ZANEMARJANJE PROSTORA V POLOVICI VIDNEGA POLJA: S TEORIJO PODPRTE STRATEGIJE ZA IZBOLJŠANJE ZAVEDANJA ZANEMARJENE STRANI

UNILATERAL SPATIAL NEGLECT: THEORY DRIVEN STRATEGIES TO ENHANCE CONSCIOUS PERCEPTION IN THE NEGLECTED SIDE

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Izvleček

Prispevek podaja pregled dveh vidikov zanemarjanja prostora v polovici vidnega polja: teoretične osnove tega stanja, ki sodi med najbolj zapletena, kar jih srečujemo v rehabilitacijski klinični praksi, in strategij za izboljšanje zavedanja zanemarjane strani. Po kratkem opisu simptomov sledi pregled kliničnih in bazičnih raziskav o tej temi, opravljenih v rehabilitacijski bolnišnici Loewenstein v Raanani v Izraelu.

Ključne besede:
zanemarjanje prostora v polovici vidnega polja, teorija, klinična rehabilitacija, raziskave

Abstract

This paper provides a review of two aspects of unilateral spatial neglect (USN): theoretical accounts of USN as one of the most puzzling conditions encountered in rehabilitation clinical practice, and strategies to enhance conscious perception in the neglected side. Following a short description of the symptom complex, there is a review of clinical and basic research on USN performed at the Loewenstein Rehabilitation Hospital in Raanana, Israel.

Key words:
unilateral spatial neglect, theory, clinical rehabilitation, research

PERCEPTUAL AND COGNITIVE DISTURBANCES IN STROKE REHABILITATION

Assessment and treatment of perceptual and cognitive impairments are of major importance in rehabilitation of patients with stroke and brain damage of other causes. Cognitive rehabilitation deals with a large variety of impairments following damage to different functional systems of the brain. These include executive disorders typically occurring after lesions to the frontal lobes; motor-control problems manifested as different types of apraxia; perceptual impairments manifested as different types of agnosia; disturbances of memory and learning as revealed in the amnestic syndrome and related disorders; aphasic language disturbances typically following damage to different perisylvian and extrasylvian regions on the left hemisphere; and disturbances of spatial cognition, as revealed in unilateral spatial neglect (USN) and related disorders occuring typically following damage to posterior perisylvian regions on the right hemisphere.

Proper understanding of such perceptual and cognitive disturbances demands a thorough knowledge of the cerebral organization of the functional systems in question. In that sense, cognitive-neuroscience and neuropsychology textbooks serve as an indispensable basic-science source for clinicians dealing with neuro-rehabilitation, providing detailed descriptions and modelling of the normal brain organization of cognitive functions (1,2), as well as theoretical models of various cognitive impairments and description of standardized assessment tools (3,4) and treatment modalities (5,6).

The functional consequences of cognitive disturbances were a subject of various studies. One such study (7) identified cognitive impairments, mainly in the domains of memory, orientation, language and attention, in about 30 % of patients with ischemic brain infarction assessed at 3 months post stroke onset. Dependency rate and overall functional disability were greater among patients with cognitive impairments, relative to those with intact cognitive functioning.

Several studies (8-11) point to an asymmetry in prevalence of functional disability among left- and right-hemisphere-damaged stroke patients (LHD and RHD, respectively). For example, it was found (10) that LHD patients are discharged earlier from hospital and are less ADL dependent compared to RHD patients, although the latter are free of the aphasic language problems often encountered by the former. The presence of USN seems to play a crucial role in creation of the relative functional disadvantage of RHD stroke patients.

Short overview of USN

A thorough survey of USN is beyond the scope of this paper. The reader is referred to a selected group of books dedicated to the subject (12-15) and review articles (16,17) which provide an account of all major aspects of USN neuroanatomy (12,1 13, 15, 17) theorizing (12, 13, 15, 16), assessment (13, 14), and treatment (13, 14, 18-21). A rather comprehensive evaluation of the evidence for the effectiveness of rehabilitation treatments for USN can be found in the Evidence-Based Review of Stroke Rehabilitation (www.ebrsr.com).

USN is of the most intriguing consequences of focal brain damage, where a patient fails to orient towards, respond to and report on significant stimuli presented in the contralesional hemispace. It is usually conceptualized in terms of failure of mechanisms whereby attentional resources are mobilized and allocated in space, or among spatially coded targets. Hypotheses emphasizing the importance of spatial representational, perceptual, intentional and premotor factors also exist (12, 13, 15, 16).

Neglect itself (i.e., the loss of conscious awareness of stimuli located in the side of space contralateral to the lesion side) reflects probably an extreme case in a series of spatial disturbances, having in common reduced processing efficiency for stimuli located in contralesional space.

The syndrome is frequently encountered in stroke patients, especially when the right-hemisphere is involved. It affects significantly the prognosis for regaining independence in activities of daily living, and therefore is of major importance in neuro-rehabilitation. Neglect may follow the occurrence of a lesion in a large variety of brain structures. Lesion location determines the cognitive processors involved and thus, the behavioural manifestations revealed in each patient.

Deranged spatial organization of data can be revealed for perceptual information, memory traces, motor and oculomotor acts aimed at spatially-tagged targets, and especially in the case of attention orienting and allocation. Inability to organize data in spatio-temporal coordinates may be revealed within the informational domain of a given cognitive processor. However, such inability is most detrimental for complex interactions between different processing modules, given the fact that spatio-temporal organization is crucial for data sharing between modules.

To summarise, the key features of unilateral spatial neglect are:

- USN, i.e., the loss of conscious awareness of stimuli located in the side of space contralateral to the lesion side, is actually a collective name given to a series of impairments having in common reduced processing efficiency in contralesional space.
- Deranged spatial organization of perceptual information, of memory traces to be stored or retrieved, of motor and oculomotor activities aimed at spatially-tagged targets, and especially of orienting and allocation of attention, is in the essence of the syndrome.
- USN may follow the occurrence of a lesion in a large variety of brain structures, mainly, but not exclusively, on the right cerebral hemisphere.
- USN is a major disabling condition. Stroke patients with USN have higher rates of severe sensory-motor as well as cognitive impairments, are usually hospitalized for longer periods of time, and they have poorer BADL function, both early after stroke onset and at late follow up assessments.
- It is not entirely clear why the presence of USN is connected with such a poor outcome. There is reason to believe that the mechanisms underlying USN play a causative role in aggravation of other sensory, motor and cognitive dysfunctions. This conjecture underlines the importance of developing newer effective means for the assessment of neglect-related phenomena and their treatment.

USN RESEARCH AT THE LOEWENSTEIN REHABILITATION HOSPITAL

The rest of this paper is a review of USN research data (22-25) obtained in our Department of Neurological Rehabilitation, at the Loewenstein Hospital, Raanana, Israel, during the last twenty years. Our research program aimed to elucidate various questions concerning the neglect syndrome, in order to assist the development of novel assessment and treatment tools. It was motivated by recognition of the importance of USN as a major source of neurological disability. The contents of this review are organized in accord with the questions – clinical and theoretical – that we posed in our research plan.

Is there a place for ipsilesional eye patching in USN rehabilitation?

USN behavior of experimental animals with unilateral posterior cortical lesions improves with the placement of a second lesion in the contralesional superior colliculus or in the inter-collicular commissure (Sprague effect). As the retinotectal fibers are mainly crossed, it has been speculated that ipsilesional eye patching, by depriving the contralesional superior colliculus of its main facilitatory visual input, might achieve similar results, and thus be used as a remediation manoeuvre in patients with USN.

We have conducted two studies in order to investigate the rehabilitation potential of ipsilesional eye patching in USN (25, 30). In the first study (25), from six patients with severe persistent USN, only one showed an unequivocal beneficial effect from ipsilesional eye patching. We suggested that our use of the line-bisection paradigm in this study played a role in this disappointing result. Midbrain visuomotor pathways provide all vertebrates with mechanisms for rapid, reflexive orienting to abrupt changes in the environment critical to survival. With the encephalization of visual function, these phylogentically ancient pathways have become integrated with cortical mechanisms involved in strategic search under endogenous control. Thus, it is possible that ipsilesional collicular activation plays a remedial role mainly with respect to involuntary (reflexive, bottom-up, stimulus-driven) orienting of spatial attention, and not in the case of voluntary (top-down, data-driven) allocation of attention. In that case, line bisection performance might not be the optimal measure for detection of colliculus-dependent amelioration in USN.

The above conjecture was corroborated by our demonstration, in a rare patient with unilateral damage to the superior colliculus, that this structure plays a crucial role in mediation of "inhibition of return" (IOR) which is an automatic mechanism whereby the attentional system favors novel spatial locations by inhibiting already scanned ones (39).

In a second study (30) on the effects of eye patching in USN, a group of 26 RHD patients with USN was given a cancellation task under binocular and monocular (left and right) viewing conditions. Thirteen patients (50 %) showed amelioration of left USN in conditions of ipsilesional eye patching, as compared to the baseline binocular state. This result is in accord with the theoretical prediction based on Sprague's findings in animals. However, eleven patients showed no significant change in either right or left viewing conditions, and two patients showed an unexpected advantage in conditions of right monocular viewing. We suggested that even if the Sprague effect contributes to the beneficial influence of ipsilesional eye patching it is hardly the single factor involved (30).

What is the role of pre-attentive factors in USN?

We have obtained in earlier research some independent evidence for the specialized role of the right cerebral hemisphere in three cognitive operations: encoding of the frequency of occurrence of a stimulus (22), of its temporal order (23) and of its spatial location (24). These three cognitive operations are considered by some prominent researchers to be carried out automatically, without the need of allocating attention voluntarily to the specific temporal and spatial features of the event, and with equal efficiency under conditions of incidental and intentional learning. Moreover, it was claimed that these processes are innate, that is, automatic from birth. Although this claim is under debate, we suspected that the role played by the right hemisphere in these operations suggests that USN, being a typical sequel of RHD, is not just an attentional problem, but may affect perceptual processes even at an early pre-attentive stage.

We have shown (26) in a patient with a right thalamic haemorrhage and left USN, that both left and right monaural sounds delivered *during sleep*, fail to elicit electroencephalographic K-complexes (conceived as signs of phasic arousal akin to the orienting response of waking) in the right cerebral hemisphere, while producing such complexes over the left hemisphere. In contrast, bilaterally symmetrical K-complexes were elicited in a control subject with a left thalamic haemorrhage and no USN (26).

In another study of *unattended* auditory processing in USN (40) we have found a fundamental *pre-attentive* deficit. USN patients did not show the normal physiological response that signals detection of environmental changes by the brain when the sound stimuli came from the left hemispace. The deficit was most notable for changes in the *spatial location* of the stimuli, as evidenced by inability of left-sided location changes to elicit the electrophysiological "mismatch negativity" (MMN) wave (40). These findings suggest that the basic impairment underlying USN may operate also in conditions and tasks that do not directly involve allocation of attention among spatially-coded targets, being the core of USN symptomatology and current USN theorizing.

What is the impact of USN in modalities other than vision?

Most of the clinical reports and neuropsychological studies on USN, have dealt with phenomena and putative mechanisms of visual neglect. Auditory neglect is seldom reported and remains a relatively unexplored feature of the syndrome. If USN means failure of a supramodal system for spatial attention, then a substantial degree of correlation should be expected between neglect manifestations in different sensory modalities.

To test this we examined the ability of RHD patients to localize and identify sound stimuli emitted from the left side of the egocentric space, using free-field auditory stimulation (36). We asked whether RHD patients are likely to manifest auditory inattention in such conditions, i.e., when both ears receive the message, and whether the magnitude of auditory inattention differ in RHD patients with and without visual neglect. To explore further the relationship between viewing and hearing in USN we employed both sound localization and identification tasks with open eyes and after blindfolding the patients. In this study we have clearly shown that RHD patients with neglect in the visual modality differ significantly from normal subjects in their ability both to identify and to localize sound signals coming from their left. This difference, being a legitimate operational definition of USN in the auditory modality, was manifested in this study, for the first time, in natural free-field stimulation conditions, i.e., without confining the sound-signal to a single ear.

The occurrence of unilateral auditory inattention, affecting both stimulus localization and identification, in free-field stimulation conditions, is puzzling, since in this condition both ears receive the contralesional message, which is then channelled to the two hemispheres. This finding emphasizes what was already known from studies of visual neglect, namely, that in this syndrome body-centred space is a critical construct in the abnormal perception of outside reality. Yet, there is a basic difference between the two modalities: in vision, one should orient toward the stimulus, that is, toward a distinct spatial location, in order to perceive it lucidly. In contradistinction, the sound stimuli used in this study were clearly heard everywhere within the examination room, irrespective of the normal listener's overt orientation.

It is of interest that left-sided auditory inattention was revealed not only by RHD patients with visual neglect, but to a lesser degree also by RHD patients who did not show visual neglect. In the most difficult hearing condition (during bilateral simultaneous stimulation), a noticeable, yet statistically insignificant, advantage for sound stimuli originating in the right side, could be recognized also among normal controls (36). These findings suggest the existence of a phenomenological continuum, based on a common attentional mechanism, between normal right-side advantage in hearing and pathological neglect behaviour. This interpretation is in accord with Kinsbourne's view of left-sided neglect as a pathological amplification of the normal state of attentional bias towards the right (12).

In the above study (36), blindfolding improved both the localization and the identification of lateralized sound stimuli. Beneficial effects of blindfolding in USN have been reported by others in a task demanding manual space exploration. Blindfolding may exert such effects through a reduction of concomitant distractory visual stimulation.

In none of the testing conditions in this study could a statistically significant difference in auditory performance be shown between RHD patients with and without visual neglect. The emergence of contralesional auditory inattention, as a consequence of right hemisphere damage, was not dependent upon the existence of neglect in the visual modality. On the other hand, the effect of blindfolding on auditory inattention suggests that separation between the auditory and visual systems is incomplete. A view of spatial attention as based on a system containing both supramodal and modal-specific components, is compatible with these results (36).

In another study of neglect in the auditory modality (41) we investigated the possibility of a dissociation between the detection and the identification of extinguished phonemes. Extinction is a frequent sequel of unilateral brain damage, manifested in conditions of bilateral simultaneous stimulation as a failure to detect the contralesional stimulus, while the same stimulus is correctly detected there when presented in isolation. The phenomenon is usually interpreted in terms of impaired mobilization of attention from an attended to an unattended object. Fourteen RHD patients with severe auditory extinction were examined using a paradigm that separated the localization of stimuli and the identification of their phonetic content. Patients reported the identity of left-sided phonemes, while "extinguishing" them at the same time, in the traditional sense of the term. This dissociation suggests that auditory extinction is more about acknowledging the existence of a stimulus in the contralesional hemispace than about the actual processing of the stimulus (41).

In a later study we were able to demonstrate the existence of a similar dissociation in processing of different stimulus attributes in the neglected hemispace also in the visual modality (48).

These studies contribute to the growing evidence in the literature suggesting that USN patients actually process contralesional information that fails to get access to conscious awareness. In these cases the impact of processing is evidenced implicitly while the patient is unable to provide an explicit account of the neglected information (16).

Can we use perceptual illusions to enhance perceptibility in the neglected side?

We explored the possibility of using perceptual illusions for the purpose of enhancing perceptibility of auditory stimuli emitted from the neglected (contralesional) side in four studies.

Using the "ventriloquist illusion" (an attribution of the sound to the sight of a fictitious source) we misled subjects to believe that auditory signals emitted from their left came from a dummy speaker on their right, and then, that right-sided stimuli came from the left. RHD patients with visual USN showed inattention also for sound emitted from the left,

but the latter improved significantly when stimulation was coupled with presentation of a dummy speaker on the right. Moreover, inattention was induced for right-sided sound stimuli when coupled with the sight of a dummy speaker on the left (27, 28).

In a different study we showed, using the McGurk illusion (the tendency of conflicting audio-visual messages to form illusory blend percepts) that visual cues (i.e., manner of articulation) in ipsilesional (right) space can help a patient with auditory USN to mentally reconstruct syllable sounds voiced in contralesional (left) space (29).

Finally, we used the "scale illusion" (hearing a distinct melody as a consequence of grouping different auditory information received from both ears into an illusory auditory stream) to test whether extinguished contralesional tones can be incorporated into the content of conscious awareness. We showed that RHD patients with severe auditory extinction were susceptible to the scale illusion while being consciously unaware of the stimuli presented on their left (52).

Altogether, the findings of the above studies suggest that the representation of space during combined audio-visual perception is established primarily on the basis of vision. Also, the position of an auditory stimulus in the representational space (where the subject believes the sound-source to be) may be even more important than its position in the physical space (where the sound source is actually located) in determining its perceptual salience (27 - 29). In addition, the scale illusion study showed that awareness is not necessary for auditory grouping, and that neglected non-conscious elements can be incorporated into a conscious percept (52). Other aspect of that complex issue can be learned from our study of spatial sequence learning in USN (33).

It is unclear yet what role illusory rightward translocation of stimuli might have in USN rehabilitation. In the visual modality, the use of vibratory stimulation of paravertebral cervical muscles, and the use of prism adaptation effects (both seemingly involving a lateralized shift of coordinate systems serving to organize spatial representations) was shown to have beneficial effects in neglect.

How can we understand impairments in recognition of small patterns (e.g., single letters) revealed by USN patients?

We have conducted a carefully controlled psychophysical research in order to explore the effect of spatial attentional constraints upon the ability of USN patients to recognize small, letter-like, patterns (35). Two RHD patients with visual USN and four normal subjects participated in the study. Small, letter-like, pre-learned patterns served as stimuli. Short exposure time prevented overt scanpaths during stimulus presentation. Attention was attracted to a central (midsagittal) fixation point by precuing this location prior to each stimulus presentation. Minute (up to 1.5 degrees of visual angle) rightward and leftward stimulus shifts caused attention to be allocated each time to a different location on the object space, while remaining in a fixed central position in viewer-centred coordinates. The task was to decide which of several pre-learned patterns was presented in each trial.

In the normal subjects, best performance was achieved when the "luminance centroid" (LC; derived from the analysis of low-spatial frequencies in the stimulus space) of each pattern coincided with the spatial position of the precue. In contrast, the patients with USN showed optimal recognition performance when precuing attracted attention to locations within the object space, to the left of the LC.

We proposed that in recognition of small patterns, the LC may serve as a center of gravity for attention allocation, i.e., as the target location where focal attention is normally directed following a primary global analysis based on the low spatial frequencies. As such, the LC of a simple pattern may serve as the origin point for an object-centred coordinate frame, dividing it into right and left. This, in turn, serves to create a prototype description of the pattern, in its own coordinates, in memory, to be addressed during subsequent recognition tasks. Best match of the percept with the stored description may explain the observed advantage of allocating attention to the LC.

The performance of the USN patients in this study can be explained in terms of neglect operating in an object-centred coordinate frame (OCCF). The paradigm used offers a novel quantitative psychophysical mode for studying the neglect phenomenon in OCCF, especially during pattern recognition (35).

How do features of ipsilesional stimuli affect extinction of contralesional stimuli?

Extinction of contralesional stimuli in conditions of bilateral simultaneous stimulation is a counterpart of USN. We have shown, using pairs of "Gabor patches" as visual stimuli, that pair detection is maximally improved when the two stimuli are proximal, co-oriented and co-axial (34).

In a second research (42) we showed that contrast isotropy of the stimulus pair is important in producing this orientation-similarity gain. The further advantage of co-oriented co-linear stimuli over co-oriented parallel (vertical) stimuli was shown exclusively with iso-contrast stimulus pairs, and was significantly enhanced when the contrast level of the stimulus pair was low (42).

Stimulus properties producing reduced extinction seem to correlate with the selectivity pattern and contrast dependence of (a) spatial lateral facilitation observed in psycho-

physical studies with normal subjects, and (b) long-range interactions observed in the primary visual cortex. Thus, two remote visual stimuli seem to be processed as a single object when the corresponding neuronal activities are linked via long-range lateral interactions.

The demonstration of contrast dependency in such processing strengthen the hypothesis that even in the presence of significant, extinction producing, parietal damage, the primary visual cortex preserves the capacity to encode, using long-range lateral interactions, an image description in which visual objects are already segregated from background (42).

Use of appropriate pairs of stimuli (i.e., stimuli showing more grouping and less competition) in signal detection tasks might help USN patients process and retrieve contralesional information otherwise lost.

What is the rate of USN-related disability among RHD patients? What is the impact of USN on the rehabilitation outcome?

We have conducted an extensive study in order to evaluate the impact of USN on patients' functioning in basic activities of daily living (B-ADL) and instrumental-ADL (I-ADL) as well as on the long term rehabilitation outcome (37).

Assessments of sensory-motor and cognitive impairment and of functional disability were conducted at 3 points in time: admission to rehabilitation; discharge from the rehabilitation hospital; and at follow-up, six months after discharge, up to a year post onset. The following outcome measures were used: Functional Independence Measure (B-ADL); The Rabideau Kitchen Evaluation (I-ADL). The study group comprised of 40 consecutive admissions to the Loewenstein Rehabilitation Hospital, of adult right-handed patients with a CT-proven, first, single, right hemispheric stroke. Based on their total score in the standardized Behavioral Inattention Test (BIT) for neglect, patients were divided into 2 groups: 19 with (USN+) and 21 without (USN-) neglect.

The findings of this study clearly differentiated the impairment and disability levels of RHD patients with and without USN. Neglect was associated with lower performance on measures of basic impairment (sensory-motor and cognitive), as well as on measures of disability in B-ADL and I-ADL. Differences were significant in all three testing periods. The recovery pattern of USN+ patients was slower and more attenuated. In both groups, most improvement occurred in the first 5 months after onset. USN was found to be the major predictor of rehabilitation outcome from admission to follow-up (37, 38).

The findings shed light on the relationship between basic impairment and disability in RHD stroke patients, contributing to our understanding of the course of functional recovery from onset to approximately one year later.

In subsequent studies we were able to shed light on the impact of USN and other cognitive impairments on the disabling phenomenon of anosognosia for hemiplegia and the problem of patients' unawareness of their own impairments and disability (43-45).

We have also shown that mechanisms operating in USN are likely to play a role also in children suffering from attention deficit disorders, i.e., from non-spatial attentional disorders (32).

The significance of USN as a major source of stroke-related long-term disability, as revealed in these studies, justifies further research efforts in order to develop more sensitive and comprehensive assessment tools, and more appropriate therapeutic modalities for this symptom complex.

Is there a place for contralesional mesh-glove electrical stimulation in USN rehabilitation?

Different studies in the last decade reported that RHD USN patients perform better on neglect tests while receiving left-sided sensory stimulation including TENS (see 14, 15, 19 - 21 for reviews of different stimulation methods).

Mesh glove (MG) stimulation was used originally by Dimitrijevic in Houston as a method of controlled afferent electrical stimulation of the neurologically affected upper limb, aimed primarily to facilitate the reestablishment of a more appropriate motor control of the hand. It employs diffuse stimulation of the affected hand by way of a wired MG made of conductive material. The novelty of this approach is that an organ, the hand, rather than a nerve or a muscle, is the target of stimulation.

Most interesting in our early observations of MG-stimulation effects (31) was the fact that visible changes in motor control could be shown in brain-damaged patients with stimulation applied below the threshold for sensory perception. We speculated that these effects are cortically mediated and widespread in nature, rather than representing time-locked reconditioning of the motor act, achieved through peripheral or spinal mechanisms. As such, MG stimulation was also expected to exert an influence on non-motor cortical dysfunctions.

To prove this conjecture, we thought to decouple the input and output modes in performance of a cortically-mediated task, i.e., to apply MG-stimulation on the contralesional hand while judging the effect through the motor performance of the ipsilesional hand. Following recent reports of benefit from contralesional TENS in USN we asked whether

contralesional application of MG stimulation below the threshold for sensory perception is likely to ameliorate the spatial-attentional deficit of patients with unilateral visual neglect.

Ten RHD patients with severe left visual neglect were asked to perform line-bisection and target-cancellation tasks, using their healthy right hand, in 3 different conditions: (a) baseline; (b) glove-on stimulation-on (applied to the left hand below the threshold for sensory perception); (c) glove-on stimulation-off (without patient's awareness of any difference between this [placebo] and the previous condition, 49).

Group performance showed significant reduction of rightward error on line bisection during stimulation, compared both to baseline and placebo conditions. In the cancellation task, the advantage shown for the stimulation condition did not reach statistical significance. We proposed that subthreshold MG stimulation ameliorates USN by causing an increment in cortical arousal in the damaged hemisphere (49). The results of this study encourage us to continue research on the therapeutic implications of MG stimulation in USN, trying to define the specifications of MG treatment that are optimal for enhancement of functional recovery.

What is the relationship between the mechanisms that produce neglect and the mechanisms involved in recovery from neglect?

Better understanding of the pathophysiology underlying USN and of the mechanisms involved in recovery from neglect is mandatory for developing efficient new treatments.

One of the most influential theories of USN claims that difficulty disengaging attention from a given stimulus, in order to relocate it on a new stimulus positioned to its left, plays a major causative role in this syndrome. This deficit, termed *disengagement failure*, is studied by Posner's "spatial cueing paradigm".

We studied the clinical importance of disengagement failure in USN by correlating patients' performance on the spatial-cueing paradigm with standardized measures of USN severity used in clinical practice (50). Assessment of this correlation done at two points in time, before and after a period of structured rehabilitation treatment, is expected to shed light on this question.

Twelve patients with recent stroke (8 RHD, 4 LHD), performed the standardized Behavioural-Inattention-Test (BIT) battery for visual neglect, line bisection tests, and two computerized response-time (RT) tests: "spatial cueing" and "target detection". A recovery pattern could be identified in both RT paradigms. However, the correlation between spatial-cueing performance (with special emphasis on the effect of disengagement failure) and other measures of neglect was week.

We concluded that disengagement failure cannot fully explain the processes underlying USN and its recovery (50). However, application of theory-based measures of the neuropsychological impairments underlying USN can be of help in development of novel therapies for the different dysfunctions expressed in this complex multifactorial syndrome.

In recent years we have expanded our theoretical research to study some other fundamental psychophysical mechanisms underlying visual behaviour in USN (51, 53). These studies shed new light on important differences between neglect and extinction phenomena, and on the subjective experience of patients with USN.

What is the role of non-spatial factors in USN?

Recent evidence points to the contribution of non-spatially lateralized mechanisms in production of clinically-relevant manifestations in USN. We have used the phenomenon of *binocular rivalry* (BR) to explore a non-spatial deficit over long temporal intervals (46). Five RHD USN patients and 4 normal controls were tested on the basic properties of BR induced by dichoptic presentation of orthogonal gratings at fixation. USN patients had much slower (factor 5) perceptual alternations compared to normal subjects, thus demonstrating a non-spatial fundamental disturbance in USN: delayed habituation to attended stimuli. This in turn may contribute to inappropriate environmental monitoring and attenuated novelty-seeking behaviour (46).

What is the best way to assess longitudinally the natural recovery of USN and the impact of treatment?

Learning effects, shown with repeated use of standard paper-and-pencil USN tests, pose a serious problem for the clinician aiming to assess longitudinally the impact of a given USN therapeutic modality.

To overcome this problem we have developed a reaction-time (RT) paradigm for purposes of clinical and experimental assessment of the distribution of attention in the visual space. The Starry Night (SN) test, designed in our department, is a computerized test involving detection of target stimuli embedded in a two-dimensional dynamic background of distractor stimuli. The spatial distribution of attention is calculated on the basis of RT and accuracy of stimulus detection in different parts of the computer monitor.

Forty-eight first-event stroke patients undergoing rehabilitation soon after the onset of stroke (32 RHD, 16 LHD), and 9 healthy controls, participated in our original study of the SN test (47). Test administration yielded distinct maps of performance in the horizontal and vertical dimensions, and permitted statistical assessments of directional biases, at the group and at the individual level. The sensitivity of the SN to the lateralized bias of spatial attention was usually higher than that of the Behavioral Inattention Test (BIT), a widely used standardized test battery for visual neglect.

The computerized SN test overcomes serious shortcomings of prevalent "paper-and-pencil" USN tests. It provides a powerful tool for monitoring the natural and treatment-induced recovery of USN patients (47, 50).

We published recently data obtained using a different and simpler computerized RT test (VISSTA) which is easily applied in the clinical setting (54)

How to assess the impact of damage to different brain regions on USN severity?

USN is quite unique in the fact that it may emerge following damage to a large variety of brain structures. This pattern of structure-function relationship reflects the complexity of operations involved in allocation of attention, and the connectivity pattern of the distributed network that forms the neural substrate for these operations.

We assessed recently the feasibility of using a multi-perturbation analysis (MPA) mathematical approach for lesion-symptom mapping. We analyzed the relative contribution of damage in different brain regions to the expression of USN as revealed in line-bisection performance (55).

The data set comprised of normalized lesion information and bisection test results from 23 first-event RHD stroke patients. Obtaining quantitative measures of task relevance for different regions of interest (ROIs), the following ROIs were found to be the most contributing: the supramarginal and angular gyri of the inferior parietal lobule, the superior parietal lobule, the anterior part of the temporo-parietal junction connecting the superior temporal and supramarginal gyri, and the thalamus (55).

Our conclusion from this study is that MPA is likely to play an important role in elucidating the anatomical substrate of complex functions and their pattern of fragmentation following localized brain damage (55).

CONCLUDING REMARKS

Research in the field of perceptual and cognitive rehabilitation, and USN rehabilitation in particular, calls for inter-disciplinary cooperation, best accomplished in the clinical setting of the rehabilitation ward. Clinical issues related to the assessment and treatment of perceptual and cognitive impairments are strongly connected to basic questions in the domains of Neuroscience and Cognitive Science. Various researchers in these fields, from different universities in Israel, collaborated with us in the studies presented in this review (see reference list).

In our experience, the model of collaboration between scientists working in the field of Stroke Rehabilitation and those working in the field of Cognitive Neuroscience proved to be very fruitful. It enriched our clinical perspective and enhanced our understanding of the perceptual and cognitive deficits underlining USN complex symptomatology and other perceptual and cognitive impairments not discussed in this paper. We learned new modes for analysing USN at the mechanistic level that increased our understanding of *USN-related Disability*.

General References:

1. Gazzaniga MS, Ivry RB, Mangun GR (Eds): Cognitive Neuroscience – The Biology of the Mind, 3rd Ed, 2009, Norton, New York.

2. Kandel ER, Schwartz JH, Jessell TM (Eds): Principles of Neural Science, 4th Ed, 2000, McGraw Hill, NY.

3. Heilman KM, Valenstein E (Eds): Clinical Neuropsychology, 4th Ed, 2003, Oxford UP, Oxford.

4. Mesulam MM (Ed): Principles of Behavioral and Cognitive Neurology, 2nd Ed, 2000, Oxford UP, Oxford.

5. Riddoch MJ, Humphreys GW (Eds): Cognitive Neuropsychology and Cognitive Rehabilitation, 1994, Lawrence Erlbaum, Hove (UK).

6. Stuss DT, Winocur G, Robertson IH (Eds): Cognitive Neurorehabilitation, 1999, Cambridge UP, Cambridge (UK).

7. Tatemichi TK, Desmond DW, Stern Y, Paik M, Sano M, Bagiella E. Cognitive impairment after stroke: frequency, patterns, and relationship to functional ability. J Neurol Neurosurg Psychiatry 1994; 57: 202-7.

8. Jongbloed L. Prediction of function after stroke: a critical review. Stroke 1986; 17: 765-6

9. Sterzi R, Bottini G, Celani MG, Righetti E, Lamassa M, Ricci S, et al. Hemianopia, hemianaesthesia, and hemiplegia after right and left hemisphere damage: A hemispheric difference. J Neurol Neurosurg Psychiatry 1993; 56: 303-7.

10. Kalra L, Smith DH, Crome P. Stroke in patients aged over 75 years: outcome and predictors. Postgrad Med J 1993; 69: 33-6.

11. Paolucci S, Antonucci G, Guariglia C, Magnotti L, Pizzamiglio L, Zoccolotti P. Facilitatory effect of neglect rehabilitation on the recovery of left hemiplegic stroke patients. J Neurology 1996; 243: 308-14.

12. Jeannerod M (Ed): Neurophysiological and Neuropsychological Aspects of Spatial Neglect, 1987, North-Holland, Amsterdam.

13. Robertson IH, Marshall JC (Eds): Unilateral Neglect: Clinical and Experimental Studies, 1993, Lawrence Erlbaum Associates, Hove (UK).

14. Robertson IH, Halligan PW: Spatial Neglect: A Clinical Handbook for Diagnosis and Treatment, 1999, Psychology Press, Hove (UK).

15. Thier P, Karnath HO (Eds): Parietal Lobe Contributions to Orientation in 3D Space, 1997, Springer-Verlag, Berlin.

16. Kerkhoff G. Spatial hemineglect in humans. Progress in Neurobiology 2001; 63: 1-27.

17. Karnath HO. New insights into the functions of the superior temporal cortex. Nature Reviews Neuroscience 2001; 2: 568-576.

18. Robertson IH. Cognitive rehabilitation: attention and neglect. Trends Cog Sci 1999; 3: 385-393.

19. Diamond PT. Rehabilitative management of post-stroke visuospatial inattention. Disability and Rehabilitation 2001; 23: 407-412.

20. Pierce SR, Buxbaum LJ. Treatments of unilateral neglect: a review. Arch Phys Med Rehabil 2002; 83: 256-268.

21. Manly T. Cognitive rehabilitation for unilateral neglect: review. Neuropsychological Rehabilitation 2002; 12: 289-310.

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22. Vakil E, Galek S, Soroker N, Ring H, Gross Y. Differential effect of right and left hemispheric damage on two memory tasks: free recall and frequency judgment. Neuropsychologia, 1991; 29: 981-992.

23. Vakil E, Soroker N, Bornstein E. The effect of right and left hemispheric lesions on effortful and automatic memory tasks. Laterality, 1998; 3: 143-159.

24. Vakil E, Soroker N, Biran N. Differential effect of right and left hemispheric lesions on two memory tasks: free recall of items and recall of spatial location. Neuropsychologia, 1992; 30: 1041-1051.

25. Soroker N, Cohen T, Baratz C, Glicksohn J, Myslobodsky MS. Is There a place for ipsilesional eye patching in neglect rehabilitation? Behavioural Neurology, 1994; 7: 159-164.

26. Weisz J, Soroker N, Oksenberg A, Myslobodsky MS. Effects of hemi-thalamic damage on k-complexes evoked by monoaural stimuli during midafternoon sleep. J Electroencephal Clin Neurophys, 1995; 94: 148-150.

27. Soroker N, Calamaro N, Myslobodsky MS. Ventriloquist effect reinstates responsiveness to auditory stimuli in the "ignored" space in patients with hemispatial neglect. J Clin Exp Neuropsychol, 1995; 17: 243-255.

28. Calamaro N, Soroker N, Myslobodsky MS. False recovery from auditory hemineglect produced by source misattribution of auditory stimuli (the ventriloquist effect). Restorative Neurol Neurosci, 1995; 7: 151-156.

29. Soroker N, Calamaro N, Myslobodsky MS. "McGurk illusion" to bilateral administration of sensory stimuli in patients with spatial neglect. Neuropsychologia, 1995; 33: 461-470.

30. Serfaty C, Soroker N, Gliksohn J, Sepkuti J, Myslobodsky MS. Does monocular viewing improve target detection in hemispatial neglect? Restorative Neurol Neurosci, 1995; 9: 77-83.

31. Dimitrijevic MM, Soroker N, Pollo FE. Mesh-Glove Electrical Stimulation. Science and Medicine, 1996; 3: 54-63.

32. Ben-Arzi A, Gliksohn J, Soroker N, Margalit M, Myslobodsky MS. An assessment of hemineglect in children with attention deficit hyperactivity disorder. Developmental Neuropsychology, 1996; 12: 271-281.

33. Cohen A, Wasserman A, Soroker N. Learning spatial sequences in unilateral neglect. Psychol Res, 1997; 60: 42-52.

34. Pavlovskaya M, Sagi D, Soroker N, Ring H. Visual extinction and cortical connectivity in human vision. Cognitive Brain Research, 1997; 6: 159-162.

35. Pavlovskaya M, Glass I, Soroker N, Blum B, Groswasser Z. Coordinate frame for pattern recognition in unilateral spatial neglect. J Cog Neurosci 1997; 9: 824-834.

36. Soroker N, Calamaro N, Glicksohn J, Myslobodsky MS. Auditory inattention in right-hemisphere damaged

patients with and without visual neglect. Neuropsychologia, 1997; 35: 249-256.

37. Katz N, Hartman-Maeir A, Ring H, Soroker N. Functional disability and rehabilitation outcome in right hemisphere damaged patients with and without unilateral spatial neglect. Arch Phys Med Rehab, 1999; 80: 379-384.

38. Katz N, Hartman-Maeir A, Ring H, Soroker N. Relationships of cognitive performance and daily function of clients following right hemisphere stroke: Predictive and ecological validity of the LOTCA battery. Occupat Therapy J Res, 1999; 19: 241-255.

39. Sapir A, Soroker N, Berger A, Henik A. Inhibition of return in spatial attention: direct evidence for collicular generation. Nature Neuroscience, 1999; 2:1053-1054.

40. Deouell LY, Bentin S, Soroker N. Electrophysiological evidence for early (pre-attentive) information processing deficit in patients with right hemisphere damage and unilateral neglect. Brain, 2000; 123: 353-365.

41. Deouell LY, Soroker N. What is extinguished in auditory extinction? NeuroReport, 2000; 11: 3059-62.

42. Pavlovskaya M, Sagi D, Soroker N. Contrast dependence of perceptual grouping in brain-damaged patients with visual extinction. Spatial Vision, 2000; 13: 403-414.

43. Hartman-Maeir A, Soroker N, Katz N. Anosognosia for hemiplegia in stroke rehabilitation. Neurorehabilitation and Neural Repair, 2001; 15: 213-222.

44. Hartman-Maeir A, Soroker N, Ring H, Katz N. Awareness of deficits in stroke rehabilitation. J Rehabil Med, 2002; 34: 158-164.

45. Hartman-Maeir A, Soroker N, Oman SD, Katz N. Awareness of disabilities in stroke rehabilitation – a clinical trial. Disability and Rehabilitation, 2003; 25: 35-44.

46. Bonneh YS, Pvalovskaya M, Ring H, Soroker N. Abnormal binocular rivalry in unilateral neglect. NeuroReport, 2004; 15: 473-477.

47. Deouell L, Sacher Y, Soroker N. A novel method for dynamic assessment of spatial attention after brain damage. J Int Neuropsychol Soc, 2005; 11: 697-707.

48. Zamir S, Henik A, Balas M, Soroker N. Differential implicit processing of word and color in unilateral spatial neglect. Cognitive Brain Research, 2005; 23(2-3): 259-269.

49. Soroker N, Dimitrijevic MM, Landa J, Serfaty C, Glicksohn J. Improvement of unilateral visuo-spatial neglect by whole-hand afferent electrical below the treshold for sensory perception. Unpublished data.

50. Sacher Y, Serfaty C, Deouell L, Sapir A, Henik A, Soroker N. Role of disengagement failure and attentional gradient in unilateral spatial neglect – a longitudinal study. Disability and Rehabilitation, 2004; 26: 746-755.

51. Pavlovskaya M, Soroker N, Bonneh Y. Extinction is not a natural consequence of unilateral spatial neglect: evidence from contrast detection experiments. Neuroscience Letters, 2007; 420: 240-244.

52. Deouell LY, Deutsch D, Scabini D, Soroker N, Knight RT. No disillusions in auditory extinction: perceiving a melody comprised of unperceived notes. Frontiers in Human Neuroscience, 2008; 1: 15.

53. Bonneh YS, Sagi D, Gorea A, Soroker N, Treger J, Pavlovskaya M. When they see, they see it almost right: Normal subjective experience of detected stimuli in spatial neglect. Neuroscience Letters, 2008; 446: 51-55.

54. Bar-Haim A, Katz N, Ring H, Soroker N. Assessment of spatial neglect using computerized feature and conjunction visual search tasks. Neuropsychological Rehabilitation, 2009; 19(5): 677-695.

55. Kaufman A, Serfaty C, Deouell L, Rupin E, Soroker N. Multi perturbation analysis of distributed neural networks: the case of spatial neglect. Human Brain Mapping, 2009; 30: 3687-3695.