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Letter to the editor

# Real-time fMRI and EEG neurofeedback: A perspective on applications for the rehabilitation of spatial neglect

A R T I C L E I N F O

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Spatial neglect is a neuropsychological syndrome characterized by a failure to orient, perceive, and act toward the contralesional side of the space after brain injury. Neglect is one of the most frequent and disabling neuropsychological syndromes following right-hemisphere damage, often persisting in the chronic phase and responsible for a poor functional outcome at hospital discharge. Different rehabilitation approaches have been proposed over the past 60 years, with a variable degree of effectiveness. In this point-of-view article, we describe a new rehabilitation technique for spatial neglect that directly targets brain activity and pathological physiological processes: namely, neurofeedback (NFB) with real-time brain imaging methodologies. In recent proof-of-principle studies, we have demonstrated the potential of this rehabilitation technique. Using real-time functional MRI (rt-fMRI) NFB in chronic neglect, we demonstrated that patients are able to upregulate their right visual cortex activity, a response that is otherwise reduced due to losses in top-down attentional signals. Using real-time electroencephalography NFB in patients with acute or chronic condition, we showed successful regulation with partial restoration of brain rhythm dynamics over the damaged hemisphere. Both approaches were followed by mild, but encouraging, improvement in neglect symptoms. NFB techniques, by training endogenous top-down modulation of attentional control on sensory processing, might induce sustained changes at both the neural and behavioral levels, while being non-invasive and safe. However, more properly powered clinical studies with control groups and longer follow-up are needed to fully establish the effectiveness of the techniques, identify the most suitable candidates, and determine how the techniques can be optimized or combined in the context of rehabilitation.



## Introduction

### *Spatial neglect syndrome*

Stroke is the most common cause of disability acquired in adulthood. More than half of all survivors are left dependent on others for everyday activities. Thus, stroke has very high economic and social costs. Besides motor and sensory losses, cognitive deficits occur in more than half of stroke survivors, among which impaired attention is the "most prominent" neuropsychological change (reported in 46–92% of patients [1]. In particular, 30–48% of patients exhibit a syndrome of chronic spatial neglect [2].

Neglect is generally defined as a failure to detect and orient to stimuli in the space contralateral to a focal brain lesion (i.e., the contralesional side), which cannot be explained by primary sensory or motor disturbances nor by any general intellectual loss or confusion [3]. It entails a complex constellation of neuropsychological deficits, which can occur in various combinations and with various degrees of severity [4–6] but characteristically leads to inattention to contralesional (e.g., sensory) information. These deficits often persist in the chronic stages many years beyond the acute neurological insult and have a major impact on the functional recovery of patients and on the burden for caregivers [7].

Neglect has been proposed to depend on an imbalance in competitive mechanisms controlling the distribution of attention in space, due to damage in one hemisphere [8,9]. Parietal and frontal cortical areas are thought to govern attention by regulating neural activity in lower-level sensory and motor areas [10,11], both enhancing responses to behaviorally relevant stimuli and suppressing responses to distracting information. Thus, after damage to fronto-parietal cortices or their white-matter interconnections within and/or between hemispheres, neural responses are reduced for stimuli arising in the opposite side of space [12,13].

Given the impact of neglect on recovery, there is an important need for identifying efficient rehabilitation methods (for review [1,14]). There is still no standardized and generally recognized effective therapy. Nevertheless, the treatment spectrum for neglect has seen a few breakthroughs in the last decades, although none of the existing approaches has shown consistent effects across patients and symptoms. The most recent Cochrane review on this issue concluded that the benefits of current rehabilitation techniques are unclear and that no approach can be supported unequivocally [15]. Many of the current rehabilitation strategies in routine use are based on behavioral training, which essentially encourages a consciously driven, strategic exploration of the neglected (typically left) space, through different types of repetitive exercises. These approaches lead to limited clinical benefits that often do not generalize outside the training context. A few other more recent procedures employ prism adaptation [16–19], caloric ear stimulation [20] or optokinetic stimulation [21] that modulate internal space representations without deliberate

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control, and others use direct neurophysiological brain stimulation with transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) [22–25], but the clinical improvements remain highly variable across patients. Furthermore, the exact neural targets of these treatments remain largely unresolved [26].

Finally, the benefits offered by current rehabilitation trainings are still inconsistent and insufficient, with short- or long-term effects that may or may not generalize across attentional tasks as a function of the different approaches and clinical characteristics. Unfortunately, no standard procedure exists that could be selected by specific clinical features or guided by objective pathophysiological parameters. Therefore, there is still an important need for novel interventions targeting precise neurophysiological or neurocognitive components, which could outperform the traditional behavioral training approaches or be combined with them to boost or maintain positive effects. Here we describe a novel approach based on neurofeedback (NFB) using real-time imaging measures of local brain activity with functional MRI (fMRI) or electroencephalography (EEG). These approaches are inspired by neuroscience literature that shows pathological functional modulations of anatomically intact sensory areas in patients with neglect due to losses in top-down attentional control signals after stroke in fronto-parietal networks [3,27]. Such approaches may usefully add to the current rehabilitation tools and allow for individual optimization through a direct assessment of its efficacy at the neural level.

Below, after we briefly review general principles of NFB, we describe our recent work to explore the feasibility of real time NFB training in patients and present preliminary results.

## Direct control of brain activity with NFB: real-time fMRI

NFB is a technique using a neural signal from the participant's brain (such as EEG or fMRI), which is not only recorded and analyzed in real-time during acquisition but also provided in real time to the participant to inform them about ongoing brain activity, through various feedback means (e.g., thermometer display, numerical score, continuous sound, virtual reality). This real-time feedback information can then be used for training, specifically, to learn how to increase or decrease activity in one (or more) target brain region(s) and thus modify its functioning. Thus, such training with NFB may serve to induce behavioral changes or modulate performance in specific tasks mediated by the target brain region(s). In other words, participants may learn to induce neural activity in a selective manner and on a voluntary basis, which may in turn also induce plasticity in the corresponding brain circuits. Various neural measures can be used for NFB. We first focus on real time-fMRI NFB and describe EEG NFB later.

Real-time NFB based on fMRI relies on anatomically localized signals of neural activity measured by local changes in oxygen demands and blood flow (BOLD signal). Recent progress in online fMRI analysis and computational power allows for real-time fMRI (rt-fMRI) analysis of BOLD activity and using this measure as an NFB signal [28]. In this way, the analysis of fMRI data is performed simultaneously with data acquisition, such that participants receive moment-to-moment feedback about levels of neural activity from one (or more) precise brain location(s) with only a short (e.g., 2–4 s) delay. Thus, while lying in the MRI scanner, the participants can see their current brain activity level on a video screen (using numbers or analogous scales such as a thermometer) and learn to modulate (increase or decrease) this activity through some mental strategy (e.g., visual imagery) across successive blocks of regulation (separated by periods of rest). Feedback information is crucial for learning: as NFB makes information about brain activity accessible to conscious perception, it opens the door to gain voluntary control over it. The advantage of rt-fMRI is that it enables learning such control for spatially well localized brain activity in the range of millimeters across the entire brain, but also for precise patterns within areas or connectivity between areas.

Recent literature has shown that healthy participants can use rt-fMRI to learn to regulate brain regions involved in visual perception, pain, motor control, linguistics, emotion, and reward processing (for review [29]). These studies show not only that successful rt-fMRI-based NFB is possible but also provide direct evidence for causal links between neural activity and mental function, with changes in behavior or performance corresponding to changes in activity for the regulated brain areas. For instance, participants trained to control activity of their motor cortex showed subsequent improvement in motor tasks.

Real-time fMRI has also been applied to clinical populations (e.g., those with chronic pain, tinnitus, depression, and Parkinson's disease [see also for a recent review (28)]). Most of these studies revealed that after NFB training, patients successfully regulated activity in the targeted brain regions and improved their clinical symptoms, which suggests that rt-fMRI is a feasible and promising method for clinical rehabilitation. However, with the exception of one study on 2 stroke patients, showing improved motor performance after training, the clinical potential of rt-fMRI NFB for stroke patients has yet to be explored more deeply [28].

## Results of fMRI NFB in neglect patients

Our group recently developed an rt-fMRI NFB method to train visuo-spatial attention by using activity in the occipital visual cortex in one hemisphere and training subjects to increase top-down regulation of this activity (Fig. 1). Abundant research has shown that visuospatial attention operates by enhancing sensory responses in early visual areas both in healthy humans and in monkey models [30]. Conversely, in patients with neglect after right parietal stroke, fMRI work has shown reduced activation of (spared) right visual areas in response to left visual inputs, which increases with attentional task demands [13]. In a first rt-fMRI study, we showed that healthy participants are able to upregulate their occipital cortex on one side only, by learning to modulate the inter-hemispheric visual cortex balance through rt-fMRI NFB [31,32]. This was achieved in 3 sessions spread over several days, and a long-term follow-up revealed that successful participants could still efficiently regulate 1 year later. However, no reliable effect was observed in behavioral performance of simple attentional tests, perhaps because of ceiling levels in healthy individuals.

Following this encouraging outcome in healthy people, we recently explored the feasibility of a similar approach for neglect syndrome [33]. In a group of patients with right parietal stroke and chronic left neglect, we assessed the ability to restore normal activity in their right visual cortex (i.e., intact areas in the damaged hemisphere) using rt-fMRI NFB. Patients underwent systematic visuo-spatial tests during the acute neglect phase as well as before and after the training. The patients were trained to upregulate activity within the right visual cortex during 3 training sessions over the course of 3 weeks. On the basis of this feedback information, patients were instructed to find the best mental strategy to induce maximal increases in neural activity in the target region (e.g., by generating and attending to visual imagery in their left visual field). To avoid contamination by the feedback display, regulation was monitored by an auditory number score (from 0 to 10) given every 6 s during the regulation blocks. Over the course of the 3 training sessions, 5 of 7 patients successfully self-regulated their visual occipital cortex activity, with improved performance in the second and third training sessions as compared with the first.

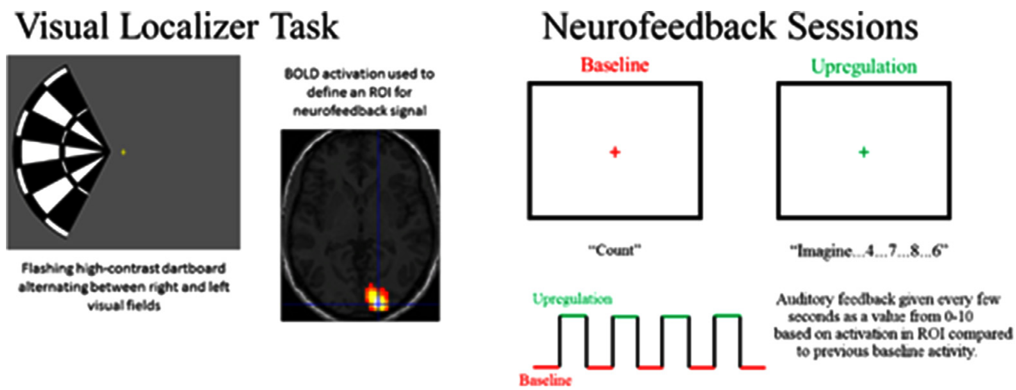


**Fig. 1.** In this functional MRI neurofeedback (NFB) paradigm, a region of interest (ROI) in right occipital cortex was identified by using a flashing dartboard localizer task (left). The high contrast dartboard was presented with inverting colors at 8 Hz, alternating between the left and right visual fields. Participants were instructed to press a button when the cross changed color, in order to maintain attention at central fixation. BOLD activation in the right primary visual cortex was used to define a spherical ROI for subsequent NFB sessions. During the NFB training (right), participants were instructed to try to increase their brain activity by imagining salient visual stimuli in the left visual field. They were presented with only a fixation cross that alternated between red and green, corresponding to the baseline and regulation blocks, which were also accompanied by an auditory cue ("Count" or "Imagine"). Feedback was provided every few seconds in the regulation blocks in the form of a spoken digit from 0 to 10, representing the strength of activation in the ROI relative to the previous baseline block.

Although this pilot sample is too small to draw definitive conclusions about the effectiveness of the training, it clearly shows that NFB with rt-fMRI is feasible in a substantial fraction of patients. In addition, we observed a modest but significant reduction in global clinical scores of neglect severity across time, as assessed with standard visuo-spatial tests such as the Bells cancellation task, a scene copy task, and line bisection. This observation is of course limited by the lack of control group, for example, providing patients with sham NFB using unrelated feedback values. However, the improvement observed after training was higher than spontaneous improvement over the preceding period since the stroke onset. The average interval between acute and pre-NFB testing was 8 months, whereas the interval between the pre- and post-NFB testing was only 3 weeks, yet neglect severity was reduced to the same extent (approximately 25%) during these 2 phases (for more detail see [33]).

Further research in larger samples with control conditions and long-term follow-up are now needed to extend these results and assess their usefulness as a potential rehabilitation tool. Future work will also establish whether NFB training of visual occipital activity leads to neural plasticity in intra- and inter-hemispheric attentional circuits mediating top-down modulation of visual perception and spatial awareness.

## Electroencephalography (EEG) NFB

Brain activity can also be recorded by EEG, which measures electrical currents and oscillations generated by cortical neurons, transmitted through the scalp. Likewise, EEG measures can be obtained in real-time and used to extract a feedback signal to train participants to up- or downregulate specific neural correlates. EEG NFB has already been used in neuropsychiatric conditions with attentional dysfunction, such as attention deficit hyperactivity disorder (ADHD), even being approved by the US Food and Drug Administration (FDA; http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm360811.htm) for therapeutic use in the latter condition. Its use in stroke rehabilitation is more recent but growing in popularity.

In general, unilateral stroke results in a significant reduction of cortical excitability and increased inhibition in the affected relative to the unaffected hemisphere. Consistent with this observation, functional recovery can be promoted by TMS and is associated with increased cortical excitability in the affected hemisphere [34]. Similarly, applying tDCS to the ipsilesional stroke region revealed clinical benefits, with a decrease in cortical inhibition in this area [35]. Stroke also results in changes in rhythmic oscillatory activity measured by EEG, as well as reduced evoked potentials, which may correlate with clinical deficits including neglect and its recovery [36].

The past decade has witnessed a significant expansion of research documenting the clinical potential of EEG NFB for neurological conditions. Of direct relevance to stroke recovery, NFB control of spontaneous low-frequency cortical oscillations (e.g., alpha rhythm) has been shown to induce neuroplastic increases of cortical excitability and decreases of intracortical inhibition. Crucially, these after-effects appear to outlast the training period for at least 30 min post-session, and their magnitude is comparable with the effect of brain (magnetic or electrical) stimulation [34]. However, brain stimulation provokes plasticity by magnetic or electric fields that are not intrinsic to the brain and must still be validated for their long-term safety, including rare seizure occurrence. In light of this evidence, EEG-based NFB acts through endogenous neural processes and has been suggested to have direct relevance for stroke rehabilitation, with growing evidence for its efficacy. However, previous EEG NFB studies have all focused on restoring motor impairment, whereas evidence about the potential application to cognitive deficits, such as neglect, is lacking.

## Results of EEG NFB in patients with neglect

A large body of work in neuroscience has demonstrated that attentional functions are intimately related to oscillatory neuronal activity across distributed brain networks [30]. Different oscillation frequency bands have been linked to distinct attentional components, for example concerning top-down modulation and communication between areas for the alpha (8–14 Hz) or beta (15–30 Hz) bands and intra-areal processing for the gamma band (>30 Hz) [34]. In particular, spatial attention is associated with robust modulation of alpha activity, which is typically suppressed over occipital areas contralateral to the focus of attention and amplified on the ipsilateral side [37].

Accordingly, to investigate the potential of EEG NFB on neglect, we first investigated oscillatory activity associated with neglect symptoms. To this aim, we collected spontaneous EEG data in chronic patients and compared them to healthy age-matched controls [38]. Patients with neglect presented a distinct right-lateralized abnormality (i.e., excess power in the theta-band and a reduction in the alpha-band). More recent work in a larger sample of patients with neglect suggests that alterations of alpha synchrony between the 2 hemispheres correlates with neglect severity in a cancellation test [39].

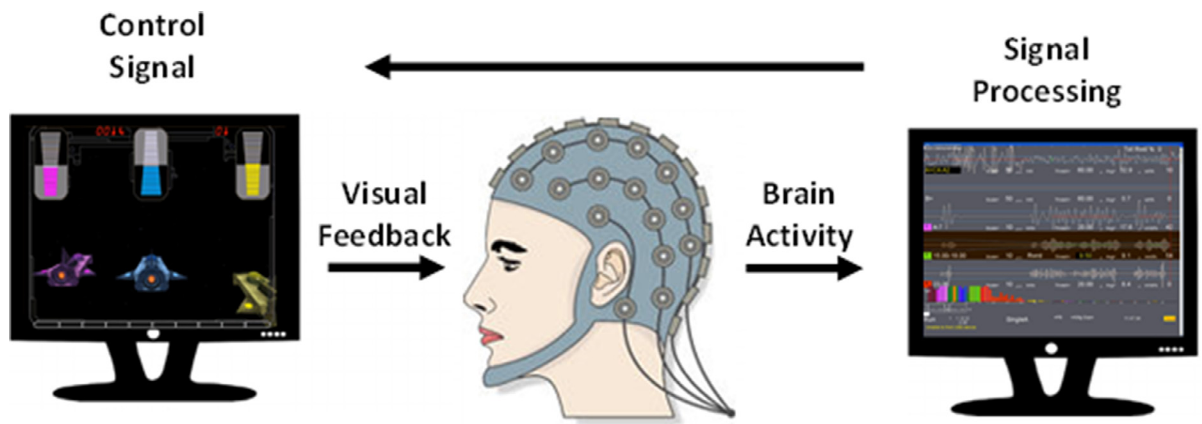


**Fig. 2.** Another neurofeedback methodology consists of a computer that records neural oscillations ("brainwaves") with non-invasive electrodes on the scalp, known as electroencephalography (EEG). Brain activity is then processed in real time and represented visually to the user (i.e., fed back) on a computer screen, for example by a colored bar or the speed of a vehicle in a video game.

In parallel, we studied a smaller group of patients with neglect who underwent 1 week of NFB training aimed at reducing the severity of their neglect symptoms (Fig. 2). The NFB training consisted of reducing the right-hemisphere alpha rhythm (8–12 Hz), focally over parietal sites (electrode P4), based on previous evidence that this constitutes a robust marker of attention orienting toward the left (contralateral) space. We hypothesized that repeated NFB would exercise the functional variability of parieto-occipital brain regions and trigger plasticity mechanisms that could normalize the interhemispheric imbalance in attentional control.

Furthermore, in a first study of patients with acute neglect [40], we showed the feasibility of this approach with 4 patients. Spatial neglect was assessed with 3 tests: line bisection, scene copying, and bell cancellation before, just following, and 1 week after the EEG NFB session, without any neuropsychological training or explicit feedback on behavioral performance. During NFB, all 4 patients could successfully reduce posterior alpha power in comparison with before NFB. The patients were instructed to find their own best mental strategy to reduce the feedback signal by trying different techniques such as creating imagery or modulating attentional focus. Behaviorally, after NFB, the clinical visuospatial tasks showed lower error rates (mean neglect score 18%) as compared with before NFB (56%; $p = 0.01$) and 1 week after (42%; $p = 0.02$). The difference between before NFB and 1 week after was not significantly ($p = 0.18$). These data demonstrate for the first time that neglect deficits can be improved after a single session of NFB in the early phase post-stroke but suggest that this is insufficient to produce a sustained improvement.

In a second study [38], we recruited a different group of patients with neglect (10 months after stroke onset) who first underwent a 1-week baseline waiting period, then were trained with rt-EEG NFB in 5 daily sessions during one full week. Again, most patients could successfully downregulate alpha activity over the right occipital region, although success varied substantially across patients. After NFB training, resting-state EEG revealed no reliable change in alpha power or any other frequency bands, but there was a significant restoration of the spontaneous alpha viability range, which was reduced as compared with healthy controls before NFB. In addition, neuropsychological testing at baseline and after the last NFB session showed moderate improvements in cancellation tasks but not other tests, and this improvement correlated with the increased alpha activity variability at rest in EEG.

Altogether, these findings are encouraging because they indicate not only the feasibility but also physiological and behavioral changes subsequent to NFB, even though these effects were modest and variable. In addition, the results may also help future studies in the choice of relevant EEG parameters to regulate with NFB because anomalies in EEG activity (including low alpha power) could hinder the use of alpha alone as an efficient feedback signal. More research is needed to optimize this approach and determine its efficacy as compared with sham controls and other training regimes.

## Rehabilitation trajectory

There are many issues regarding the rehabilitation of spatial neglect across several levels. First, we need to know the prevalence of neglect in stroke. A recent study showed that the prevalence of spatial neglect was 30% in the acute phase [41]. The presence of spatial neglect in the chronic phase can be estimated at 20%, depending on lesion site [11] and differences in brain activity related to attentional networks between the acute and chronic phase [27].

Additionally, the reported presence of spatial neglect depends on the type of clinical evaluation (attentional, representational, egocentric, object-centered, far/near, stimulus-specific). A recent study demonstrated that diagnostic measures are highly variable, but the principal cognitive tests used were cancelation, drawing tests and neuroimaging/neuromodulation [42]. Another recent study asked experts who have assessed or treated patients with spatial neglect to provide their opinions on how they address spatial neglect [43]. The experts reported ideal and real scenarios for treatment as a function of recovery phase (earliest, acute, subacute, and chronic). The data showed that the ideal treatments were prioritized above the reality scenario for all recovery phases except the chronic phase. Both the reality and ideal treatments included visual scanning, active limb activation, and sustained attention training in the top-five selections, as well as prism adaption in all cases except for the earliest phase of the reality scenario. However, as shown recently [18], prism adaptation does not seem well adapted to patients with parietal lesions.

In sum, the perfect assessment should use ecological evaluations and multi-test methods to detect spatial neglect symptoms, allowing to dissociate the different features of neglect [10,11,44] as a function of the lesion site. Thus, the choice of the rehabilitation program should depend on these 2 points: the type of neglect and the location of the lesion. Some types of patients may benefit from traditional approaches, whereas others may be best treated using novel NFB approaches that directly target specific brain areas or processes.

In comparison with other emerging therapies, such as TMS and tDCS, the advantages of EEG-based NFB approaches are their low cost, their safety (only the natural operation of the brain is implicated, and no seizures have been documented to date), their ease of implementation, and the fact that they are painless (some patients report repetitive-TMS as painful depending on the stimulation site). rt-FMRI NFB is similarly non-invasive, but it does require a costly MRI scanner that is accompanied by certain exclusion criteria (e.g., metal implants, claustrophobia), so it is impractical for many patients. Nonetheless, 3T scanners are increasingly common in hospital and research facilities and the spatial resolution of fMRI allows for targeting patient-specific brain regions that are spared by their lesion or critical to individualized attention network activity. In contrast, EEG can be implemented easily in clinical settings. In fact, for several years, technological advances have allowed for moving the necessary equipment from universities to hospital departments and even to practitioners' offices.

Moreover, a similar EEG/fMRI methodology could be applied to a host of other neurological deficits in the future (hemianopia, hemiparesis, epilepsy) and even some psychiatric conditions (depression, anxiety, impulsivity). What most distinguishes an NFB approach such as ours is that it is strictly endogenous and non-pharmacological, whereby measures of neural function are directly used to guide neuroplastic changes autonomously and in a self-organized way through self-regulation. There are no risks for side effects or immediate withdrawal symptoms. These benefits agree with recent longitudinal studies reporting a stabilization of NFB effects after 1 year.

## Conclusion

In this perspective paper, we introduce NFB as a novel and potentially promising technique for rehabilitation of spatial neglect, in complement to other existing therapies. We illustrate our preliminary results with both fMRI and EEG, primarily aiming to show the possibilities of this approach while acknowledging several methodological limits. Our rt-fMRI NFB data demonstrated that the upregulation of activity in right visual cortex and associated attentional networks might result in increased neuronal sensitivity to visual stimuli in the left hemifield. Alternatively, NFB might rebalance functional top-down interactions between the damaged attentional networks in the fronto-parietal cortex and the spared visual areas in the occipital cortex, thus leading to reduced neglect symptoms in behavioral tests. Second, our EEG NFB data demonstrated a rebalancing of alpha activity over parieto-occipital sites between the 2 hemispheres and/or the restoration of spontaneous dynamic variability in alpha range, resulting in significant improvement in neglect tasks that persisted for 1 week after the intervention.

Nonetheless, these findings need to be confirmed, extended, and refined. Future double-blind randomized experiments should include a much larger number of stroke patients to permit group-level inferences about the efficacy of NFB. Also, systematic behavioral outcome measures should be used, possibly relying on a standardized battery of clinically relevant tests, and, critically, the transfer of any improvements to daily life activities. Finally, both short- and long-term effects of NFB should be assessed in follow-up studies to shed light on the degree to which NFB can trigger sustained changes in brain activity and, consequently, behavioral and functional amelioration. These preliminary findings suggest that NFB approaches may be effective in reducing spatial neglect deficits in some patients, but they do not allow to draw conclusions about the general efficacy and effectiveness of these techniques, which still need to be thoroughly evaluated in future studies. Taken together, the evidence we present constitutes a promising background to design more properly powered studies to better characterize the effectiveness of this novel technology for rehabilitation of spatial neglect after stroke and potentially, domains of neurorehabilitation in general.

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