The potential of real-time fMRI neurofeedback for stroke rehabilitation: A systematic review

Tianlu Wang a, Dante Mantini b,c,d and Celine R. Gillebert a,b,*

a Department of Brain & Cognition, University of Leuven, Leuven, Belgium
b Department of Experimental Psychology, University of Oxford, Oxford, United Kingdom
c Research Center for Movement Control and Neuroplasticity, University of Leuven, Leuven, Belgium
d Department of Health Sciences and Technology, ETH Zurich, Zurich, Switzerland

Abstract
Real-time functional magnetic resonance imaging (rt-fMRI) neurofeedback aids the modulation of neural functions by training self-regulation of brain activity through operant conditioning. This technique has been applied to treat several neurodevelopmental and neuropsychiatric disorders, but its effectiveness for stroke rehabilitation has not been examined yet. Here, we systematically review the effectiveness of rt-fMRI neurofeedback training in modulating motor and cognitive processes that are often impaired after stroke. Based on predefined search criteria, we selected and examined 33 rt-fMRI neurofeedback studies, including 651 healthy individuals and 15 stroke patients in total. The results of our systematic review suggest that rt-fMRI neurofeedback training can lead to a learned modulation of brain signals, with associated changes at both the neural and the behavioural level. However, more research is needed to establish how its use can be optimized in the context of stroke rehabilitation.

© 2017 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. Introduction
The number of stroke survivors is continuously increasing with the ageing of the population: about 15 million people worldwide suffer from stroke every year, of whom 5 million die, whereas another 5 million become chronically disabled (WHO, 2012). Behavioural deficits in cognitive and motor domains are highly prevalent and persistent in stroke survivors (Bickerton et al., 2014; Demeyere, Riddoch, Slavkova, Bickerton, & Humphreys, 2015; Demeyere et al., 2016; Jaillard, Naegele, Trabucco-Miguel, LeBas, & Hommel, 2009; Planton et al., 2012; Verstraeten, Mark, & Sitskoorn, 2016). Neurophysiological and neuroimaging studies suggested that stroke causes network-wide changes across structurally intact regions, directly or indirectly connected to the site of infarction (Carrera & Tononi, 2014; Carter et al., 2010; Gillebert & Mantini, 2013; Grefkes et al., 2008; Ward & Cohen, 2004). Disruptions in even one of the many networks or brain regions implicated in the different aspects of motor function and cognition can have a major impact on quality of life (Achten, Visser-Meily, Post, & Schepers, 2012; Hochstenbach, Mulder,
1.1. Neurofeedback

Neurofeedback works as a closed loop system that provides real-time information regarding the participant’s own brain activity and/or connectivity, which can be used to develop self-learning strategies to modulate these brain signals (Weiskopf, Mathiak, et al., 2004). It follows the principle of operant conditioning, a method of learning that occurs through reinforcing specific behaviour with rewards and punishments (Skinner, 1938). If the participant learns to control activity of the brain areas targeted through neurofeedback, this may ultimately lead to a measurable behavioural change that is related to the function of those areas (DeCharms et al., 2005; Haller, Birbaumer, & Veit, 2010; Hartwell et al., 2016).

The origins of neurofeedback are rooted in electroencephalography (EEG), which measures dynamic changes of electrical potentials over the participant’s scalp (Nowlis & Kamiya, 1970). This technique is portable and inexpensive, and provides estimates of brain activity at high temporal resolution. EEG neurofeedback has been widely used over the years to induce long-lasting behavioural changes, both in healthy volunteers and in patients (Gruzelier, 2014; Nelson, 2007). However, because of the low spatial resolution associated with this technique, it is very challenging to selectively target brain areas of interest. As such, the effects of EEG neurofeedback are often not specific (Rogala et al., 2016; Scharnowski & Weiskopf, 2015). Other neuroimaging techniques used for neurofeedback include magnetoencephalography (MEG) (Buch et al., 2012; Okazaki et al., 2015) and functional near-infrared spectroscopy (fNIRS) (Kober et al., 2014; Mihara et al., 2013). However, as also for EEG, their spatial resolution is relatively limited and they do not permit to target precise brain regions.

The field of neurofeedback has rapidly developed and delved into new avenues by the introduction of real-time functional magnetic resonance imaging (rt-fMRI) technology (Cox, Jesmanowicz, & Hyde, 1995). Accordingly, in the past years there has been a steady increase of studies focussing on rt-fMRI neurofeedback applications to induce behavioural changes (Sulzer et al., 2013). Rt-fMRI neurofeedback uses the blood-oxygenation level-dependent (BOLD) signal to present contingent feedback to the participant and to enable modulation of brain activity (Fig. 1). Various acquisition parameters are available, and chosen based on a trade-off between spatial and temporal resolution, and signal-to-noise ratio (Weiskopf, Scharnowski, et al., 2004). The analysis is performed almost immediately or with a delay of a few seconds depending on the available computational resources. With a much higher spatial resolution than EEG, fMRI allows for a refined delineation of both cortical and subcortical target regions. These properties can be valuable for neurofeedback applications (Stoeckel et al., 2014). Recent studies suggest that rt-fMRI is a mature technology to use in the context of neurofeedback training (for a review, see e.g., Ruiz, Buyukturkoglu, Rana, Birbaumer, & Sitaram, 2014; Weiskopf, 2012). As a result, doors are being opened to the application of rt-fMRI neurofeedback in ameliorating disrupted brain functions in stroke survivors.

1.2. Stroke rehabilitation

The last two decades have witnessed a proliferation of rehabilitation strategies to promote functional recovery after stroke, such as task-specific exercises, task repetition, mental and motor imagery, imitation and – among technological approaches – robot-assisted training, muscle stimulation, magnetic and electrical stimulation, and the use of virtual environments (Cicerone et al., 2000; Loetscher & Lincoln, 2013). However, none of these approaches has yet yielded satisfactory results. Most likely, this is because they do not properly account for the structural, metabolic, and electrophysiological consequences of stroke, and are based on theories of neural plasticity that mainly focus on damage and reorganization of local circuitry, without considering brain-wide effects (Baldassarre et al., 2014; Langhorne, Bernhardt, & Kwakkel, 2011). Furthermore, current rehabilitation protocols do not sufficiently account for across-subject variability. Large across-subject differences have indeed been reported in the type and degree of behavioural impairment and in the spontaneous functional reorganization after stroke (Gillebert & Mantini, 2013; Stoeckel et al., 2014). Based on these considerations, it could be argued that rt-fMRI neurofeedback may be effective for reducing stroke-induced behavioural deficits because the feedback is based on individual brain dynamics, and the brain signals can be derived at high spatial resolution.

1.3. Objectives of the systematic review

This systematic review examines whether rt-fMRI neurofeedback can induce neural and behavioural changes related to motor function or cognition. It thereby evaluates the potential of rt-fMRI neurofeedback-based therapy for stroke rehabilitation. More specifically, we aim to (1) provide an overview of empirical studies investigating the effectiveness of rt-fMRI neurofeedback in modulating brain function and behaviour in healthy individuals and stroke survivors; (2) evaluate the quality of the studies against pre-set methodological and theoretical criteria; (3) provide indications for investigating the use of rt-fMRI neurofeedback in the field of stroke rehabilitation.

2. Methodology

2.1. Search methods

We searched 4 databases (Web of Knowledge/Web of Science, Pubmed, Scopus, and the recently released Real-time Functional Imaging and Neurofeedback (rtFIN) literature database (http://www.rtfin.org/literature.html)) from 1970 to July 2017.
and screened reference lists. We used the following keywords: FMRI AND (real-time OR neurofeedback) AND (stroke OR cognition OR attention OR memory OR perception OR language OR motor OR behaviour). For the rtFIN database, we searched for relevant studies by selecting the categories fMRI and Multiple modalities.

2.2. Inclusion and exclusion criteria

We sought all studies in which the aim was to use real-time fMRI neurofeedback to modulate brain activity, connectivity, and/or the ensuing behaviour related to cognition and motor function in healthy individuals and/or stroke survivors. We restricted the search to the motor and cognitive domains, as these have been shown to be frequently affected after stroke (Hochstenbach et al., 1998; Langhorne, Coupar, & Pollock, 2009). Studies evaluating patients with progressive brain diseases, neurodevelopmental or neuropsychiatric disorders were not included. Due to the novelty of this field, we also retained studies with small sample sizes that were labelled as feasibility, proof-of-concept, or pilot studies. We only considered published manuscripts in English.

2.3. Outcome measures

Two outcome variables were considered in the study. The first involved measures of learned self-regulation of brain function (Sulzer et al., 2013), as assessed by the activation level in the target region-of-interest (ROI) or across the brain, or the functional connectivity between two or more ROIs (Sulzer et al., 2013). The second outcome variable involved measures of behavioural change in cognitive and motor domains. For any of the aforementioned outcome measures, successful learning can be inferred from comparing participants who received neurofeedback to participants who did not receive real feedback (sham-neurofeedback). Alternatively, it can be inferred from within-group comparisons between neurofeedback training runs and transfer runs (i.e., runs during which no feedback is presented) (Weiskopf, Scharnowski, et al., 2004).

2.4. Quality assessment

Two experimenters (TW and CRG) independently assessed the methodological quality of the studies according to the Joanna Briggs Institute (JBI) critical appraisal tools (JBI, 2016). We used the checklist for quasi-experimental studies, which includes 9 criteria (established temporal relationship between the variables; similar participants; similar treatment; control group; multiple outcome measurements; follow-up; similar outcome measurements; reliable outcome measurements; and appropriate statistical analysis). One point was given for the fulfilment of each of the criteria above. Studies scoring between 0 and 3, and those scoring between 4 and 6 were considered to be of low and moderate quality, respectively. If a study scored a 7 or

Fig. 1 – Real-time fMRI neurofeedback is a closed-loop system that can be used to voluntarily modulate brain-activity through the principle of operant conditioning. (A) The participants use self-generated or prior instructed strategies to attempt to change their brain activity. (B) fMRI data are acquired and (C) processed in real-time. Computer programs select the relevant signals and (D) return these to the participants after varied degrees of pre-processing to allow them to adjust their control strategies.
higher, it was considered a high quality study (Luchtka-Flude & Groll, 2015).

3. Results

Application of inclusion and exclusion criteria led to the identification of 33 studies that used rt-fMRI neurofeedback in healthy participants and/or stroke survivors (Fig. 2). These studies included a total of 651 healthy participants and 15 stroke survivors. The total sample size per study ranged between 4 and 80 individuals. The age of the healthy participants ranged between 18 and 77, and the age of the stroke patients between 41 and 75 years. The targeted domain, the presence of a control group, the duration and planning of the neurofeedback training, and the assessment of training outcomes differed considerably between the studies and are summarized in Tables 1 and 2. About half of the studies (N = 17) explicitly examined the effect of rt-fMRI neurofeedback on behavioural outcome measures (Table 2).

3.1. Quality assessment

According to the JBI criteria, two studies were deemed of low quality and 14 studies of moderate quality. The remaining 17 were rated as high-quality studies. Noteworthy, only few studies assessed the long-term effects of the neurofeedback training on the participants (Table 3).

3.2. Modulation of brain activity and connectivity

Most of the studies in healthy individuals showed successful regulation of brain activity in the target ROI, or of the functional connectivity between two or more target ROIs; six studies reported no neural effects of rt-fMRI neurofeedback at the group level (Blefari, Sulzer, Hepp-Reymond, Kollias, & Gassert, 2015; Chiew, LaConte, & Graham, 2012; Johnson et al., 2012; Ramot, Grossman, Friedman, & Malach, 2016; Robineau et al., 2014; Scharnowski, Hutton, Josephs, Weiskopf, & Rees, 2012) (Tables 1 and 2).

Three studies in the cognitive domain (Amano, Shibata, Kawato, Sasaki, & Watanabe, 2016; Robineau, Meskaldji, et al., 2017; Yoo et al., 2007) and one study in the motor domain (Yoo, Lee, O’Leary, Panycz, & Jolesz, 2008) followed up on the participants after the rt-fMRI neurofeedback training over long periods (between 2 weeks and 14 months). The results suggest that the ability to self-modulate brain activity can be preserved up to 14 months after the initial neurofeedback training.

The studies that applied rt-fMRI neurofeedback to ameliorate stroke-induced behavioural impairments provided evidence that stroke patients can modulate the neural activity...
| Study                  | ROI(s) and definition                  | Participants b,c                                                                 | Training sessions and feedback                                                                                       | Results                                                                                                                                                                                                 | Quality |
|-----------------------|----------------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| Auer et al. (2015)    | Bilateral M1; functional localizer     | 32 young healthy adults (16 controls)                                            | 24 runs of 5.8 min each, 12 days over 4 weeks;                                                              | Significant transfer of self-regulated control in most of the participants, with a high spatial specificity to the ROI                                                                                       | High    |
| Berman et al. (2012)  | Left M1; functional localizer          | 15 young healthy adults (no controls)                                            | 2–4 runs of 4 min each, 1 day                                                                               | Successful up-regulation of ROI activity during both NF and transfer runs with motor execution, but not with motor imagery                                                                                       | Moderate |
| DeCharms et al. (2004)| Left M1 and S1; functional localizer  | 9 young healthy adults (3 controls)                                             | Continuous line graph, or virtual reality interface of a corresponding dynamic virtual object; Sham NF from a background region at an earlier time-point in the same session | Successful regulation of ROI activity, specific to the experimental group                                                                                                                                     | High    |
| Hampson et al. (2011)| Bilateral SMA; functional and anatomical localizer | 8 young healthy adults (no controls)                                            | 24 runs over 2 weeks;                                                                                          | Successful regulation of ROI activity in sessions 2–4, but no significant increase over the sessions                                                                                                      | Moderate |
| Johnson et al. (2012)| Left PMC; functional localizer         | 13 young healthy adults (no controls)                                            | 4 runs of 10.3 min each, 1 day;                                                                              | Participants preferred intermediate over continuous feedback                                                                                                                                          | Low     |
| Liew et al. (2016)    | Left M1 and thalamus; functional localizer | 4 elderly chronic stroke patients with right hemiparesis (no controls)        | 18 ± 3 runs of 4 min each, 2 days                                                    | Increased connectivity between the start and the end of the NF training in 3/4 participants                                                                                                               | Moderate |
| Marins et al. (2015)  | Left PMC; anatomical localizer         | 28 young healthy adults (14 controls)                                           | 3 runs of 6.5 min each, 1 day; Controls receive random signals 'without meaning, displayed for experimental purposes' | Increased activation in the ROI in the last NF run compared to the first run; Associated increases in activity of motor control regions, not present in the control group | High    |
| Study                        | Region(s)                      | Participants                                                                 | Methods                                                                 | Results                                                                                       | Rating |
|------------------------------|-------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|--------|
| Neyedli et al. (2017)        | Bilateral M1; functional localizer | 26 young healthy adults, (13 controls); 18 elderly healthy adults (9 controls) | 4 runs of 6 min each, 1 day, Continuous horizontal bar, Sham NF from a non-activated region | Young and older adults increased their lateralized activity between the motor cortices. Only young adults could maintain the lateralized activity during transfer. Motor imagery-related haemodynamic and electrophysiological activity are both modulated during EEG-, fMRI- as well as EEG-fMRI-NF. | Moderate |
| Perronnet et al. (2017)      | Left M1; functional localizer  | 10 young healthy adults (no controls)                                         | 3 runs of 6.7 min each, 1 day, Moving ball                              | Successful regulation of ROI activity through focused visual motor imagery in most of the participants. Recruitment of a novel circuit including putative V6 and medial cerebellum. Induced modulation of FFA/PPA or PPA/FFA activity ratio in 10/16 participants without them being aware. Associated changes in functional connectivity in the auditory cortex. Required target level of regulation (40% increase from baseline) reached by 10/11 resp. 7/11 experimental and control participants. No significant difference between the pre- and post-training scans in either group. The experimental group showed a significant increase in activated volume and BOLD signal in the last NF run. | Moderate |
| Xie et al. (2015)            | Right dorsal PMC; functional localizer | 24 young healthy adults (12 controls)                                          | 4 runs of 7.5 min each, 1 day, Continuous line graph, Sham NF from the experimental group | Associated decrease in connectivity between bilateral PMC and right posterior parietal lobe. All achieved a 3-fold increase in the number of activated voxels in motor and somatosensory areas. Successful regulation of ROI activity, retained after a 2 week long daily practice without NF. Recruitment of additional circuitries implicated in motor skill learning, unique to the experimental group. | High    |
| Yoo and Joelsz, 2002         | Left M1 and S1, parts of premotor areas; functional and anatomical localizer | 5 young healthy adults (no controls)                                           | 1 run of 8 min, 1 day, Intermittent statistical map of pixel-by-pixel brain activity, 7 runs of 1.2 min, 1 day, follow-up after 2 weeks, Continuous line graph, Sham NF from a non-activated region in an earlier session | Successful regulation of ROI activity through focused visual motor imagery in most of the participants. Recruitment of a novel circuit including putative V6 and medial cerebellum. Induced modulation of FFA/PPA or PPA/FFA activity ratio in 10/16 participants without them being aware. Associated changes in functional connectivity in the auditory cortex. Required target level of regulation (40% increase from baseline) reached by 10/11 resp. 7/11 experimental and control participants. No significant difference between the pre- and post-training scans in either group. The experimental group showed a significant increase in activated volume and BOLD signal in the last NF run. | High    |
| Yoo et al. (2008)            | Left M1; functional and anatomical localizer | 24 young healthy adults (12 controls)                                          | 4 runs of 7.5 min each, 1 day, Continuous line graph, Sham NF from the experimental group | Associated decrease in connectivity between bilateral PMC and right posterior parietal lobe. All achieved a 3-fold increase in the number of activated voxels in motor and somatosensory areas. Successful regulation of ROI activity, retained after a 2 week long daily practice without NF. Recruitment of additional circuitries implicated in motor skill learning, unique to the experimental group. | High    |
| Cognitive domain             |                               |                               |                                                                          |                                                                                                                                                         |        |
| Banca et al. (2015)          | hMT+/V5 complex; functional localizer | 20 young healthy adults (no controls)                                         | 1 run of 8 min, 1 day, Intermittent statistical map of pixel-by-pixel brain activity, 7 runs of 1.2 min, 1 day, follow-up after 2 weeks, Continuous line graph, Sham NF from a non-activated region in an earlier session | Successful regulation of ROI activity through focused visual motor imagery in most of the participants. Recruitment of a novel circuit including putative V6 and medial cerebellum. Induced modulation of FFA/PPA or PPA/FFA activity ratio in 10/16 participants without them being aware. Associated changes in functional connectivity in the auditory cortex. Required target level of regulation (40% increase from baseline) reached by 10/11 resp. 7/11 experimental and control participants. No significant difference between the pre- and post-training scans in either group. The experimental group showed a significant increase in activated volume and BOLD signal in the last NF run. | Moderate |
| Ramot et al. (2016)          | FFA and PPA; functional localizer | 16 young healthy adults (no controls)                                         | 25 runs of 10 min each over 5–7 days, Auditory feedback with positive/ negative sounds | Successful regulation of ROI activity through focused visual motor imagery in most of the participants. Recruitment of a novel circuit including putative V6 and medial cerebellum. Induced modulation of FFA/PPA or PPA/FFA activity ratio in 10/16 participants without them being aware. Associated changes in functional connectivity in the auditory cortex. Required target level of regulation (40% increase from baseline) reached by 10/11 resp. 7/11 experimental and control participants. No significant difference between the pre- and post-training scans in either group. The experimental group showed a significant increase in activated volume and BOLD signal in the last NF run. | Moderate |
| Yoo et al. (2006)            | Left primary and secondary auditory areas; anatomical and functional localizers | 22 young healthy adults (11 matched controls)                                 | 5 runs, 40 min total, 1 day, Intermittent auditory feedback of PSC, No neurofeedback information for the controls | Successful regulation of ROI activity through focused visual motor imagery in most of the participants. Recruitment of a novel circuit including putative V6 and medial cerebellum. Induced modulation of FFA/PPA or PPA/FFA activity ratio in 10/16 participants without them being aware. Associated changes in functional connectivity in the auditory cortex. Required target level of regulation (40% increase from baseline) reached by 10/11 resp. 7/11 experimental and control participants. No significant difference between the pre- and post-training scans in either group. The experimental group showed a significant increase in activated volume and BOLD signal in the last NF run. | High    |
in, and connectivity between brain areas implicated in the impaired functions. In Liew et al. (2016), stroke patients learned to modulate functional connectivity between the primary motor cortex and the thalamus in the ipsilesional hemisphere. Half of the patients were able to maintain control of this cortical–subcortical connectivity during the transfer run, and all showed an increased resting-state connectivity between the two regions following the training. Sitaram et al. (2012) successfully used rt-fMRI neurofeedback on the ventral premotor cortex to remediate mild upper limb motor impairments in chronic stroke survivors. After three days of training, three times a day, the patients were able to regulate activity in the ventral premotor cortex, and maintained it during the transfer run. In Robineau, Saj, et al. (2017), patients with hemispatial neglect were able to control activity in the ipsilesional early visual cortex, but not the differential activity between the contra- and ipsilesional early visual cortex.

3.3. Training-induced behavioural modulation of motor function

In almost all studies using rt-fMRI neurofeedback to train motor function (Blefari et al., 2015; Bray, Shimojo, & O’Doherty, 2007; Chiew et al., 2012; Hui, Zhang, Ge, Yao, & Long, 2014; Scharnowski et al., 2015; Sitaram et al., 2012; Zhao et al., 2013), experimenters encouraged the participants to perform motor imagery as a strategy to self-regulate cortical activity. Studies in healthy participants reported neurofeedback-related improvements in motor performance when participants were trained to regulate activity in the supplementary motor area, the sensorimotor cortex, and the ventral and dorsal premotor cortex. Similarly, Sitaram et al. (2012) showed improvements in visuomotor functioning following rt-fMRI neurofeedback training on the ventral premotor cortex in stroke survivors with right hemiparesis. No significant behavioural change was found in the studies aimed at regulating activity in the primary motor area (Blefari et al., 2015; Chiew et al., 2012) (Table 2).

3.4. Training-induced behavioural modulation of cognition

A substantial number of studies assessing the effect of rt-fMRI neurofeedback on cognitive performance were in the domain of visual perception. Most of these targeted early visual areas V1 and V2 (Amano et al., 2016; Robineau et al., 2014; Robineau, Saj, et al., 2012; Scharnowski et al., 2012; Shibata, Watanabe, Sasaki, & Kawato, 2011), whereas one study targeted the higher visual areas parahippocampal place area and fusiform face area (Habes et al., 2016). Four of these studies observed behavioural changes after the training (Table 2). For instance, Robineau, Saj, et al. (2017) showed that rt-fMRI neurofeedback training can reduce symptoms of hemispatial neglect in chronic stroke patients. Consistent with the observations at the neural level (Section 3.3), the study reported a reduction of hemispatial neglect assessed with a line bisection task when participants learned to upregulate ipsilesional visual cortex activity. This is the first neurofeedback study to suggest that exerting control over the activity in the ipsilesional visual
### Table 2 – Overview of the studies examining the effect of rt-fMRI neurofeedback on neural and behavioural outcome measures.a

| Study | ROI(s) and definition | Participants b,c | Training sessions and feedback | Results | Quality |
|-------|-----------------------|------------------|--------------------------------|---------|---------|
| **Motor domain** | | | | | |
| Blefari et al. (2015) | Left M1; anatomical and functional localizers | 14 young healthy adults (no controls) | • 3 runs of 6 min each, 1 day | • Left M1 activity was lower during neurofeedback | Moderate |
| | | | • Continuously vertically moving ball | • Isometric pinching task showed no change during pre- and post-training | |
| | | | | • Correlations between left M1 activation and performance | |
| Bray et al. (2007) | Left M1 and S1; functional localizer | 40 young healthy adults (9 controls) | • 4 runs of 8 min each, 1 day | • Overall brain activity increase in the NF group, and no significant change in the control group | High |
| | | | • Intermittent feedback, monetary reward | • Participants receiving NF showed significant faster reaction times with a coherent cue | |
| | | | • Sham NF from the experimental group | • Increased laterality index between left and right M1 in 6/13 NF participants | High |
| Chiew et al. (2012) | Bilateral M1; functional localizer | 18 young healthy adults (5 controls) | • 4 runs of 8.5 min each, 1 day | • Participants receiving NF showed significant faster reaction times with a coherent cue | |
| | | | • Continuous arrow vector; length represents brain activity | • Increased laterality index between left and right M1 in 6/13 NF participants | |
| | | | • Sham NF from the experimental group | • Button press reaction time test showed no difference pre- and post-training in both NF and sham-feedback groups. | |
| Hui et al. (2014) | Right PMC; functional localizer | 28 young healthy adults (13 controls) | • 4 runs of 7.5 min each, 1 day | • Significant correlation between changes in ROI activity in the last run and network connectivity | High |
| | | | • Continuous line graph | • Significant increased performance in finger tapping task in both groups, but only correlated with functional connectivity in the NF group | |
| | | | • Sham NF from the experimental group | | |
| Scharnowski et al. (2015) | SMA and PHC; functional localizer | 7 young healthy adults (no controls) | • 12–22 runs of 8 min each, 4–6 days; | • Significant increases in differential feedback signal associated with training, maintained in the absence of neurofeedback in transfer runs | Low |
| | | | • Continuous graph of differential SMA–PHC or PHC–SMA signal | • Increased negative coupling between SMA and PHC | |
| | | | | • Improved reaction times during the motor task correlated with SMA activity, and performance in word memory correlated with in PHC activity | |
| | | | | • Increased ROI activity and decreased intracortical inhibition over the course of the training | Moderate |
| | | | | • The visuomotor pinch-force task showed improved performance across trials in 1 patient and 3 healthy participants | |
| Sitaram et al. (2012) | PMv; functional localizer | 2 elderly chronic stroke patients with right hemiparesis 4 young healthy controls | • 10 runs of 7.5 min each over 3 days | • Increase in connectivity from the dorsal PMC to other motor-related areas in the experimental group and progressive decrease in the control group | High |
| Zhao et al. (2013) | Right dorsal PMC; functional localizer | 24 young healthy adults (12 controls) | • 4 runs of 7.5 min each, 1 day | • Significant improvements in the behavioural finger tapping task, higher in the experimental compared to the control group | |
| | | | • Continuous line graph | | |
| | | | • Sham NF from the experimental group | | |

(continued on next page)
| Study                           | ROI(s) and definition                                       | Participants \(b,c\) | Training sessions and feedback                                                                 | Results                                                                                                                                                                                                 | Quality |
|--------------------------------|------------------------------------------------------------|-----------------------|-----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| **Cognitive domain**           |                                                            |                       |                                                                                               |                                                                                                                                                                                                       |         |
| Amano et al. (2016)            | V1/V2; functional localizer for fMRI decoder              | 18 young healthy adults (6 controls)                                                     | • 3 runs on 3 days; • Intermittent visual disc size • No NF training for the controls                                                     | • Induced associative learning between colour and grating orientation in the early visual cortex (V1/V2) • Assessed with a forced-choice test after training, persisting for 3–5 months after training | High    |
| DeBettencourt et al. (2015)    | Frontoparietal attention network, functional localizer    | 80 young healthy adults (Experimental group + 4 control groups, 16 subjects each)         | • 3 runs of max 2 h each, 3–5 days • Composite faces/scenes stimuli, proportion of task-relevant information related to how well the participant paid attention • Sham NF from the experimental group • No-NF: no feedback, outside the scanner • RT-feedback: response time feedback, outside the scanner • RT-sham control: random feedback from the RT-feedback group | • Activity patterns for the faces versus scenes attentional states became more separable after training as assessed by MVPA • Sustained attention abilities improved in participants who received NF training | High    |
| Habes et al. (2016)            | PPA/FFA; functional localizer                             | 9 young healthy adults, (8 controls)                                                     | • 6 runs of 3 min each, 1 day • Continuous thermometer • No feedback for the controls, training in a mock scanner • 3 runs of 60 min each, 3 days • Continuous thermometer | • Successful upregulating differential PPA/FFA activity • Binocular rivalry task performance showed no behavioural changes after training • Consistent up-regulation of the target ROI activity in 8/14 participants • No significant improvement in bilateral target detection task and line bisection task (Robineau et al. 2014) • The successful learners achieved similar activity levels 14 months after the training without any neurofeedback (Robineau, Meskaldji, et al. 2017) | High    |
| Robineau et al. (2014) and Robineau, Meskaldji, et al. (2017) | Visual areas in left and right occipital cortex; functional localizer                   | 14 young healthy adults (no controls)                                                    | • 12–15 runs of 3 min each, 3 days over 3 weeks • Auditory feedback between 0 (lowest) and 10 (highest) on ipsilesional V1 activity (unilateral group) or differential V1 feedback (bilateral group) every 6 s | • No effects in the bilateral group, positive results in the unilateral group • Significant increase in activity levels over the training sessions • Recruitment of bilateral frontoparietal areas, increased localization to the contralesional hemisphere over the sessions • Significant decrease in errors in the line bisection task between the pre-training and session 3, significant reduction of neglect severity according to conventional tests taken pre- and post-training | Moderate |
| Robineau, Saj, et al. (2017)   | Unilateral right V1/bilateral V1; functional localizer     | 9 elderly chronic stroke patients with left hemispatial neglect (2 experimental groups with 6 and 3 participants) |                                                                                               |                                                                                                                                                                                                       | High    |
| Study            | Task Description                                                                 | Participants       | Procedure Details                                                                                                           | Findings                                                                                           | Improvement |
|------------------|----------------------------------------------------------------------------------|--------------------|----------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|------------|
| Rota et al. (2009) | Right IFG; anatomical and functional localizers                                 | 12 young healthy adults (5 controls) | 4 runs of 9 min each, 1 day; Continuous thermometer; Sham NF from unrelated regions | Progressive increase in ROI activation specific to the NF group; Improvements in the experimental group in interpreting emotional prosody but not syntax | High       |
| Scharnowski et al. (2012) | Early visual cortex representing the left or right visual field; functional and anatomical localizer | 16 young healthy adults (5 controls) | 6 runs of 8.3 min each, 3 days; Continuous thermometer; Sham NF from an unrelated region | Significant increases in visual cortex activity in 7/11 experimental participants; Associated increase in connectivity between the visual cortex and the superior parietal lobe; Significantly enhanced perceptual sensitivity in successful learners | High       |
| Sherwood et al. (2016) | Left DLPFC activity; functional localizer                                      | 25 young healthy adults (7 controls) | 5 runs of 8 min each, 5 days over 2 weeks; Continuous line graph; No feedback information for the controls | Ability of ROI activity regulation significantly increased in the experimental group; Associated increase in working memory performance assessed with the 2-back task and dual-task scenario | High       |
| Shibata et al. (2011) | V1/V2; functional localizer for fMRI decoder                                | 10 young healthy adults (no controls) | 10 runs of 5 min each, 5–10 days; Intermittent, solid green disk | Learned estimation of target-orientation likelihood, even during the first neurofeedback day; Performance in orientation discrimination task significantly improved | Moderate   |
| Zhang et al. (2013) | Left DLPFC; functional localizer                                               | 30 young healthy adults (15 controls) | 8 runs of 6.5 min each, 2 days; Continuous thermometer; Sham NF from the experimental group | ROI activity significantly increased between the first and last training session; Experimental group showed improved performance on the digit span and letter memory task | High       |

a Abbreviations in alphabetical order: DLPFC, dorsolateral prefrontal cortex; FFA, fusiform face area; M1, primary motor cortex; MVPA, multi-variate pattern analysis; NF, neurofeedback; PHC, parahippocampal cortex; PMC, premotor cortex; PMv, ventral PMC; PPA, parahippocampal place area; ROI, region of interest; RT, response time; S1, primary somatosensory cortex; SMA, supplementary motor area; V1/V2, primary/secondary visual cortex.
b Where applicable, the number of controls is included in the total number.
c The age of young adults ranged from 18 to 46; the age of elderly adults ranged from 41 to 77.
Table 3 – Quality assessment of the included studies based on the JBI checklist for semi-experimental studies, which includes 9 criteria (established temporal relationship between the variables; similar participants; similar treatment; control group; multiple outcome measurements; follow-up; similar outcome measurements; reliable outcome measurements; and appropriate statistical analysis).

| Study | 1. Cause and effect | 2. Similar participants | 3. Similar treatment | 4. Control group | 5. Multiple outcome measures | 6. Follow-up | 7. Similar outcome measures | 8. Reliable outcomes | 9. Appropriate statistical analysis | Score |
|-------|------------------|--------------------------|---------------------|-----------------|-------------------------------|-------------|--------------------------|------------------|---------------------------------|-------|
| **Studies with neural measures only** |
| **Motor domain** |
| Auer et al. (2015) | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 7 |
| Berman et al. (2012) | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 4 |
| DeCharms et al. (2004) | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 1 | 1 | 4 |
| Hampson et al. (2011) | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 3 |
| Johnson et al. (2012) | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 5 |
| Liew et al. (2016) | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 5 |
| Marins et al. (2015) | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 1 | 5 |
| Neyedli et al. (2017) | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 6 |
| Perronet et al. (2017) | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 5 |
| Xie et al. (2015) | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Yoo and Jolesz (2002) | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 2 |
| Yoo et al. (2008) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
| **Cognitive domain** |
| Banca et al. (2015) | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 4 |
| Ramot et al. (2016) | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 4 |
| Yoo et al. (2006) | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 7 |
| Yoo et al. (2007) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
| **Studies with behavioural and neural measures** |
| **Motor domain** |
| Blefari et al. (2015) | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 4 |
| Bray et al. (2007) | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 8 |
| Chiew et al. (2012) | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 8 |
| Hui et al. (2014) | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 8 |
| Scharnowski et al. (2015) | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 3 |
| Sitaram et al. (2012) | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 1 | 6 |
| Zhao et al. (2013) | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 8 |
| **Cognitive domain** |
| Amano et al. (2016) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
| DeBettencourt et al. (2015) | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 7 |
| Habes et al. (2016) | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 7 |
| Robineau et al. (2014) and Robineau, Meskaljii, et al. (2017) | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 5 |
| Robineau, Saj, et al. (2017) | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 7 |
| Rota et al. (2009) | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 8 |
| Scharnowski et al. (2012) | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 8 |
| Sherwood et al. (2016) | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 7 |
| Shibata et al. (2011) | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 4 |
| Zhang et al. (2013) | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 8 |
cortex may enable stroke patients to reduce the spatial attention bias characteristic of hemispatial neglect.

The rt-fMRI neurofeedback studies focusing on other cognitive functions were all performed in healthy participants. They reported an improved behavioural performance after rt-fMRI neurofeedback training (DeBettencourt, Cohen, Lee, Norman, & Turk-browne, 2015; Rota et al., 2009; Sherwood, Kane, Weisend, & Parker, 2016; Zhang, Yao, Zhang, Long, & Zhao, 2013). Zhang et al. (2013) and Sherwood et al. (2016) reported an improvement in working memory performance after neurofeedback training to modulate dorsolateral prefrontal cortex activity. DeBettencourt et al. (2015) developed a sustained attention training paradigm using rt-fMRI neurofeedback, and behavioural performance in a go/no-go task improved after just one training session. Finally, Rota et al. (2009) examined how emotion processing by the right inferior frontal gyrus influenced language and speech processing, and showed that increasing activity in this region was correlated with improvements in interpreting emotional prosody in a linguistics task, but not in a syntax task.

4. Discussion

Previous research demonstrated correlational links between brain function and behaviour, and the use of neurofeedback enabled causal links to be substantiated through the voluntary modulation of one’s own brain activity. With the correct strategy, this knowledge can be used by clinicians to ameliorate behavioural deficits by facilitating endogenous control over brain activity, likely with higher specificity and fewer side effects than pharmaceutical therapies (Weiskopf, 2012). Accumulating evidence suggests the efficacy of rt-fMRI neurofeedback in the treatment of neurodevelopment and neuropsychiatric disorders, such as attention deficit disorders, anxiety, depression, addictions, and autism spectrum disorders (for a review, see Stoeckel et al., 2014). However, rt-fMRI neurofeedback is still relatively new in the field of stroke rehabilitation. Due to the high costs of MR scanning, rt-fMRI is expected to become a clinically used approach only if it is proven that it can bring clear benefits to the patients’ quality of life. To address this issue, here we conducted a systematic review assessing the potential of rt-fMRI neurofeedback for the rehabilitation of motor and cognitive impairments following stroke. Effective modulation of cognitive and motor performance through self-regulated brain activity was shown in some — but not all — rt-fMRI neurofeedback studies conducted so far in healthy individuals and stroke patients. It should be noted that only three neurofeedback studies on stroke patients met the inclusion criteria (Liew et al., 2016; Robineau, Saj, et al., 2017; Sitaram, Lee, Ruiz, & Birbaumer, 2011). Accordingly, the effectiveness of this non-invasive therapy for stroke rehabilitation needs to be more extensively evaluated.

4.1. Effects of rt-fMRI neurofeedback on brain function and behaviour

Overall, the findings from studies conducted in healthy individuals suggest that neurofeedback training has the potential to improve performance in motor and cognitive functions. At the same time, we observed that the effectiveness of real-time fMRI neurofeedback varies considerably across target regions. For instance, most of the studies targeting early visual areas showed significant neural or behavioural effects after the training (Banca, Sousa, Catarina Duarte, & Castelo-Branco, 2015; Robineau et al., 2014; Scratchnowski et al., 2012; Shibata et al., 2011). In contrast, the studies targeting higher visual areas did not observe any significant effects (Habes et al., 2016; Ramot et al., 2016). Also, successful regulation has been observed in most of the studies targeting the sensorimotor or premotor cortex (Auer, Schweizer, & Frahm, 2015; Bray et al., 2007; DeCharms et al., 2004; Hui et al., 2014; Zhao et al., 2013), but limited success has been obtained in modulating primary motor cortex activity through motor imagery (Berman, Horovitz, Venkataraman, & Hallett, 2012; Blefari et al., 2015; Chiew et al., 2012; however, see; Perronnet et al., 2017; Yoo et al., 2008). Noteworthy, it’s still a matter of debate whether primary motor cortex is recruited during motor imagery (Sharma, Pomeroy, & Baron, 2006).

For stroke patients, rehabilitation protocols that do not require the patients to make overt movements, which is the case for neurofeedback-based training, may be beneficial since prolonged physical effort can be avoided. The results of this systematic review indicate that stroke patients, like healthy individuals, can learn to control brain activity through neurofeedback, and this might ultimately lead to an improvement of stroke symptoms. This postulation is also confirmed by studies aiming at modulating brain activity and connectivity in stroke with fNIRS (Mihara et al., 2012, 2013), MEG (Boe, Gionfriddo, Kraeutner, Tremblay, & Bardouille, 2014; Buch et al., 2012), or EEG (Ramos-Murguialday et al., 2014; Shindo et al., 2011; Young et al., 2014). Notably, evidence exists for a successful use of EEG neurofeedback for cognitive and motor rehabilitation in stroke, but the effects are not consistent across participants (Bearden, Cassisi, & Pineda, 2003; Cannon, Sherlin, & Lyle, 2010; Doppelmayr, Nosko, & Fink, 2007; Reichert et al., 2016; Rozelle & Budzynski, 1995). We posit that, thanks to its superior spatial resolution, rt-fMRI can provide more accurate feedback than EEG/MEG and fNIRS to the participants, who may more easily learn to control their brain activity or connectivity.

4.2. Important factors for the design of rt-fMRI neurofeedback studies

Use of control groups/treatments. The use of appropriate control treatments is particularly important when assessing behavioural changes induced by rt-fMRI neurofeedback training. In this regard, it should be noted that about one third of the reviewed studies did not include a control group, and this impedes quantitative analyses concerning the effectiveness of the intervention. Studies with a control group mostly included sham-feedback groups, where feedback was presented based on brain activity recorded in a different participant (e.g., Hui et al., 2014; Xie, Xu, Long, Yao, & Wu, 2015; Zhang et al., 2013) or from a brain region of the same participant but unrelated to the function of interest (e.g., DeCharms et al., 2004; Neyedli et al., 2017; Rota et al., 2009; Yoo et al., 2007, 2008).
Others included no-neurofeedback behavioural training groups either inside or outside the MR scanner (e.g., Amano et al., 2016; Auer et al., 2015; Yoo et al., 2006). Taken together, the use of sham-neurofeedback was crucial to demonstrate the importance of real, contingent neurofeedback in learning to modulate brain activity in a wide range of brain regions (DeCharms et al., 2004; Linden & Turner, 2016; Scharnowski & Weiskopf, 2015; Sepulveda et al., 2016). However, the effectiveness of rt-fMRI neurofeedback-based therapy for stroke rehabilitation is still to be compared to conventional stroke therapy. Likewise, comparisons between experimental groups with different demographics might reveal factors that influence both the ability to learn self-regulation and the emergence of behavioural effects (e.g., age, Neydli et al., 2017). To this end, carefully designed rt-fMRI neurofeedback studies should be conducted in stroke patients and age-matched control subjects, as already done in EEG neurofeedback studies (Becerra et al., 2011; Cho, Kim, & Jung, 2016; Kober et al., 2015; Shindo et al., 2011; Staufenbiel, Brouwer, Keizer, & van Wouwe, 2014).

Potential biases in participant allocation. Most of the studies were single-blinded and validated in the sense that participants who did not receive real feedback did not notice it, or were unaware that the experiment involved multiple groups of participants. The degree of blinding of the experimenter during the training and of the assessor during the post-training assessment was not specified, with an exception of two studies. Notably, these studies implemented a double-blind procedure by letting a different researcher conduct the participant recruitment and scheduling (DeBettencourt et al., 2015; Neydli et al., 2017). This double-blind procedure would be an appropriate approach for the unbiased assessment of rt-fMRI neurofeedback effects (Stoeckel et al., 2014), in particular in randomized control trials.

Duration/intensiveness of the training. Almost all studies that failed to find an effect of rt-fMRI neurofeedback on behavioural performance, also did not show clear signs of neural modulation (Blefari et al., 2015; Chiew et al., 2012; Robineau et al., 2014). Studies without behavioural effects were typically conducted within a single day, though there does not seem to be a strong link between the absence of effects at the neural level and training duration (ranging from 1 to 7 days). Other studies with short training protocols showed significant pre-post behavioural learning effects after sessions as short as 30 min (Hui et al., 2014; Zhao et al., 2013), and neural effects after a single run of 8 min (Yoo & Jolesz, 2002). These results are promising for clinical applications of rt-fMRI neurofeedback, possibly in combination with other interventions outside the scanner (Yoo et al., 2007, 2008). Most studies with multi-day sessions showed increasing control of ROI activity over the course of the training. None of the reviewed studies compared the magnitude of the learning effects across training days to that from multiple training sessions on the same day. However, other neurofeedback studies have found a sleep consolidation effect where performance increased significantly more between training days compared to between runs on the same day (Megumi, Yamashita, Kawato, & Imamizu, 2015; Scheinost et al., 2013). Although no golden standard exists, it has been suggested that successful transfer of learned self-regulation in the absence of neurofeedback can be expected if at least half of the training runs reach a significantly increased activation (Auer et al., 2015).

Training design. Almost all studies made use of a block design, alternating blocks aimed at regulating neural activity with resting-state blocks. In contrast, Banca et al. (2015) built in a semi-event-related feature that allowed the participant to ‘self-pace’ the training by choosing the order and the duration of the blocks. This self-paced design could potentially improve participant engagement and increase the effectiveness of the training. Notably, the optimal way to learn to control one’s own brain activity varies greatly between participants. For example, Scharnowski et al. (2015) found that explicit cognitive strategies worked best in facilitating neurofeedback learning over the supplementary motor area, whereas Sepulveda et al. (2016) showed best learning effects in the same region when providing a monetary reward without explicit instructions. Further investigations on the mechanisms of operant conditioning in neurofeedback paradigms are warranted for the design of protocols that can give rise to successful learned self-regulation of the targeted brain activity (Birbaumer, Ruiz, & Sitaram, 2013; Sulzer et al., 2013).

Type of feedback. In general, the type of neurofeedback given can vary in modality (auditory and visual feedback), degree of processing (presenting raw brain activity or a derived measure), and timing of the presentation (continuous or intermittent). A few studies gave feedback in the auditory modality (Banca et al., 2015; Ramot et al., 2016; Robineau, Saj, et al., 2017; Yoo et al., 2006), whereas the majority provided visual feedback. The feedback is typically designed to minimize distraction from the task at hand, however, the effect of feedback modality on training efficacy has not been systematically investigated (Emmert et al., 2016). About half of the studies that trained visual perception opted for auditory feedback since it is in a different modality. Regardless of the modality, the majority of the studies provided continuous feedback such that subjective experience could be linked to a ‘tangible’ output. Interestingly, Johnson et al. (2012) showed that participants preferred intermittent compared to continuous feedback in a motor imagery task. The authors suggested that intermittent feedback is more effective in promoting self-regulation of activity in the premotor cortex, however, this study did not directly compare the effect of continuous versus intermittent feedback on training efficacy. There are no best-practice guidelines in the literature concerning the use of continuous or intermittent feedback (Sulzer et al., 2013).

Behavioural outcome measures. The reviewed studies that investigated behaviour included a variety of outcome measures chosen to fit the experimental paradigms of each study. An important factor to consider is the sensitivity of the outcome measures used: if a study does not report significant behavioural changes, it may simply be due to the fact that the outcome measure is not sufficiently sensitive. From this perspective, recent studies have highlighted the importance of using computerized tests for a refined quantification of the participants’ performance on a variety of motor and cognitive tasks (Bonato & Deouell, 2013; Nordin, Xie, & Wunsche, 2014; Pedrol, Serino, Cipresso, Pallavicini, & Riva, 2015). Also, the use of standardized neuropsychological test batteries suitable for stroke patients may be particularly helpful. They enable
qualitative and quantitative comparisons across experiments using different brain areas as targets for rt-fMRI neurofeedback, and allow for predictions on quality of life following the training (Bickerton et al., 2014; Demeyere et al., 2015; Fugl-Meyer, Jääskö, Leyman, Olsson, & Steglin, 1975). Overall, the use of reliable indices that can show clinically significant changes due to the training is crucial to the development of rt-fMRI neurofeedback as a novel therapeutic tool (Stoeckel et al., 2014).

Follow up/transfer. The current review included only a limited number of long-term follow-up studies in healthy participants, and none in stroke patients (Amano et al., 2016; Robineau, Meskalďi, et al., 2017; Yoo et al., 2007, 2008). Previous fNIRS and EEG studies investigating the long-term effects of neurofeedback in stroke patients show that the improved motor function could be retained up to four weeks after training (Mihara et al., 2013; Mottaz et al., 2015), but this has not yet been shown for rt-fMRI neurofeedback training in stroke patients.

4.3. Caveats and future directions

The findings of this systematic review suggest that rt-fMRI neurofeedback may be effective in ameliorating motor and cognitive deficits in stroke patients. Nonetheless, the limited number of patient studies does not allow to draw conclusions about the efficacy and effectiveness of this technique, which still need to be thoroughly evaluated in future studies. The use of different neurofeedback training approaches and outcome measurements complicates any direct comparison between studies aimed at ameliorating the same function. Although no golden standard exists for the assessment of cognitive and motor impairments in stroke patients, a more consistent selection of methods would ease the comparison of the results obtained across studies. Based on the considerations above, we suggest that future double-blind randomized experiments should include a relatively large number of stroke patients to permit group-level inferences about the efficacy of rt-fMRI neurofeedback. Also, systematic outcome measures on behavioural functions should be used, possibly relying on a standardized battery of clinically-relevant tests (Bickerton et al., 2014; Demeyere et al., 2015; Fugl-Meyer et al., 1975). Finally, both short- and long-term effects of rt-fMRI neurofeedback should be assessed in follow-up studies to shed light on the degree with which neurofeedback can trigger sustained changes in brain activity and consequently, behaviour.

5. Conclusion

Effective rehabilitation approaches to improve motor and cognitive function of stroke patients are still lacking. The results emerging from this systematic review suggest that rt-fMRI neurofeedback permits self-regulation of brain activity and can lead to behavioural effects. As such, a more widespread application in the field of stroke rehabilitation is warranted. Neurofeedback may prove particularly useful in early stages after stroke, when physically strenuous interventions are not possible or recommended. In particular, neurofeedback can show the participants that they can take control over seemingly volitionless aspects of their impairment. This feeling of increased control will most likely benefit the individual through the recovery process. Additionally, neurofeedback training in the chronic stage of stroke, where spontaneous recovery has stopped, may trigger functional reorganization in structurally intact parts of the brain, possibly leading to a behavioural recovery that would otherwise not occur.

Acknowledgements

We would like to thank Prof. Glyn Humphreys for guidance and inspiring scientific discussions. We would also like to thank Hanne Huygeliel as well as two anonymous reviewers for their constructive comments on the manuscript. This work was supported by the Wellcome Trust (grant number 101253/A/13/Z to DM) and the Research Foundation Flanders (G072517N to CRG).

References

Achten, D., Visser-Weil, J. M. A., Post, M. W. M., & Schepers, V. P. M. (2012). Life satisfaction of couples 3 years after stroke. Disability and Rehabilitation, 34(17), 1468–1472. https://doi.org/10.3109/09638288.2011.645994.
Amano, K., Shibata, K., Kawato, M., Sasaki, Y., & Watanabe, T. (2016). Learning to associate orientation with color in early visual areas by associative decoded fMRI neurofeedback. Current Biology, 26(14), 1861–1866. https://doi.org/10.1016/j.cub.2016.05.014.
Auer, T., Schweizer, R., & Frahlm, J. (2015). Training efficiency and transfer success in an extended real-time functional MRI neurofeedback training of the somatomotor cortex of healthy subjects. Frontiers in Human Neuroscience, 9(October), 547. https://doi.org/10.3389/fnhum.2015.00547.
Baldassarre, A., Ramsey, L., Hacker, C. L., Callejas, A., Astafiev, S. V., Metcalf, N. V., et al. (2014). Large-scale changes in network interactions as a physiological signature of spatial neglect. Brain: A Journal of Neurology, 137(12), 3267–3283. https://doi.org/10.1093/brain/awu297.
Banca, P., Sousa, T., Catarina Duarte, I., & Castelo-Branco, M. (2015). Visual motion imagery neurofeedback based on the hMT+/V5 complex: Evidence for a feedback-specific neural circuit involving neocortical and cerebellar regions. Journal of Neural Engineering, 12(6), 66003. https://doi.org/10.1088/1741-2560/12/6/066003.
Bearden, T. S., Cassisi, J. E., & Pineda, M. (2003). Neurofeedback training for a patient with thalamic and cortical infarctions. Applied Psychophysiology and Biofeedback, 28(3), 241–253. https://doi.org/10.1023/A:1024689315563.
Becerera, J., Fernández, T., Roca-Stapping, M., Díaz-Comas, L., Galian, B., Bosch, J., et al. (2011). Neurofeedback in healthy elderly human subjects with electroencephalographic risk for cognitive disorder. Journal of Alzheimer’s Disease, 28(2), 357–367. https://doi.org/10.3233/JAD-2011-11055.
Berman, B. D., Horovitz, S. G., Venkataraman, G., & Hallett, M. (2012). Self-modulation of primary motor cortex activity with motor and motor imagery tasks using real-time fMRI-based neurofeedback. NeuroImage, 59(2), 917–925. https://doi.org/10.1016/j.neuroimage.2011.07.035.
Bickerton, W.-L., Demeyere, N., Francis, D., Kumar, V., Remoundou, M., Balani, A., et al. (2014). The BCoS cognitive...
profile screen: Utility and predictive value for stroke. 
Neuropsychology, 29(4), 638–648. https://doi.org/10.1037/ 
neu0000160.

Birbaumer, N., Ruiz, S., & Sitaram, R. (2013). Learned regulation of 
brain metabolism. Trends in Cognitive Sciences, 17(6), 295–302. 
https://doi.org/10.1016/j.tics.2013.04.009.

Blefari, M. L., Sulzer, J., Hepp-Reymond, M.-C., Kollias, S., 
& Gassert, R. (2015). Improvement in precision grip force control 
with self-modulation of primary motor cortex during motor 
imagery. Frontiers in Behavioral Neuroscience, 9(February), 1–18. 
https://doi.org/10.3389/fnebh.2015.00018.

Boe, S., Gionfriddo, A., Kraeutner, S., Tremblay, A., 
& Bonato, M., & Deouell, L. Y. (2013). Hemispatial neglect: 
Efficacy in the treatment of a 43-year-old female stroke victim: 
A case study. Journal of Neurotherapy, 14(2), 107–121. 
https://doi.org/10.1080/108416272015.

Carrera, E., & Tononi, G. (2014). Diaschisis: Fast, present, future. 
Brain: a Journal of Neuroscience, 135(2), 596–614. 
https://doi.org/10.1093/brain/awr331.

Cannon, K. B., Sherlin, L., & Lyle, R. L. (2010). Neurofeedback 
efficacy in the treatment of a 43-year-old female stroke victim: 
A case study. Journal of Neurotherapy, 14(2), 107–121. 
https://doi.org/10.1080/108416272015.

Cechlář, M., Martinů, D., Gillebert, C. R., & Humphreys, G. W. 
(2015). Asymmetrical white matter networks for attending to 
global versus local features. Cortex; a Journal Devoted To the 
Study of the Nervous System and Behavior, 72, 54–64. 
https://doi.org/10.1016/j.cortex.2015.01.022.

Cechlář, M., Rothsstein, P., Hansen, P. C., Deb, S., Riddoch, M. J., 
& Humphreys, G. W. (2013). The central role of the tempo-
parietal junction and the superior longitudinal fasciculus in 
supporting multi-item competition: Evidence from lesion-
symptom mapping of extinction. https://doi.org/10.1016/j. 
cortex.2011.11.008.

Chiew, M., LaConte, S. M., & Graham, S. J. S. (2012). Investigation of 
fMRI neurofeedback of differential primary motor cortex 
activity using kinesthetic motor imagery. Neurolmage, 61(1), 
21–31. https://doi.org/10.1016/j.neuroimage.2012.02.053.

Cho, H.-Y., Kim, K.-T., & Jung, J.-H. (2016). Effects of 
neurofeedback and computer-assisted cognitive rehabilitation 
on relative brain wave ratios and activities of daily living of 
stroke patients: A randomized control trial. Journal of Physical 
Therapy Science, 28(7), 2154–2158. https://doi.org/10.1589/ 
jpts.28.2154.

Cicerone, K. D., Dahlgem, C., Kalmar, K., Langenbahn, D. M., 
Malec, J. F., Bergquist, T. F., et al. (2000). Evidence-based 
cognitive rehabilitation: Recommendations for clinical 
practice. Archives of Physical Medicine and Rehabilitation, 81(12), 
1596–1615. https://doi.org/10.1016/s0003- 
e167.2003.08.041.

Doppelmayer, M., Nosko, H., & Fink, A. (2007). An attempt to 
increase cognitive performance after stroke with 
neurofeedback. Biofeedback, 35(4), 126–130. Retrieved from 
http://www.ncbi.nlm.nih.gov/pubmed/22081825.

Emmert, K., Kopel, R., Sulzer, J., Brühl, A. B., Berman, R. D., 
& Linden, D. E. J., et al. (2016). Meta-analysis of real-time fMRI 
neurofeedback studies using individual participant data: How is 
brain regulation mediated? Neurolmage, 124, 806–812. 
https://doi.org/10.1016/j.neuroimage.2015.09.042.

Fugl-Meyer, A. R., Jääskos, L., Leyman, I., Olsson, S., & Steljing, S. 
(1975). The post-stroke hemiplegic patient. 1. a method for 
evaluation of physical performance. Scandinavian Journal of 
Rehabilitation Medicine, 7(1), 13–31. Retrieved from http://www. 
ncbi.nlm.nih.gov/pubmed/1155616.

Gillebert, C. R., & Maintini, D. (2013). Functional connectivity in 
the normal and injured brain. The Neuroscientist: A Review Journal 
Bringing Neurobiology, Neurology and Psychiatry, 19(5), 509–522. 
https://doi.org/10.1177/1073858412463168.

Grefkes, C., Nowak, D. A., Eickhoff, S. B., Dafotakis, M., Kust, J., 
Karbe, H., et al. (2008). Cortical connectivity after subcortical 
stroke assessed with functional magnetic resonance imaging. 
Annals of Neurology, 63(2), 236–246. https://doi.org/10.1002/ 
aan.21228.

Gruzelier, J. H. (2014). EEG-neurofeedback for optimising 
performance. 1: A review of cognitive and affective outcome in 
healthy participants. Neuroscience and Biobehavioral Reviews, 
44(5), 124–141. https://doi.org/10.1016/j. 
neubiorev.2013.09.015.

Habes, I., Rushton, S., Johnston, S. J., Sokunbi, M. O., Barawi, K., 
Brosnan, M., et al. (2016). fMRI neurofeedback of higher visual 
areas and perceptual changes. Neurophysiology, 85, 206–215. 
https://doi.org/10.1016/j.neuropsychologia.2016.03.031.

Hallas, S., Birbaumer, N., & Veit, R. (2010). Real-time fMRI 
feedback training may improve chronic tinnitus. European
Neurology, 74(1), 100–108. https://doi.org/10.1002/ana.23879.Brain-Machine-Interface.

Ramot, M., Grossman, S., Friedman, D., & Malach, R. (2016). Covert neurofeedback without awareness shapes cortical network spontaneous connectivity. Proceedings of the National Academy of Sciences of the United States of America, 113(17), E2413–E2420. https://doi.org/10.1073/pnas.1516857113.

Reichert, J. L., Kober, S. E., Schweiger, D., Griesshofer, P., Neuper, C., & Wood, G. (2016). Shutting down sensorimotor interferences after stroke: A proof-of-principle SMR neurofeedback study. Frontiers in Human Neuroscience, 10, 348. https://doi.org/10.3389/fnhum.2016.00348.

Robineau, F., Meskaljdi, D. E., Kouch, Y., Rieger, S. W., Mermoud, C., Morgenthaler, S., et al. (2017). Maintenance of voluntary self-regulation learned through real-time fMRI neurofeedback. Frontiers in Human Neuroscience, 11(March), 1–8. https://doi.org/10.3389/fnhum.2017.00131.

Robineau, F., Rieger, S. W., Mermoud, C., Pichon, S., Kouch, Y., Van De Ville, D., et al. (2014). Self-regulation of inter-hemispheric visual cortex balance through real-time fMRI neurofeedback training. NeuroImage, 100, 1–14. https://doi.org/10.1016/j.neuroimage.2014.05.072.

Robineau, F., Sai, A., Neveu, R., Van De Ville, D., Scharnowski, F., & Vuilleumier, P. (2017). Using real-time fMRI neurofeedback to restore right occipital cortex activity in patients with left visuo-spatial neglect: Proof-of-principle and preliminary results. Neuropsychological Rehabilitation, 1–22. https://doi.org/10.1080/09602011.2017.1301262.

Rogala, J., Jurwicz, K., Paluch, K., Kublik, E., Cetnarski, R., & Wrobel, A. (2016). The do’s and don’ts of neurofeedback training: A review of the controlled studies using healthy adults. Frontiers in Human Neuroscience, 10. https://doi.org/10.3389/fnhum.2016.00301. Article 301.

Rota, G., Sitaram, R., Veit, R., Erb, M., Weiskopf, N., Dobig, G., et al. (2009). Self-regulation of regional cortical activity using real-time fMRI: The right inferior frontal gyrus and linguistic processing. Human Brain Mapping, 30(5), 1605–1614. https://doi.org/10.1002/hbm.20621.

Rozelle, G. R., & Budzynski, T. H. (1995). Neurotherapy for stroke rehabilitation: A single case study. Biofeedback and Self-Regulation, 20(3), 211–228. https://doi.org/10.1007/BF01474514.

Ruiz, S., Buyukturguloglu, K., Rana, M., Birbaumer, N., & Sitaram, R. (2014). Real-time fMRI brain computer interfaces: Self-regulation of single brain regions to networks. Biological Psychology, 95(1), 4–20. https://doi.org/10.1016/j.biopsycho.2013.04.010.

Scharnowski, F., Hutton, C., Josephs, O., Weiskopf, N., & Rees, G. (2012). Improving visual perception through neurofeedback. Journal of Neuroscience, 32(49), 17830–17841. https://doi.org/10.1523/JNEUROSCI.6394-11.2012.

Scharnowski, F., Veit, R., Zopf, R., Studer, P., Bock, S. W., Diedrichsen, J., et al. (2015). Manipulating motor performance and memory through real-time fMRI neurofeedback: Biological Psychology, 108, 85–97. https://doi.org/10.1016/j.biopsycho.2015.03.009.

Scharnowski, F., & Weiskopf, N. (2015, August). Cognitive enhancement through real-time fMRI neurofeedback. Current Opinion in Behavioral Sciences. https://doi.org/10.1016/j.cobeha.2015.05.001.

Scheinost, D., Stoica, T., Saksja, J., Papademetris, X., Constant, R. T., Pittenger, C., et al. (2013). Orbitofrontal cortex neurofeedback produces lasting changes in contamination anxiety and resting-state connectivity. Translational Psychiatry, 3(4), e250. https://doi.org/10.1038/tp.2013.24.

Sepulveda, P., Sitaram, R., Rana, M., Montalba, C., Tejos, C., & Ruiz, S. (2016). How feedback, motor imagery, and reward influence brain self-regulation using real-time fMRI. Human Brain Mapping, 37(9), 3153–3171. https://doi.org/10.1002/hbm.23228.

Sharma, N., Pomeroy, V. M., & Baron, J. C. (2006). Motor imagery: A backdoor to the motor system after stroke? Stroke; A Journal of Cerebral Circulation, 37(7), 1941–1952. https://doi.org/10.1161/01.STR.0000269202.43357.fc.

Sherwood, M. S., Kane, J. H., Weisend, M. P., & Parker, J. G. (2016). Enhanced control of dorsolateral prefrontal cortex neurophysiology with real-time functional magnetic resonance imaging (rt-fMRI) neurofeedback training and working memory practice. NeuroImage, 124, 214–223. https://doi.org/10.1016/j.neuroimage.2015.08.074.

Shibata, K., Watanabe, T., Sasaki, Y., & Kawato, M. (2011). Perceptual learning incepted by decoded fMRI neurofeedback without stimulus presentation. Science, 334(December), 1413–1415. https://doi.org/10.1126/science.1212003.

Shindo, K., Kawashima, K., Ushiba, J., Ota, N., Ito, M., Ota, T., et al. (2011). Effects of neurofeedback training with an electroencephalogram-based brain-computer interface for hand paralysis in patients with chronic stroke: A preliminary case series study. Journal of Rehabilitation Medicine, 43(10), 951–957. https://doi.org/10.2340/16501977-0859.

Sitaram, R., Lee, S., Ruiz, J., & Birbaumer, N. (2011). Real-time regulation and detection of brain states from fMRI signals. In R. Cohen, & J. R. Evans (Eds.), Neurofeedback and neuro modulation techniques and applications (pp. 227–438). Elsevier. https://doi.org/10.1016/B978-0-12-382235-2.00009-3.

Sitaram, R., Veit, R., Stevens, B., Caria, A., Gerloff, C., Birbaumer, N., et al. (2012). Acquired control of ventral premotor cortex activity by feedback training: An exploratory real-time fMRI and TMS study. Neurorehabilitation and Neural Repair, 26(3), 256–265. https://doi.org/10.1177/1545968311418345.

Skinner, B. F. (1938). The behaviour of organisms: An experimental analysis. D. Appleton-Century Company Incorporated.

Staufenbiel, S. M., Brouwer, A. M., Keizer, A. W., & van Wouwe, N. C. (2014). Effect of beta and gamma neurofeedback on memory and intelligence in the elderly. Biological Psychology, 95(1), 74–85. https://doi.org/10.1016/j.biopsycho.2013.05.020.

Stoelckel, L. E., Garrison, K. A., Ghosh, S. S., Wighton, P., Hanlon, C. A., Gilman, J. M., et al. (2014). Optimizing real-time fMRI neurofeedback for therapeutic discovery and development. NeuroImage: Clinical, 5, 245–255. https://doi.org/10.1016/j.nicl.2014.07.002.

Sulzer, J., Haller, S., Scharnowski, F., Weiskopf, N., Birbaumer, N., Befari, M. L., et al. (2013). Real-time fMRI neurofeedback: Progress and challenges. NeuroImage, 76, 386–399. https://doi.org/10.1016/j.neuroimage.2013.03.033.

Verstraeten, S., Mark, R., & Sitskoorn, M. (2016). Motor and cognitive impairment after stroke: A common bond or a simultaneous deficit? JMedPub Journals, 1(1), 1–10. Retrieved from http://www.imedpub.com.

Ward, N. S., & Cohen, L. G. (2004). Mechanisms underlying recovery of motor function after stroke. Archives of Neurology, 61(12), 1844–1848. https://doi.org/10.1001/archneur.61.12.1844.

Weiskopf, N. (2012). Real-time fMRI and its application to neurofeedback. NeuroImage, 62(2), 682–692. https://doi.org/10.1016/j.neuroimage.2011.10.009.

Weiskopf, N., Mathiak, K., Bock, S. W., Scharnowski, F., Veit, R., Grodd, W., et al. (2004). Principles of a brain-computer interface (BCI) based on real-time functional magnetic resonance imaging (fMRI). IEEE Transactions on Biomedical Engineering, 51(6), 666–670. https://doi.org/10.1109/TBME.2004.827063.

Weiskopf, N., Scharnowski, F., Veit, R., Goebel, R., Birbaumer, N., & Mathiak, K. (2004). Self-regulation of local brain activity using real-time functional magnetic resonance imaging.
(fMRI). *Journal of Physiology Paris*, 98(4–6 Spec. Iss.), 357–373. https://doi.org/10.1016/j.jphysparis.2005.09.019.

WHO, G. W. H. O. (2012). Global Health Estimates.

Xie, F., Xu, L., Long, Z., Yao, L. L., & Wu, X. (2015). Functional connectivity alteration after real-time fMRI motor imagery training through self-regulation of activities of the right premotor cortex. *BMC Neuroscience*, 16(1), 29. https://doi.org/10.1186/s12868-015-0167-1.

Yoo, S.-S., & Jolesz, F. A. (2002). Functional MRI for neurofeedback: Feasibility study on a hand motor task. *NeuroReport*, 13(11), 1377–1381. https://doi.org/10.1097/00001756-200208070-00005.

Yoo, S.-S., Lee, J. H., O’Leary, H. M., Lee, V., Choo, S.-E., & Jolesz, F. A. (2007). Functional magnetic resonance imaging-mediated learning of increased activity in auditory areas. *NeuroReport*, 18(18), 1915–1920. https://doi.org/10.1097/WNR.0b013e328350a601.

Yoo, S.-S., Lee, J. H., O’Leary, H. M., Panych, L. P., & Jolesz, F. A. (2008). Neurofeedback fMRI-mediated learning and consolidation of regional brain activation during motor imagery. *International Journal of Imaging Systems and Technology*, 18(1), 69–78. https://doi.org/10.1002/ima.20139.

Yoo, S.-S., O’Leary, H. M., Fairneny, T., Chen, N.-K., Panych, L. P., Park, H., et al. (2006). Increasing cortical activity in auditory areas through neurofeedback functional magnetic resonance imaging. *NeuroReport*, 17(12), 1273–1278. https://doi.org/10.1097/01.wnr.0000227996.53540.22.

Young, B. M., Nigogosyan, Z., Walton, L. M., Song, J., Nair, V. A., Grogan, S. W., et al. (2014). Changes in functional brain organization and behavioral correlations after rehabilitative therapy using a brain-computer interface. *Frontiers in Neuroengineering*, 7(26), 15. https://doi.org/10.3389/fneng.2014.00026.

Zhang, G., Yao, L. L., Zhang, H., Long, Z., & Zhao, X. (2013). Improved working memory performance through self-regulation of dorsal lateral prefrontal cortex activation using real-time fMRI. *PLoS One*, 8(8), e73735. https://doi.org/10.1371/journal.pone.0073735.

Zhao, X., Zhang, H., Song, S., Ye, Q., Guo, J., & Yao, L. L. (2013). Causal interaction following the alteration of target region activation during motor imagery training using real-time fMRI. *Frontiers in Human Neuroscience*, 7(Dec). https://doi.org/10.3389/fnhum.2013.00866.