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Topical review

Impact of cognitive neuroscience on stroke rehabilitation

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Introduction

For over two decades cognitive neuroscience has been shaping our understanding of perception, cognition and consciousness [1]. The term has been coined to describe the translation between cognition, the biological processes of the brain and computational modeling [2,3]. From early on several fields of high clinical relevance were developed under the umbrella of cognitive neuroscience: neuropsychology [4], neuroimaging [5], neural plasticity [6] and neurorehabilitation [7].

Stroke rehabilitation should benefit substantially from cognitive neuroscience in the coming years. To illustrate this point we draw here upon a series of well established studies and outline clinical trials which would be useful to perform. The conceptual shift from classical aphasic syndromes to cognitive models of speech and language processing [8] opened new vistas for rehabilitation, and the new therapeutic interventions are or will be soon ready for clinical trials. Predicting outcome is, however, still difficult [9], partially due to the poor understanding we have of neural mechanisms supporting recovery of cognitive functions. The investigation of simpler models such as the dual-stream model for auditory processing, rather than the very complex networks involved in speech and language processing, may offer useful insights into postlesional plasticity and reorganization. A very intriguing development is the use of brief behavioral interventions, such as prismatic adaptation in neglect, which are believed to enhance plasticity and/or alter the organization of the contralesional hemisphere [10]. There is currently a "translational gap" between the demonstrated effects of prismatic adaptation in specific tasks and the clinically relevant reduction of neglect-related disability [11]. To bridge this gap we need to understand better the mechanisms which underlie the effect of prismatic adaptation and to define

more precisely the indications for this treatment so that more focused randomized controlled trials can be carried out.

From the Wernicke-Lichtheim-Geschwind model to current concepts of language processing

Geschwind's very influential re-analysis of aphasic syndromes emphasized a mechanistic model of language processing by Wernicke's areas for comprehension and Broca's area for production as well as by the connecting white matter pathways [12]. Together with a large body of lesion studies, it determined the diagnostic tools we still use and shaped our bedside approach to aphasia. Its relevance for neurorehabilitation was, however, rather limited. The rehabilitation strategies that we use for aphasia today are based on models of speech and language processing which combine cognitive and biological approaches.

Over four decades after Geschwind's seminal paper, combined evidence from imaging and lesion studies, supported by data from non-human primates, offers a much more complex picture of the neural organization underlying language functions. Based on research in non-human primates, the dual-stream model for auditory processing offers a useful framework for understanding the neural substrates responsible for speech and language in humans [13,14]. It posits the existence of a ventral stream, involved in comprehension, and of a dorsal stream, linking the auditory cortex to articulatory networks. In contrast to the Wernicke-Lichtheim-Geschwind model, the dual-stream model includes a right hemispheric contribution for the ventral, but not the dorsal, stream [13]. The neurocognitive approach to grammatical functions, based on

neuroimaging and lesion studies, highlights the importance of specialized networks, which are partially co-extensive with the ventral and dorsal streams in the left hemisphere [15,16].

The rehabilitation of aphasias benefits largely from cognitive neuroscience [17]. To name a few examples, the understanding of Hebbian mechanisms, i. e. the increase of synaptic efficacy by repeated activation of the postsynaptic neuron by the corresponding presynaptic input [18], suggested the use of intensive practice in rehabilitation, which indeed proved to be efficient [19,20]. The link between the auditory and motor cortices, highlighted in the dual-stream model, was the starting point of constrained induced aphasia therapy [21]. For other approaches which have been practiced for decades, cognitive neuroscience helped to understand the mechanisms of action; this is the case for melodic intonation therapy, which appears to rely on the mirror neuron system and multimodal interactions as well as on postlesional plasticity within the language and music systems [22].

Functional imaging in aphasic patients reveals changes in language organization, which is believed to underlie recovery and to reflect the effects of treatment [23]. After stroke in left hemispheric language areas, the non-injured language networks, which tend to be poorly activated in the acute stage, are transiently up-regulated two weeks later, including the recruitment of additional regions in the right hemisphere [24]. In the chronic stage neural activity induced by language tasks involves a complex network; within the left hemisphere this network corresponds to a reconstituted language-specific system, and in the right hemisphere to the recruitment of the homotopic regions. Based on a large body of activation studies, the latter has been interpreted either as an important contribution to recovery or a detrimental side-effect due

to the loss of transcallosal inhibition; a third option needs yet to be tested, namely that parts of the activated networks are not language-specific, but reflect the much greater cognitive load which the task represents for the aphasic patient [25].

Long-term recovery of language after stroke is variable. The ischemic penumbra allows a fair prediction of functional improvement, which will take place during the acute stage [26]. The recovery during the following months cannot, however, be predicted reliably on the basis of lesion size, language performance in the acute stage, age or education [9]. Current research in predictive models of recovery aims at large scale databases, comparing anatomical and functional data [27,28]. The lack of predictive power is possibly due to our still limited understanding of postlesional reorganization and the mechanisms that govern it.

The evidence for the effectiveness of speech and language therapy is encouraging but not conclusive. Although a considerable number of studies were found to be indicative of empirical support for aphasia therapy [20,29], a critical review of the whole body of randomized controlled trials is more reserved. The latter concludes that there is "some evidence of the effectiveness of speech and language therapy ... in terms of improved functional communication, receptive and expressive language" [30]. Furthermore, the same review draws attention to methodological issues, which should be avoided in future trials.

In clinical practice our rehabilitation programs should use the new aphasia interventions for which the current evidence is encouraging. There is, however, a great need for clinicians to participate in research projects, so that the state of evidence can be improved. Collaborative

research with cognitive neuroscientists should help to sharpen indications for specific therapeutic interventions. The clinical relevance of interventions needs to be tested in large-scale randomized controlled trials with appropriate outcome measures.

Analyzing postlesional plasticity by means of the dual-stream model of auditory processing

Specialized perceptual networks which rely on finely tuned parallel and hierarchical processing offer a unique opportunity to investigate postlesional plasticity. In contrast to the highly complex networks which underlie speech and language processing, these models are simpler and allow addressing specific questions: What happens when a specialized network is damaged? Are the effects different in the acute and in the chronic stages? What happens to specialized networks (within an intact hemisphere) if the contralateral hemisphere is damaged? Work on non-verbal auditory processing offers such an insight. The two processing streams, which were originally described in non-human primates [31,32], were subsequently demonstrated in man in a series of fMRI studies (e. g. [33,34]). A very similar organization was found in both hemispheres of normal subjects, where the temporal convexity is predominantly involved in sound recognition and the parietal convexity in auditory spatial aspects. The organization of the ventral stream is highly complex and proceeds in hierarchical steps from the analysis of spectro-temporal features of sounds within the early-stage auditory areas on the supratemporal plane [35] to semantic encoding near the temporal pole (e. g. [36–38]). Specific classes of auditory stimuli involve other areas, in addition to the auditory regions on the temporal cortex, such as environmental sounds related to actions, which co-activate parts of the motor, premotor and prefrontal cortices (e.g. [37,39–41]; Fig.1).

The recognition of an environmental sound follows a temporal sequence of processing steps, as demonstrated in a series of electrophysiological studies [43]. The neuronal networks within the temporal lobe differentiate between sounds of living vs man-made categories as early as 70 ms post stimulus onset [44] and between the (non-verbal) vocalizations of humans vs animals at ca 170 ms [38]. Sounds related to actions yield different neural activity in the premotor cortex at ca 300 ms [40]. The neural networks within the temporal lobe keep track of prior exposure to the same sound object, even if other sounds have been heard in between; the so called repetition priming effect occurs very early, at 165-215 ms [45]. It is essentially semantic [38] and persists even after frequent exposure to the implicated sound objects [46]. The auditory representations within the two streams are highly plastic and can be modulated by even brief training [47].

Large focal lesions centered on one or the other stream were shown to disrupt selectively the corresponding function, thus confirming the critical role and the specificity of the two streams. In cases of large lesions, these deficits persist into the chronic stage. Damage to one stream but not the other can lead to situations where a patient recognizes environmental sounds perfectly well, but is unable to indicate where they are, or another patient cannot recognize environmental sounds but can indicate with precision where they come from [48–52].

The specificity of the two streams is lost during the acute and postacute stages of stroke. This was demonstrated by the effects of small focal lesions in the acute . Although specific deficits were sometimes associated with lesions of the corresponding stream this was often not the case; a striking example of this is provided by patients with normal sound recognition but with auditory localization deficits associated with small focal lesions of the ventral stream [53].

Auditory deficits associated with small focal lesions in the acute stage have been shown to

recover subsequently, independently of whether there was congruence between the deficit and the specialized network [51]. Sound recognition or localization deficits present during the postacute stage (14-30 days post-stroke) tended to be associated with larger lesions that tended to encroach onto the corresponding specialized network; the recovery rate was lower (about 43%). Similarly, sound recognition or localization deficits present during the early chronic stage (> 1 month post stroke) tended to be associated with even larger lesions that tended to be centered on the corresponding specialized network; the recovery rate was low (about 33%; [51]).

Focal unilateral lesions were shown to have an impact on the organization of the ventral and dorsal streams in the contralateral, intact hemisphere. The same fMRI paradigm that revealed the ventral and dorsal stream specificity in normal subjects [33] was applied to patients with a first focal lesion. Within the contralesional hemisphere sound recognition tasks no longer activated specifically the ventral stream, nor did auditory spatial tasks the dorsal stream; both types of tasks co-activated a common region within the upper temporal lobe [42]. This loss of specificity is very likely the result of profound changes in transmitter receptors which were shown to occur throughout the cerebral cortex after focal lesions in animal models, including an up-regulation of NMDA receptors and a down-regulation of GABAA receptors [54]. The GABAA receptors were shown to be modulated in the human cortex; in postacute and chronic stroke the anatomically intact auditory cortex displayed a layer-selective downregulation of the α2 subunit, whereas the α1, α3 and β2/3 subunits of the GABAA receptor and the GABAB receptors maintained normal levels of expression [55].

Whereas impairments of non-verbal auditory functions have a clinical impact, e. g. auditory agnosia as indicator of the severity in aphasia [56] and auditory spatial deficits in unilateral neglect [57], the understanding of the underlying plasticity and reorganization is of conceptual importance. One take-home message is that the anatomically intact, contralesional hemisphere changes its intrinsic organization and opens a window of increased plasticity. This concept is driving currently research on therapeutic interventions in neglect.

Bottom-up approaches to neglect rehabilitation – understanding the underlying mechanisms

Left unilateral neglect is a frequent, albeit heterogeneous condition in right hemispheric stroke. Patients fail to respond or to orient spontaneously to stimuli presented on the left side and seem unaware of this part of space [58–60]. The intriguing nature of the deficit, its high incidence and its negative impact on recovery have initiated a highly productive research field in cognitive and clinical neuroscience which has led to the development of several rehabilitation techniques [11,61–64].

Several reviews and meta-analyses noted that although therapeutic interventions tended to alleviate neglect symptoms, this was not the case in all studies [20,61,63,65–68] . As pointed out by a recent Cochrane meta-analysis, "the effectiveness of cognitive rehabilitation interventions for reducing the disabling effects of neglect and increasing independence remains unproven ", partially because available studies do not always report long term outcome and effects on activities of daily living [69]. An additional challenge for randomized controlled trials and their meta-analyses is the heterogeneity of neglect syndromes, of which each may respond differently

to specific therapeutic paradigms. There is a great need to understand the mechanisms underlying these paradigms and to define indications for specific treatments.

Rehabilitation methods for neglect rely either on top-down approaches, i. e. on increasing voluntarily attentional load to the left side, or on bottom-up mechanisms, i. e. on the modulation of spatial representations by means of sensory stimulations (for review e. g. [70]). Bottom-up approaches include vestibular stimulation [71], neck muscle vibration [72], optokinetic stimulation [73] and prismatic adaptation [74]. The latter is based on a large body of evidence from basic and clinical studies, which offer an interesting insight into the plasticity of spatial representations in normal subject and in stroke patients.

The prismatic adaptation therapy consists of a visuo-motor adaptation to right-deviating prisms during a pointing task, which induces an aftereffect characterized by pointing errors to the left. During the aftereffect neglect symptoms were shown to decrease on several standard neuropsychological tests such as line bisection, copying a simple drawing, drawing of a daisy from memory or reading [74]. Further studies have demonstrated positive effects on wheelchair navigation [75], postural control [76], mental imagery [77,78], haptic spatial judgments [79], visual search [80], tactile [81] and auditory attention [82,83] and activities of daily living [84]. When prismatic adaptation is applied in a single brief session, the alleviation of neglect symptoms is limited to a few hours [74,77,85]. In several studies prismatic adaptation was administered daily over 2 weeks and the improvement lasted for up to 6 months [84,86–89]. However, one study failed to show any significant improvement [90] and another found only a transient one [91].

The wide range of tasks and activities which can be improved by prismatic adaptation makes it a very desirable tool for neglect rehabilitation [92]. However, not all neglect patients respond equally well to prismatic [84,93]. Different types of neglect may be more or less susceptible to its effects [94], which may explain contradictory results in prospective studies [84,86,90,91,95]. A recent review advocated against a general administration and proposed to apply prismatic adaptation specifically to neglect patients with motor-intentional aiming deficits [11]. A better understanding of the neural mechanisms underlying the therapeutic effect of prismatic adaptation may indeed help to identify patients who will be good responders (Fig. 2).

Activation studies in normal subjects revealed two types of neural mechanisms which may underlie the beneficial effects of prismatic adaptation in neglect patients. A series of studies focusing on the adaptation task itself showed that, during the pointing with prisms, normal subjects experience a profound modulation of neural activity within the posterior parietal cortex and cerebellum [96–99]. Such a modulation may occur in neglect patients and favour postlesional reorganization of the attentional parieto-frontal networks [92]. A recent study compared visual field representations before and after a brief exposure to prismatic adaptation; significant changes were found bilaterally in the inferior parietal lobule, corresponding to an increase of the ipsilateral field representation in the left and a decrease in the right inferior parietal lobule [100]. Thus, in normal subjects prismatic adaptation reverses the right hemispheric dominance for visual space and the left hemisphere becomes competent both for right and left space. Increasing left hemispheric competence for the whole space would be highly beneficial to neglect patients. Two activation studies in neglect patients have demonstrated that prismatic adaptation enhances left hemispheric involvement in visual tasks. A PET study has shown that the beneficial effect of

prismatic adaptation on neglect symptoms correlates with bilateral modulation of cortical regions involved in spatial cognition [101] and a recent fMRI study has shown an increase in fronto-parietal regions bilaterally during bisection and visual search tasks [102]. Both studies involved small numbers of patients (6 and 7) and further investigations are needed to assess fully the effects on the representation of visual space.

Conclusions

Cognitive neuroscience has had so far a very positive impact on stroke rehabilitation. To increase this impact in the future we need to implement the translation from bed to bedside to large scale clinical trials. The refinement of cognitive models, as witnessed for speech and language processing during the last two decades, led to very efficient, new rehabilitation strategies for aphasia. For neglect, bottom-up and top-down approaches introduced a wide range of new therapeutic options. Several issues remain, however, to be explored. Not all patients respond equally well to the one or the other therapeutic intervention. The current challenges lie in identifying correctly the indications for specific approaches, ie. in defining the profile of patients who will respond well to a specific treatment. This requires a better understanding of the mechanisms underlying the effects of treatments. Although studies in normal subjects contribute decisively to this, more hypothesis-driven studies need to be carried out in patients, since the finely tuned parallel and hierarchical processing networks which underlie cognitive functions experience profound reorganization after stroke, even in regions spared by the lesion and the penumbra. The therapeutic interventions with their indications need then to be tested in large-scale randomized controlled trials, which take into account long-term outcome in terms of activities of daily living and of social and professional integration.

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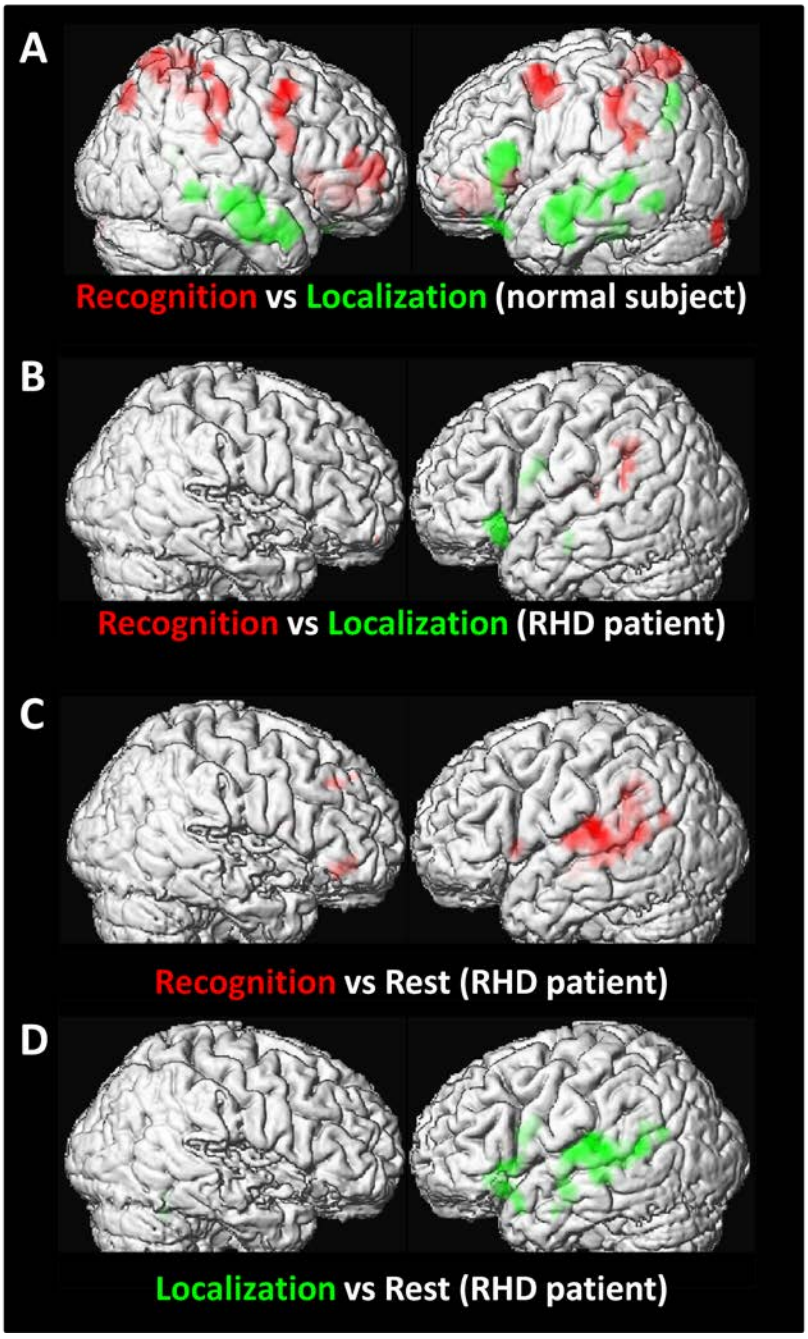

Figure 1. The ventral and dorsal auditory streams in a normal subject (A; adapted from [33] and in a patient with a right temporal lesion (B-D; adapted from [42]). In the top two panels, areas more activated in recognition than in localization are shown in green, areas more activated in localization than in recognition are shown in red. Note the loss of the dual-stream dichotomy within the anatomically intact left hemisphere in B, due to the overlap of the regions which were activated by the sound recognition (C) and by the sound localization tasks (D).

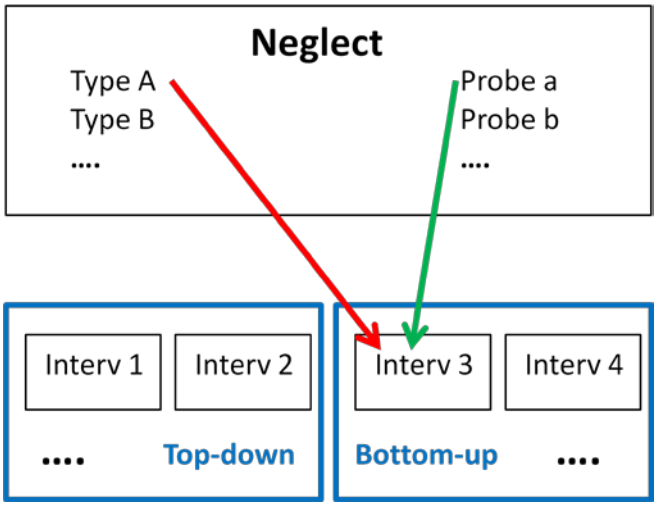

Figure 2. Refining indications for neglect interventions. Instead of enrolling all neglect patients in a trial with a specific therapeutic intervention (e. g. Interv 3), only specific types of neglect (e. g. type A) may be included. Such an approach has been proposed for prismatic adaptation in neglect characterized by motor-aiming deficits [11]. Alternatively a "probe" may be used to identify good responders to the treatment; for prismatic adaptation this could be the presence of the aftereffect after a single presentation [84].