

Editorial

Plasticity in Spatial Neglect – Recovery and rehabilitation

G. Kerkhoff^{a,*} and Y. Rossetti^b

^a*Clinical Neuropsychology Unit, Department of Psychology, Saarland University, Postbox 151150, 66041 Saarbrücken, Germany*

^b*Espace et Action, UMR-S 534 INSERM et Université Claude Bernard, 16 avenue Lepine, 69676 Bron, France
Tel.: Lab: +33 4 72 91 34 16; Hospital: +33 4 78 86 50 23; Fax: +33 4 72 91 34 01;
E-mail: rossetti@lyon.inserm.fr/yves.rossetti@chu-lyon.fr*

1. Scientific perspective

Hemineglect (synonymous: unilateral spatial neglect) denotes the impaired or lost ability to react to or process sensory stimuli (visual, auditory, tactile, olfactory, imaginal) presented in the hemispace contralateral to a lesioned cerebral hemisphere or to act upon such stimuli motorically (motor neglect). Despite recovery of the most obvious signs of hemineglect in the first 2–3 months after stroke a considerable portion of neglect patients – especially those with *large* right-hemispheric lesions – remains severely impaired in cognitive and motor tasks, as well as in functional activities of daily living (ADL). Apart from its clinical significance, neglect has attracted many researchers from different faculties because of its multifaceted nature, the associated breakdown of conscious awareness found in victims with this disease, as well as the multimodal nature of the syndrome which provides fascinating opportunities to study crossmodal integration and attention as well as spatial orientation and representation.

Although much progress has been made in the understanding of the basic impairments in spatial neglect

in the past two decades, which is documented by many conferences held, numerous conference proceedings and text books, only recently significant progress has been made in the development and evaluation of novel treatment approaches for patients with neglect. This lag is partially explained by the fact that theory-based treatment-approaches can only be developed when new theories for the explanation of the basic mechanisms have been formulated and tested experimentally. Another reason may be the fact that controlled and randomized large-scale treatment studies require tremendous efforts and resources, both with respect to the availability of clinics, patients, treatments, potential financial incomes and researchers designing and coordinating such studies.

Clinically, spatial neglect and associated disorders are a major neurological handicap in many societies. The incidence of stroke in man is relatively high in all societies and will probably rise with increasing age, at least in most societies. Spatial neglect occurs in some 25–30% of all stroke patients, which means that 3–5 million *new* victims will suffer from neglect every year worldwide. Despite recovery of the most obvious signs of the disease in a portion of these, chronic impairments will persist in the remaining persons for years or even the rest of their life. While motor system plasticity as well as language recovery following stroke have been repeatedly a scientific topic the recovery of spatial

*Corresponding author: Clinical Neuropsychology Unit, Department of Psychology, Saarland University, Postbox 151150, 66041 Saarbrücken, Germany. Tel.: +49 681 302 57380; Fax: +49 681 302 57382; E-mail: kerkhoff@mx.uni-saarland.de.

neglect – both naturally and by treatment interventions – has only recently moved into the focus of researchers.

Therefore, as guest editors of this special issue of RNN we thought that time is mature to focus especially on those topics of neglect which are related to plasticity (both behavioural and neural), recovery, improved diagnostics, novel treatment techniques and their outcome. We therefore invited many of the leading researchers in this field from Australia, Canada, Finland, France, Germany, Great Britain, Italy and Japan, to collate lab reviews or broader topical reviews that might guide the reader to novel, influential ideas, improved diagnostic and treatment techniques as well as to fruitful concepts for future research and applications in this field. While a complete coverage of all relevant research was definitely beyond the scope of this special issue we selected 18 different contributions dealing with basic mechanisms of neglect, extinction and unawareness, diagnostic issues, treatment techniques, and perspectives for future research. We trust that this broad collection of papers will be stimulating both for researchers interested in basic mechanisms of spatial neglect as well as clinicians involved in the clinical management of patients with neglect. Furthermore, this broad focus may facilitate the scientific cross-talk between specialists in basic science and others primarily interested in clinical applications and treatment.

2. Basic mechanisms of neglect and associated disorders

The review by Jehkonen, Laihosalo and Kettunen from Tampere/Finland [9] addresses major aspects regarding the impact of neglect on functional outcome after stroke. While the negative impact of neglect on the patient's outcome is common knowledge, few is known about the long-term outcome. The available studies with respect to the long-term outcome of neglect have often relied on test scores instead of measuring functional activities, motor or cognitive functions related to daily life. In the light of the international classification of diseases (ICF) it is essential for future studies not only to collect test scores, but also to include motor, cognitive and social activity measures when studying the effects of neglect and neglect therapy. This will provide a more accurate figure of the limits but also of the resources of the patients suffering from spatial neglect, as well as their families caring for them. By the same logic, treatment studies should in the future also include measures of activities and participation to

measure outcome in order to show whether these can be improved by a specific intervention. This could – in the long run – improve the management of neglect patients. Furthermore, homogenous patient groups should be used, and the knowledge about right-sided neglect after left-hemisphere lesions is very limited.

In the second article Brozzoli, Demattè, Pavani, Frassinetti and Farné (Lyon/France, Trento/Italy, Bologna/Italy) [4] deal with the complex interplay of neglect and extinction within and between sensory modalities. While formerly extinction has been considered as a minor form of neglect during its recovery stage this view is no longer tenable. Neglect occurs without extinction and vice versa. These double dissociations and the interplay of different modalities show that both disorders have different mechanisms (both behavioural and neural), but share similar principles of multimodal and crossmodal integration. Thus, most patients with visual neglect will also have auditory or somatosensory neglect. Furthermore, the authors highlight novel findings about neglect and extinction in the so-called “lower senses”, olfaction and taste. The final message of this review is that a deeper understanding of the multisensory nature of the deficits in neglect and extinction will eventually lead to more powerful, multisensory-based rehabilitation approaches.

In the following review Snow (Birmingham/UK) and Mattingley (Melbourne/Australia) [16] point to the need to distinguish between stimulus-driven and goal-driven aspects of patients' selective attention deficits. They discuss the interaction between bottom-up factors, such as stimulus salience, and top-down factors, such as task goals, in the manifestations of spatial neglect and extinction. They argue that these conditions are characterised by a failure to integrate bottom-up and top-down neural signals, with specific reference to impairments of stimulus selection that affect the ipsilesional side of space.

A special issue about neglect would be incomplete without dealing with one of the most conspicuous features of neglect patients: their unawareness (anosognosia) of the(ir) disease. Vallar and Ronchi (both at Milano/Italy) [18] summarize all relevant published studies on unawareness of hemiplegia and hemianopia after brain damage including a recent neuroanatomic analysis of the lesions in patients showing neglect with and without anosognosia. In summary, these data show that although neglect and unawareness are indeed often combined, they may dissociate in single cases. Analysis of the lesions shows that anosognosia for hemiplegia most often is found after lesions to the motor

cortex, hence lesions causing the hemiplegia. The authors frame their review with a theory of unawareness according to which awareness of motor functions (i.e. intactness of one's own limbs) is generated within the same cortical regions that are involved in motor control. Put differently, motor functions and motor awareness are coded in neighbouring or even identical cortical regions.

3. Diagnostic issues

While the bedside-assessment of neglect phenomena in acute stroke patients does not require very sophisticated instruments such tests have only limited value in detecting nonvisual neglect, and are often useless in detecting chronic or more subtle neglect phenomena. Therefore, other techniques are required. A more sophisticated analysis of visual neglect phenomena is dealt with in the review by Ishiai (Tokio/Japan) [8]. His results indicate that in patients with neglect, the representational image of a horizontal line may be formed on the basis of the attended segment between the right endpoint and the favored point of fixation. As the favored point of fixation is nearly always shifted to the ipsilesional side, the resulting bisection is mostly shifted to this side. Furthermore, these eye movement analyses show clearly that neglect patients do not explore the contralesional part of a line during line bisection tasks. Thus, the combination of eye tracking devices with line bisection tasks may further elucidate the mechanisms underlying neglect. This elegant combination of behavioural and oculomotor techniques might eventually be used for other domains of neglect as well.

The comparison of neglect in different studies is often difficult due to the use of different screening tests for the diagnosis of neglect. The lack of standardized, internationally adapted measures that all researchers agree on often lead in the past to largely diverging results between different studies. We therefore believe that it is necessary in the future – as in other areas of medicine or psychology – to use standardized, internationally available test instruments. One such new instrument is the test battery developed and normed by the French group on neglect including Azouvi (Garches/France), Bartolomeo (Paris/France), Beis (Nancy/France), Pérennou (Dijon/France), Pradat-Diehl (Paris/France) and Rousseau (Lille/France) [2]. They collected normative values on a large patient sample ($n = 456-472$) in a test battery including paper-and-pencil-tests, an assessment

of personal neglect, extinction, anosognosia and a behavioural rating of neglect by staff. Their results show that a multifaceted diagnostic approach is more sensitive to neglect and that paper-and-pencil-tests may miss neglect phenomena that are readily detected by behavioural ratings or behavioural tests of neglect. Another important finding is that age, education and acting hand may influence the performance already in normal subjects and therefore these factors have to be controlled for.

The complex interplay between lateralized and non-lateralized attentional capabilities in neurodegenerative diseases is highlighted in the contribution by Bublak (Jena/Germany) and Finke (München/Germany) [5]. While spatially non-lateralized impairments of attention and working memory have been reported in a number of recent studies in neglect patients suffering from stroke, there exist only few methods to delineate these deficits in greater detail. Furthermore, subtle disturbances – as seen frequently in slowly progressive degenerative disease – can not be precisely mapped with these methods. Bublak and Finke suggest the assessment of nonlateralized and lateralized attentional capacities by techniques based on Bundesen's theory of visual attention. This is a parameter-based estimation of visual perceptual processing speed, visual working memory storage, and spatial attentional weighting. Their lab-review shows that this method is highly sensitive to detect subtle pathological impairments in neurodegenerative disease, and to delineate different profiles of impairments in different diseases (i.e. Alzheimer's versus Huntington's disease).

In the next article Glocker, Bittl (both from Eichstätt/Germany) and Kerkhoff (Saarbrücken/Germany) [7] describe the development, psychometric validation and clinical results of a novel test designed to assess body representational neglect. Little is known about body neglect and its relationship to other forms of neglect. One reason is the lack of standardized tests to detect it. The authors show that the novel test is highly reliable and sensitive and that nearly 80% of right-brain and 47% of left-brain damaged patients are impaired in this apparently simple test. Apart from this clinical significance, preliminary data show that body neglect and other neuropsychological disorders that also involve knowledge of the own body (apraxia) can be dissociated. This result may be taken as an indication of multiple cortical mechanisms devoted to different aspects of body knowledge (i.e. pantomiming hand gestures versus searching the own body surface).

In the last chapter of the diagnostic section Pérennou (Dijon/France) [13] provides a comprehensive review

examining the association between postural disorders and neglect. While it is long known that patients with right-brain-damage have a poor motor outcome after stroke the reasons for this finding have been less clear. Unawareness, neglect and spatial disorders have been identified as influential factors. This review provides also a description of the most useful tasks and devices suitable for the measurement of postural deficits in stroke patients with neglect. Pérennou theorizes that postural disorders are so prominent in neglect because of disturbed graviceptive and visuospatial informations both subserving postural control. This review should encourage neglect researchers to incorporate postural measurements into their research as well as clinical assessment routines.

4. Treatment techniques

The treatment section covers five different types of treatment approaches for spatial neglect. In the first contribution, Pizzamiglio, Guariglia, Antonucci and Zoccolotti (all from Rome/Italy) [14] give a topical as well as historical review about the development of a rehabilitative program for unilateral neglect. This review, covering a period of the past 30 years, summarizes the major milestones in the development of the so-called visual scanning training, the first systematic and effective treatment for patients with neglect. Furthermore, typical problems in neglect rehabilitation are addressed (i.e. limited transfer to daily life). Rode (Lyon/France), Klos (Erlangen/Germany), Courtois-Jacquin (Lyon/France) and Rossetti (Lyon/France) [15] report novel findings of the prism-adaptation technique for the rehabilitation of spatial cognition disorders, i.e. spatial dysgraphia. Spatial dysgraphia and constructional apraxia are known for many decades but have been largely neglected by researchers. This contribution shows that prism adaptation improves spatial-cognitive abilities relevant for spatial writing number processing and constructional abilities.

In the subsequent contribution by Kerkhoff (Saarbrücken/Germany), Keller (Bad Aibling/Germany), Ritter and Marquardt (both Munich/Germany) [10] it is shown that optokinetic stimulation with active tracking of the moving targets by the patient yields significantly greater and lasting improvements as compared to the conventional scanning training procedure. While this does not necessarily imply to abandon scanning training it shows that this form of optokinetic training may be particularly useful in acute ne-

glect patients because it does not require a conscious, top-down-directed strategy for compensation. Sturm (Aachen/Germany), Thimm and Fink (both Aachen and Jülich/Germany) [17] summarize ongoing studies of alertness training in neglect patient and its effect on behavioural and neural measures of neglect. They show that alertness training leads to a reduction of neglect by recruitment of frontal cortical areas in both cerebral hemispheres, whereas optokinetic stimulation of the type designed by Kerkhoff et al. [10]. These results suggest the complementary use of attentional and optokinetic training procedures, which in turn might produce a combined and possibly greater behavioural recovery in neglect patients. Finally, in the last contribution of the treatment section Eskes and Butler (both Halifax/Canada) [6] show that the use of functional electrical stimulation may yield promising results in activating contralateral limb movements in those neglect patients with severely impaired motor functions due to hemiplegia. This novel combination approach might be an interesting avenue for future research and shows the potential when combining behavioural treatments with prosthetic or technical devices in neglect rehabilitation. Though space was too limited to deal with all currently available techniques in the treatment section, it summarizes novel ideas, provides updates of currently used techniques and suggests novel treatment combinations. Furthermore, the treatment potential when *combining* such single treatments – a common strategy in other areas of medicine and psychology – is not at all exhausted at the moment. The partially divergent profiles of action of the different treatments strongly suggest that an intelligent combination (not necessarily at the same time) could produce more, quicker and more stable treatment-induced recovery. This is not only clinically relevant, but poses also central basic science questions of how such integrative effects are enabled on the neuroanatomic and neurophysiological level.

5. Future directions for research and treatment

In this section Bowen and Lincoln (Nottingham/UK) [3] give a meta-analysis of the overall effects of neglect therapy. Their critical conclusion is also formulated in their title: there is a need for randomized treatment studies in neglect research because few studies so far used a randomized allocation to treatments. The most likely explanation for this is that the collection of large, homogenous patient groups takes years to complete – when one centre performs the study alone. This prob-

lem probably could be solved by conducting multi-centre studies. Furthermore, the stability of the treatment effects is often evaluated only in short time intervals after the cessation of treatment. Finally, as already pointed out in the first contribution by Jehkonen et al. [9] functional tasks documenting treatment-induced recovery after a specific intervention have been used only very rarely. Hence, the best we can say at the moment is that neglect rehabilitation reduces neglect in neglect tasks – whether or not functional gains follow from such improvements is an open research question for the next years.

In the subsequent contribution Luauté (Lyon/France), Halligan (Cardiff, UK), Rode, Jacquin-Courtois and Boisson (Lyon/France) [11] give a comprehensive review of prism-adaptation studies in neglect rehabilitation. This therapeutic intervention is probably the best evaluated technique among the other novel treatment approaches, although no randomized control trial is available yet. Prism adaptation has been shown to affect patients with spatial neglect as well as normal subjects. C. Michel (Dijon/France) [12] studied neglect-like behaviour in healthy individuals and in particular the use of prism adaptation as a procedure for simulating various symptoms of clinical neglect in normals. Such neglect-like symptoms offer insights as to the mechanisms of spatial neglect and provides an understanding of the interaction between low level sensorimotor processes and spatial cognition. Implications for the functional mechanisms and the anatomical substrates of prism adaptation are discussed in terms of inter-sensory plasticity and sensorimotor coordination.

In the final contribution by Ansuini (Padova/Italy), Pierno (Padova/Italy), Lusher (Melbourne/Australia) and Castiello (London/UK and Padova/Italy) [1] the authors describe the effect of virtual reality applications for the remapping of contralesional (neglected) space in patients. The authors show that patients with lesions sparing the parietal cortex benefit from this novel technique. Their results also highlight the pivotal role of the parietal cortex for this induced remapping of neglected space.

6. Concluding remarks and further perspectives

Brain repair, adaptive reorganisation, compensatory strategies, prostheses and medications all can contribute to functional recovery from spatial neglect and associated disorders after brain damage. Animal experiments, functional imaging studies and longitudinal

outcome studies suggest that injured brains can change their function and connectivity, both on the behavioural and neural level, and both spontaneously (i.e. without intervention) as well in response to specific treatments. However, many questions in this context remain still open. Some of these are: Is spontaneous recovery similar to treatment-induced-recovery? Which treatments are best in which type of neglect, and when after stroke? How often and how long should a treatment be applied? Could an enriched environment improve the outcome additionally, as suggested by animal experiments? Another interesting question is whether top-down-compensatory strategies and bottom-up stimulation maneuvers can be combined to yield a better outcome? Despite significant progress in the development of novel and more effective treatments in the past 10 years little is known about the long-term-stability of such treatment-related improvements (over a time-scale of years after treatment). How can transfer to daily life be improved? What is the relative role of the anatomically intact and of the lesioned hemisphere in recovery? Furthermore, patients differ considerably in their individual response to the same type of treatment. Although lesion size, location, diffuse lesions and related factors are without doubt relevant here, individual psychological factors like motivation, intelligence and affective style have not been considered until now. As they all influence cognitive functioning and the underlying neural circuitry in the healthy brain these parameters might be relevant prognostic factors when researchers try to tailor individually optimized treatments. Finally, how can the unawareness issue be successfully addressed?

In conclusion, the study of these questions in spatial neglect provides excellent opportunities for an interdisciplinary exchange of research ideas between basic neuroscience, applied clinical neuropsychology, neurorehabilitation and neuro-technology.

Acknowledgements

This issue would have not been possible without the help of others. We are grateful to all authors for their dedicated contributions. We also gratefully acknowledge the reviewers work, the continuous help of St. Matzke from the editorial office of RNN, as well as the support of IOS press.

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