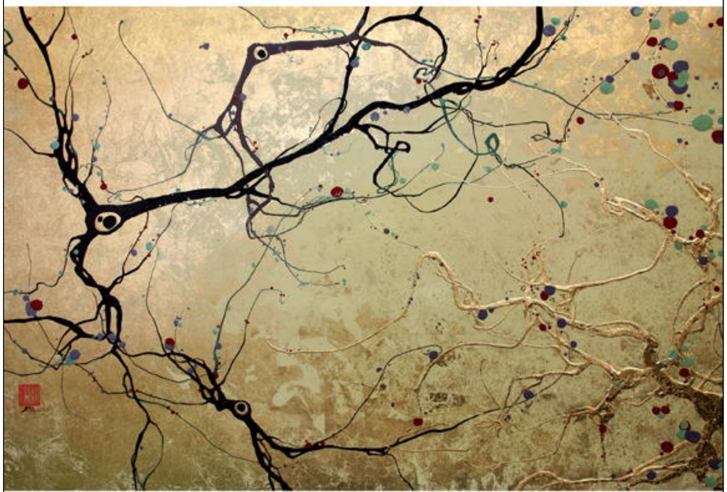
Volume 50 Issue 6 May 2012

ELSEVIER

NEUROPSYCHOLOGIA

An international journal in behavioural and cognitive neuroscience



Special Issue
Spatial Neglect and Attention

Guest Editors
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Neuropsychologia 50 (2012) 1072–1079

Contents lists available at SciVerse ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Review

Rehabilitation of neglect: An update

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ARTICLE INFO

Article history:
Received 6 September 2011
Received in revised form 11 January 2012
Accepted 12 January 2012
Available online 28 January 2012

Keywords:
Brain damage
Extinction
Treatment
Optokinetic stimulation
Vestibular
Brain stimulation
Motor
Dysphagia
Review

ABSTRACT

Spatial neglect is a characteristic sign of damage to the right hemisphere and is typically characterized by a failure to respond to stimuli on the left side. With about a third of stroke victims showing initial signs of neglect, it is a frequent but also one of the most disabling neurological syndromes. Despite partial recovery in the first months after stroke one third of these patients remain severely disabled in all daily activities, have a poor rehabilitation outcome and therefore require specific treatment. The last decades have seen an intensive search for novel, more effective treatments for this debilitating disorder. An impressive range of techniques to treat neglect has been developed in recent years. Here, we describe those techniques, review their efficacy and identify gaps in the current research on neglect therapy.

Contents

Abbreviations: OKS, optokinetic stimulation; CVS, caloric vestibular stimulation; FES, functional electrical stimulation; GVS, galvanic vestibular stimulation; NMV, neck muscle vibration; PA, visuo-motor prism adaptation; TMS, transcranial magnetic stimulation; TDCS, transcranial direct current stimulation; VR, virtual reality; VST, visual scanning therapy.

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doi:10.1016/j.neuropsychologia.2012.01.024

1. Introduction

Neglect is a challenging and complex disorder. Typically, it is defined as the impaired or lost ability to respond to sensory stimuli (visual, auditory, tactile, olfactory) presented in the contralesional hemispace of a neurological patient (Kerkhoff, 2001). In addition to sensory neglect, motor neglect may occur and manifest itself as the reduced use or nonuse of the contralesional extremities during walking or bimanual activities.

But neglect is not just challenging to define and understand it also poses a challenge to our health system. The clinical, sociodemographic as well as epidemiological relevance of spatial neglect as a disease is substantial: every year about 3–5 million patients suffer from neglect after stroke (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005), and this incidence will continuously increase due to a rising incidence of cerebro-vascular diseases in our aging western societies and a shift to western life habits in the newly industrialized countries. Spontaneous recovery occurs but will not necessarily eliminate all signs of neglect. More importantly about a third of all patients manifest a chronic form of neglect and show clear signs of neglect even more than a year after their neurological incident (Karnath, Rennig, Johannsen, & Rorden, 2011; Rengachary, He, Shulman, & Corbetta, 2011). Neglect interferes with rehabilitation attempts aimed at improving other symptoms of the patients (such as hemiparesis) and if left untreated will therefore lead to a poor rehabilitation outcome. It seems clear that the development of effective treatments for neglect should be a high priority. For the purpose of this special issue on unilateral neglect, we provide an overview over existing treatment options but also identify some of the gaps in current research on neglect-therapy. It is sobering to observe that while significant progress has been made, many of the gaps that were identified in previous reviews can still be found today. For this reason we will ask at the end of our review whether there are structural reasons that can explain the persistence with which important questions remain not only unanswered but effectively unexamined.

2. Early exploration

The first attempts to treat patients with unilateral neglect focused on the obvious problem that these patients seemed to explore only half of their visual world. The therapeutic answer to this problem was provided by Diller and Weinberg (1977) who used visual displays that contained multiple items and asked their patients to find specific items on these displays. It was hoped that through practice and guiding feedback from the therapist patients would learn to guide their eyes to the hitherto neglected contralesional space. This approach was borrowed from Poppelreuter (1917) who had used a similar approach in his treatment of patients with visual field defects. Visual scanning or visual exploration therapy (VST or VET) as it came to be known rapidly established itself as the treatment of choice. Today many different versions are available. These versions differ mainly in three respects: size of the display and method of presentation and instructions. The display can either be as small as a magazine or as big as the screen in a home-cinema. The stimuli might be presented on a piece of paper, presented on a computer screen or projected with a beamer. Patients might be instructed to describe all items on a display or only search for a specific object embedded among other distractor items. While for many years it has become the de-facto standard for neglect therapy only a few studies examined its efficacy. Kerkhoff, Münβinger, Haaf, Eberle-Strauss, and Stögerer (1992) compared the impact of VST on patients with visual field deficits and those with neglect and found that patients with visual field deficits benefit significantly more from this treatment than patients with neglect. A similar finding was reported by Antonucci, Guariglia, Judica, Magnotti, Paolucci, and Pizzamiglio (1995). The same group could however show that VST is better than an unspecific cognitive training (Antonucci et al., 1995).

However a major weakness of the VST therapy is its specificity, i.e. some but not all neglect-associated symptoms seem to improve with VST (Kerkhoff, 1998a). Typically, VST training improves visual scanning and related visual tasks like reading and line bisection performance, but fails to improve non-visual neglect. For example, in the study by Schindler, Kerkhoff, Karnath, Keller, and Goldenberg (2002) visual scanning training led to measurable improvements in reading and visual search, but not in tactile search. In contrast neck-muscle vibration in combination with visual scanning training led to significantly greater improvements in reading and visual search, but also in tactile search. Likewise, Kerkhoff et al. (2012, this issue) found improvements in visual *and* auditory neglect after optokinetic training with pusuit eye movements in 3 neglect patients, but only *unimodal* (visual) improvements after visual scanning training in 3 other neglect patients, without any effect on auditory neglect.

VST is also quite time-consuming and thus quite costly. A minimum of 40 treatment sessions (each about 50 min long) are needed to achieve stable results (Antonucci et al., 1995; Kerkhoff, 1998a). This requires a substantial commitment from the therapist and the patient. Commitment from the patient is often difficult to obtain given the well-known association between anosognosia (lack of insight) and unilateral neglect (Vallar, Bottini, & Sterzi, 2003). Given these shortcomings of VST it is therefore hardly surprising that many researchers in the field were looking for alternatives. These came in the form of several sensory stimulation techniques. Those stimulation techniques have two things in common, they require less compliance and cooperation from the patient and they all aim to restore the patient's eye-, head- and body-orientation to the veridical straight-ahead direction.

3. Seeing straight

Karnath (2006) argued that the core-deficit in unilateral neglect is an orientation bias to the right. Even at rest right brain-damaged patients with neglect will show a 30° deviation of eye and head orientation to the right (Fruhmann-Berger & Karnath, 2005). On the basis of these and similar findings Karnath and Dieterich (2006) suggested that neglect results from damage to the multisensory cortex (localized in the right superior temporal cortex, insula and temporo-parietal junction) in which vestibular, auditory, neck-proprioceptive and visual input is combined to create higher order spatial representations of our body's position in relation to our environment. Given the multisensory nature of this representation Karnath (2006) suggested that it should be possible to use sensory signals from different modalities to counteract the rightward bias in neglect patients. Research in the past identified a number of possible cues which the brain can use to compute the body's position in space (e.g. vestibular, visual or proprioceptive signals) and identified numerous ways to induce a bias in that system. The four best researched techniques are caloric, galvanic or optokinetic stimulation and neck vibration. There is a fifth technique which uses a more indirect way to affect our sense of where we are in relation to the world around us and it is called prismatic adaptation. All five techniques can be used to induce a leftward orientation bias and might therefore be used to neutralize the pathological rightward bias found in neglect patients. Most studies who examined the influence of those manipulations on neglect demonstrated at least transient improvement of neglect symptoms and thus provided general support for the idea that a rightward orientation bias lies at the heart of the neglect syndrome. But do these interventions provide viable treatment options? This question will be addressed in the following subsections.

3.1. Optokinetic stimulation (OKS)

The technique of optokinetic stimulation (OKS) exploits the fact that for the perception of our body in space we also use visual information, in particular visual motion information. If we look at a large visual display that fills our field of vision and moves to the left, we have the impression that our body rotates toward the right. We accordingly try to compensate for this perceived rotation to the right by re-orienting ourselves to the left. This phenomenon could be exploited to counteract the rightward-orientation-bias in neglect. Pizzamiglio, Frasca, Guariglia, Incoccia, and Antonucci (1990) tested this idea and found a significant reduction of neglect symptoms. However, these benefits were of a transient nature. (Kerkhoff, 2002) and colleagues later tested with much smaller moving visual displays presented on conventional PC-monitors (17″) potential therapeutic effects in patients with neglect. Such smaller devices leave the periphery of the visual field free of motion and primarily test the pursuit system. This technique evokes an optokinetic nystagmus but not the subjective impression of body rotation. Kerkhoff (2002) investigated in a pilot study with three right-brain damaged neglect patients whether the repetitive application of small-field OKS may induce lasting improvements in visual neglect. All subjects received standard visual exploration training (3 sessions per week) throughout the complete course of the pilot study. During a 2-week baseline period all subjects were tested four times in a variety of neglect tests to exclude effects of spontaneous recovery and/or test repetition. During this period, no significant improvements in any test were seen (despite the visual exploration training being performed). After the fourth baseline test, repetitive optokinetic stimulation was given for 5 sessions (each with 45 min duration, delivered in a period of 10–14 days). After OKS-training, auditory neglect and neglect dyslexia were substantially improved. Likewise, visual cancellation performance had significantly improved in all three patients after OKS. These improvements remained stable after a 2-week-follow-up in all cases. Interestingly, these improvements were obtained in two modalities of neglect (vision and audition) which underlines the multimodal efficiency of small-field OKS as already documented with short-term optokinetic stimulation. These positive findings were mostly confirmed in later studies, all using small-field OKS stimulation stimulating the pursuit system (Keller, Lefin-Rank, Losch, & Kerkhoff, 2009, Kerkhoff et al., this issue; Kerkhoff, Keller, Ritter, & Marquardt, 2006; Schröder, Wist, & Hömberg, 2008; Thimm et al., 2009). There is however an interesting exception: Pizzamiglio et al. (2004) found no significant benefits with full-field OKS training. It is therefore interesting to look at the features which distinguish Pizzamiglio et al.'s study from studies which achieve positive results. It turns out that in the Pizzamiglio-study patients were asked to refrain from pursuit eye-movements whereas in the other studies such eye-movements were encouraged. It therefore appears that smooth pursuit eye movements are an important therapeutic ingredient of the OKS training. This conclusion is corroborated by functional imaging data: Konen, Kleiser, Seitz, and Bremmer (2005) showed that active tracking of OKS displays yields more widespread activations in the parieto-temporal cortex of healthy subjects than passive "stare-gazing". In summary it seems that OKS is an effective treatment for neglect but it is also clear that even this technique requires some amount of active patient-participation.

3.2. Neck-muscle vibration (NMV)

The logic underlying neck-muscle vibration is not dissimilar to that underlying OKS. We only feel that our head is looking straight if the proprioceptive signals from our neck-muscles indicate that both muscles are stretched to the same extent. Vibration over the left neck-muscles induces an illusory lengthening of the stimulated muscles. The effect is a paradoxic illusion of a continuous, constant movement to one side. This illusion is present as long as the vibratory stimulus is applied on the muscle(s). Vibration over the left neck muscles does not only evoke the impression that the head is rotated toward the right but also that the trunk is rotated toward the left. The type of (verbally reported) illusion depends on the experimental setup. The setup determines whether subjects have the impression (and verbally report) that the head is moving relative to the fixed trunk or the trunk is moving relative to the fixed head. Both types of mechanisms induced by NMW neutralize the rightward orientation bias and thereby reduce neglect symptoms. The validity of this prediction has been demonstrated in a series of studies by Karnath and his colleagues (Karnath, Christ, & Hartje, 1993; Karnath, Fetter, & Dichgans, 1996; Karnath, 1995). Unsurprisingly these effects are transient with some after-effect and one might therefore ask whether repetitive application of this technique might lead to stable benefits. Unfortunately treatment based on neck vibration has attracted little research. At the moment only two studies have been published.

Schindler et al. (2002) evaluated in a controlled crossover treatment study whether repetitive application of contralesional neck vibration (NMV) in combination with standard visual exploration training is superior to visual exploration training given *without* neck vibration. Twenty neglect patients were randomly allocated to two groups ($n = 10$ each). Each group received 15 sessions of the respective training for 3 weeks (5 per week), after which the two treatments were reversed and another 15 treatment sessions with the other treatment were given (crossover design). The results show uniformly larger treatment gains during the neck vibration + exploration training (regardless of the time when it was received) as compared to exploration training without concomitant neck vibration. Significant improvements in the visual straight ahead, cancellation and reading were obtained after the combined treatment. Furthermore, the improvements transferred to a tactile search task in peripersonal space thus showing multimodal efficacy. Moreover, the improvements transferred to several activities of daily living as rated before and after the treatment blocks by nurses who were 'blind' to the treatment type. According to these ratings, combined neck vibration and visual exploration treatment led to greater improvements in reaching, grasping, transfers from/to bed and wheelchair, and dressing as compared to pure visual exploration treatment. In a subsequent study with 5 neglect patients studied in a single case experimental design it was shown that NMV alone yielded comparable and lasting improvements in visual neglect, without concurrent visual exploration training (Johannsen, Ackermann, & Karnath, 2003). In summary it appears that NMV provides a viable treatment option for neglect. To apply NMV vibrating equipment is required and in the past this may have deterred clinicians from employing this treatment procedure more frequently.

3.3. Caloric- and galvanic-vestibular stimulation

Cold water (caloric) vestibular stimulation (CVS) of the contralesional ear (usually the left) or warm water stimulation of the ipsilesional ear (the right in patients with left neglect) stimulates the horizontal ear canal of the vestibular system and induces a vestibular nystagmus, i.e. reflexive, rhythmical oscillations of the eyeballs consisting of quick and a slow phase, together with a deviation of the so-called 'Schlagfeld' of the nystagmus. CVS reduces sensory neglect in visual exploration and straight ahead tests for some 10–15 min. This procedure also improves neglect-related disturbances of the body scheme, unawareness of hemiplegia and postural imbalance as well (Rode et al., 1992; Rode, Perenin, Honoré, & Boisson, 1998; Rode, Tiliket, Charlopain, & Boisson, 1998). CVS also improves the deviation of the subjective visual straight ahead (Karnath, 1994) and improves somatosensory neglect phenomena for a similar time period (Vallar, Guariglia, & Rusconi, 1997; Vallar et al., 2003). Hence, this type of sensory stimulation exerts *multimodal* positive effects on many aspects of the neglect syndrome. CVS in healthy subjects leads to a strong activation of a large cortico-subcortical network including parietal, temporal, insular and subcortical regions of the hemisphere contralateral to the cold-water-stimulated ear (Bottini et al., 1994, 2001). Despite its short-term effectiveness, caloric stimulation has not been evaluated as a tool for long-term or repetitive stimulation. This is largely due to the vestibular habituation phenomenon associated with repeated caloric stimulation. The typical side effects of this stimulation like vertigo and vomiting encountered in normal subjects are not experienced by neglect patients (Rode, Perenin, et al., 1998).

Galvanic-vestibular stimulation (GVS) stimulates the vestibular system electrically via small intensities of current from two electrodes (one anode and one cathode) applied to the left and right mastoids (or vice versa) behind the ears of the subject (see Utz, Dimova, Oppenlander, & Kerkhoff, 2010, for a detailed recent review). Underneath the mastoids the vestibular nerve runs from the inner ear toward vestibular brain stem nuclei, which in turn are interconnected with thalamic relay stations (nucleus ventroposterolateralis). From there, ascending vestibular fiber pathways reach a number of cortical vestibular areas including area 2cv near the central sulcus, area 3a,b in the somatosensory cortex, parietal area 7a, and the parieto-insularvestibular-cortex (PIVC; Guldin & Grüsser, 1998). Although for the vestibular modality there seems to be no primary cortex as in the visual, auditory or tactile modality, the above-mentioned array of multiple, interconnected vestibular cortical areas is thought to be under the control of the PIVC. GVS is an attractive technique for research and treatment since the application is relatively easy and safe as long as safety guidelines are adhered to (Utz, Korluss, et al., 2011). Studies with neglect patients show that CVS and GVS have a similar immediate effect on neglect symptoms (Utz, Keller, Kardinal, & Kerkhoff, 2011). Studies with neglect patients show that CVS and GVS have similar effects on neglect symptoms. One might speculate that repetitive application of CVS and GVS might induce improvements which outlast the stimulation period. However, currently there is only one study where this approach has been tried. Kerkhoff et al. (2011) used repetitive GVS to treat tactile extinction. They found stable treatment effects which outlasted the stimulation period (see Section 6.2). But in general it is too early to judge the long-term therapeutic potential of this technique.

3.4. Prism adaptation

Prism adaptation is another technique that can be used to correct the rightward orientational bias of patients with neglect. In the typical case of prism adaptation, as applied to neglect patients, subjects wear right-shifting wedge prisms. As a consequence everything is seen as shifted to the right. However, when subjects point to where they see the visual target they will notice that their hand ends up to the right of the real target location. Given the opportunity to observe at least part of their hand movements, they can compensate for the right-shifting errors and over time achieve more accurate pointing movements. After the adaptation period the prism goggles will be removed and subjects will be asked to point to visual targets but this time they cannot see their own hand and therefore cannot judge the accuracy of their pointing movements. In this situation a so-called post-prismatic after-effect is observed. Subjects will now point consistently to the left of the visual target. Another way to assess this after-effect is to ask subjects to close their eyes and indicate with their outstretched arm what they perceive as the straight-ahead direction. It can be observed that after the adaptation phase, the direction of their straight-ahead is rotated toward the left (for a review of the prism adaptation procedure, see (Redding & Wallace, 2006; Redding, Rossetti, & Wallace, 2005). This observation suggests that prism adaptation with right-shifting goggles could also be used to neutralize the rightward bias of neglect patients. Rossetti et al. (1998) tested this idea and found not only a significant reduction of neglect symptoms but also found that the prism-induced alleviation of neglect symptoms will last for at least 2 h and thus much longer than the alleviation obtained with OKS, NMV and caloric stimulation. It is partly the simplicity of the procedure but also the fact that the effects on neglect seem so stable which accounts for the fact that this procedure has attracted in recent years more research than all of the other treatment options combined. Another article in this special issue deals with the theoretical and clinical insights that have been produced by this intense research activity. We will therefore only provide a brief summary on the use of prism adaptation as a tool for neglect rehabilitation in this section.

Despite its early promise it now appears that a single session or even a few sessions of prism adaptation are insufficient to produce stable benefits. Using a single session of prism adaptation and comparing this to a single session of pointing without prism goggles, Rousseaux, Bernati, Saj, and Kozlowski (2006) found no significant improvement of neglect symptoms specific to prism adaptation. More recently Nys, Seurinck, and Dijkerman (2008) used a protocol which included four training sessions and found a short-term but no long-term advantage for training with prismatic goggles. In contrast protocols using 10 or more sessions of prism adaptation found reliable, generalizable benefits which lasted for at least 5 weeks after the end of the therapy (Frassinetti, Angeli, Meneghello, Avanzi, & Ladavas, 2002). This finding was again confirmed in a more recent study (Serino, Barbiani, Rinaldesi, & Ladavas, 2009). One study using a randomized placebo-controlled design did not find a significant treatment advantage for the prismatic training, but the goggles used in this study were much weaker (6° as compared to 10° or even 20°) than in other studies (Turton, O'Leary, Gabb, Woodward, & Gilchrist, 2010). The number of sessions (i.e. 10 training sessions) used in the study by Turton et al. (2010) was the same as in two studies which provided evidence of positive effects (Ladavas, Bonifazi, Catena, & Serino, 2011; Serino et al., 2009). We, therefore, think it is most likely that weak goggles rather than too few trainings sessions are responsible for the negative outcome of the Turton et al. study.

In summary it appears that repetitive prism adaptation can produce significant treatment benefits. But by now it is also clear that a treatment using prism adaptation is not necessarily less time-consuming than other forms of neglect therapy.

4. Classics and newcomers

Recent reviews have typically focused on the sensory stimulation methods which we reviewed in Section 2. This is understandable and reflects the fact that sensory stimulation methods have recently attracted significantly more research than other treatment techniques. However, a review on neglect-therapy would be incomplete without mentioning some of the newer and some of the classic but now often neglected treatment options. Those options range from low-tech eye-patch techniques to high tech TMS treatments. The clinical evidence base for all of these techniques is currently too sparse to judge their potential and efficiency. We therefore decided to simply provide a table which provides some details on the techniques and list relevant studies (see Table 1).

5. Mix and match

During the last two decades a significant number of new options for the treatment of neglect patients have been introduced. The challenge today is thus to decide how to mix and match the

Table 1
List of novel and promising modulation or treatment techniques for patients with spatial neglect Harvey.

Technique	Reference	Sample	Outcome
Repetitive TMS (theta-burst) of the left parietal cortex	Nyffeler, Cazzoli, Hess, and Muri (2009)	$N = 11$ patients with left visual neglect	Transient improvements in visual exploration in left hemispace after 2–4 sessions of Theta-Burst TMS; positive after-effects maintained up to 32 h post-stimulation after 4 TBS. Theta-Burst TMS may thus promote faster recovery from neglect, when repetitively applied
20 sessions of left parietal TMS	Song et al. (2009)	2 × 7 patients with left visual neglect	rTMS improved line cancellation and line bisection selectively in the group receiving rTMS in addition to conventional neglect rehabilitation (scanning). rTMS might thus promote treatment-induced recovery from neglect
Transcranial direct current stimulation (TDCS) of the left- vs. right parietal cortex	Sparing et al. (2009)	10 patients with left visual neglect	Direct current stimulation of the parietal cortex transiently modulated visual neglect in a polarity-specific way. Repetitive stimulation may potentially reveal therapeutic effects in neglect patients
Visuomotor feedback training (patients are presented with horizontally extended wooden rods and asked to lift them)	Harvey, Hood, North, and Robertson (2003)	2 × 7 patients with left visual neglect (one group of 7 took part in the visuomotor feedback training, the other group of 7 was assigned to the control condition (no treatment))	Assessment after the experimenter-led 3-day intervention showed that patients in the intervention group improved in a third of all neglect tests. Patients performed a further 2-week patient-led training. The 1-month post-training assessment showed improved in 46% of the neglect tests. These are promising results which so far have largely been neglected
Combination of visual scanning training plus functional electric stimulation (FES) of the left hand	Polanowska, Seniow, Paprot, Lesniak, and Czlonkowska, (2009)	2 × 20 patients with left visual neglect, most of them with leftsided paresis/plegia	Additional left-hand electrical somatosensory stimulation increased the effects of visual scanning training at 1-month post-test; leftsided somatosensory deficits did not weaken the positive effect. This may be particularly helpful for the treatment of patients with hemisensory loss
Functional electric stimulation (FES) of the left forearm	Harding and Riddoch (2009)	4 patients with left visual neglect and hemiparesis/-plegia	FES improved visual neglect in 3 of the 4 patients; stable results at 6-months-post treatment
Right-half field eye-patching in combination with conventional occupational therapy vs. sole occupational therapy	Tsang, Sze, and Fong (2009)	2 × 17 patients with left visual neglect	Greater improvements of the group that received right-half field eye patching in addition to conventional occupational neglect therapy than in the group without eye patching in conventional neglect tests, but only partially in impairment tests (partially in eating, bathing, dressing)
Interactive virtual environment training for safe street crossing of neglect patients	Katz et al. (2005)	8 vs. 11 patients with left visual neglect	Both groups improved, but the group receiving virtual reality training of street crossing improved more in some measures of the virtual reality tests and in some measures of real street crossing. VR-training may be an additional helpful tool to address problems of daily life such as street crossing, moving in traffic situations

treatment options that are available. Mixing and matching in this context means matching the treatment options to the patient, selecting those treatments which are superior to others and combining them in ways that will enhance the treatment outcome. Currently this process is based on instinct and also – we suspect – on habit and available resources. This is unavoidable since there are currently no evidence-based recommendations which could help the clinicians to match the treatment to the patient, select the best treatment and combine it with other techniques in the most advantageous way. However, there is some progress with respect to the last question. In this section we will describe four studies that examined whether multi-component treatments are more effective than mono-therapies. Schindler et al. (2002) combined NMV with visual scanning and compared this combination to visual scanning therapy on its own. They found a clear superiority for the combined therapy. More recently Saevarsson, Kristjansson, and Halsband (2010) showed that combining NMV with prism adaptation is again significantly more effective than NMV on its own and Schröder et al. (2008) reported that combining visual exploration therapy either with OKS or with TENS yields better results than visual exploration therapy on its own. They also found that adding OKS is more advantageous than adding TENS. Thus, at the moment it might appear that any multi-component therapy is better than any mono-therapy. This presumption is however contradicted by a recent study from Keller, Lefin-Rank, Losch, and Kerkhoff (2009). They compared OKS + PA with OKS alone and found that the combined treatment provides no significant benefits. A different view could therefore be that what matters more is not how you combine treatment but which treatment you choose. It appears that OKS is a fairly effective treatment and its benefits seem to be largely independent of the context in which it is presented. Other treatments such as PA, NMV and TENS seem to produce significant benefits but in less reliable ways and VET on its own is consistently inferior to any multi-component therapy. This suggests a hierarchy of treatments with OKS at the top, PA, NMV and TENS in the middle and VET at the bottom of the efficiency scale. However, this is largely speculative at the moment and just goes to show that what is really needed are studies which directly compare different treatment options against each other and against a placebo treatment.

6. Scotomas in neglect research

6.1. Nonvisual neglect

Most treatment studies focus on visual neglect and pay little attention to other aspects of the neglect syndrome, namely auditory, somatosensory, haptic forms of neglect, body-neglect, motor neglect or representational neglect. This is most likely due to the easy availability and practical assessment of visual neglect by conventional screening tests (i.e. Bells test, Mesulamš test) and neglect test batteries (Wilson, Cockburn, & Halligan, 1987). In contrast tests for the assessment of auditory, somatosensory, haptic or motor neglect are not widely available and the distinction between basic deficits (e.g. hearing loss in the case of auditory neglect or hemiplegia in the case of motor neglect) and neglect-related deficits in the auditory, haptic, somatosensory and motor domain can be difficult. Despite these difficulties it should be borne in mind that non-visual forms of neglect can be very disabling and should therefore be considered in the evaluation and development of neglect treatments. In the case of motor neglect mirror therapy could prove useful. During mirror therapy, a mirror is placed in the patientš midsagittal plane, presenting the patient with the mirror image of his or her nonaffected arm (Dohle et al., 2009). The mirror image of the ipsilesional right arm activates the right hemisphere because it is perceived as the contralesional left arm in the mirror. Several studies have shown that mirror therapy improves arm function (Dohle et al., 2009), hand function (Yavuzer et al., 2008), and leg function (Sutbeyaz, Yavuzer, Sezer, & Koseoglu, 2007) in patients with unilateral acute hemiparesis after stroke. Interestingly, the study by Dohle et al. (2009) noted also significant improvements in visuospatial neglect after mirror therapy. Mirror therapy might therefore provide an effective add-on treatment to rehabilitate motor functions *and* sensory neglect at the same time.

Dysphagia (swallowing disorders) is often observed in patients with right-hemisphere stroke and left-sided neglect (Andre, Beis, Morin, & Paysant, 2000). These patients tend to neglect food and saliva in their mouth, display a lack of exploratory movements of their tongue toward their left part of the mouth, just as in ocular or manual exploration of the contralesional space. The clinical signs of the disorder include dribbling, choking, retention of food and an impairment of tactile detection and taste sensation in the affected part of the mouth. Affected patients appear to be unaware of their left body (mouth) side, which so far has been largely ignored in studies looking at the efficacy of neglect therapy. Importantly, neglecting food during swallowing can cause aspiration (i.e. food/saliva getting into the trachea and from there into the lungs) of food or saliva and can thereby lead to life-threatening situations. Despite its clinical relevance there is little empirical research on this topic. It is currently unclear whether these problems are caused by loss of sensory or motor function or unilateral neglect. If neglect contributes to the swallowing problems in these cases the application of sensory stimulation techniques, which proved effective in the treatment of visual and auditory neglect, might also ameliorate signs of dysphagia in these patients.

6.2. Sensory extinction

A phenomenon which is often associated with the neglect syndrome or sometimes considered to be a minor form of neglect by some researchers is extinction. Extinction of sensory stimuli is defined as the inability to process or attend to the more contralesionally located stimulus when two stimuli are simultaneously presented. By definition, the processing of a single stimulus should be only marginally impaired, thereby ruling out gross elementary sensory deficits (i.e. hemianopia, hemianaesthesia, unilateral hearing loss).

Although extinction is frequently found in different modalities (visual, haptic, auditory) only a few studies examined the impact of neglect therapy on extinction. Those studies used mostly a single session approach and found regardless of whether they used CVS (Vallar, Bottini, Rusconi, & Sterzi, 1993), OKS (Nico, 1999), peripheral magnetic stimulation (Heldmann, Kerkhoff, Struppler, Havel, & Jahn, 2000) or PA (Maravita et al., 2003) a transient improvement of signs of sensory stimulation. In a recent multi-session study it was shown that GVS can lead to reduced tactile extinction, an effect that lasts for more than 3 months (Kerkhoff et al., 2011). The findings are based on a small group of patients and should be considered preliminary, but they suggest that multiple-session sensory stimulation therapy could also be usefully employed to improve signs of sensory extinction.

6.3. Transfer and treatment intensity

Bowen and Lincoln (2007) pointed to the dearth of evidence demonstrating a clear transfer of treatment benefits into the daily lives of patients. Part of the problem is that there are hardly any objective and standardized measures that would allow researchers to assess how patients cope with real life activities. Most activities of daily life (ADL) measures use reports or questionnaires which target a wide range of activities and disabilities (e.g. FIM, Granger, Hamilton, Linacre, Heinemann, & Wright, 1993), for an exception, see the Catherine Bergego Scale (Azouvi et al., 2003). As a consequence these questionnaires are not only lacking in objectivity, they are also often too crude to detect neglect-specific improvements. To put it simply a patient with recovered neglect and hemiplegia will still require help in many situations as a consequence of the remaining hemiplegia and thus her score on a functional independence measure might therefore not look much improved. But does that mean that the therapy leading to the recovery from neglect was useless? This patient may still need help, but this help will be easier to administer because the patient will cooperate, the patient will be able to read and entertain herself better (typically not an item on most disability scales), will be less likely to bump into obstacles and in general will be less frustrated by experiencing her external environment as strange, confusing and unobliging. The transfer of benefits into the real life is certainly an important issue, but the problem here is not just a reluctance of researchers to apply appropriate measures, it is the lack of valid, objective and sensitive measures and the lack of an agreed consensus on what we should consider as a significant and relevant improvement.

However, another problem might also be that evidence for transfer of treatment benefits into the patients' daily lives is missing because such transfer might require a different form of treatment. Sohlberg and Mateer (2001) have argued that transfer does not happen, transfer needs to be trained. Such training of transfer which involves the therapy-guided application of treatment gains to ADL situations is not a standard component of any of the reviewed neglect therapies. However, it might have to become one if we wish to see evidence of transfer to ADL situations. In this context it is also worth pointing out that transfer might be related to treatment intensity. As previously mentioned early neglect treatment studies found that a minimum of 40 treatment sessions are required to obtain significant and lasting effects on ADL tasks (Antonucci et al., 1995; Kerkhoff, 1998b). The difficulty with more recent treatment studies might lie in the fact that even multi-session protocols rarely used more than 20 treatment sessions. This points to a more general shortcoming of current research on neglect therapy, namely that there is no systematic effort to establish which intensity (massed or distributed practice) or duration of treatment is needed to achieve long-lasting and transferable treatment benefits.

6.4. Funding for rehabilitation research

However, the most relevant scotoma is perhaps not a blindness of researchers but a blindness of funding agencies. We tend to return to the same questions (reviews) and bemoan the same shortcomings: lack of randomized control studies, studies with too few training sessions, lack of long-term follow-up, no objective measures of transfer into ADL, no direct comparison of different treatments, no large-scale, multi-center studies (e.g. Bowen & Lincoln, 2007). We could go on describing these shortcomings. But if researchers fail to address those questions it is surely not because of ignorance but because of structural weaknesses in the system and we all know what these structural weaknesses are. Long-term studies can only be performed if the time is provided to carry out these long-term treatments. However, in the current health-funding climates, the trend for ever shorter hospital and rehabilitation times make it increasingly difficult, if not impossible, to study treatment regimes which last for more than two or three weeks. Hence, it appears that in countries using the DRG-system (Diagnostic-Related-Groups) as for instance Germany and in the near future also Switzerland, longer-lasting treatment studies are extremely difficult to carry out, because the patients stay only for some 3–6 weeks in the clinic. Apart from reducing the possible number of treatment sessions und thus limiting efficacy of treatment, this makes long-term follow-up investigations also difficult. Large-scale studies also require large-scale funding. But with funding for rehabilitation currently being a low priority (as communicated from colleagues in Germany, Switzerland, Netherlands, UK), large-scale funding for rehabilitation projects is currently out of the question. Given the current demographic trends it is clear that stroke and its disabling consequences will become an ever larger problem. In this context the current failure to provide sufficient funding for research on neurorehabilitation can no longer be called a scotoma, it is a form of complete blindness.

7. Conclusion

The last two decades have seen a dramatic increase in the number of techniques available for the treatment of unilateral neglect. Many of these techniques were developed from experimental interventions designed to influence the rightward orientation bias of neglect patients. These sensory stimulation techniques have some obvious advantages. They are easy to apply, their effects tend to generalize to a number of different neglect symptoms and they only require minimal patient-compliance – a huge benefit in the case of a disorder that is frequently associated with anosognosia. The induced improvements can last for several weeks when *multiple* treatment sessions are applied. However, the initial hope for a quick cure for neglect after only one or a handful of treatment sessions has turned out to be unrealistic. The challenge today is to select the best tool for a given patient and to know how to combine the different available treatments for maximum effect. To answer this challenge we need empirical evidence which identifies the best treatment, the optimal amount of treatment sessions, the best combination of treatments and provides treatment-specific predictors for therapy-responders. While in recent years some progress has been made in this respect, much more research is needed. This is also true for a number of other topics. While in the past most research focused on visual neglect other equally relevant aspects such as auditory, motor or buccal neglect received little attention. Moreover, neglect in childhood has received little attention, and treatment of children with neglect even less (Bollea et al., 2007). We have no doubt that some of these ignored topics will be duly addressed by future research. However, there are some gaps in neglect research, which have a longer history. Reviewers have criticized for some time that too little research into the long-term effects of neglect-therapy and its transferability into daily life are conducted. The fact that little has changed despite these reminders suggests that the underlying problem is not ignorance but lack of available funding resources. Along with many others we are convinced that today the biggest obstacle to progress in neglect rehabilitation is not the lack of ideas but the lack of funding.

Acknowledgment

This work was partially supported by a grant from the Deutsche Forschungsgemeinschaft (IRTG 1457 "Adaptive Minds") to Georg Kerkhoff.

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