

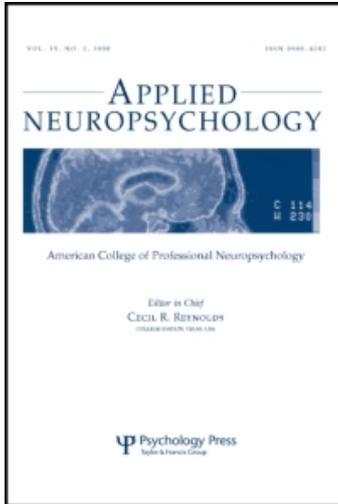
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### Designing Rehabilitation Programs for Neglect: Could 2 Be More Than 1+1?

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# Designing Rehabilitation Programs for Neglect: Could 2 Be More Than 1+1?

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Unilateral neglect is a multimodal neuropsychological disorder that has puzzled scientists for a long time. Many interventions have been developed, but only a handful has proven to be effective. This review examines whether applying different therapeutic techniques in combination will increase therapeutic benefits. Studies were reviewed where therapies are applied sequentially or in combination with other techniques. The results indicate that combining different interventions leads to increased general improvement compared with other noncombined designs, even when the number of treatment sessions is not constant. Practical and theoretical aspects of different treatments are discussed. The combined approach to treatment may have direct relevance to disorders other than neglect. This report introduces a new classification scheme for different interventions with the aim of facilitating more focused therapy. Finally, suggestions are made as to what the focus of future studies of neglect therapy should be and how therapeutic benefits might be maximized.

*Key words: classification scheme, sequential and combined designs, therapeutic designs, unilateral neglect*

## INTRODUCTION

Unilateral neglect is a multimodal neuropsychological disorder where patients fail to respond to stimuli in their contralesional hemifield (Heilman, Watson, &

Valenstein, 2003; Mesulam, 1985). A patient with neglect may fail to read the left part of a sentence, may read only the right pages of a book, or may fail to notice that someone passes them by on their left side (Weinstein, 1981). Although neglect is severely disabling for patients, effective treatment strategies for the disorder have remained elusive.

One out of three stroke victims shows symptoms of neglect, and new cases of neglect are estimated to be 3

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to 5 million per year worldwide (Appelros, Karlsson, Seiger, & Nydevik, 2002; Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Pedersen, Jørgensen, Nakayama, Raaschou, & Olsen, 1997). Right-hemisphere stroke patients with neglect are more likely to show deficits in daily functioning compared with right-hemisphere stroke patients *without* the disorder, even when lesion size is taken into account (Buxbaum et al., 2004; Denes, Semenza, Stoppa, & Lis, 1982; Freund, 1987; Katz, Hartman-Maeir, Ring, & Soroker, 1999). Effective treatment would clearly be of value to patients and their families and would reduce the costs of health care. Note that only a decade ago, some standard textbooks argued that neglect was essentially untreatable (see Robertson, 2002).

A number of therapeutic interventions for neglect have been developed in the last few decades, but very few have conclusively been shown to be of value in treating the syndrome. Some have speculated that stronger and more durable intervention effects might result from combining different treatments or applying different treatments repeatedly (e.g., Kerkhoff, 2003; Rossetti & Rode, 2002; Singh-Curry & Husain, 2008). This raises the important question of whether the particular therapeutic *design* may play as large a role in neglect rehabilitation as the individual intervention techniques.

The aim is to compare the effects of combining different therapies (either simultaneously or sequentially) with other therapy approaches, and to understand what benefits might be gained by using combinations of therapies to treat neglect, as compared to single-session and sequential applications of the same rehabilitation techniques. This topic has not been systematically addressed in earlier reviews. The review also introduces a new classification scheme for different types of therapy, with the aim of assisting clinicians in making informed decisions about which therapies are best suited to the treatment of individual patients with idiosyncratic symptoms.

### MULTIMODALITY OF NEGLECT

Neglect is a multimodal *syndrome* where various types of dysfunction vary greatly between patients (e.g., Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2009) and the critical neural tissue damage varies between individuals. The affliction is “at its core” a disorder of attention, and the neural systems damaged correspond well with regions that have been shown to play key roles in attentional orienting (Awh & Jonides, 2001; Geng et al., 2006; Jovicich et al., 2001; Kristjánsson, Vuilleumier, Schwartz, Macaluso, & Driver, 2007; Ruff, Kristjánsson, & Driver, 2007; Yantis & Serences, 2003). Neglect is therefore not connected with damage to sensory areas of the brain. For example, neglect is not necessarily confined to vision and manifests itself in

many different types of deficits. The best intervention will therefore involve treatment of the multifaceted symptoms of neglect with different interventions, each of which could target the individual deficits. For example, the syndrome seems to involve dysfunctional attentional orienting toward one hemifield; other researchers have argued that the deficits are not necessarily confined to one visual field (Duncan et al., 1999; Husain et al., 2001, but see Kristjánsson & Vuilleumier, 2010). Furthermore, some studies have shown that many aspects of the perceptual process remain intact for the affected hemifield (see e.g., Conci et al., 2009; Driver & Vuilleumier, 2001; Finke et al., 2009; Kristjánsson, Vuilleumier, Malhotra, Husain, & Driver, 2005; Mattingley, Davis, & Driver, 1997; Saevarsson, Jóelsdóttir, Hjaltason, & Kristjánsson, 2008). Interventions that only focus on rectifying the rightward bias or only address the deficiencies in search behavior might then fail to address crucial aspects of the syndrome. A therapeutic approach that attacks both these aspects could be much more effective (e.g., Saevarsson, Kristjánsson, & Halsband, 2010).

### PROGNOSIS AND RECOVERY

Full or partial spontaneous recovery of neglect may occur for some patients after onset, while the syndrome remains chronic for a sizable number. Stone, Halligan, and Greenwood (1993) have reported that 82% of right-hemisphere and 65% of left-hemisphere stroke patients show *acute* neglect symptoms, while Halligan and Marshall (1989) found that 48% of right-hemisphere and 15% of left-hemisphere stroke patients show symptoms of the disorder for at least 2 months following stroke. The degree to which this recovery was confounded with poststroke therapy is not known. How the effects of neglect therapy may interact with spontaneous recovery is unclear and is a notoriously difficult issue to address experimentally. Some degree of recovery usually occurs spontaneously in the weeks or months following stroke, typically within the first 3 months, while at other times, recovery is not seen until a few years following the brain injury. Different aspects of the syndrome may also recover at different rates (such as motor dysfunction and anosognosia; Cramer, 2008).

Corbetta and colleagues (2005) studied changes in neural plasticity connected with recovery in neglect. They found that recovery from symptoms caused by right frontal lesions was correlated with structural changes of this area and physiological changes in intact dorsal and ventral networks of attention that are functionally related to, but anatomically distinct from, the locus of the brain injury. However, they did not explicitly address the extent to which this recovery was

therapy based versus spontaneous. Both behavioral measurements and functional imaging were performed at an acute stage of the syndrome (3 to 4 weeks following stroke) and were repeated more than 6 months poststroke, when the symptoms had become more stable. Some of the patients received some kind of neglect therapy during this period. Robertson, McMillan, Edgeworth, and Brock (2002) speculated that the plasticity changes produced by recovery following rehabilitation and spontaneous recovery could be quite similar, making any distinct effects of the two difficult to disentangle. Many questions remain unanswered regarding recovery rates for different therapies (Cramer, 2008).

### INTERVENTIONS FOR NEGLECT

There appears to be a general consensus that interventions of clinical value for neglect should lead to benefits lasting at least a day or longer. There is, however, much less agreement on *how* the syndrome should be treated. Long-term clinical benefits have not been sufficiently evaluated for all methods (Robertson, 2002). Nevertheless, those treatments that have not yet been found to be clinically useful in terms of the duration of beneficial effects might still be found to play a role in treating neglect—for instance, if they can facilitate any benefits from using another intervention by shrinking the neglected space at the time of intervention and strengthen the overall clinical effects when used in conjunction with other therapies. *Caloric vestibular stimulation*, to cite one example, might increase the alertness of neglect patients as other interventions, such as prism adaptation (PA) or eye patching, when simultaneously applied (see e.g., Saevarsson, Kury, et al., 2008, for some preliminary findings).

Only a few functional brain imaging studies have been performed to explore the neurophysiological bases of therapies for neglect (see Arene & Hillis, 2007, for an overview). For instance, a positron emission tomography study by Luauté, Michel, et al. (2006) showed that low-level visuomotor adaptation (i.e., automatic modifications of visuomotor correspondence following a prism-exposure phase) resulted in modulations of neuronal activity in the right cerebellum, the right posterior parietal cortex, the left thalamus, the left temporo-occipital cortex, and the left medial temporal cortex (see also Luauté et al., 2009). Similar rehabilitation studies on animals show how behavioral recovery is correlated with plasticity changes in the brain (e.g., Nudo, Wise, SiFuentes, & Milliken, 1996). These studies give some indication of what sort of reorganization of the dysfunctional neural networks takes place following the application of these interventions. How these findings on the neurophysiological underpinnings of different methods relate to the selection of interventions and thera-

peutic designs for patients as a function of their individual brain lesions remains to be systematically studied.

### WHAT DETERMINES THE SUCCESS OF THERAPY FOR NEGLECT?

A large number of unrelated factors can affect the outcome of a particular treatment. As with many other health problems, the symptoms of neglect can vary over time. Because different interventions have different limitations and merits, some interventions can be more therapeutically relevant than others for different subgroups of patients, or for similar groups at different times. For instance, one therapy might be more relevant when rapid effects of intervention are important (Saevarsson, Kristjánsson, Hildebrandt, & Halsband, 2009). However, what kind of therapy is most effective at different points in time following the onset of neglect remains unclear.

Regrettably, a sizeable number of patients do not seem to receive any benefits from therapy. The patients' level of functioning may be too severely disrupted for them to undergo treatment, or the selected therapies may not target their clinical symptoms sufficiently (see e.g., Vuilleumier, 2007). Because neglect is multifaceted and some interventions seem to be quite task specific, the choice of intervention is of great importance (Rossetti & Rode, 2002). Visual scanning training has for instance been found to help patients with reading, but the benefits of this training are remarkably specific to this single task (Manly & Mattingley, 2004). Some medical problems can exclude certain interventions, therapy combinations, or therapy sequences. For instance, neck vibration (NV) is not recommended for patients wearing a pacemaker or for epileptic patients without medication. Eye patching should be avoided if a patient suffers from hemianopia, and PA should be avoided if the patient suffers from dizziness. A few guidelines can be pointed out that are useful in designing individualized therapy sessions. For one, it is important to consider the nature and degree of the patient's cognitive impairment because impairments can vary greatly between patients in terms of arousal levels, sustained attention, and spatial orienting (Robertson, 2002). For instance, some patients show improvements from visuospatial motor cueing training but not from visual scanning training (Samuel et al., 2000).

The symptoms of the vast majority of neglect patients fall under more than one subcategorization (e.g., motor, visual, tactile, olfactory, or auditory), and different interventions seem to affect different subtypes of the disorder (see Rossetti & Rode, 2002, for an overview). Thus, when an individual therapy is designed, such differences in the individual symptomology of differing patients must be taken into account. When a patient's

fitness, or general ability level, is too low, sequential application of interventions in which patients can rest between sessions might be more advisable than simultaneous combined interventions, because the patient may simply cope more easily with the therapy (although the results of Keller, Lefin-Rank, Lösch, & Kerkhoff, 2009, may suggest some important caveats to this). Simultaneous combined interventions may be preferable when the patient's fitness level is high, because the total intervention time is shorter as compared with the sequential approach, and some research indicates that this may be a more effective intervention type overall. Future research should address differences in therapeutic effects when two interventions are applied in combination or in sequence.

### CLASSIFYING THE DIFFERENT INTERVENTION DESIGNS

Systematic classification of the different rehabilitation schemes may lead to more informed choices of therapy designs. The following three classification criteria are proposed: (1) *passive* versus *active* therapies, (2) *restorative* versus *compensatory* therapies, and (3) *top-down* versus *bottom-up* therapies. *Passive* interventions do not necessarily require the patient's attention and collaboration. This type of intervention can be used in combination with any other type of intervention if the patient's fitness level is high enough to allow this. NV is an example of such a passive intervention. For instance, PA is an *active* intervention technique that requires the patient's collaboration, attention, and vigilance. While passive intervention techniques can be combined with other passive or active techniques (see e.g., Saevarsson et al., 2010), there may be problems with applying two or more active intervention techniques simultaneously (see e.g., Keller et al., 2009). Interestingly, Luauté, Halligan, Rode, Rossetti, and Boisson (2006) recommended mostly active neglect interventions (such as PA and visual scanning training) in their comprehensive review of therapeutic techniques for neglect. Only one of the interventions recommended in their review was a combination of active and passive techniques (NV combined with an extensive training program). More research involving combinations of passive and active therapy types might reveal a more important role for passive therapy approaches. To provide an example, Saevarsson et al. (2010) and Saevarsson, Kristjánsson, Hildebrant, et al. (2009) recently found more improvement in neglect symptoms when NV and PA were used in combination, as compared with NV or PA applied on their own.

*Compensatory* interventions involve feedback upon performance or some form of support provided by the

therapist. Interventions of this sort can be both passive and active. For instance, visual scanning (Weinberg et al., 1977) is an active compensatory training technique, while limb activation is passive compensatory. Limb activation might be categorized as passive for hemiplegic (paralyzed on the left side of their body) patients and active for those without hemiplegia. A *restorative* intervention is aid or medicine based and is not necessarily dependent on help from a therapist. NV (Karnath, Christ, & Hartje, 1993) and repetitive transcranial magnetic stimulation (TMS; Oliveri et al., 2001) are examples of passive–restorative interventions, and PA is an example of an active–restorative intervention.

The aim with *top-down* approaches is to get the patient to voluntarily reduce or compensate for their neglect symptoms by providing them with strategies to improve their functioning. Such approaches do not always require the use of external devices. Top-down methods can be passive–compensatory (e.g., music training) or active–compensatory (e.g., mental imagery; Smania, Bazoli, Piva, & Guidetti, 1997). Passive–restorative and active–restorative top-down approaches that have been used for the treatment of neglect were not found. The aim with *bottom-up* approaches is to alter underlying causes, normally through the use of a device that manipulates stimuli in the patient's environment or enhances their awareness of their neglected side. Bottom-up interventions do not necessarily require the patient's cooperation and can, with relative ease, be combined simultaneously with many other interventions. Bottom-up approaches can be subdivided into passive–compensatory (such as dimming the lights; Hjaltason & Tegner, 1992), active–compensatory (limb activation; Halligan & Marshall, 1989), passive–restorative (NV; Karnath et al., 1993) and active–restorative (caloric stimulation; Rubens, 1985).

Table 1 presents brief descriptions of 10 interventions that have been developed for neglect. The table categorizes each rehabilitation technique in terms of the three criteria that have been explained here. The focus is on interventions that have either been used in combination with other methods or sequentially with the same or different therapies. This categorization of therapy techniques can be used as a guide when a rehabilitation program for a particular patient is designed, and may aid in the development and design of future studies of the efficacy of neglect interventions, particularly as they are applied with other methods. While evidence for the efficacy of each of these methods is quite variable, the main point here is that it is important to attack the symptoms from different angles. Although the efficacy of a specific method may not be supported by strong evidence, it may nevertheless be of value when used in combination with other therapy types (see e.g., Saevarsson, Kury, et al., 2008).

TABLE 1

Brief Rationale and Description of Specialized Neglect Interventions That Have Been Used in Combination and Sequentially With Other Methods

<i>Name of Intervention</i>	<i>Procedure/Rationale</i>	<i>Mechanism</i>	<i>Attentional Load</i>	<i>Compensatory/Restorative</i>	<i>Can be Used Simultaneously with</i>
1. CVS	Injection of cold water in the external ear canal produces correction of spatial coordinate frame.	Bottom-up	Passive	Restorative	2–10
2. EP & RHB	Eye patches are worn to produce Sprague effect (visually guided behavior to the contralateral space).	Bottom-up	Passive	Restorative	1, 3–10
3. LAT	Active and passive movements with a left limb to the left to increase the function of the right hemisphere.	Bottom-up	Active/Passive	Compensatory	1–2, 4–10
4. NV	Vibration applied to posterior part of left neck muscles to recalibrate egocentric/spatial coordinates.	Bottom-up	Passive	Restorative	1–3, 5–10
5. OPKS	Leftward moving background of a screen that causes recalibration of spatial coordinates.	Bottom-up	Active	Restorative	1–4, 9
6. PA	Successive pointing movements while wearing prisms that produce visuomotor adaptation.	Bottom-up	Active	Restorative	1–4, 9
7. SAT	Examiner touches different locations on a patient's back and the patient has to indicate the touched location on a mannequin in front of them.	Top-down	Active	Compensatory	1–4, 9
8. SATG	Sequential sound stimulation to alert spatial attention to left.	Top-down	Active	Compensatory	1–2, 9
9. TENS	Surface stimulation with electrical impulses that generate tingling sensation.	Bottom-up	Passive	Compensatory	1–8, 10
10. VST	Uncued and cued voluntary scanning eye movement training to the left side of a scanning board.	Top-down	Active	Compensatory	1–3, 9

*Note.* Abbreviations for interventions: CVS = Caloric vestibular stimulation; EP = Eye patching; LAT = Limb activation training; NV = Neck vibration; OPKS = Optokinetic stimulation; PA = Prism adaptation; RHB = Right hemifield blinding; SAT = Sensory awareness training; SATG = Sustained attention training; TENS = Transcutaneous electrical nerve stimulation; VST = Visual scanning training.

### CAN THE USE OF EXTANT THERAPY TYPES BE IMPROVED?

Only a handful of therapies have been developed that have been shown to result in significant, relatively long-lasting reductions in symptoms, in terms of neuropsychological testing and functional effectiveness (see e.g., Luauté, Halligan, et al., 2006, for a comprehensive overview; see also Bowen & Lincoln, 2002). Although some single-session interventions have shown relatively long-term clinical benefits on neglect symptoms, many authors have argued that combined applications of different interventions (even applied repeatedly) could increase the therapeutic effects of various interventions that have already been developed (e.g., Kerkhoff, 2001, 2003; Manly & Mattingley, 2004; Rossetti & Rode, 2002). In this context, Kerkhoff (2001, p. 21) asked: “How can different treatment approaches be combined effectively to reach a maximal outcome for the patient?” Singh-Curry and Husain

(2008, p. 449) echoed this question: “Both spatial and nonspatial mechanisms contribute to neglect and may represent different targets for treatments aimed at rehabilitating the condition.” In the future, it is likely that new interventions, new combinations of extend methods, and new sequences of known methods will be developed and may become standard tools for treating neglect. It is suspected that the design of such methods will (and should) be the focus of research in the coming years because current interventions have not proved to be sufficiently effective at relieving neglect symptoms, while evidence that combining therapies can lead to *additive* therapeutic benefits upon neglect continues to emerge.

Recent years have seen an increased number of studies where different therapies are used both in combination and sequentially. In an attempt to measure the effects of such approaches, a literature search aimed at identifying and classifying studies of this sort was performed. The Medline, PsychInfo, ScienceDirect, and

TABLE 2  
Studies That Have Applied Simultaneous Combined Therapeutic Methods for One Session in Neglect Rehabilitation

Study	Interventions	Number of Patients	Duration of Intervention	Therapeutic Results
Butter & Kirsch (1992)	EP, VST	31	Unspecified	The group that received both interventions showed stronger improvement than either of the two groups that only received training on one of the treatments.
Saevarsson, Kristjánsson, & Halsband (2010)	PA, NV	12	20 min	More improvement from combined NV and PA compared with PA and NV applied in isolation.
Saevarsson, Kristjánsson, & Halsband (2008)	PA, RHB	4	10–15 min	Some indication of improvement in the PA–RHB group, but not in the PA–LHB group.

Note. Abbreviations in the table: EP = Eye patching; LHB = Left hemifield blinding; NV = Neck vibration; PA = Prism adaptation; RHB = Right hemifield blinding; VST = Visual scanning training.

TABLE 3  
Studies That Used Combined Therapeutic Designs in Neglect Rehabilitation With Treatment Applied More Than Once

Study	Interventions	Number of Patients	Duration of Intervention	Therapeutic Results
Brunila et al. (2002)	LAT, VT	4	6 weeks	Combined approach suggests additive therapeutic effects.
Polanowska et al. (2009)	LSS, VST	40	1 month	LSS combined with VST showed more benefits than VST alone.
Schindler et al. (2002)	LAT, ET	10	1 week	The group that received both treatments showed superior therapeutic effects compared with VST.
Schröder (2008)	ET, TENS	30	1 week	Combined approach led to larger improvement than exploration training on its own.
Wiert et al. (1997)	VST, TR	25	1 month	Combined approach resulted in more improvement than the control group, which received regular neurorehabilitation.
Wiebecke (2007)	PA, RPMS	26	3–4 weeks	Combined approach showed the same improvement as the PA on standard tests. Only the PA group showed improvement in daily function.

Note. Abbreviations in the table: ET = Exploration training; LAT = Limb activation training; LSS = Left-hand somatosensory stimulation; PA = Prism adaptation; RPMS = Repetitive peripheral magnetic stimulation; TENS = Transcutaneous electrical nerve stimulation; TR = Trunk rotation; VST = Visual scanning training; VT = Visual training.

Web of Science databases were used to identify studies where one of four types of therapeutic design was employed (see Tables 2 to 5). Thirty-nine relevant studies using this search criteria were found. An attempt to estimate the success of different therapeutic designs in neglect was made based on the results of these identified studies.

Table 2 lists the studies where two different treatment approaches (*combined design*) have been applied simultaneously in one session. Table 3 shows approaches where a combination of treatments (*sequential combined design*) is applied for more than one session. Table 4 shows studies that have used *sequential designs*, where a single therapeutic approach is applied repeatedly. Table 5 shows *sequentially mixed designs*, where dissimilar treatments are applied at different times.

What can be learned from the findings on combined and sequential approaches to neglect therapy tabulated here? The most important conclusion is that combined

sequential designs (as shown in Table 3) seem to be the most effective form of treatment.<sup>1</sup> All sequentially combined therapy studies (see Table 3) appeared to result in larger improvement for the experimental group as compared with a control group. In addition, the three studies in which the single-session combined approach was used show some evidence of additive therapeutic effects, as compared with the control groups (see Table 2). The results from Tables 2 and 3 suggest that combining two or more treatment methods and applying them simultaneously, preferably with repeated application, is a quite promising avenue for neglect therapy and rehabilitation.

<sup>1</sup>At present, the low number of relevant studies prevents us from drawing strong conclusions about *individual* combinations of therapies and designs. Our aim is rather to highlight some trends in the findings—in particular that combinations of approaches hold the greatest promise—and to point the way forward in terms of research into different therapeutic designs.

TABLE 4  
Studies That Have Used Sequential Interventions (Same Method Applied Repeatedly) in Neglect Rehabilitation

<i>Study</i>	<i>Intervention(s)</i>	<i>Number of Patients</i>	<i>Duration of Intervention</i>	<i>Therapeutic Results</i>
Bailey et al. (2002)	VST or LAT	7	3 weeks	Patients in both groups showed improvements 3 weeks after intervention.
Cherney et al. (2003)	VST, AT, or OR	4	8–9 weeks	No clear conclusions could be drawn about the success of the intervention.
Dijkerman et al. (2004)	PA	1	1 month	Results are not reported on whether the second PA session produced stronger improvement than the first session of PA.
Frassinetti et al. (2002)	PA	13	5 weeks	Improvement was found on many different neglect tests following 5 weeks of repeated application of PA.
Harvey et al. (2003)	VFT	14	6 weeks	Significantly more improvement than that seen for a control group of neglect patients.
Humphreys et al. (2006)	PA	1	14 weeks	Results indicate long-term improvement following prolonged PA.
Johannsen et al. (2003)	NV	10	10 days	Improvement from symptoms of neglect 1–4 years following therapy.
Katz et al. (2005)	IVET	19	1 month	Some indication of improvement.
Kerkhoff et al. (2001)	OPKS	3	2 weeks	Improvement of neglect symptoms 18–24 months following therapy.
Kerkhoff et al. (2006)	OPKS or VST	10	2 weeks	Significant improvement in the OPKS group unlike the VST group.
Maddicks et al. (2003)	LAT	1	10 days	Improvements were found in the locomotor space but not in peripersonal space.
McCarthy et al. (2002)	IT	2	Unspecified	Imagined movement of left arm improved neglect, and the effect was specific to the arm that was imagined.
Nys et al. (2008)	PA	16	1 month	No clear difference between the PA and the control group was found.
Robertson et al. (2002)	LAT	39	3 months	The intervention was linked to long-term improvement of neglect.
Serino et al. (2009)	PA	20	2 weeks	Stronger effects compared with a control group of patients. Beneficial effects were confirmed 1 month following the PA.
Shiraishi et al. (2008)	PA	7	2 months	Long-term improvement of eye movements to the neglected side.
Song et al. (2009)	rTMS	14	2 weeks	Some indication of improvement of neglect symptoms.
Sturm et al. (2006)	CAT, OPKS	14	3 weeks	The CAT and the OPKS groups both showed 3 weeks improvement following 3 weeks of training.
Thimm et al. (2006)	CAT	7	3 months	Limited improvement of neglect symptoms.

*Note.* Abbreviations in the table: AT=Attention training; CAT=Computerized alertness training; IT=Imagination training; IVET=Interactive virtual imaging training; LAT=Limb activation training; NV=Neck vibration; OPKS=Optokinetic stimulation; OR=Oral reading; PA=Prism adaptation; rTMS=Repetitive transcranial magnetic stimulation; VFT=Visuomotor feedback training; VST=Visual scanning training.

On the other hand, the results from the 19 studies in which only a single therapy type was used (see Table 4) are rather heterogeneous. While some studies show evidence of moderate improvement, others do not. Finally, the 11 studies that used sequentially mixed designs (see Table 5) show improvements in symptoms for most patients, in basic agreement with the findings in Tables 2 and 3.

The most important conclusion from Tables 2 through 5 is that the three approaches (Tables 2, 3, and 5), which mix different therapy types, appear to result in larger improvements of neglect symptoms than sequential designs where a single therapy type is applied repeatedly (Table 4). What is particularly interesting is that in some cases the design seems to play as large a role as the intervention itself, regardless of the number or intensity of therapeutic sessions that are applied for both types of designs. This indicates that the particular therapy type employed is not the only important factor

with regard to neglect rehabilitation, but that the therapeutic design and how it interacts with a particular therapy type are equally important. If true, this finding should transform the agenda for future studies on neuropsychological rehabilitation.

Although the vast amount of single-session studies on the different interventions were not reviewed here (i.e., therapies not used in combination with other methods as in Table 2), all four categories of design tabulated in Tables 2 through 5 seem to show superior therapeutic effects compared with single-session baseline interventions (most of the studies provide such baselines). The main limitation of the information given in these tables is the relatively low number of studies.<sup>2</sup> Furthermore, neglect was assessed in many nonuniform ways across these studies, which may have affected the outcome evaluations. Additionally, because only a small number of

<sup>2</sup>This scarcity of studies precludes a meta-analysis at this point.

TABLE 5  
Studies That Have Used Different Interventions Applied at Different Times to Explore Neglect Rehabilitation

Study	Interventions	Number of patients	Duration of Intervention	Therapeutic Results
Antonucci et al. (1995)	GCI, VST, RT, CT, FD	20	2 months	Experimental and control (no special intervention) groups showed similar improvement of neglect symptoms.
Hildebrandt et al. (1998)	VCT, CS	25	4 weeks	The approach resulted in additive therapeutic effects.
Hildebrandt et al. (1999)	VCT, TENS, AS	>32	4 weeks	Additive effects were revealed with the approach.
Karnath (1995)	TENS, NV	4	Unspecified	Only short-term improvement was found after NV at the time of intervention.
Keller et al. (2009)	PA, OPKS	10	Ca. 30 minutes	OPKS alone resulted in more improvement compared with when PA was also applied.
Pizzamiglio et al. (2004)	OPKS, VST	3	6 weeks	The mixed sequential application of VST and OPKS was not found to produce additive therapeutic effects.
Robertson et al. (1992)	PCL, LAT, AVP	3	5 days	All sequences of intervention showed improvement.
Samuel et al. (2000)	VSMC, VST	2	2 days	Patients showed improvement of neglect symptoms 1 month after intervention.
Weinberg et al. (1979)	SAT, SOT, VST	53	4 weeks	The experimental groups showed stronger improvement compared with the control group.
Wilson et al. (2000)	LAT, SATG	1	20 days	Additional sequential benefits from sequential mixed therapy compared with LAT alone.
Wilson & Manly (2003)	SATG, EL	1	20 days	Improvements were found 2 weeks following intervention.

*Note.* Abbreviations in the table: AS=Acoustical stimulation; AVP=Avoidance conditioning procedure; CS=Contralesional stimulation; CT=Copying training; EL=Errorless learning; FD=Figure description; GCI=General cognitive intervention; LAT=Limb activation training; NV=Neck vibration; OPKS=Optokinetic stimulation; PA=Prism adaptation; PCL=Perceptual anchoring training; RT=Reading training; SAT=Sensory awareness training; SATG=Sustained attention training; SOT=Spatial organization training; TENS=Transcutaneous electrical nerve stimulation; VCT=Visual compensatory training; VSMC=Visuospatial-motor cueing; VST=Visual scanning training.

studies have used sequentially combined approaches (Table 3), the tables are incomplete, and a large majority of the studies that were reviewed here has been devoted to the study of therapeutic benefits of repeated individual sessions of a single treatment method (Table 4). Also, a large portion of the studies covered in Tables 2 through 5 are focused on the visual modality in neglect. Therefore, any conclusions that can be drawn from the review with regard to other modalities must come with this caveat.

It is particularly interesting to see that some of the interventions that have been found to be successful when used in combined or sequential designs have not been found to be particularly successful when used in isolation (such as NV; Luauté, Halligan, et al., 2006). This suggests that therapeutic methods that may not be particularly effective on their own can still be of clinical value when used in conjunction with other therapy types. The importance of this point should not be underestimated. Such synergistic effects are of particular interest and deserve further study.

One of the main suggestions made here is that more studies of various designs of therapeutic techniques are strongly needed for an in-depth analysis and interpretation of different approaches. The claim is that the results suggest that the importance of the design of neglect therapy is underestimated in the literature and that scientists appear to be magnetically drawn to single-session applications of individual methods. Much

more research is needed to explore the interactive relationship between therapy designs on the one hand and the different therapies on the other. The current results (in Tables 2, 3, and 5) do nevertheless give some hope that the number of studies of therapy designs where different methods are applied in combination is increasing.

There are other arguments for using combinations of therapies applied simultaneously rather than single therapeutic techniques. If combined interventions work better in terms of therapeutic effects and speed of both application and therapeutic success, it is not unreasonable to assume that the amount of time the patients need to spend in rehabilitation clinics might be reduced and used in a more efficient manner. This may then be an important and useful strategy because simultaneous combined therapies are less likely to tire out patients and consequently diminish their fitness levels. The results of a recent study conducted by Keller et al. (2009) are particularly telling. The researchers found that applying two *active* interventions (optokinetic stimulation and PA) at different times, albeit with almost no break in between, resulted in *fewer* therapeutic effects than optokinetic stimulation applied on its own. This might suggest that long and difficult therapy sessions tire patients out, leading to fewer clinical effects from the combination of methods. Fatigue may lead to a strengthening of neglect symptoms, which could overwrite any beneficial effects from the

combination of therapies<sup>3</sup> (e.g., Saevarsson, Kristjánsson, & Hjaltason, 2009).

Different patients with a diagnosis of neglect show diverse symptoms, and these symptoms may have various degrees of overlap. In theory, this point could be employed to argue for the use of very strategically picked single therapies based on patients' particular symptoms. However, the vast majority of neglect patients do not have a single group of symptoms that are particularly sensitive to a single intervention. Furthermore, the current state of knowledge of specific aspects of neglect and their interaction for individual patients is not sufficient to serve as a basis for selecting a particular therapy.

Many possible combinations and sequences of interventions have not been studied experimentally and could be of great interest. For instance, studies of the simultaneous combined use of two active therapies are for the most part missing, and the same is true for combinations of two passive therapy types. Also, repetitive TMS has neither been explored in combination nor sequentially with NV. Furthermore, neuropsychological interventions, such as transcranial direct current stimulation, remain unexplored for neglect. Future research could include neuroimaging during a combined intervention study. Such research might reveal greater activity modulations in the human brain than have already been found in functional brain imaging studies on isolated or sequential therapies, especially in light of the fact that combined approaches have shown larger behavioral improvements from rehabilitation than single therapy designs. Meanwhile, it is important to continue the development of new interventions for neglect due to the relatively limited success of currently available therapy techniques. This continued development should be guided by an increased understanding of the disorder and the underpinnings of current interventions. Although current therapeutic techniques for neglect have regrettably shown only limited benefits, the progress that has nevertheless been made in recent years affords us some cautious optimism for the future.

The principal claim here is that combined or sequentially combined applications of different therapies are the most promising avenues for future intervention procedures for neglect. Apart from the growing scientific evidence (as seen in Tables 2, 3, and 5), another reason for this claim is that neglect is a multimodal, multicomponent disorder that can be caused by dysfunction or damage in several cortical and subcortical neural circuits. Note that discussion of the importance of therapeutic designs and other practical suggestions in

the current review might be equally applicable to other health problems, such as aphasia, which shares the diverse and heterogeneous symptomology of neglect. However, the authors are not aware of any scientific reviews on therapeutic designs for other disorders.

## CONCLUSIONS

While neglect continues to be an immense burden for patients, their families, and the world's health care systems, effective therapies and designs for the disorder remain elusive. The main argument in the current review is that more attention should be paid to the design of rehabilitation programs. Different therapeutic techniques used in combination that are applied repeatedly may currently be the most promising approach to treating the disorder and most likely produce the strongest and longest-lasting effects. The primary reason for this is that neglect symptoms tend to vary considerably between individuals, and the clinical symptoms can normally be seen in different modalities, heterogeneous behaviors, and on various types of tasks.

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