behavioral Inattention Test (Halligan, Cockburn, & Wilson, 1991) was shown to be a significant independent variable for predicting rehabilitation outcomes in individuals with either right or left hemisphere stroke. Moreover, although in line with other studies (for reviews, see Beis et al., 2004; Bowen et al., 1999; Chen, Chen, et al., 2015), the authors observed a higher rate of neglect after right than after left hemisphere stroke (48.5% vs. 31.7%), the occurrence rate among people with left brain damage was clearly not negligible but instead frequent. This strongly suggests that every individual with stroke should be screened for spatial neglect. In fact, a promising new method of doing exactly this is the technology-enhanced platform developed by ***Cerrato et al.*** (this issue). These authors re-developed the classic baking tray task (Tham & Tegner, 1996), an ecologically valid assessment of spatial neglect, in which

patients are asked to distribute cubes equally across a board (and patients with left neglect typically make these placements more towards the right side of space). The traditional way of scoring this task is by assessing the configuration of the final placement of the cubes. However, a characteristic behaviour of neglect patients - starting tasks from the right side rather than the left - cannot be quantified using this standard measure. The new E-TAN platform represents a novel method of quantifying the sequence and timing of the cube placements using a convenient, fast, and relatively automated procedure while maintaining the ecological validity of the original task.

An important message regarding the diagnosis of neglect comes from the work of ***Evald et al.*** and ***Checketts et al.*** (this issue). The main objective of ***Evald et al.'s*** study was to describe current knowledge and practices in the assessment and treatment of spatial neglect among healthcare professionals in Denmark by conducting a nationwide internet survey. Similar to ***Checketts et al***., who led an international online survey spanning 33 countries, they found that occupational therapists, physiotherapists, and psychologists are more involved in neglect assessment than other professional disciplines. Both survey studies further reported, though, that rather than using a standardized assessment method or scale, clinicians most often relied on subjective observation to make the diagnosis of spatial neglect. In addition, the authors of both studies report great variations in the diagnostic approaches used across the different care disciplines, possibly reflecting the different understanding of the syndrome and its presentations. As a result, the researchers call for multi-disciplinary collaboration in clinical practice and improved research-to-practice translation to determine best practice for neglect diagnosis.

Multisensory and Auditory Rehabilitation

Regardless of the diagnostic methods used, it has long been documented that spatial neglect significantly impedes rehabilitation progress and slows functional recovery (Appelros, 2007; Buxbaum et al., 2004; Chen, Hreha, et al., 2015; Denes et al., 1982; Gillen, Tennen, & McKee, 2005; Jehkonen et al., 2000; Kalra et al., 1997; Nijboer, van de Port, Schepers, Post, & Visser-Meily, 2013; Paolucci, Antonucci, Grasso, & Pizzamiglio, 2001; Wee & Hopman, 2008) and stroke rehabilitation guidelines across the world all advocate that spatial neglect needs treatment (Bryer et al., 2010; Hacke et al., 2008; Hebert et al., 2016; Philippine Academy of Rehabilitation Medicine CPG Committee, 2011; Winstein et al., 2016).

Both ***Zigiotto et al.*** and ***Ladavas et al.*** (this issue) describe interesting multisensory approaches, successfully building on current evidence that indicates that, although spatial neglect may affect every sensory modality, jointly or separately, multisensory mechanisms devoted to the integrated coding of

spatial information may be preserved, thus providing a potential route for compensating modality-specific (visual) symptoms of neglect (Bolognini, Convento, Rossetti, & Merabet, 2013). In a prospective, randomized, single-blind study, ***Zigiotto et al.*** compared the effects of an intensive audio-visual multisensory stimulation (MS) to prism adaptation (PA), allocating twenty spatial neglect patients either to the MS or PA treatment group (two daily 20-min sessions over two weeks). The authors show very good feasibility, as well as MS effects comparable to the positive effects of PA, with neglect in the personal space improved only by MS and not PA. Using the same technique, and applying a comparable extent of training, ***Ladavas et al.*** found these effects to be stable at an average of 6.5 months post-training among the 53% of the participants who were available for follow-up. In a related approach, across 2 pilot studies, ***Schenke et al.*** (this issue) investigated the effects of dynamic auditory cueing on egocentric neglect. In Study 1, 15 intervention sessions were delivered over 3 weeks, with 11 early-acute patients listening to either music or audio books, delivered dynamically from the right to the left ear. This induced a reduction in neglect severity as indexed by line bisection performance at the end of the final therapy session compared to a historic control group. In Study 2, 8 patients received dynamic auditory cuing in combination with optokinetic stimulation (Kerkhoff et al., 2014; Kerkhoff, Keller, Ritter, & Marquardt, 2006) over 15 sessions. The number of left and central omissions was reduced post-intervention on a visual scanning test. These three studies all underpin the findings that although spatial neglect presents most dominantly in the visual domain, its treatment should not be restricted to a single (visual) modality.

Barrett et al. (this issue) review the behavioural and anatomical evidence for the presence of an aiming (motor-intentional) bias in patients with neglect, a deficit in the unaffected (right) arm that is characterised by a slowness or failure to initiate movements towards contralesional space. The authors also present preliminary data from a small trial in which bromocriptine (a dopaminergic medication) was administered in 10 patients with neglect, twice daily for 7 weeks. Although larger studies are now required, the results of this trial look promising, with bromocriptine selectively improving functional disability in patients with motor-intentional neglect, but not in those with perceptual-attentional deficits.

Complimentary to ***Barrett et al***., in a perplexing single-case exploratory study, ***Foncelle et al.*** (this issue) describe an atypical complex regional pain syndrome patient who presents *hyper*-attention to the affected left side. Using a longitudinal design (with repeated outcome testing before, during and after prism adaptation therapy) the authors report a significant pain decrease in this patient following therapy with the painful hand towards the opposite direction, to the pathological side. While these results will need to be replicated in a larger sample, this single-case study sheds light into the effects of prism

adaptation showing that response to treatment may be associated with a modification of spatial behaviour of the two hands.

transcranial Direct Current Stimulation (tDCS)

Olgiati and Malhotra (this issue) provide a most insightful, comprehensive and critical overview of the possible use of transcranial direct current stimulation (tDCS) for improving neglect and associated attentional deficits after right-hemisphere stroke. They argue convincingly that, at present, there are many unknowns in terms of how parameters such as current polarity, online vs off-line stimulation, state-dependency, dose and timing of the stimulation, number of sessions, blinding and extensive brain damage affect rehabilitation outcome. They then make important suggestions for improving the design of future clinical trials to measure tDCS efficacy.

Even if the perfect study design were to be achieved, ***Learmonth et al*.** (this issue) add an even more sobering note about feasibility. The authors found that despite a very large recruitment base and high referral rates (N = 288), only 8% of the patients (24 rather than the envisaged 60) could be randomized over a 29-month study period. The largest number of exclusions (n = 91/288; 34%) were due to medical comorbidities that prevented patients from undergoing 10 intervention or control sessions. As a result, no meaningful secondary outcome measures in terms of neglect recovery could be collected for their 4-arm PROBE design. ***Oligati and Malhotra*** further highlight that apart from ***Learmonth et al.***, other studies that report feasibility (unfortunately most neglect tDCS studies do not report feasibility), also note this to be poor (Ladavas et al., 2015; Smit et al., 2015). Altogether this suggests that tDCS may not yet be a realistic tool to be integrated in spatial neglect care and rehabilitation.

Virtual and multi-context interventions, return to work

On a much more positive note though, new treatment approaches continue to be developed, and most relevant for the current, and almost certainly also the post-COVID 19 period, ***Morse et al.*** (this issue) report the first phase of a treatment approach leveraging virtual reality (VR) technology and tele-rehabilitation. Patients with spatial neglect trialed a home-based self-initiated treatment program, and the authors further conducted focus group discussions and in-person interviews with patients and family caregivers, assessing the usability/development of the VR equipment and surveying the user experience, as this is most important for future adherence and efficacy. The authors also collected qualitative and

quantitative information from clinicians for their acceptance of VR technology being used in treating such patients remotely. The results are encouraging and the study seems prescient, bearing in mind the current large focus on tele-rehabilitation as a central new topic of many neuropsychological workshops and conferences (e.g., OPSYRIS http://opsyris.org/, the British Neuropsychological Society https://www.the-bns.org/ and Gesellschaft fuer Neuropsychologie 2020 (https://www.gnp.de/aktuelles/jahrestagung-der-gnp) virtual meetings). A similarly enlightened approach is described in ***Toglia and Chen*** (this issue) who implemented a multi-context treatment approach aiming to remediate spatial neglect through supportive guidance and collaborative interaction between the patient and therapist, and thus facilitating self-awareness and control over the neglect symptoms. The results are encouraging as even after only a single training session the treatment group showed a reduced ipsilesional spatial bias (relative to a control group, although it did not improve detection overall) as well as improved self-awareness. In fact, ***Kerkhoff***'s study (this issue) enables us to finish with a most positive message never reported as yet: describing three individuals, all with extensive right hemisphere lesions and left-sided spatial neglect, Kerkhoff reports that, after a series of neglect and cognitive treatments, all of them managed to return to work successfully.

Concluding remarks

It is clear already that in current and future years more people will suffer from stroke, whether related to COVID-19 or not, and given its prevalence, many more people's lives will be affected by neglect. Here we hope to have contributed to its possible amelioration with highlights of the latest thinking on neglect diagnosis, prevalence and treatment.

We would also very much like to express our sincerest gratitude to all our contributors. They dealt with illness and/or family dependencies and were cut off from local infrastructure and/or web access, and it speaks for the great tenacity and resilience of researchers that not a single contributor dropped their contribution, and that all still responded positively and efficiently to the numerous communications and, at times, annoying quirks of the editorial process. Many, many thanks again all of you!

Monika, Gemma, Stephanie and Peggy

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