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faculty of behavioural and social sciences

Systematic Review on Treating Neglect with Prism Adaptation – The Relative Impact of Realignment and Recalibration

Marie Charline Lipinsky

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Department of Psychology
University of Groningen
Supervisor / Examiner: Prof. dr. Helmut Hildebrandt
Second reviewer: Prof. dr. Joost Heutink

Abstract

Prism Adaptation (PA) is a treatment procedure aiming at reducing unilateral visuo-spatial neglect. In recent years, research reported mixed results regarding the effectiveness of PA (Rousseaux et al., 2016; Turton et al., 2010; Qiu et al., 2021; Li et al., 2021). This systematic review investigated two cognitive processes that play a crucial role in adapting to prisms. First, realignment, which relies on an adjustment of egocentric reference frames (Redding & Wallace, 2006), and second, recalibration, which relies on strategic control to correct for errors (Redding et al., 2005). Effects of PA were classified as aftereffects (positions of pointings after PA) or treatment effects (performance on functional and visuospatial tests), yet since aftereffects are said to confirm adaptation to prisms (McIntosh et al., 2019), treatment effects were expected to only emerge when aftereffects were observed. This review proposed that aftereffects are dependent on the dosage of realignment, reflected by the number of pointings, whereas treatment effects are dependent on the dosage of recalibration, reflected by the number of sessions. Further, effects are hypothesized to be facilitated, or restricted by clinical and methodological factors. Literature was obtained from online databases, such as PsychINFO and PubMed and selected based on subject matters. Subsequently, suitable studies were analysed (*n*=29) and compared based on effect sizes and p-values and observed frequencies of significant results were calculated. Findings show that the facilitation of realignment predicts the emergence of aftereffects, while treatment effects cannot be explained by the increase of either process. Recalibration did have an impact on both types of effects, yet only when patients generally responded to PA, the number of sessions influenced outcomes. Effects are not solely attributable to dosages of either component, as neglect severity and duration, type of exposure, and spatial extent of pointing space moderate the effectiveness of PA.

Keywords: prism adaptation, neglect, realignment, recalibration, dosage

Introduction

Unilateral neglect is a neuropsychological disorder marked by an attentional deficit to respond, report, or orient to stimuli on the contralesional side (Karnath & Dieterich, 2006; Heilman et al., 2000). It emerges in 29% of patients following unilateral stroke, most prevalent after suffering brain damage to the right hemisphere (Esposito et al., 2020). Neglect is a very disabling visuospatial disorder, associated with functional impairment in activities of daily living (ADL; Kerkhoff & Schenk, 2012), and about a third of patients continues to experience symptoms until it manifests as a chronic condition (Karnath et al., 2011). One frequently applied form of treatment in neglect rehabilitation is prism adaptation training (PA; Rossetti et al., 1998). During PA, patients wear goggles with implemented prism glasses that displace the visual field in a rightward direction, usually by a shift of 10°, and patients are asked to repeatedly point to visually presented targets (Goedert et al., 2018). Due to the shift induced by wedged goggles, patients' pointing will result in a terminal error, which after repetitive trials, they will adapt to compensate for (Panico et al., 2020). After exposure to the prismatic displacement, a temporal aftereffect emerges where patients will now reach to the left of targets, showing the desired effect (Angeli et al., 2004).

A positive response to treatment can be observed in 50-75% of patients (Barrett et al., 2012), which suggests that PA is an efficacious procedure in treating neglect. However, recent meta-analyses question the effectiveness of PA in neglect amelioration (Qiu et al., 2021), and further the sustainability in the long-term (Li et al., 2021). In virtue of these inconsistencies within existing literature, this review aims at finding explanations for mixed results by investigating different treatment strategies and analyzing potential moderators by means of clinical and methodological characteristics that could impact the effectiveness of PA treatment.

PA training is known to involve at least two separate components while adapting to prisms, namely recalibration and realignment (Redding et al., 2005). When prism googles are donned, patients start to reach to targets and initially experience the direct effect, missing the target due to the spatial discrepancy between the felt limb and the seen target (Newport & Schenk, 2012). Subsequently, first, patients adapt through recalibration by strategically controlling their movements to compensate for errors (Redding et al., 2005). This strategy is implemented immediately, as soon as the error is detected (Panico et al., 2020). Second, following 30 and more continuous pointing movements towards stimuli, spatial realignment takes place (Newport & Schenk, 2012), where egocentric maps of reference frames are adjusted (Redding & Wallace, 2006).

Whether realignment or recalibration is the dominant process in fostering adaptation to prisms partially depends on the type of exposure, as visibility of the reaching movement can impact both processes (Petitet et al., 2018). In concurrent prism adaptation (CPA), patients rely on visual feedback as some, or all, of their movement is visible (Newport & Schenk, 2012). Thus, the discrepancy between visual and proprioceptive pointing becomes unconsciously reduced to realign the reaching movement (Redding & Wallace, 2006). In terminal prism adaptation (TPA), only the final part of the movement is visible, and patients must strategically calibrate their movement to reach to the target (Newport & Schenk, 2012). This method of exposure fosters a conscious correction (Rossetti et al., 1993), which is shown to lead to superior results in reducing neglect (Ladavas et al., 2001). Additionally, Saevarsson et al. (2009) argue that beneficial effects from PA can disappear through receiving feedback as the cognitive load increases, which in turn hinters patients from strategically controlling the adaption to prisms. These results suggest that applying TPA rather than CPA, thereby fostering recalibration, has a superior effect on neglect recovery.

In neglect therapy, typical experimental paradigms consist of three stages (Petitet et al., 2018). First, baseline assessments (pre-exposure) are carried out, second, the intervention (exposure) is applied, and final, a second assessment follows the end of treatment (post-exposure). Neglect amelioration is measured by means of aftereffects and treatment effects, comparing scores in the pre-exposure condition to post-exposure measurements. The strength of aftereffects is assessed by the spatial deviation of pointing movements with respect to the pointing position prior to the intervention (Fernandez-Ruiz & Diaz, 1999). Positions of reach are indicated by measurements such as straight-ahead pointing (SAP) or open-loop pointing (OLP). In SAP, patients are usually blindfolded and asked to point to their subjective straight-ahead, whereas in OLP, patients point to a visual target, also without visual access to their movement (Sarri et al., 2008).

Treatment effects are distinguished between measurements in neglect assessment, and functional assessment (ADL). Standard neglect tests include the Apples Cancellation Test (ACT; Bickerton et al., 2011) and the Behavioral Inattention Test (BIT; Halligan et al., 1989). The latter is composed of two subscales, namely the conventional subscale (BIT-C), which includes tasks such as Letter Cancellation and Line Bisection (LB), and the behavioral subscale (BIT-B), containing tasks such as telling and setting the time. Common scales assessing functional improvement include the Functional Independence Measure (FIM; Oczkowski & Barreca, 1993) and the Catherine Bergego Scale (CBS; Azouvi et al., 2003). It is suggested to include scales of both classifications since standard visuospatial tests are limited in presenting only partial information of the clinical picture, ignoring patients' abilities regarding aspects of daily living (Champod et al., 2018). Moreover, the BIT-B as well as the CBS reflected functional improvements after PA treatment, whereas different results have been reported on other questionnaires on ADL.

PA seems to be successful in facilitating functional improvement (Chen et al., 2014; Mizuno et al., 2011; Serino et al., 2009; Spaccavento et al., 2016), and various paper-and-pencil tests assessing visuospatial bias to the right have also shown beneficial effects on impairments after PA treatment (Farné et al., 2002; Ladavas et al., 2011; Rossetti et al., 1998; Serino et al., 2006, 2007, 2009). Furthermore, positive effects are shown to be reliable among a variety of tasks (Frassinetti et al., 2002). To inspect whether the prismatic shift is responsible for amelioration of deficits, the study by Serino et al. (2009) compared PA treatment with a placebo treatment. Patients in both groups showed recovery in neglect, yet, when patients were exposed to prisms, amelioration of symptoms was stronger (Serino et al., 2009). Contradicting to these findings, Qiu et al. (2021) argue against positive effects of PA, as their review concludes to find no difference in improvement between patients receiving PA treatment compared with placebo treatment, however, the applied statistical anlaysis relies on a very small sample size. The review by Newport and Schenk (2012) summarizes that on one hand, most studies that applied PA found beneficial effects after treatment, but on the other hand, some randomized controlled trail (RCT) studies failed to find positive effects overall (Nys et al., 2008; Rode et al., 2015; Rousseaux et al., 2006; Ten Brink et al., 2017; Turton et. Al., 2010). Although most findings argue that PA is an effective treatment in reducing neglect, there must be factors influencing neglect amelioration, as Chen et al. (2014) conclude that some groups of patients benefit from treatment, while others do not.

Dosage of Realignment and Recalibration

Previous research suggests that increased amounts of visual and motor interactions in PA treatment facilitate motor-based realignment, resulting in longer aftereffects (Fernandez-Ruiz & Diaz, 1999; Pochopien & Fahle, 2015), which argues for the notion that a higher frequency of pointing movements leads to superior effects. In contrast, it is hypothesized that through repeated donning and doffing of prism goggles, patients are forced to strategically calibrate for the visuo-motor discrepancy imposed by prism glasses (Scheffels et al., 2021), which advocates repetitive interruptions through taking off the goggles. With respect to this review, disruptions of adaptation can be conceptualized as taking off goggles within, or after one session, thus applying multiple consecutive sessions are also regarded as intermittent PA. A few years ago, Barrett et al. (2012) challenged researchers by stating that so far, no dose-response research had been conducted, which seems crucial in optimizing patients' rehabilitation, specifically considering the bigger picture of composing future therapeutic interventions.

Existing literature comparing the effects of different dosages of induced realignment suggest that a minimum of 50 pointing movements leads to an aftereffect and result in sizeable reductions in neglect (Luauté et al., 2006; McIntosh et al., 2002; Rossetti et al., 1998). Interestingly, the combination of 60 pointings and an additional CPA approach, leads to very large aftereffects (Farné et al., 2002; Gutierrez-Herrera et al., 2020; Sarri et al., 2011), arguing for an increased adaptation induced by spatial realignment. This is in accordance with the notion that more pointings increase the chance of truly adapting to prisms (Redding & Wallace, 2006). The most incisive argument advocating an increased number of pointing comes from a study by Serino et al. (2009), where measurements were also taken in intervals within prism exposure. Pointing errors decreased as the number of pointings increased when the first 30 pointings were compared to additional 30 pointings and these results were compared to measurements after the intervention, when a total of 90 pointings were completed.

Rather than relying on implicit processes (i.e., realignment), neglect rehabilitation may be improved by focusing on explicit processes (i.e., recalibration), since it was illustrated that increased strategic control, thus, increased recalibration by donning goggles twice instead of once, leads to constant accuracy in tests after two, instead of one, sessions (Gutierrez-Herrera et al., 2020) and a single session may lead to no improvements at all (Rousseaux et al., 2006). Nevertheless, in the past, studies with low dosage (one session only; Angeli et al., 2004; Rossetti et al., 1998) were compared with studies that implemented a higher dosage (five sessions per week; Turton et al., 2010; Mancuso et al., 2012) and no differences in improvements were found due to higher intensity of treatment (Ten Brink et al., 2017). However, the amount of studies listed was small and there are studies advocating against this claim (Frassinetti et al., 2002; Ladavas et al., 2011; Serino et al., 2007; Spaccavento et al., 2016; Vangkilde & Habekost, 2010). Furthermore, it has been argued across studies that over a period of two weeks, daily repetitive sessions of 15-20 minutes are the key to obtain a reduction in neglect (Barrett et al., 2012; Chen et al., 2014; Frassinetti et al., 2002), lasting for up to five weeks (Frassinetti et al., 2002), or even six months with 10 sessions (Serino et al., 2007). Goedert and colleagues (2015) argue however, that instead of 10 sessions, four to six sessions could be effective in decreasing neglect as well. Overall, a tendency suggesting repetitive PA sessions lead to better neglect recovery is observable, although significant treatment effects were also reported following a small amount of PA sessions (Champod et al., 2018).

Link Between Aftereffect and Treatment Effect

So far, it has been established that prism-induced aftereffects stem from slow-processing visual-motor realignment, and that a conscious correction by means of strategic recalibration is responsible for quickly reducing error during PA (Redding & Wallace, 2006). However, the link between emerging aftereffects and treatment effects is still to be inspected and may depend on various training aspects (Fernandez-Ruiz & Diaz, 1999). Aftereffects are the expected sensorimotor change following PA that confirms effective adaptation to prismatic displacement (McIntosh et al., 2019), measured immediately after PA. Although some effects may persist, those effects are limited to a sensorimotor response to pointing movements, whereas treatment effects are measures of general neglect amelioration reflected by visuospatial tests and functional performance. This implies that aftereffects must be evident, showing that adaptation was successful, and only then treatment effects are able to emerge.

Furthermore, previous research demonstrates that the emergence of aftereffects after PA and treatment effects may be stronger correlated than previously assumed (Farné et al., 2002). Additionally, patients who show improvements in cancellation tasks were found to exhibit larger aftereffects than patients who did not improve on these neglect assessments (Sarri et al., 2008). There is however much contradicting evidence, showing that aftereffects of individual patients do not necessarily reflect treatment effects (Dijkerman et al., 2003; Goedert et al., 2018; Ladavas et al., 2011; Serino et al., 2006) and may even be a bad predictor (Serino et al., 2007).

Long-Term Effects

PA demonstrates to not only be an effective treatment in reducing symptoms of neglect, but also imposing long-term amelioration (Frassinetti et al., 2002; Humphreys et al., 2006; Serino et al., 2006) even up to six months (Serino et al., 2007). Recent reviews however question the effectiveness of PA, as studies have shown that effects induced by prisms last only temporarily (Li et al., 2021; Nys et al., 2008). This is difficult to accept per se, since not many studies investigated longer-lasting effects. Moreover, studies that do include follow-up measurements vary in aspects such as temporal distance to the end of treatment (i.e., Farné et al., 2002; Rode et al., 2015). Nevertheless, it is of great importance to consider the persistence of treatment effects, so that therapies can be composed in ways that offers patients sustainable amelioration. Interestingly, Goedert et al. (2018) argue that effects after PA treatment may develop and strengthen over time, which is in accordance with findings by Fortis et al. (2010) where patients showed improvements in the first week that continued in the second week and became stable at follow-up measurements after three months. The question of intensity of treatment seems to play a role in long-term effects, since it is suggested that PA effects may only be stabilized by repetition (Serino et al., 2009), as error reduction seems to increase after multiple consecutive sessions. It has been argued that long-lasting improvements manifest after at least 10 sessions of PA treatment have been administered (Newport & Schenk, 2012). This is difficult to falsify since only a few studies that applied a single treatment session and included follow-up measurements exist, however present studies do show significant improvements after a single session, with improvements being present two hours after the intervention (Rossetti et al., 1998), lasting up to a day, nonetheless showing a significant reduction by one week (Farné et al., 2002). Although these are interesting results, there seems to be no clear consensus whether PA produces effects that cumulate with repetitions or if effects are maximized after a single session (Jacquin-Courtois et al., 2013).

Moderators

Apart from type of exposure, there are several forces within the environment and the individual that can influence the effectiveness of PA. Some patients respond better to treatment than others while others do not respond at all (Chen et al., 2014). These differences in findings are not entirely explained by different number of sessions, or pointings that are carried out during PA. Hence, some clinical and methodological characteristics seem to play a moderating role in the responsiveness to prisms that determine the overall course and success.

Clinical Characteristics

Severity of Neglect. Most standard neglect tests assess the severity of the disorder, distinguishing patients in suffering from mild, moderate, or severe neglect. Previous research established that patients affected by severe neglect do not appear to improve significantly in functional abilities compared to patients suffering from mild neglect (Mizuno et al., 2011). Additionally, severe neglect may hinder patients to guide eye movements towards targets on the neglected side (Chédru, Leblanc, & Lhermitte, 1973; Girotti, Casazza, Musico, & Avanzino, 1983; Walker & Findlay, 1996) and has shown to limit neglect recovery (Chen et al., 2014). In contrast, PA demonstrates to reduce neglect symptoms even in patients suffering from severe neglect (McIntosh et al., 2002). This is in accordance with the pioneering work by Rossetti et al. (1998), arguing that patients affected by severe neglect are able to adapt to prisms and strongly improve after PA, which is also evident two hours after the intervention. Thus, neglect severity may play a role in responsiveness to PA, however it does not seem to be the sole dominant factor. Moreover, it is difficult to measure effects based on neglect severity, since standardized cut-offs to appropriately categorize patients have yet to be established. These are available for the CBS, where predefined scores indicate cut-offs for respective classifications, but not for other assessment methods.

Duration of Neglect. Patients may also differ regarding the duration of illness since stroke-onset, which can be distinguished between the acute (within four weeks, Nys et al., 2008), sub-acute, or chronic (between one and three months, and more than three months, respectively, Mizuno et al., 2011) phase. While it was recently observed that patients in different phases show no differences in effects (Vaes et al., 2018), Luauté et al. (2006) concluded that shorter durations of neglect result in better adaptation to prisms. This can be ascribed to larger capacities for neuroplasticity, which are found in patients early after stroke, and are said to facilitate the rehabilitative process (Mizuno et al., 2011). Such findings imply that patients in the acute stage, rather than chronic patients, benefit from PA treatment. However, it may be difficult to attribute neglect amelioration in acute patients solely to PA effects, since spontaneous recovery takes place within the first weeks after the incident (Nys et al., 2008). Nevertheless, the notion that improvements following PA treatment are ascribed to spontaneous recovery entirely is confounded through significant improvements found in patients suffering from chronic neglect (Jacquin-Courtois et al., 2013). Although chronic neglect seems to be particularly difficult to rehabilitate (Robertson, 1999), sizeable reductions in neglect can indeed be attributed to adaptation to prisms in these patients who suffer several months from their deficits (Champod et al., 2018, McIntosh et al., 2002). Moreover, further research suggests that time-since-lesion-onset does not restrict the beneficial effects experienced after PA (Sarri et al., 2008). In virtue of these findings in recent years, further analysis is advisable.

Lesion Localization. There is consensus across literature that lesions in the parietal (and temporal) lobe restrict the effectiveness of PA (Goedert et al., 2018; Gossmann et al., 2013; Lunven et al., 2019; Rousseaux et al., 2006; Sarri et al., 2008; Striemer & Danckert, 2010), since adaptation is said to be mediated to a large extent by cerebellar and parietal areas (Newport & Schenk, 2012; Panico et al., 2020). Also, parietal networks are involved in both cognitive processes, realignment, and recalibration (Panico et al., 2020), which may explain the hampered effects of PA when respective areas are involved. Nevertheless, neglect recovery was evident in patients presenting with stroke in parietal lobes (Pisella et al., 2004), whereby functionality of the cerebellum was intact. In turn, damaged cerebellar areas, but intact parietal areas hindered adaptation to the displacement induced by prisms (Redding et al., 2006). This suggests that although parietal areas seem to be important in experiencing beneficial effects following PA, presentation of an intact cerebellum is even more crucial.

The study by Gossmann et al. (2013) adds to previous findings, as patients with intact parietal (and temporal) areas exhibited good neglect recovery. These patients rather had lesions in frontal and subcortical (basal ganglia) areas, which led to conclude that cortical impairments of the parietal-temporal-frontal network (dorsal pathway) restricts patients in adapting to PA, whereas impairments in frontal and subcortical lesions did not. Moreover, patients who present with lesions in frontal areas show better adaptation, thus, exhibit larger improvements in neglect rehabilitation with PA (Chen et al., 2014). In accordance with these findings is evidence that patients receiving PA with damage to frontal lobes showed larger functional improvement, suggesting that lesion localization in frontal areas moderates the beneficial effects induced by PA (Goedert et al., 2018).

Age. Stroke usually affects patients of advanced age; hence, existing literature focuses on generally older populations. Nonetheless, older patients seem to present with more severe forms of neglect (Chen et al., 2014), which however does not automatically assume stronger debilitation. Additionally, a study inspecting PA in healthy subjects found that older subjects perform worse on tasks than younger subjects, which may be a result of diminished motor control, commonly observed in older people (Fernandez-Ruiz et al., 2000). Despite age-related disturbances, older participants still achieved the same magnitude of adaptation compared to younger participants, they only took longer in adapting to prisms, which in turn lead to long-lasting aftereffects.

Methodological Characteristics

Visual Shift. Prism goggles commonly produce an optical shift of 10°, which can be observed among various studies. The review by Champod et al. (2018) raises the question of whether differences in the amount of optical shifts can impact the efficacy of PA. The notion is based on findings from a study that uses a visual shift of only 6°, and this study failed to find significant results (Turton et al., 2010). Additionally, the study by Fernandez-Ruiz and Diaz (1999) examined healthy participants to investigate differences of optical shifts. Their research implies that greater prism diopters result in larger movement displacements and more visuo-motor interactions are needed to correct for previous errors. Hence, with regard to this review, the amount of visual shift seems to be another potential moderator, as there may be a threshold of optical displacement that needs to be reached in order for PA to be effective.

Spatial Extent of Pointing Space. Performing saccades to the contralesional side is impaired in neglect patients, as they struggle to acknowledge a quarter of all targets that are presented within the neglected field (Girotti et al., 1983). Although Serino et al. (2006) found a positive correlation between saccade deviations and increased performance on tasks assessing visuospatial abilities following PA, another study concludes that PA does not lead to increased leftward saccades, which in turn did not influence improvement in neglect (Nys et al., 2008). One explanation for the failed recognition of targets, and differences in previous results may be the spatial extent targets are presented in. Previous studies vary in spatial space, although 42° seems to be most often used across years of research (Angeli et al., 2004; Fortis et al., 2010; Spaccavento et al., 2016; Gutierrez-Herrera et al., 2020). In clinical practice, patients may fail to respond to targets, which are presented too far to the left because of visuospatial deficits and a large angle of reach may be one responsible factor. As the study by Farné et al. (2002) shows different magnitudes in aftereffects depending on the position of targets, the extent of pointing space seems to require more attention, which was not previously inspected.

Current Study

So far, experimental studies focused on the effectiveness of PA itself but did not distinguish between dosages of treatment strategies in terms of pointings and sessions. The study by Scheffels et al. (2021) is the first RCT to inspect differences regarding amounts of realignment and recalibration by means of continuous and intermittent PA, and no systematic review has been conducted on comparing studies based on dosages. Finding evidence for lower dosages to produce as much or more beneficial effects makes frequent treatment more available and probabilistic (Goedert et al., 2015). Moreover, the effectiveness of PA has been studied extensively, but literature on effectiveness distinguished by strategies and based on statistical data has been lacking. Recent reviews ignore to analyze effects by means of statistical manners or were forced to rely on a very small sample size, since experimental studies rarely report statistics to calculate effect sizes. Nevertheless, a few studies allow doing so, whereas for the remaining studies p-values seem to be a suitable indicator to compare effects based on levels of significance. This has its downsides, yet comparisons based on statistical data seem necessary to suggest directions for future therapeutic sessions.

In this paper, I am interested in differences of dosages of treatment components and the consequential magnitude of effects following PA. To what extent strategic control, thus, recalibration indicated as the number of sessions are accountable in rehabilitation, and to what extent realignment, consequently, the number of pointings, and other moderating factors contribute to the effectiveness of PA is the central aspect of this review. If realignment is the crucial part of PA, I expect that an increased number of pointings result in larger effects. If, however, recalibration is the crucial process of PA, I expect an increased number of sessions to prompt larger effects. As I am interested in how both processes affect the effectiveness of PA, I hypothesize that first, the magnitude of aftereffects is dependent on the number of pointings, reflected by all effects established through measurements based on pointing movements. Second, I propose that the magnitude of treatment effects is dependent on the number of sessions within PA treatment, evidenced by visuospatial tests and functional assessment. Lastly, I will inspect the potential link between the emergence of aftereffects and treatment effects, and if effects are moderated by clinical and methodological factors. Thus, the following hypotheses will be tested:

1. An increased dosage of realignment (frequency of pointings), rather than recalibration (frequency of sessions), results in larger aftereffects.
2. An increased dosage of recalibration (frequency of sessions), rather than realignment (frequency of pointings), results in larger treatment effects.
3. Various clinical and methodological factors moderate the effectiveness of PA in different manners, thereby facilitating, or restricting the emergence of aftereffects and treatment effects.

Methods

Search Strategy and Study Selection

Literature was obtained by searching online databases, such as PsychINFO, PubMed and Google Scholar. Selected papers were empirical journal articles that contain the keywords ‘prism adaptation’ and ‘neglect’, and discuss subject matters, such as the amount and kind of exposure in PA treatment, which are crucial for statistical analyses. Additionally, papers that discuss clinical factors in the effectiveness of PA, such as severity or duration of neglect, lesion localizations, or age, or methodological factors such as the type of exposure, visual shift, or spatial extent of the pointing space, were also considered. Regarding types of studies, RCTs were preferred, but the inclusion of a control group was not required for the present review, as only active arms of studies were focused on in data analysis, and existing control groups were ignored. Case reports that fulfilled the abovementioned criteria were also appropriate for analysis.

Data Collection and Inclusion Criteria

Articles found on online databases were screened regarding patient and intervention characteristics. Included studies were compared based on intensity of treatment (i.e., duration and frequency of PA), considering moderating clinical factors. Additionally, another necessity was the inclusion of statistical analyses, preferably standard deviations and means, so effect sizes could be computed accordingly. Alternatively, effects by means of p-values were also accepted, as otherwise the number of included studies would have been too small. Effect sizes of aftereffects and treatment effects were calculated and contrasted under consideration of influencing variables.

Excluded were theoretical papers and reviews that do not contain original experimental data. Moreover, collected data stemmed from studies conducted with patients suffering from neglect, thus, studies that yield data from healthy controls were excluded from analysis. Additionally, studies that were missing statistical analyses, or that reported extraordinary statistical analyses or raw scores only, had to be excluded, as they could not be used for analytical comparisons. Finally, another reason for exclusion was the withholding of the absolute number of sessions, since the amount of recalibration could not be identified.

Participants

Eligible studies included patients with left visuospatial neglect, as determined by neuropsychological assessment measures. In order to examine differences in the severity and duration of neglect, patients with neglect in different stages of severity and chronicity were suitable for this review. Severity was expected to be divided categorically, from mild to moderate to severe, and ultimately relied on the phrasing of authors. Chronicity, denoted by the amount of time that has passed since the stroke occurred, was also expected to be categorized, but depended on the way authors reported this information. Patients were distinguished between illness in the acute phase, the sub-acute phase and the chronic phase. In terms of lesion localizations, variations in cortical and subcortical structures were of interest, to assess whether lesions in one area affected rehabilitation differently compared to lesions in other areas. Relevant were studies that explicitly discussed different lesion localizations as clinically impacting the effectiveness of PA, which again was reliant on the intention of authors in previous studies. Finally, age was another potential moderator, therefore inclusion of distinguishment between younger vs. older participants was preferred.

Interventions

Included studies were required to apply a PA procedure to achieve neglect amelioration. One central aspect was the dosage of realignment (frequency of pointing movements), to inspect whether the number of pointing movements in PA is crucial for neglect rehabilitation. The dosage of recalibration (amount of donning the goggles) was also of major interest, which was operationalised through the number of sessions, to investigate the effects of variations in the amount of strategic control.

Several methodological factors were investigated as potential moderators in the effectiveness of PA. While carrying out pointing movements, patients were obligated to wear wedged prism goggles that shifted the visual field by a certain amount. Differences in improvements were inspected on the grounds of different magnitudes of shifts of the prismatic displacement. Moreover, the selection of type of exposure was used as another indicator for potential differences of effects in PA treatment. First, a terminal feedback design was of interest to investigate the extent of recalibration used during exposure. Second, studies that used a concurrent feedback method were also legitimate, to inspect the impact of realignment during PA. Another important factor of interventions was the spatial extent of pointing movements. In practice, this may have large implications regarding the extent patients are able to reach, especially considering the left side of their body midline. Thus, the angle of reach seemed to be an important indicator and reporting of these was of importance, but not a necessity, for comparisons.

Outcomes

Outcomes that were used in studies included first, aftereffects measured by pointing errors pre- and post-intervention, and second, scores on at least one objective measure of either the extent of neglect, or a measure of ADL. Clinical scales were divided into two separate classifications, namely functional assessment (ADL) and neglect assessment, since they rely on different cognitive capacities, and therefore indicate different areas of deficits.

Also considered in analysis, was the time of measurement of the last assessment. Required was a post-intervention assessment to establish the amount of neglect amelioration by comparing scores on baseline assessments with final measurements, considering the temporal distance to the last intervention. Measurements directly after the final session of PA and assessments weeks or months later were of interest to assess differences in immediate outcomes and long-term effects of PA treatment. Studies that contain patients who had to drop out because of various reasons were included, nevertheless, reasons for not completing the treatment procedure were listed, to inspect whether certain components of interventions were responsible for a discontinuation of treatment.

Statistical Analysis

Effect sizes of aftereffects and treatment effects were calculated using Cohen's *d*, by dividing the mean difference of measurements by its pooled standard deviation. Adapted from Cohen (1988), effect sizes were considered small when values were exceeding 0.2, moderate when exceeding 0.5, and effects exceeding 0.8 were considered large. Unfortunately, the minority of studies offers data that can be calculated by these means, which is why p-values were also accepted as a measure to compare levels of significance. The significance level was set to $\alpha < 0.05$, and significance at $\alpha \leq 0.01$ and $\alpha \leq 0.001$ was also highlighted.

To compare effect sizes between studies, Forest Plots were created. Therefore, effects were split according to different outcome measures, and confidence intervals were calculated. If confidence intervals intersected at the midline, a non-significant effect was indicated, objecting the effectiveness of the intervention. In comparing effects indicated by p-values visually, tables were created for each outcome measure separately. To display results, studies were assigned to columns according to the number of pointing movements (≤60 vs. ≥80) and sessions (one vs. up to four vs. 10 or 20), and non-significant results were highlighted.

Regarding the impact of methodological characteristics, frequencies of significant results were calculated, to inspect whether non-significant results were due to respective factors, namely type of exposure and spatial extent of pointing space.

To inspect whether there is a link between the emergence of an aftereffect following PA and treatment effects on neglect rehabilitation, effects of both measurements were compared to another and between studies, under consideration of contributing factors. The availability of statistical data for analysis was unexpectedly limited, and many moderating factors may have an impact on effects observed between studies.

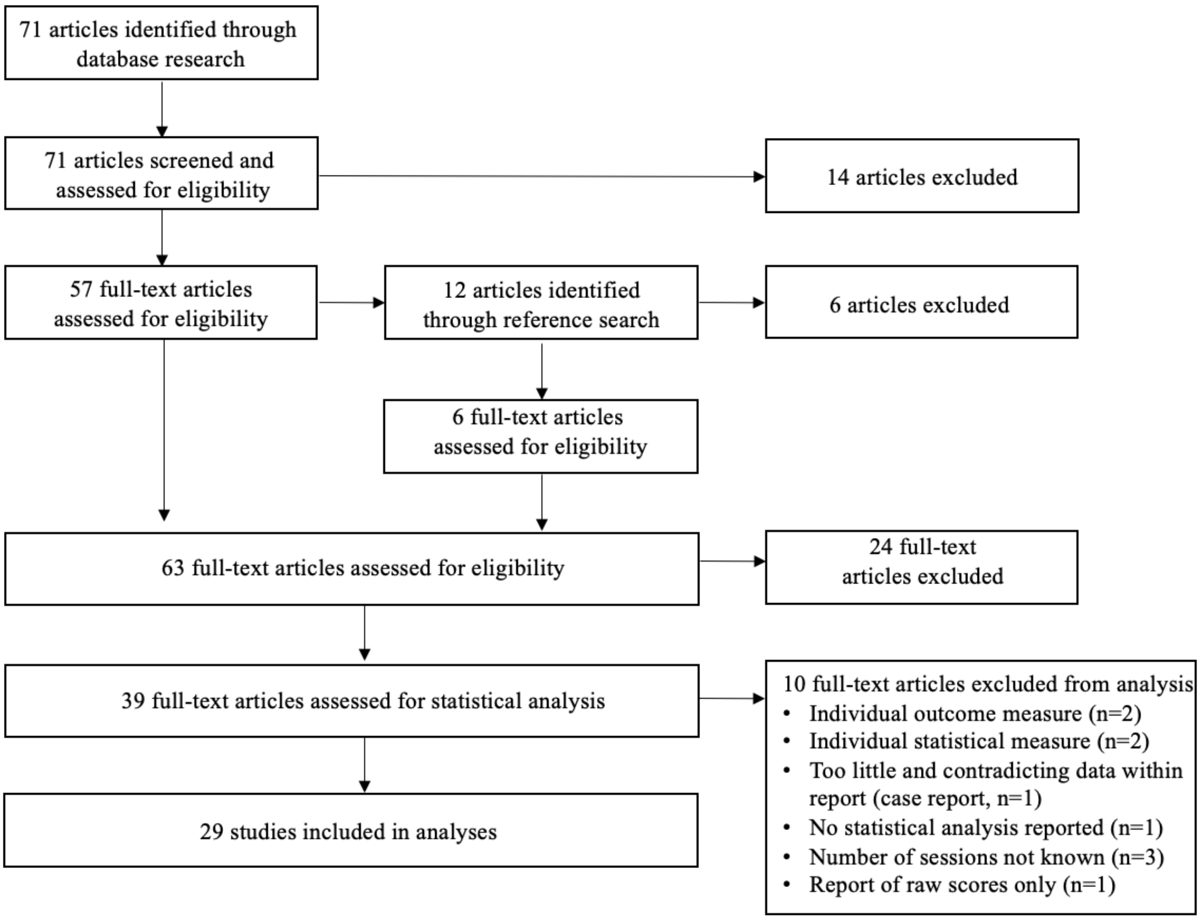
Results

Study Selection

A total of 71 articles had been found by searching through online databases, and 12 supplementary articles were added by screening reference lists of preliminary included articles. Of these 83 papers, 20 were excluded after reading the abstract, which resulted in a total of 63 papers that were full-text reviewed for eligibility. Subsequently, of the 39 eligible papers, 10 were excluded due to unsuitability for statistical analyses, which left 29 studies in total for analysis (Figure 1). Analysed studies were group studies, however, two case reports (McIntosh et al., 2002; Striemer & Danckert, 2010) were also appropriate for analysis.

Figure 1

Flowchart of the selection process of studies



Sample & Design

Appendix A contains all characteristics of included studies that were part of analysis.

Participant Characteristics

All studies included patients that suffered from lesions to the right hemisphere, resulting in left-sided neglect, except for one study that included patients, which presented with left-sided or right-sided neglect (Ten Brink et al., 2017). Severity of neglect varied between and within studies from mild to severe neglect. The duration of neglect since stroke-onset ranged from a few days (i.e., Nys et al., 2008) to an average of 40 months (Vangkilde & Habekost, 2010), therefore including patients with acute, sub-acute, as well as chronic neglect. In terms of lesion localization, all patients suffered damage to the right hemisphere, and some studies differentiated among frontal, temporal, occipital, parietal, and subcortical lesions. Due to limited depth in information of lesion localization within studies, this factor was excluded from further analysis. Across studies, sample sizes were relatively small, ranging from five (Luauté et al., 2007) to 34 (Ten Brink et al., 2017) participants (mean=13; excluding case reports). In total, data of 377 participants was inspected and the mean age of patients was 65 years (mean range=56-75), ranging from 23 years to 89 years of age among patients. Due to limited variation in information of age between studies, this factor was excluded from further analysis.

Intervention Characteristics

Included studies applied a PA procedure to decrease abnormal rightward bias by means of aftereffects and subsequently investigate the amount of neglect amelioration in terms of either or both, aftereffects, and treatment effects, considering long-term persistence. Between studies, the treatment consisted of different dosages of realignment (frequency of pointings) per session, as one study used approximately 33 movements (Gossmann et al., 2013), while in other studies patients performed up to 100 pointing movements per session. In terms of recalibration (frequency of donning goggles), studies were distinguished by one versus multiple treatment sessions. With a minimum of a single session and a maximum of 20 sessions, the number of donning goggles ranged from once (in a minimum of 50 pointing movements) to up to 20 times (in 1800 movements). In cases where treatment was applied 20 times, patients received PA across two weeks, thus, twice a day. However, one study extended treatment of 20 sessions over the course four weeks, applying PA once a day (Spaccavento et al., 2016). Yet, noteworthy, one other study carried out the PA procedure across four weeks (Rode et al., 2015) and another over the course of three weeks (McIntosh et al., 2002), although in these cases, PA was applied once a week only.

Patients were asked to carry out pointing movements while wearing wedged prism goggles that shifted the visual field by usually 10˚. In one study, a visual shift of only 6˚ (Turton et al., 2010) was used, while in others a bigger shift of 11.4˚ (Goedert et al., 2018), or 12˚ (Aimola et al., 2012; Chen et al., 2014; Mizuno et al., 2011, 2021) was used. Due to limited variation in information of visual shift between studies, this factor was excluded from further analysis. Regarding the type of exposure, two thirds of included studies used a terminal feedback design, where patients were obstructed to see their pointing movement and only the terminal error was visible. Remaining studies applied a concurrent feedback method and patients were able to see some, or all, of their movement. Another separate factor that varied between interventions was the spatial extent of pointing movements, depending on where targets were presented. The space ranged from a 10˚ angle of reach to up to a ~50˚ angle of reach, while a width of 42˚ was used mostly, where targets appeared 21˚ to the left, at the center, and 21˚ to the right of the patient's midline.

Outcome Characteristics

Most of the 29 eligible studies reported outcome measures of both, the aftereffect, and the treatment effect. One study reported solely aftereffects (Aimola et al., 2012) and 11 studies reported only treatment effects (Gossmann et al., 2013; Luauté et al., 2007; Lunven et al., 2019; McIntosh et al., 2002; Mizuno et al., 2011, 2021; Nys et al., 2008; Serino et al., 2007; Spaccavento et al., 2016; Ten Brink et al., 2017; Turton et al., 2010). Effects by means of effect sizes were compared between six studies, effects indicated as p-values between 23 studies. Generally, comparisons of effect sizes were preferred. However, when effects were indicated by both, effect sizes and p-values, and if p-values were more indicative regarding the goal of this review, they were chosen over effect sizes (i.e., Mizuno et al., 2011; Nys et al., 2008). Also, if effect sizes could be computed for one measure only (e.g., aftereffects), but at the same time, both measures (aftereffects and treatment effects) were indicated by p-values, the latter analysis was chosen to investigate the relation between the magnitude of the aftereffect and neglect amelioration (i.e., Gutierrez-Herrera et al., 2020; Ladavas et al., 2011).

Aftereffects were listed by 18 studies and usually measured by one of two measures, either by straight-ahead pointing or open-loop pointing. Common scales to assess functional assessment (ADL) were the CBS (n=7) and the FIM (n=5), reported among nine studies. Neglect assessment was reported in 23 studies, most often represented by either or both subscales of the BIT (n=13). Further similar outcome measures of neglect were ‘neglect tests’ (n=2), cancellation tasks (n=6), line bisection (n=6), ‘neglect dyslexia amelioration’ (n=1), and the ACT (n=1). All included studies assessed participants at baseline and after the intervention, whereof most studies took follow-up measurements directly after the treatment had ended. 17 studies carried out a later follow-up, ranging from a minimum of two hours after the intervention (McIntosh et al., 2002; Rossetti et al., 1998) to up to six months after the treatment (Goedert et al., 2018; Rode et al., 2015; Serino et al., 2007), to establish the extent of long-term effects of PA on neglect amelioration. Drop-outs were not common, as only 10 out of 29 studies were affected, whereof three studies were missing patients merely for follow-up measurements. In general, the availability of data was surprisingly rare and difficult to interpret, thus, it was challenging to compare between studies appropriately.

Statistical Analysis

Table 1 shows the quantity of significant aftereffects and treatment effects of included studies. (For more detail see *Appendix A*.)

Table 1

Observed frequencies of significant effects

Number of Sessions x Pointings	<10 x ≤60	<10 x ≥80	≥10 x ≤60	≥10 x ≥80
Observed Frequencies (*n* total studies)				
Aftereffects (*n*=18)	100% (5)	100% (5)	50% (2)	67% (6)
Treatment effects (*n*=27)	100% (7)	50% (6)	50% (2)	75% (12)

Note. Table favors intervention

Aftereffects

All studies that were compared based on effect sizes (*n*=5) showed significant improvements across frequencies of pointings and sessions after PA treatment (Table 2). Intergroup comparisons indicated increasing effect sizes as number of pointings increased (*Appendix B),* thus, we found support for the first hypothesis. When keeping the number of sessions and time interval after the final intervention constant and varying the number of pointings on the smallest level, we found evidence for a larger aftereffect when patients carried out 80 pointing movements (Sarri et al., 2008: *d*=1.16, 95% CI [0.33, 1.99]) instead of 60 movements (Sarri et al., 2011: *d*=0.86, 95% CI [0.06, 1.66]). The effect increases by a larger amount as movements were added, and even more when prism goggles are additionally donned multiple times through increasing the number of repeated interventions across several days (Aimola et al., 2012: *d*=2.17, 95% CI [1.12, 3.22]). This is confirmed by an intragroup comparison, as Fortis et al. (2010) measured aftereffects twice, after one session (*d*=0.84, 95% CI [-0.07, 1.75]) and again after the tenth session (*d*=1.93, 95% CI [0.87, 2.99]), which extends the supported argument of the first hypothesis.

Table 2

Observed frequencies of significant aftereffects measured immediately after PA as indicated by effect sizes

Number of Sessions x Pointings	1 x 60	1 x 80	10 x 90
Observed Frequencies (*n* measures)	100% (1)	100% (1)	100% (3)

Note. Table favors intervention; significant aftereffects were found across all dosages of recalibration and realignment

P-values of the remaining studies (*n*=13) were also in favour of PA, since most studies found significant effects (Table 3). Based on the quantity of significant effects, significance was rather found when the number of pointings and sessions was held low. However, focusing on *levels* of significance in immediate measurements, the biggest effect was found when the dosage of treatment components was maximized, through executing 90 pointings in each of the 20 sessions, spread over two weeks (Frassinetti et al., 2002; $p<0.0001$) and overall, effects increased in significance with increasing number of sessions (*Appendix B)*, which showed partial evidence in favor of my hypothesis. Nevertheless, studies with lower dosages also found significance at the 0.05 up to the 0.001 level, whereas some were carried out under deviating circumstances. Furthermore, when multiple sessions are incorporated, a difference was found in the length of intervals that lies between individual sessions. One study applied only two sessions of PA, however, they were assigned over the course of four days, and a significant effect was found (Gutierrez-Herrera et al., 2020; $p=0.002$). Comparable was the study by Rode et al. (2015), which found an effect of $p<0.05$ after applying four sessions of PA, spread over the course of four weeks, thus, patients received treatment only once a week, which seemed to be less efficient.

Table 3

Observed frequencies of significant aftereffects measured immediately after PA as indicated by p-values

Number of Sessions x Pointings	<10 x ≤60	<10 x ≥80	≥10 x ≤60	≥10 x ≥80
Observed Frequencies (*n* measures)	100% (5)	100% (3)	50% (2)	50% (4)

Note. Table favors intervention; aftereffects favor low dosage of realignment and recalibration

Treatment Effects

Functional Assessment (ADL). Unfortunately, there is not much to conclude based on the effects of PA on ADL, neither when comparing studies based on effect sizes (*n*=2; Table 4), nor when evaluating studies based on p-values (*n*=7; Table 5), as the availability of data on functional assessments is rare across studies. Regarding effect sizes, the FIM seemed to be an insensitive measure, as Fortis et al. (2010) found effect sizes close to 0 in all consecutive follow-up measurements (*d*=-0.14, 95% CI [-1.02, 0.74]; *d*=-0.3, 95% CI [-1.17, 0.57]; *d*=-0.18, 95% CI [-1.14, 0.78]), similar to measurements on the CBS (*Appendix C*). In the study by Fortis et al. (2010), improvements on the CBS were observable, however, only the assessment one week after the final intervention was found to be significant (*d*=-1.12, 95% CI [-1.92, -0.32]). Nevertheless, assessments immediately after PA (*d*=-0.66, 95% CI [-1.51, 0.19]) and the late follow-up (*d*=-0.57, 95% CI [-1.52, 0.38]) showed moderate effects. Despite the apparent unsuitability of ADL measures, intergroup comparisons indicated a significant effect when the dosage of sessions was increased above a certain threshold, showing support for my second hypothesis. The number of pointing movements was equal in both studies, yet Spaccavento et al. (2016) extended their treatment of 20 sessions over the course of four weeks, whereas Fortis et al (2010) applied PA treatment 10 times within one week, twice a day. Effect sizes in Spaccavento et al. (2016) were significant in both measures (FIM: *d*=-1.63, 95% CI [-2.35, -0.91]; CBS: *d*=1.29, 95% CI [0.33, 2.25]). Results are in favor of the intervention, and significance was rather found when the number of sessions was increased.

Table 4

Observed frequencies of significant treatment effects in ADL measured immediately after PA as indicated by effect sizes

Number of Sessions x Pointings	10 x 90	20 x 90
Observed Frequencies (*n* measures)	50% (2)	100% (2)

Note. Table favors intervention; treatment effects in ADL favour higher dosage of recalibration

Table 5

Observed frequencies of significant treatment effects in ADL measured immediately after PA as indicated by p-values

Number of Sessions x Pointings	$<10 \times \leq 60$	$<10 \times \geq 80$	$\geq 10 \times \geq 80$
Observed Frequencies (*n* measures)	0% (1)	0% (1)	20% (5)

Note. Table does not favor intervention

Nonetheless, most studies indicating effects by p-values failed to find a significant interaction between the treatment sessions and groups ($p>0.05$), independent of the number of pointings and sessions (Mizuno et al., 2011, 2021; Ten Brink et al., 2017; Turton et al., 2010; Rode et al., 2015; Gossmann et al., 2013). Thus, I did not find evidence for the second hypothesis based on p-values. The only study that did find a significant interaction was the experiment by Chen et al. (2014, $p=0.01$), measured four weeks after the intervention (*Appendix C*). They used a procedure that included 60 pointing movements in each of the 10 sessions, and significant effects may be due to other moderating factors, which will be discussed later. Most importantly, the interaction that was found does not distinguish between PA vs. control treatment, as both groups received PA. However, this study focused on the differences of lesion localizations, specifically, frontal vs. non-frontal lesions. (For more detail see significance table in *Appendix C*.)

Neglect Assessment. Measurements on neglect rehabilitation that were indicated by effect sizes did not show the expected improvements (Table 6). Although patients did improve to some extent, effect sizes of studies (*n*=4) were not significant, as most effects were close to 0 (*Appendix D*). Especially in the study by Fortis et al. (2010), the Line Bisection task did not show meaningful effects immediately after PA (*d*=-0.1, 95% CI [-0.98, 0.78]) or a week later at follow-up (*d*=0.09, 95% CI [-0.79, 0.97]). However, this may have been due to components of the study itself since intergroup comparisons showed that patients in the study of Sarri et al. (2011) did improve by a significant amount (*d*=1.12, 95% CI [0.22, 2.02]). Nevertheless, these findings contradict my second hypothesis, as the study by Sarri et al., (2011) included one of the smallest dosages of treatment, having only one treatment session.

Table 6

Observed frequencies of significant treatment effects in neglect measured immediately after PA as indicated by effect sizes

Number of Sessions x Pointings	1 x 60	10 x 90	20 x 90
Observed Frequencies (*n* measures)	100% (1)	50% (2)	0% (1)

Note. Table does not favor intervention

Contrary to findings from effect sizes, p-values display significant effects of improvement in neglect amelioration across studies (*n*=19) between six different measures (Table 7). Studies that included a smaller number of sessions were more successful than studies that included more sessions, whereas the different numbers of pointings did not have an impact. Therefore, I did not find evidence to support my second hypothesis. Some studies chose highest dosages of treatment, where patients took part in 10 or 20 sessions and carried out 90 pointing movements per session. Two of those studies did not reach significance (Mizuno et al., 2011; Turton et al., 2010) in the immediate measurement after the final treatment (p>0.05), whereas two of the remaining measurements were even significant at the p<0.001 level (Frassinetti et al., 2002; Serino et al., 2007) and continued on that level at follow-up assessments (*Appendix D*). Across studies and conditions, significant and non-significant effects were found, and *levels* of significance tended to increase with increasing numbers of sessions, however, this did not pertain to all studies. Direct comparisons of studies with similar amounts of sessions found that the number of pointing movements did not have a major impact. On one hand, McIntosh et al. (2002) used an experimental design where patients were assigned to PA three times, carrying out 50 movements, and effects were significant (p<0.001). On the other hand, Rode et al. (2015) and Nys et al. (2008) incorporated 80 and 100 pointings, respectively, within 4 sessions each and effects did not reach significance (p>0.05). Concluding, the number of pointings was not determining, as expected, and separate clinical or methodological factors may moderate the effectiveness of PA to a bigger extent than anticipated.

Table 7

Observed frequencies of significant treatment effects in neglect measured immediately after PA as indicated by p-values

Number of Sessions x Pointings	<10 x ≤60	<10 x ≥80	≥10 x ≤60	≥10 x ≥80
Observed Frequencies (*n* measures)	89% (9)	57% (7)	0% (1)	60% (5)

Note. Table favors intervention; treatment effects favor neither low nor high dosage of realignment, and favor low dosage of recalibration

Clinical and Methodological Factors (Moderators)

Several factors appeared to moderate the effectiveness of PA in rehabilitation by facilitating or hindering adaptation, as differences of effects between studies were not always explained by the number of pointing movements, or sessions (for more detail see *Appendix A*). This shows support for my third hypothesis, and four out of seven moderators were analysed in detail (data of the remaining three factors had to be excluded from further analysis).

Severity of Neglect. Patients in the study by Goedert et al. (2018) all suffered from mild or moderate neglect. Although results found a significant aftereffect (p=0.001), no interaction between session and groups was detected (*p*>0.05). The study by Gossmann et al. (2013) included patients with severe neglect, showing improvements in the ACT (*p*=0.041), which also remained significant at follow-up (*p*<0.006). Contradicting, one intragroup comparison (Mizuno et al., 2011) showed a significant interaction when patients with mild neglect were treated (*p*<0.01) but these effects did not hold for patients with severe neglect (*p*>0.05).

Duration of Neglect. Most studies include chronic patients (59%) and all respective studies showed significant effects in patients for at least one, if not both, of aftereffects and treatment effects. Sub-acute patients were also present across studies (37%), and mixed results were found for these patients. Studies on acute neglect were rare (15%), as only one study exclusively investigated patients with an illness duration of a maximum of four weeks (Nys et al., 2008) whereof most effects found failed to reach significance (*p*>0.05). Additionally, a few other studies were assumed to contain patients in the acute, as well as the sub-acute phase. Moreover, studies inspecting sub-acute neglect only, did not find significant effects (*p*>0.05; Mizuno et al., 2011, 2021; Rode et al., 2015; Ten Brink et al., 2017).

Type of Exposure: Terminal vs. Concurrent Exposure. Intergroup comparisons showed no major differences in improvement with respect to the type of exposure. For most studies that applied TPA, results showed significant aftereffects (67%), and treatment effects (70%) with respect to neglect amelioration and functional improvement. Nonetheless, these were also found for studies using the concurrent exposure method (aftereffects: 90%, treatment effects: 54%). One intragroup comparison was conducted by Ladavas et al., (2011) and findings showed significant treatment effects for a terminal exposure approach (*p*<0.0001). Nevertheless, effects for PA with a concurrent exposure were also significant (*p*<0.001). Direct comparisons for post-intervention measurements showed larger improvement for TPA than CPA (*p*<0.01), however, regarding aftereffects, no difference between both modalities were found.

Spatial Extent of Pointing Space. Intergroup comparisons showed significant improvements in aftereffects (100%) and neglect amelioration (57%) when a spatial extent of 10˚ or 20˚ was used, however, in some measurements no significant effects were found. Most studies that presented targets in a pointing space of >20˚ also found significant results in aftereffects (70%) and treatment effects (63%), but some analyses failed to reach significance in other studies.

Discussion

The aim of this review was to investigate the effectiveness of PA in neglect rehabilitation by inspecting dosages of realignment and recalibration. Realignment may be dependent on the number of visuomotor interactions, thus, pointings, as well as the approach of a concurrent exposure to PA. By contrast, recalibration may be dependent on the number of donning the prism goggles, operationalized through number of sessions, as well as the approach of a terminal exposure to PA. This implies that both processes may be dependent on frequencies of treatment components, and the type of exposure being used. Recently, a trend has been observed to increase the frequency of pointing movements and the number of sessions, however, negative results are still reported (Mizuno et al., 2011, 2021; Turton et al., 2010). This review suggests that if realignment was more important, therapy units employing higher numbers of pointing movements resulted in superior effects. However, if recalibration was more essential in adapting to prisms, studies using repeated sessions showed larger effects. Consequently, dosages of realignment and recalibration regarding deviating number of pointings and sessions, respectively, were discussed first. Nevertheless, besides the type of exposure, further factors may impact the effective extent of PA training (Fernandez-Ruiz & Diaz, 1999), which were considered as potential moderators and subsequently discussed.

Aftereffects

Beneficial effects were observed across studies that varied in dosages and patient characteristics, which supports the general notion that PA is an appropriate method in treating neglect. The first hypothesis proposed that the magnitude of aftereffects increases as the dosage of number of pointings increased. Evidence was found across studies to support this notion, as patients indeed experienced larger aftereffects as the number of pointings increased. This confirmed previous research indicating that larger aftereffects may be induced through higher numbers of visuo-motor interactions through fostering realignment (Fernandez-Ruiz & Diaz, 1999; Pochopien & Fahle, 2015), and many studies that used designs where patients were asked to point to targets 90 or 100 times, found significant aftereffects (Abbruzzese et al., 2019; Angeli et al., 2004; Fortis et al., 2010; Frassinetti et al., 2002; Vangkilde & Habekost, 2010). This seems to be a tendency only, as it did not hold for all studies. An increased number of sessions did not appear to play a major role in the *quantity* of significant aftereffects, which confirmed the assumption that aftereffects rather rely on realignment. However, significant aftereffects were also found with fewer pointings, or more pointings *and* sessions. One example is the intragroup comparison by Fortis et al. (2010), as aftereffects increased when comparing outcomes after one session to scores after 10 sessions, thus, based on this study, recalibration seems to have an impact. In studies that found significant effects, *levels* of significance also increased with more sessions, yet looking across all studies, significant effects were rather found when the number of sessions was held low. This reinforces the notion of including large sample sizes, as one study compared to another can evoke very different results. Concluding, significance of aftereffects rather depends on an increased number of pointings, hence, realignment, rather than recalibration plays the central role. Only when patients adapt well to PA after one session, the number of sessions should be increased, subsequently, recalibration can be important in increasing the magnitude of aftereffects, but it depends on predisposing factors.

Treatment Effects

The significance of treatment effects differed with respect to the choice of outcome measures. The second hypothesis suggested that the magnitude of treatment effects increases as the dosage of number of sessions increased. Looking at outcome measures of ADL, only two studies used fewer than 10 sessions, and both found non-significant results. Additionally, when more sessions were implemented, mixed results were found, thus, results partially contradict the effectiveness of PA. Within significant results, effects slightly favor an increased number of sessions, which showed partial evidence in favor of my second hypothesis. No conclusions can be made regarding the dosage of realignment since variations in pointing quantities among studies were limited. All in all, ADL assessments alone are not sensitive enough to guide therapeutic decisions but slightly advocate an increased number of sessions, thus, the dosage of recalibration seems to be important.

Outcomes on neglect assessment partially contradicted measurements on ADL, as overall, significant effects were found, yet not all studies show these results. Further, no relation between treatment effects, and number of pointings and sessions was found, showing no evidence for my second hypothesis. The Forest Plot inspecting intergroup and intragroup comparisons did not favor PA as a treatment for neglect, as most effects failed to show significance. P-values however, indicated significant effects across studies, varying in quantities of pointings and sessions. Largest effects were found when dosages in recalibration were maximized, yet most effects from lower dosages were also significant. When the size of significance was ignored and merely the number of significant effects was focused on, a tendency that fewer sessions, yet more pointings, were responsible for larger treatment effects can be observed, which implies that realignment may also have a larger impact than recalibration. Unfortunately, this can be regarded as fishing, and I object this conclusion.

Based on these results, it can be inferred that regarding treatment effects reflected in neglect assessment, neither realignment, nor recalibration was dominant or decisive in fostering neglect amelioration.

When combining both, assessments in ADL and neglect assessment, there was a trend observed that when recalibration was increased, higher *levels* of significance were found, while neither more nor less realignment led to more significance. However, these results need to be interpreted with caution, since comparisons based on quantity and quality of significant effects led to contradicting results, as the *number* of significant effects was not increased, but rather decreased, when multiple sessions were administered. Overall, I did not find support for my second hypothesis that treatment effects rely on the number of sessions. The surprising result that treatment effects did not rely on recalibration to the expected extent can be explained by the notion made by Saevarsson et al. (2009), proposing that cognitive load hinders adaptation to prisms. Although this statement referred to visibility of reach, this may also hold for administering multiple sessions a day, since recalibration, which fosters a conscious correction (Redding & Wallace, 2006), also was fatiguing and can be responsible for poorer outcomes. Concluding, neither an increased number of pointings, nor sessions did result in *more* treatment effects, yet an increase in number of sessions led to *larger* effects. Similar to what was found for aftereffects, the amount of recalibration seems to only matter if patients are proven to adapt well to PA and then recalibration may play a central role. This is in accordance with the argument made by Frassinetti et al. (2002), stating that daily repetitive sessions led to a reduction in neglect symptoms, also proposing that treatment effects may be dependent on recalibration.

Link between Aftereffect and Treatment Effect

It was argued that there seems to be a link between the presence of an aftereffect, and treatment effects in neglect rehabilitation (Farné et al., 2002), hence, this review also aimed at investigating whether a consistent relation between aftereffect and treatment effects was apparent. Since the emergence of aftereffects confirms adaptation to prisms (McIntosh et al., 2019), it is expected that treatment effects only follow when adaptation is evident through significant aftereffects. Gutierrez-Herrera et al. (2020) previously investigated this hypothesized link and found a significant correlation between aftereffect and treatment effect after one, as well as two, sessions. However, other research raises doubts with regard to this link as further evidence for this notion was not found and the opposite may hold; aftereffects may be even badly predictive of treatment effects (Serino et al., 2007). This was supported by multiple studies showing that aftereffects may emerge, though, no treatment effects were evident in ADL or neglect assessment (Goedert et al., 2018; Rode et al., 2015; Saevarsson et al., 2009; Sarri et al., 2008), and vice versa (Chen et al., 2014; Ladavas et al., 2011; Serino et al., 2009).

As previously mentioned, there are several factors that may moderate the effectiveness of PA, and considering potential moderators aims to put prior conclusions into perspective. The third hypothesis proposed that some clinical, and methodological variables have a systematic effect on the effectiveness of PA in neglect rehabilitation by facilitating or hindering the emergence of effects. Neglect symptoms are very heterogeneous in their manifestation (Adair & Barrett, 2008) and a large heterogeneity can also be observed among patient and intervention characteristics. This review investigated neglect severity, duration of neglect, the type of exposure (TPA vs. CPA), and the spatial extent of pointing space in greater detail to find explanations for mixed results, as effects were not always attributable to varying frequencies of pointings (dosage of realignment) and sessions (dosage of recalibration). Significant differences were found analyzing the impact of those moderators, supporting the last hypothesis.

Clinical Patient Characteristics

Severity of neglect was frequently discussed in the past and two recent studies including patients with mild (Ten Brink et al., 2017) and severe (Vilimovsky et al., 2021) neglect both found negative results regarding the effectiveness of PA. Since many other studies found positive results, severity cannot be the sole deciding factor, but assuredly impacts adaptation to prisms, as evident in the following study. Mizuno et al. (2011) reported interesting results, since they distinguished patients in terms of neglect severity. Intragroup comparisons showed that patients with severe neglect were unable to respond to the prismatic displacement and experienced no effects, while patients suffering from mild neglect adapted well and showed reliable treatment effects in the FIM, as observed in follow-up measurements at their discharge. Incorporating what has been investigated so far, treatment administered twice a day may be too fatiguing for patients with severe neglect, due to increased cognitive load. Other studies examining patients with severe neglect did find significant results, though, they only administered one session a day (one session in total: Rossetti et al., 1998; or 10 sessions in total: Chen et al., 2014; Fortis et al., 2010). This was further extended by results from studies by Goedert et al. (2018) and Gossmann et al. (2013). The former included patients with mild to moderate neglect only, whereas the latter investigated patients suffering from severe neglect, yet patients in both groups were in the (sub-)acute phase of illness duration. Goedert et al. (2018) found a significant aftereffect but no improvements in neglect, while patients from the study by Gossmann et al. (2013) exhibited neglect amelioration, which remained significant up to five to six days at follow-up. Differences in effects can be partially ascribed to the deviations in neglect severity, yet based on current evidence, it seems difficult to interpret results due to multiple fluctuating factors that can additionally impact PA.

Duration of neglect has become a relevant aspect of recent studies, yet so far it has been argued that patients in different stages do not respond differently to treatment (Vaes et al., 2018). However previously, shorter illness durations were argued to lead to superior effects over longer durations (Luauté et al., 2006), which can be explained by two mechanisms. First, capacities for neuroplasticity are enlarged in patients in the early stage of illness (Mizuno et al., 2011), and second, spontaneous remission may be a substantial part at the (sub-)acute stage (Nys et al., 2008). Nevertheless, the argument that acute patients, rather than chronic patients, respond well, or even better to PA, was not supported. Although spontaneous recovery is commonly observed, this does not restrict the effectiveness of PA regarding functional recovery (Chen et al., 2014). While some studies inspecting (sub-)acute patients did not find any significant effects (Mizuno et al., 2011; Nys et al., 2008 Rode et al., 2015; Ten Brink et al., 2017), other studies with patients in the chronic phase of their illness found a great response to PA and improvements in daily functions (Vangkilde & Habekost, 2010). Looking at current analyses, a trend can be observed that patients in the chronic phase respond even better to PA treatment than patients in illness durations of below three months. This supports the earlier notion that time-since-lesion onset does not hinder the effectiveness of PA (Sarri et al., 2008), and suggests that chronic patients benefit most from PA, thus, duration of illness plays a role in the effectiveness of PA.

Methodological Characteristics

As previously mentioned, aftereffects were argued to stem from the discrepancy of visual and proprioceptive pointing, which fosters spatial realignment (Fernandez-Ruiz & Diaz, 1999; Pochopien & Fahle, 2015). Across studies, significant aftereffects were observed when PA was administered with concurrent exposure, even when the number of pointings was small. This demonstrates that CPA also facilitated realignment, which explained the large amounts of studies finding significant aftereffects when using CPA. However, visibility of pointings impacted realignment (Petitet et al., 2018) through fostering unconscious corrections of spatial reference frames (Redding & Wallace, 2006), while simultaneously hindering strategic control by increasing the cognitive load through additional visual stimulation (Saevarsson et al., 2009). Although CPA led more consistently to significant aftereffects than TPA, studies using TPA found more significant effects in treatment outcomes, even exceeding the amount of significant results for aftereffects. Ladavas et al. (2011) added to this by stating that although both modalities resulted in neglect amelioration, TPA was superior to CPA. TPA led patients to recalibrate their reaching movement when the terminal error was noticed (Newport & Schenk, 2012), which seemed to produce better treatment effects. Studies by Chen et al. (2014) and Goedert et al. (2018) added to that as both administered the same dosage of realignment and recalibration in terms of pointings and sessions. Goedert et al. (2018) implemented a concurrent exposure and found a significant aftereffect but failed to show reduction in neglect, whereas patients in the study by Chen et al. (2014) showed significant neglect recovery after TPA, even four weeks after finalizing the treatment. This implies that CPA, while facilitating realignment and resulting in large aftereffects, hinders patients to consciously adapt to the shift induced by prisms in the long-term, whereas TPA, facilitates recalibration through focusing on strategic control, results in more consistent treatment effects. Hence, the type of exposure seems to play a central role in the effectiveness of PA, as facilitation of recalibration leads to better outcomes.

Finally, spatial space in PA was not investigated by studies or reviews so far, although promising results were found conducting this systematic review. Significant findings were observed across studies employing larger (i.e., 42˚ or 50˚) and smaller (≤20˚) angles of reach. Largest aftereffects were found when the smallest (10˚) extent was used, as visual targets were not presented far to the neglected side. However, looking at treatment effects, neglect amelioration was superior when angles of >20˚ were used. This implies that aftereffects were inhibited by very wide spatial spaces, whereas treatment effects were not hindered, possibly even enlarged through wide spaces. A spatial extent of 20˚ implies that patients pointed 10˚ to their right and 10˚ to their left side, however, the prism goggles displace the visual field by 10˚ to the right, thus, for targets that were visualized to the patient's left side, patients actually pointed straight ahead, and movements did not interfere with the neglected side. This may explain the larger aftereffects, as all targets were visible and all movements could be executed, while in larger spatial extents, some targets may be missed, thus, realignment (through number of pointing movements) will not be practiced as much as if every target can be responded to. In turn this suggests that for bigger extents, if patients do acknowledge targets within their neglected field and train their reaching behavior towards the neglected side, this results in stable neglect recovery. This implies that by using a bigger spatial space, reaching to the far left becomes a therapeutic aspect itself, as patients have to interact with their neglected side, thus, directly train the core of their deficit, and this may have large implications for future therapy. Nevertheless, comparing studies by Serino et al. (2007, 2009), which were equal regarding training aspects but differed in a 42˚ and 50˚ pointing space, respectively, both studies found significant effects, yet effects in the latter were smaller. This suggested that in severely affected patients, a very large angle of reach may obstruct desired results, as patients missed targets and thus, did not experience the same effects.

Long-Term Measurements

The persistence of effects varies depending on the temporal distance of the follow-up measurement with regard to the final intervention. Frassinetti et al. (2002) found that neglect amelioration can last several weeks, which was extended in the study by Serino et al. (2007), showing that effects can persist for six months. Half of aftereffects observed directly after PA were still present at follow-up, while the same applied for 83% of treatment effects. This implies that treatment effects may be a better predictor of neglect recovery than aftereffects. Previous research suggested that aftereffects decay within 60 seconds (Fernandez-Ruiz et al., 2004). Although they did decrease in some studies (Frassinetti et al., 2002; Rode et al., 2015), effects showed a stable persistence at measurements a day later in the study by Farné et al. (2002), nevertheless they were significantly reduced after one week. Nonetheless, significant aftereffects were observed at a follow-up four to five days after treatment (Gutierrez-Herrera et al., 2020), still, the notion that aftereffects decrease within a week was supported, yet they were more persistent than previously assumed.

Finally, drop-outs due to negative side effects were very rare. Some were evident at follow-up measurements, simply because patients were already discharged (Fortis et al., 2010; Goedert et al., 2018; Serino et al., 2007, Ten Brink et al., 2017). Aspects of the intervention were rarely responsible for leaving the treatment prematurely, as only one study reported that patients discontinued treatment because of unwillingness or tiredness. Further drop-outs in other studies were justified by bad health conditions or medication, which in turn did not necessarily reflect poor intervention characteristics.

Limitations and Strengths

This review had some limitations, which should be considered. First, the initial idea of comparing studies based on effect sizes had to be discarded in most cases, as most previous studies did not report relevant statistics. Yet, systematic comparisons by contrasting p-values are highly controversial, as the addition of non-significant p-values will lead to a significant outcome in the long-term. For example, if two non-significant results are multiplied, they will produce a significant value (e.g., 0.07 x 0.07 = 0.0049). In the following, significant results will be reported without ever establishing significant values through initial analysis, therefore, this strategy seems illusive. Thus, effects of studies that coincide in dosage or aspects were not added and only compared upon magnitude, which does not seem statistically appropriate. Second, observed frequencies of significant effects only consider the quantity, not the quality of effects. Frequencies merely check if a significant effect is present, whereas the strength of effects was ignored. This in turn lead to mixed results between tables and figures and highlighted the importance of distinguishing *levels* of significance. Third, because of small numbers of participants within studies, inferences must be considered with caution as they explain a broad picture that cannot be applied to every individual. Finally, inferences of conclusions regarding moderators must be considered with caution, as focusing on one factor neglected the simultaneous influence of several others. There are numerous factors that can impact adaptation to prisms, which makes it hard to determine a justification for why a patient showed a particular effect.

Nevertheless, this review also had strengths. Although comparisons by means of p-values had some flaws, this left the opportunity of increasing the sample size (n=29 instead of n=5), which resulted in more precise conclusions. In total, measurements of 377 patients were part of this review, and 18,564 pointings were executed over 218 sessions (μ=85 pointings per session) of PA treatment Thereby, this paper adds to current research as it investigated dosages of cognitive processes under consideration of variations of clinical characteristics. This has not been done previously, although it has been prompted by Champod et al. (2018). Moreover, the effectiveness of PA treatment was assured, which reinforces the integration of this treatment in neglect rehabilitation. This seems especially important, since PA is also feasibly for home use (Fortis et al., 2010), and does not require much clinical training (Goedert et al., 2015), which facilitates rehabilitation in the individual through continuation of training after discharge.

Future Research

First and foremost, the reporting of necessary statistics to calculate effect sizes is urgently advised in future RCTs. Second, studies that include follow-up measurements, should also assess patients directly after the final intervention. Non-significant effects at follow-ups days or weeks later cannot be put into meaning without an indication of effects immediately after PA to compare whether the effect has decreased or never existed in the first place. Third, the study by Fortis et al. (2010) demonstrates larger aftereffects after 10 compared to one session. Studies that administer multiple sessions should consider assessing patients not only at baseline, but also after the first session, to be able to ascribe effects to a higher dosage if the effect accumulates. Fourth, the dosage of recalibration can be inspected further by conducting studies either with intermittent training (see Scheffels et al., 2021) or by asking patients to point to targets only 20 times, since realignment takes place from 30 pointings onwards (Newport & Schenk, 2012). This will add to the small body of research on dosages of adaptation processes. Fifth, future studies should consider investigating comorbidities and anosognosia, as they can be a big obstacle in compliance and adhering to treatment. Moreover, assessments of ADL should not be the only measure to indicate treatment effects. Preferred is a combination of both classifications but ADL measurements alone are not sensitive enough for clinical interpretation. Finally, this review highlights the need for further exploration of clinical and methodological characteristics, which may play a central role in impacting PA, including particularly the further investigation of the spatial extent of pointing space. However, in order to investigate moderating characteristics, randomization of participants must be excluded, as non-significant results cannot be attributed to causes. If randomization is prohibited, yet appropriate blinding of researchers assured, this should be approached. Additionally, with respect to the spatial extent of pointing space, future therapy sessions should systematically increase the extent and observe whether effects change, increase, or diminish.

Conclusion

With this review I hope to serve the purpose of directing future research on neglect rehabilitation including RCT studies. Despite clinical and methodological heterogeneity across studies, most studies reported improvements in neglect symptoms, reflected by aftereffects or treatment effects, which generally advocates the utilization of PA in neglect rehabilitation. However, these improvements were not always attributable to an increased number of pointings or sessions. Increased realignment was found to be indicative of larger aftereffects, while recalibration in terms of donning goggles (frequency of sessions) did not seem of importance at first. Nevertheless, some patients simply do not seem to respond to PA and their treatment procedure should be adjusted. Yet other patients do benefit from PA in general, and since increased recalibration led to increasing levels of significance with regard to aftereffects and treatment effects, session should be repeated when patients respond well to treatment. This implies that treatment needs to be adjusted to individual patients and in case they respond, recalibration should be facilitated. Furthermore, realignment and recalibration are not only facilitated by means of more pointings and sessions, but also through types of exposure, namely CPA and TPA, respectively. Instead of focusing on increasing dosages of recalibration through repetitive sessions, the type of exposure, TPA respectively, may be another important factor to facilitate recalibration. Effectiveness of PA seems to be dependent on the individual patient, thus, future rehabilitation should be adjusted accordingly in terms of intervention characteristics, and number of sessions to maximize adherence. Neglect severity and duration, appeared to influence adaptation to prisms, while type of exposure and spatial extent of pointing space seemed to be a core facilitator, which should be focused on in future studies.

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Appendix A

Characteristics of included studies

Study	Patient Characteristics				Intervention Characteristics					Outcome Characteristics			
	N (μ age)	Duration of Illness	Severity of Illness	Localisation of Lesion	Nr. of Pointings	Nr. of Sessions (once a day unless stated otherwise)	TPA/ CPA	Spatial Extent	Visual Shift	After-effects	Treatment Effect	Latest Follow-up	Drop-outs
Abbruzzese et al., 2019	n=28 (μ=66)	-	-	-	**90**	**10** within 2 weeks	TPA	-	10˚	$d=0.76$++	BIT: $d=-0.52$++	directly	0
Aimola et al., 2012	n=11 (μ=71)	average 21 months	-	-	**96**	**2** within 1 session	CPA	10˚	12˚	after 1 donning: $d=2.17$+++	-	directly	0
Angeli et al., 2004	n=8 (μ=70)	2-19 months	-	F/P/T/O/ TH/IC/BG	**90**	**1**	TPA	42˚	10˚	$p<0.0004$***	Neglect Dyslexia: $p<0.001$***	directly	0
Chen et al., 2014	n=21 (μ=62)	maximum of 2 months	moderate-severe	frontal vs. non-frontal	**60** LB	**10** within 2 weeks	TPA	~50˚	12.4˚	$p>0.05$	CBS 4 weeks: $p=0.01$*	following week, 2, 3 & 4 weeks	0
Farné et al., 2002	n=6 (μ=68)	2-8 months	-	F/P/T/O/IC/ TH/BG/WM	**60**	**1**	CPA	40˚	10˚	directly, 1 day: $p<0.0002$***	BIT directly, 1 day: $p<0.0002$***	directly, 1 day, 1 week	0
Fortis et al., 2010	n=10 (μ=73)	average 3.4 months	mild-severe	overlap in WM & BG	**90**	**10** within 1 week twice a day	CPA	42˚	10˚	after 1 donning: $d=0.84$+++ after 10th donning: $d=1.93$	directly CBS: $d=-0.66$++ FIM: $d=-0.14$ LB: $d=-0.1$ 1 week CBS: $d=-1.12$+++ FIM: $d=-0.3$+ LB: $d=0.09$ 1, 2, 3 months CBS: $d=-0.57$++ FIM: $d=-0.18$	directly 1 week, 1, 2 & 3 months)	3
Frassinetti et al., 2002	n=7 (μ=65)	3-27 months	-	F/P/T/O/ BG/IC	**90**	**20** within 2 weeks twice a day	TPA	42˚	10˚	directly: $p<0.0001$*** up to 12h: $p<0.03$* from 4th day on: $p>0.05$	BIT 2 days: $p<0.0003$*** 5 weeks: $p<0.0002$***	directly, 2 days, 1 week, 5 weeks	1
Goedert et al., 2018	n=8 (μ=62)	9-50 days	mild-moderate	frontal vs. non-frontal, insula	**60** LB	**10** within 2 weeks	CPA	~50˚	11.4˚	directly: $p=0.001$**	BIT 5 weeks: $p>0.05$	directly, 1, 2, 3, 4 & 5 weeks, 12 & 24 weeks	High rate at 12 & 24 weeks

Gossmann et al., 2013	n=16 (μ=67)	average 36 days	severe	cortical vs. subcortical	**~ 33**	**4** within 1 week	CPA	-	10°	-	ACT: p=0.041* FIM: *p*>0.05	directly, 5-6 days	0
Gutierrez-Herrera et al., 2020	n=15 (μ=66)	2-8 months	-	F/P/T/O/I/ BG/C	**60**	**2** within 4 days	CPA	42°	10°	*p*=0.002**	Correlation of aftereffect and treatment effect after 1st session Cancellation: *p*=0.001** after 2nd session Cancellation: *p*=0.01*	directly, 4-5 days	4
Ladavas et al., 2011	n=20 (μ=64)	2-30 months	-	cortical vs. subcortical	**90**	**10** within 2 weeks	TPA vs. CPA	50°	10°	*p*>0.05	BIT-C (BIT-B similar): *p*<0.05* [TPA: *p*<0.0001 CPA: *p*<0.001]	1 week	0
Luauté et al., 2006	n=5 (μ=74)	2-14 months	-	F/P/T/O/ subcortical	**50**	**1**	TPA	-	10°	-	BIT: *p*=0.04*	directly	1
Lunven et al., 2019	n=14 (μ=64)	3-37 months	-	F/P/T/O/C	**~100**	**1**	TPA	-	10°	-	Neglect Tests high-responder: *p*=0.012* low-responder: *p*=0.5	directly	0
(CR) McIntosh et al., 2002	n=1 (μ=74)	9 months	severe	parietal (+ parts of occipital)	**50**	**3** within 3 weeks	TPA	20°	10°	-	Cancellation, LB: *p*<0.001***	2 hours	0
Mizuno et al., 2011	n=17 (μ=66)	1-3 months	mild or severe	-	**90**	**20** within 2 weeks twice a day	TPA	~50°	12°	-	BIT, CBS, FIM: p>0.05 [FIM mild neglect directly, follow-up: *p*<0.01**]	directly, at discharge (average 95 days)	3
Mizuno et al., 2021	n=15 (μ=64)	maximum of 3 months	mild or severe	-	**90**	**20** within 2 weeks twice a day	TPA	~50°	12°	-	CBS: p>0.05	directly, at discharge (average 127 days)	0
Nys et al., 2008	n=10 (μ=64)	maximum of 4 weeks	severe (+ 1 mild)	F/P/T/O/IC/ TH/BG/I	**100**	**4** within 4 days	TPA	20°	10°	-	directly LB: p>0.05 Cancellation: *p*=0.045* 1 month BIT-C: *p*>0.05	directly, 1 month	0
Rode et al., 2015	n=9 (μ=56)	1-3 months	mild or severe	F/P/T/O/ subcortical	**80**	**4** within 4 weeks	CPA	20°	10°	directly: *p*<0.05* follow-up: p>0.05	FIM, BIT: p>0.05	directly, 1, 3 & 6 months	1

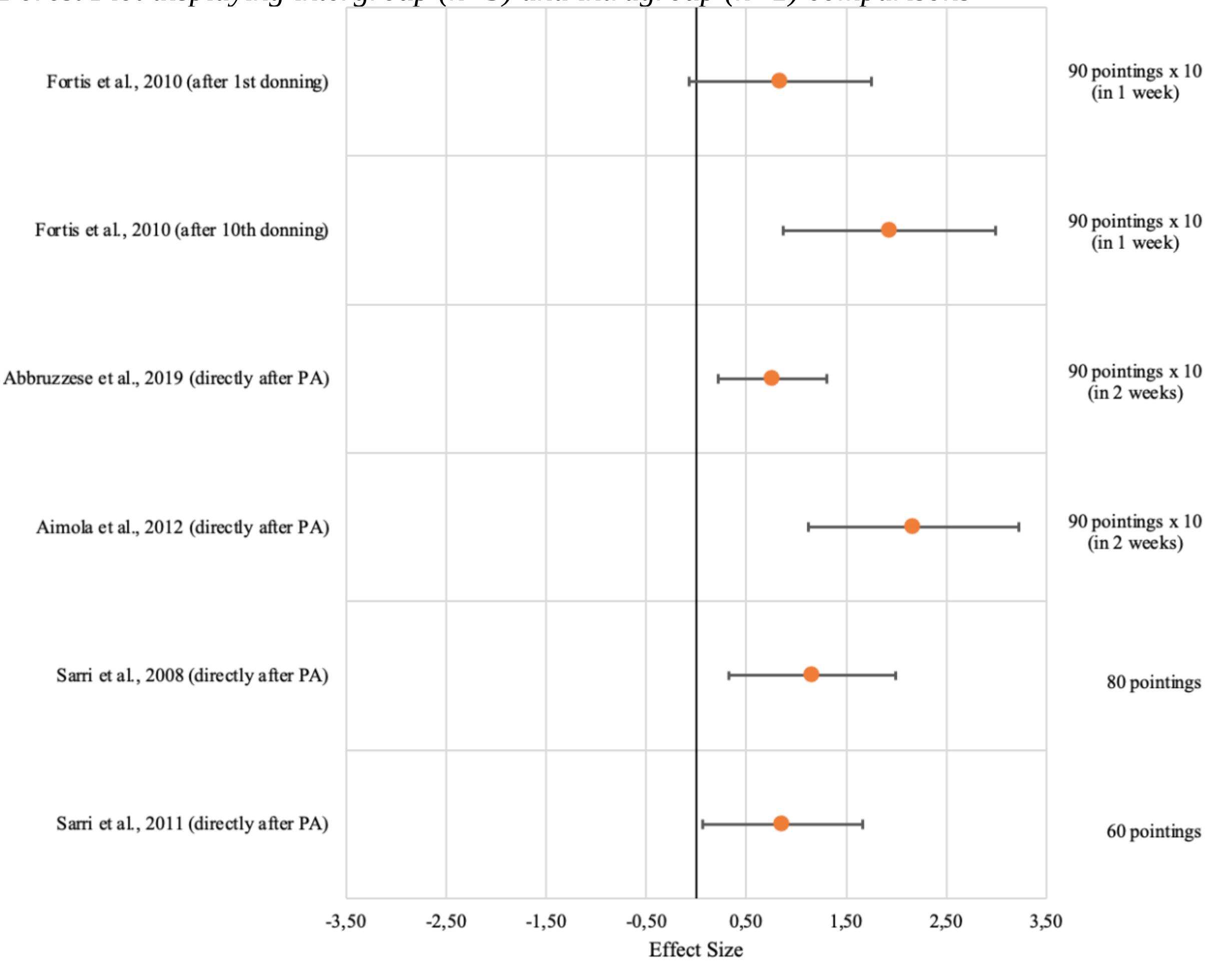
Rossetti et al., 1998	n=8/6 (μ=62)	average 9 weeks	severe	F/subcortical/ cortico-subcortical	**50**	**1**	CPA	20˚	10˚	*p*<0.05*	LB, Cancellation directly, 2 hours: *p*<0.01**	directly, 2 hours	0
Saevarsson et al., 2009	n=4/4 (μ=59)	3-61 months	-	F/P/T/O/ TH/BG/I	**60**	**1**	TPA	-	10˚	E1: *p*<0.05* E2: *p*<0.05*	Neglect Tests E1: *p*>0.05 E2: *p*=0.018*	directly	0
Sarri et al., 2008	n=13 (μ=57)	average 20 months	-	F/P/T/O/ BG/WM/I	**80**	**1**	CPA	20˚	10˚	*d*=1.16+++	Cancellation: *non-significant*	directly	1
Sarri et al., 2011	n=11 (μ=59)	average 22 months	-	F/P/T/O/IC/ BG/WM/I	**60**	**1**	CPA	20˚	10˚	*d*=0.86+++	LB: *d*=1.12+++	directly	0
Serino et al., 2007	n=21 (μ=67)	average 15 months	-	F/P/T/O/IC/ TH/BG	**90**	**10** within 2 weeks	TPA	42˚	10˚	-	BIT-C (BIT-B similar) 1 week, 3 months: *p*<0.0002*** [when follow-up at 6 months included 6 months: *p*<0.0004***]	1 week, 1, 3 & 6 months	High rate at 6 months
Serino et al., 2009	n=20 (μ=62)	average 5 months	-	-	**90**	**10** within 2 weeks	TPA	50˚	10˚	p>0.05	BIT directly: *p*<0.05* 1 month: *p*>0.05	directly, 1 month	0
Spaccavento et al., 2016	n=10 (μ=67)	average 90 days	-	-	**90**	**20** within 4 weeks	CPA	42˚	-	-	BIT: *d*=-0.37+ CBS: *d*=1.29+++ FIM: *d*=-1.63+++	directly	0
(CR) Striemer & Danckert, 2010	n=3 (μ=75)	-	-	P-WM, TH/ F-P-WM, P, BG/O-T, P	**~100**	**1**	-	-	10˚	*p*<0.05*	LB: *p*<0.05*/ *p*<0.001***	directly	0
Ten Brink et al., 2017	n=34 (μ=59)	average 41.5 days	mostly moderate-severe	-	**~100**	**10** within 2 weeks	TPA	20˚	10˚	-	CBS 6 weeks: p>0.05	1, 2, 3, 4, 6 & 14 weeks	2
Turton et al., 2010	n=16 -	minimum of 20 days	-	-	**90**	**10** within 2 weeks	TPA	42˚	6˚	-	BIT, CBS directly, follow-up: p>0.05	directly, 4 days, 8 weeks	0
Vangkilde & Habekost, 2010	n=6 (μ=58)	average 40 months	-	F/P/T/O/ IC/TH	**90**	**20** within 2 weeks twice a day	TPA	42˚	10˚	*p*<0.001*	Cancellation: *p*<0.003**	directly	0

Note. Effects are indicated by effect sizes and p-values, treatment effects are distinguished by improvements in neglect and ADL; (CR) = case report; - = not reported; F = frontal; P = parietal; T = temporal; O = occipital; TH = thalamus; IC = internal capsule; BG = basal ganglia; WM = white matter; I = insula; C = cerebellum; TPA = terminal prism adaptation; CPA = concurrent prism adaptation; BIT = Behavioral Inattention Test; ACT = Apples Cancellation Test; LB = Line Bisection; CBS = Catherine Bergego Scale; FIM = Functional Independence Measure; * = *p*<0.05; ** = *p*<0.01; *** = *p*<0.001; + = *d*>0.2; ++ = *d*>0.5; +++ = *d*>0.8

Appendix B

Aftereffects following PA

Forest Plot displaying intergroup (n=5) and intragroup (n=1) comparisons



Note. Figure favors intervention; effects increased in significance with increased realignment and recalibration; PA = Prism Adaptation

P-values displaying intergroup (n=13) and intragroup (n=3) comparisons

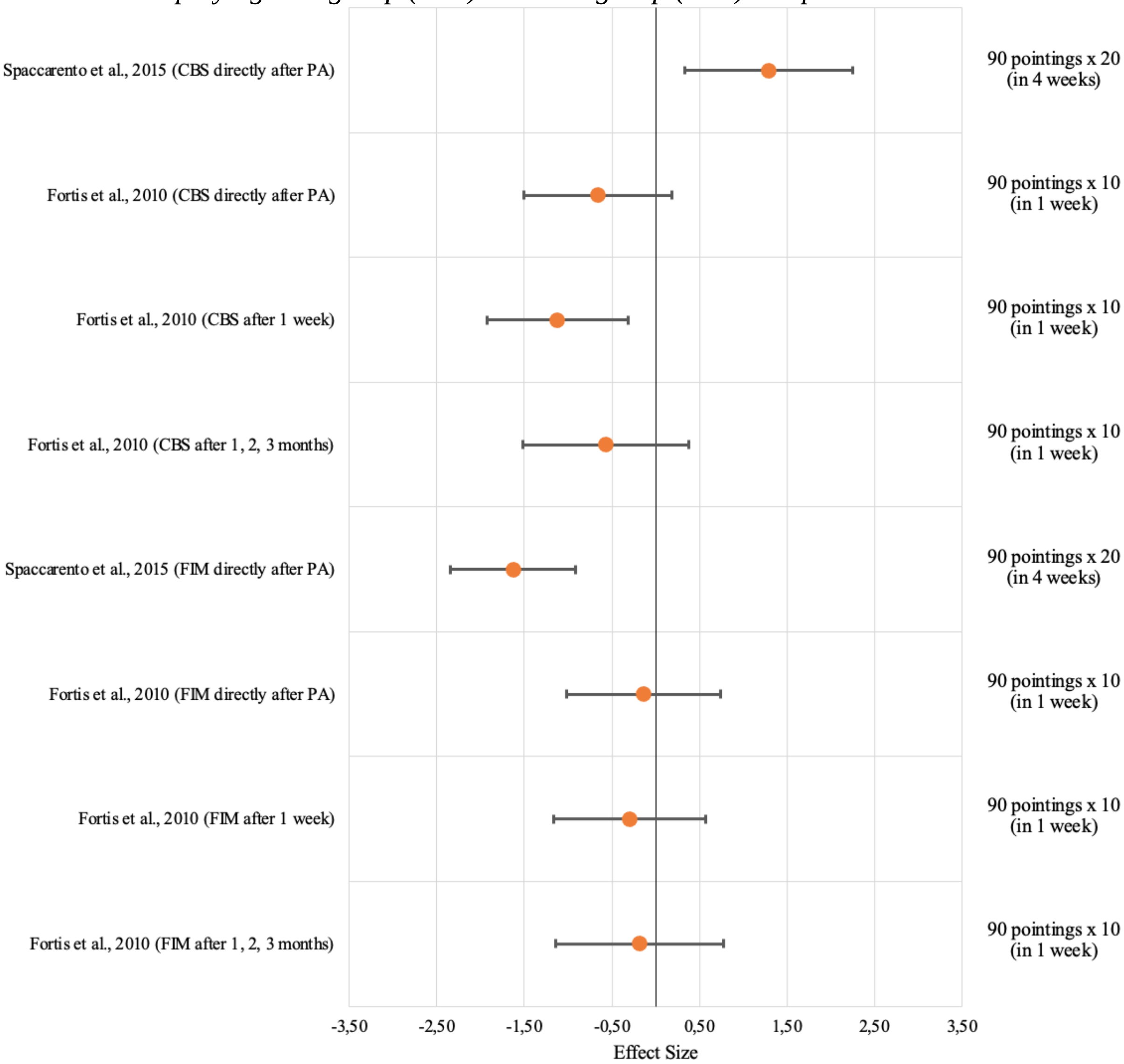
Study	1 session		up to 4 sessions		10 or 20 sessions	
	≤ 60 pointings	≥ 80 pointings	≤ 60 pointings	≥ 80 pointings	≤ 60 pointings	≥ 80 pointings
Frassinetti et al., 2002						20x90: *p*<0.0001***
12 hours follow-up						*p*<0.03*
4 days follow-up						*p*>0.05
Vangkilde & Habekost, 2010						20x90: *p*<0.001***
Ladavas et al., 2011						10x90: *p*>0.05
Serino et al., 2009						10x90: *p*>0.05
Chen et al., 2014					10x60: *p*>0.05	
Goedert et al., 2018					10x60: *p*=0.001**	
Rode et al., 2015				4x80: *p*<0.05*		
6 months follow-up				*p*>0.05		
Gutierrez-Herrera et al., 2020			2x60: *p*=0.002**			
Striemer & Danckert, 2010		1x100: *p*<0.05*				
Angeli et al., 2004		1x90: *p*<0.0004***				
Farné et al., 2002	1x60: *p*<0.0002***					
1 day follow-up	*p*<0.0002***					
Saevarsson et al., 2008	1x60: E1: *p*<0.05*					
	E2: *p*<0.05*					
Rossetti et al., 1998	1x50: *p*<0.05*					

Note. Table favors intervention; effects increased in significance with increased recalibration; E1/2 = experiment 1/2; * = *p*<0.05; ** = *p*<0.01; *** = *p*<0.001

Appendix C

Treatment effects following PA on two measures of ADL

Forest Plot displaying intergroup (n=2) and intragroup (n=2) comparisons



Note: Scores on the CBS in Fortis et al. (2010) are reversed-coded and need to be interpreted accordingly; figure partially favors intervention; effects increased in significance with increased recalibration; CBS = Catherine Bergego Scale; FIM = Functional Independence Measure; PA = Prism Adaptation

P-values displaying intergroup (n=7) and intragroup (n=2) comparisons

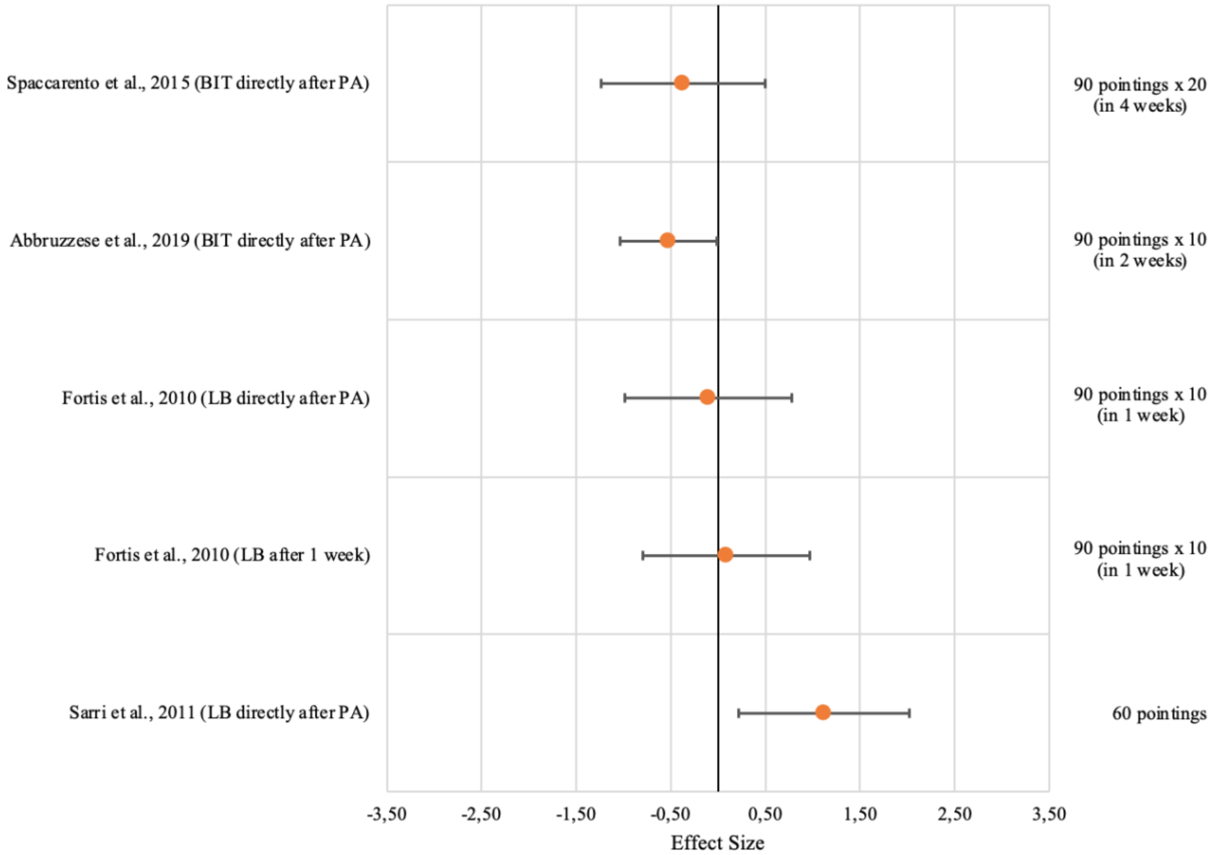
	Study	<10 sessions		10 or 20 sessions	
		≤ 60 pointings	≥ 80 pointings	≤ 60 pointings	≥ 80 pointings
CBS	Mizuno et al., 2011				20x90: $p>0.05$
	Mizuno et al., 2021				20x90: $p>0.05$
	Ten Brink et al., 2017; 6 weeks follow-up				10x100: $p>0.05$
	Turton et al., 2010				10x90: $p>0.05$
	8 weeks follow-up				$p>0.05$
	Chen et al., 2014; 4 weeks follow-up			10x60: $p=0.01$**	
FIM	Mizuno et al., 2011				20x90: $p>0.05$
	mild neglect only				$p<0.01$**
	follow-up at discharge; mild neglect only				$p<0.01$**
	Rode et al., 2015		4x80: $p>0.05$		
	Gossmann et al., 2013	4x33: $p>0.05$			

Note: Table does not favor intervention; CBS = Catherine Bergego Scale; FIM = Functional Independence Measure; * = $p<0.05$; ** = $p<0.01$; *** = $p<0.001$

Appendix D

Treatment effects following PA on two and six measures of neglect

Forest Plot displaying intergroup (n=4) and intragroup (n=1) comparisons



Note: Figure does not favor intervention; BIT = Behavioral Inattention Test; LB = Line Bisection; PA = Prism Adaptation

P-values displaying intergroup (n=19) and intragroup (n=6) comparisons

	Study	1 session		up to 4 sessions		10 or 20 sessions	
		≤ 60 pointings	≥ 80 pointings	≤ 60 pointings	≥ 80 pointings	≤ 60 pointings	≥ 80 pointings
BIT	Frassinetti et al., 2002; 2 days follow-up						20x90: $p<0.0003$***
	5 weeks follow-up						$p<0.0002$***
	Mizuno et al., 2011						20x90: $p>0.05$
	Ladavas et al., 2011						10x90: $p<0.05$*
	Serino et al., 2007; 1 week follow-up						10x90: $p<0.0002$***
	3 months follow-up						$p<0.0002$***
	6 months follow-up						$p<0.0004$***
	Serino et al., 2009						10x90: $p<0.05$*
	1 month follow-up						$p>0.05$
	Turton et al., 2010						10x90: $p>0.05$
	8 weeks follow-up						$p>0.05$
	Goedert et al., 2018; 5 weeks follow-up					10x60: $p>0.05$	
	Nys et al., 2008				4x100: $p>0.05$		
	Rode et al., 2015				4x80: $p>0.05$		
	Farné et al., 2002	1x60 $p<0.0002$***					
	1 day follow-up	$p<0.0002$***					
	Luauté et al., 2007	1x50: $p=0.04$*					
Line Bisection	Nys et al., 2008				4x100: $p>0.05$		
	McIntosh et al., 2002			3x50: $p<0.001$***			
	Striemer & Danckert, 2010		1x100: $p<0.05$*				
	Rosetti et al., 1998	1x50: $p<0.01$**					
	2 hours follow-up	$p<0.01$**					
Cancellation	Vangkilde & Habekost, 2010						20x90: $p<0.003$**
	Nys et al., 2008				4x100: $p=0.045$*		
	McIntosh et al., 2002			3x50: $p<0.001$***			
	Rosetti et al., 1998	1x50: $p<0.01$**					
	2 hours follow-up	$p<0.01$**					
Neglect Tests	Lunven et al., 2019		1x100: $p=0.012$*				
	Saevarsson et al., 2008	1x60: E1: $p>0.05$ E2: $p=0.018$*					
ACT	Gossmann et al., 2013			4x33: $p=0.041$*			
Neglect Dyslexia	Angeli et al., 2014		1x90: $p<0.001$***				

Note: Table favors intervention; effects partially increased in significance with increased recalibration; BIT = Behavioral Inattention Test; LB = Line Bisection; E1/2 = experiment 1/2; ACT = Apples Cancellation Test; * = $p<0.05$; ** = $p<0.01$; *** = $p<0.001$