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Modulating the interhemispheric activity balance in the intraparietal sulcus using real-time fMRI neurofeedback: Development and proof-of-concept

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ABSTRACT

The intraparietal sulcus (IPS) plays a key role in the distribution of attention across the visual field. In stroke patients, an imbalance between left and right IPS activity has been related to a spatial bias in visual attention characteristic of hemispatial neglect. In this study, we describe the development and implementation of a real-time functional magnetic resonance imaging neurofeedback protocol to noninvasively and volitionally control the interhemispheric IPS activity balance in neurologically healthy participants. Six participants performed three neurofeedback training sessions across three weeks. Half of them trained to voluntarily increase brain activity in left relative to right IPS, while the other half trained to regulate the IPS activity balance in the opposite direction. Before and after the training, we estimated the distribution of attention across the visual field using a whole and partial report task. Over the course of the training, two of the three participants in the left-IPS group increased the activity in the left relative to the right IPS, while the participants in the right-IPS group were not able to regulate the interhemispheric IPS activity balance. We found no evidence for a decrease in resting-state functional connectivity between left and right IPS, and the spatial distribution of attention did not change over the course of the experiment. This study indicates the possibility to voluntarily modulate the interhemispheric IPS activity balance. Further research is warranted to examine the effectiveness of this technique in the rehabilitation of post-stroke hemispatial neglect.

1. Introduction

Given the limited capacity of our brain to simultaneously process incoming information, selective attention is important to efficiently interact with our environment in everyday life. It enables us to prioritise the processing of behaviourally relevant stimuli from cluttered visual scenes, and as such to achieve our goals. Previous studies showed that selective attention is mediated by a distributed network of brain regions in the frontal and parietal cortex, sometimes referred to as the dorsal attention network (DAN; Corbetta and Shulman, 2002; Ptak, 2012). More specifically, it has been shown that the intraparietal sulcus (IPS), which holds a topographic representation of the visual field, plays a key role in orienting attention towards a spatial location in anticipation of a visual target stimulus (Gillebert et al., 2011; Molenberghs et al., 2008; Silver and Kastner, 2009; Szczepanski et al., 2010). In healthy individuals, the degree of lateralization of the left and right IPS, which reflects the extent to which each area responds to the contra- versus ipsilateral visual field, has been found to predict the behavioural spatial bias when distributing attention across the visual field (Szczepanski and Kastner, 2013; Thut et al., 2006). Furthermore, suppressing left or right parietal cortex excitability using non-invasive brain stimulation can impair contralateral stimulus detection (e.g. Andres et al., 2020; Hilgetag et al., 2001; Szczepanski and Kastner, 2013).

Understanding how interhemispheric regions of the dorsal attention

Abbreviations: BOLD, blood oxygen level-dependent; dPSC, differential percent signal change, EPI: echoplanar image; fMRI, functional magnetic resonance imaging; FWHM, full-width at half maximum; GLM, general linear model; IPS, intraparietal sulcus; MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; NF, neurofeedback; PANAS, Positive and Negative Affect Scale; QCM, Questionnaire for current Motivation; ROI, region-of-interest; SE, standard error; TE, echo time; TR, repetition time, TVA: Theory of Visual Attention.

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network, in particular the left and right IPS, interact in the control of spatial attention is of considerable clinical interest due to the high prevalence of post-stroke spatial attention disorders such as hemispatial neglect (Buxbaum et al., 2004; Demeyere and Gillebert, 2019; for a review, see Corbetta, 2014). Hemispatial neglect is characterised by an imbalance in the distribution of attention, biased towards the ipsilesional side of space, accompanied by non-spatial deficits such as a reduction in arousal. It has a severe effect on the activities of daily living and predicts poor functional outcome (e.g. Nijboer et al., 2013, 2014). Hemispatial neglect typically occurs after structural damage to perisylvian regions in the right hemisphere, such as the inferior parietal lobule, the ventrolateral frontal cortex and the superior/middle temporal cortex (Karnath and Rorden, 2012; Karnath et al., 2004, 2011). This structural damage in turn induces functional abnormalities in structurally intact brain areas, more specifically, decreased task-evoked activity in ipsilesional and increased task-evoked activity in contralesional IPS, as well as a decreased functional connectivity between left and right IPS (Corbetta et al., 2005; Corbetta and Shulman, 2011; He et al., 2007). Furthermore, inhibitory non-invasive brain stimulation of the contralesional or excitatory stimulation of the ipsilesional parietal cortex can improve hemispatial neglect symptoms and accelerate recovery in activities of daily living (e.g. Nyffeler et al., 2019; Sparing et al., 2009; Sunwoo et al., 2013; for a review, see Cotoi et al., 2019).

In this study, we aimed to assess whether real-time functional magnetic resonance imaging (fMRI) neurofeedback can be used to endogenously modulate the interhemispheric IPS activity balance. Neurofeedback is a technique that provides participants with information about their ongoing brain activity. It is based on the theory of operant conditioning, where activity changes towards a desired state are rewarded (Fetz, 2007; Skinner, 1938). When participants learn to volitionally regulate their brain activity to reach the desired state, accompanying behavioural changes are to be expected (deCharms et al., 2005; for a review, see Sitaram et al., 2017). Over the past decades, neurofeedback has been of increasing interest to researchers from various disciplines for its broad fundamental and clinical applications, as well as its potential to provide tailored interventions accounting for inter-individual variability and accommodating individual characteristics of the participants (Ordikhani-Seyedlar et al., 2016; Thibault et al., 2018; Wang et al., 2018). For instance, a neurofeedback study based on electroencephalography (EEG) has successfully trained right-hemisphere stroke patients with hemispatial neglect to control alpha oscillations from their right posterior parietal cortex, the degree of which significantly correlated with performance on a cancellation test (Ros et al., 2017). Furthermore, neurofeedback based on real-time fMRI has been successfully used to train hemispatial neglect patients with right-hemisphere stroke to upregulate right visual cortex activity (Robineau et al., 2017), since reduced activity in the intact ipsilateral visual cortex is thought to be due to the top-down influence of the functionally disrupted IPS (Koivisto et al., 2017; Ruff et al., 2009; Vuilleumier et al., 2008). After three training sessions, the patients successfully learnt to increase activity in the ipsilesional visual cortex and showed an improvement in performance on clinical neglect tests. Robineau and colleagues also attempted to train stroke patients with hemispatial neglect to control the interhemispheric activity balance between the left and right visual cortices. However, while this was successful in an earlier study with healthy participants, the patients did not learn volitional control over the differential activity (Robineau et al., 2014, 2017).

Despite the lower temporal resolution in comparison to EEG neurofeedback, real-time fMRI is more suited to conduct neurofeedback experiments where a high spatial precision is required, e.g., to reliably delineate the IPS. To date, multiple real-time fMRI neurofeedback studies have used the IPS as a control region-of-interest (ROI), a functionally unrelated region to the target region (e.g. Young et al., 2014, 2017, 2018; Yuan et al., 2014; Zotev et al., 2011, 2013, 2016, for a review, see Young et al., 2018). These studies focused on the potential of neurofeedback training of amygdala activity in healthy individuals and patients with major depressive disorder to improve mood and alleviate symptoms of major depressive disorder, and provided participants in the control group with feedback from the left horizontal segment of the IPS (hIPS). The results showed no increase in hIPS activity over the course of the training, nor any behavioural effects in the control group, while improvements were observed in both the neural and the behavioural outcome measures of the experimental group, receiving veridical feedback from the amygdala (Young et al., 2014, 2017, 2018; Yuan et al., 2014; Zotev et al., 2011, 2013, 2016). However, no neurofeedback study has directly investigated whether interhemispheric IPS activity balance can be volitionally controlled. The shift from subcortical regions and primary motor and sensory regions, which constitute a large part of the neurofeedback literature, towards higher-order brain regions involved in complex cognitive processes such as attention could provide a more varied and versatile usage of neurofeedback, but requires additional considerations (Ekanayake et al., 2018; Thibault et al., 2018). Mainly, it is important to disentangle which activation changes in the regions associated with higher-order cognitive process are due to neurofeedback-guided self-regulation, and which are reflective of higher-order cognitive processes involved in feedback processing or recruited through exogenous stimulation.

The current study describes the development and implementation of a real-time fMRI neurofeedback pipeline to train individuals to volitionally control interhemispheric brain activity in the IPS. Six neurologically healthy participants were recruited for a proof-of-concept study to assess, on an individual subject level, the feasibility of increasing the differential activation between left and right IPS using real-time fMRI neurofeedback information about the activity in the target relative to the contralateral IPS. We probed for changes in functional connectivity due to the training by acquiring resting-state fMRI scans. We also analysed the effect of real-time fMRI neurofeedback training on the behavioural spatial bias in the distribution of attention using a whole and partial report paradigm within the framework of the Theory of Visual Attention (TVA; Bundesen, 1990), a quantitative model of visual attention. We hypothesised that participants could learn to modulate the interhemispheric IPS activity balance using neurofeedback, and that this ability would be maintained in the absence of neurofeedback. The aim of the neurofeedback training was to increase the activity of the target IPS relative to the contralateral IPS. If successful, we expected the hemispheric asymmetry in the BOLD activity of the IPS to be accompanied by a reduced correlation between the time courses of the target and contralateral IPS, and thus by a decreased functional connectivity between left and right IPS during rest (e.g. Scharnowski et al., 2015). Finally, we expected the training to change the distribution of attention across the visual field mirroring the learnt changes in interhemispheric IPS activity balance. The purpose of this study is to test whether volitional modulation of the interhemispheric IPS activity balance can be achieved in individual participants. This study aims to provide further evidence for a causal relationship between interhemispheric IPS activity balance and spatial attention, and to constitute an important step to establish how neurofeedback can be used to promote the functional recovery of individual stroke patients with hemispatial neglect.

2. Methods

2.1. Participants

Six neurologically healthy individuals were recruited from the student body of KU Leuven to participate in the study (4 women, aged 23 to 29 years). General exclusion criteria were a previous history of neurological, neurodevelopmental, or psychiatric disorders, colour blindness, or contraindications for MRI. All participants had good or contact-lens corrected sight and were right-handed (Edinburgh Handedness Inventory score greater than 60; Oldfield, 1971; Veale, 2014; Table 1). Participants provided written informed consent in accordance with the

Table 1
Participants' group allocation and demographic data. Participants in the left-IPS group were asked to shift the interhemispheric IPS activity balance leftward, participants in the right-IPS group were asked to shift the interhemispheric IPS activity balance rightward. Handedness is expressed with the Edinburgh Handedness Inventory score (Oldfield, 1971; Veale, 2014); ranging from −100: extreme left-handedness to +100: extreme right-handedness).

Group	Participant	Age	Sex	Handedness
Left-IPS	P1	27	F	88
	P3	25	M	81
	P5	27	F	88
Right-IPS	P2	29	F	75
	P4	23	M	100
	P6	23	F	100

Declaration of Helsinki and received financial compensation for participation in the study. The study was approved by the Ethics Committee Research UZ/KU Leuven (Reference number: S60136).

2.2. Study design

2.2.1. General procedure

The participants were randomly assigned to one of two groups (Table 1). Participants in the left-IPS group were asked to shift the interhemispheric IPS activity balance leftward by up-regulating the left IPS (IPS_{target}) and/or down-regulating the right IPS (IPS_{contra}) activity. In turn, the participants in the right-IPS group were asked to shift the interhemispheric IPS activity balance in the opposite direction by up-regulating the right IPS (IPS_{target}) and/or down-regulating the left IPS (IPS_{contra}) activity.

The study was conducted across five weeks (Fig. 1). In the first pre-training assessment (Fig. 1A), participants were informed that they would learn to modulate their own brain activity in regions that play an important role in spatial attention. Strategies that involve covert allocation of attention were suggested (e.g. focusing covertly on the space inside the scanner bore opposite to IPS_{target}, visual imagery of objects or scenes on the side opposite to IPS_{target}), but participants were also encouraged to explore other ones. Afterwards, the participants performed the whole and partial report task to assess the baseline spatial bias in the distribution of attention across the visual field (see section 2.2.3).

In the following three weekly sessions, participants received neurofeedback (NF) training (Fig. 1B–D). At the start of the first training session, participants were informed about the scanning procedures (Fig. 1B). They viewed an example of the feedback display, and were explained that the feedback would correspond to the differential brain activity between IPS_{target} and IPS_{contra} with a delay of about 6 s, based on the time course of the hemodynamic response function. To account for this delay, participants were suggested to maintain any self-regulation strategy for at least 10 s. At the start of each training session, participants filled in the pre-training questionnaires (see section 2.2.4). An anatomical scan, lasting 7 min, was then acquired to automatically define the target and contralateral IPS ROI in native space (see section 2.4.1). Five neurofeedback scans were performed in which the participants used mental strategies to increase the difference in brain activity between IPS_{target} and IPS_{contra} (see section 2.2.2). Each training session was concluded with the whole and partial report task outside the scanner, and the post-training questionnaires. Additionally, resting-state fMRI scans, each with 7 min duration, were acquired before the neurofeedback scans in the first training session, and after the neurofeedback scans in the final training session (Fig. 1B, D).

In the fifth and last week, participants performed the whole and partial report task once again during the post-training assessment (Fig. 1E). Sessions were scheduled with 7 days in between and around the same time of the day, but some flexibility was required to adapt to scanner availability. The consensus on the reporting and experimental design of clinical and cognitive behavioural neurofeedback studies can be found in Supplementary Table S1 (Ros et al., 2020).

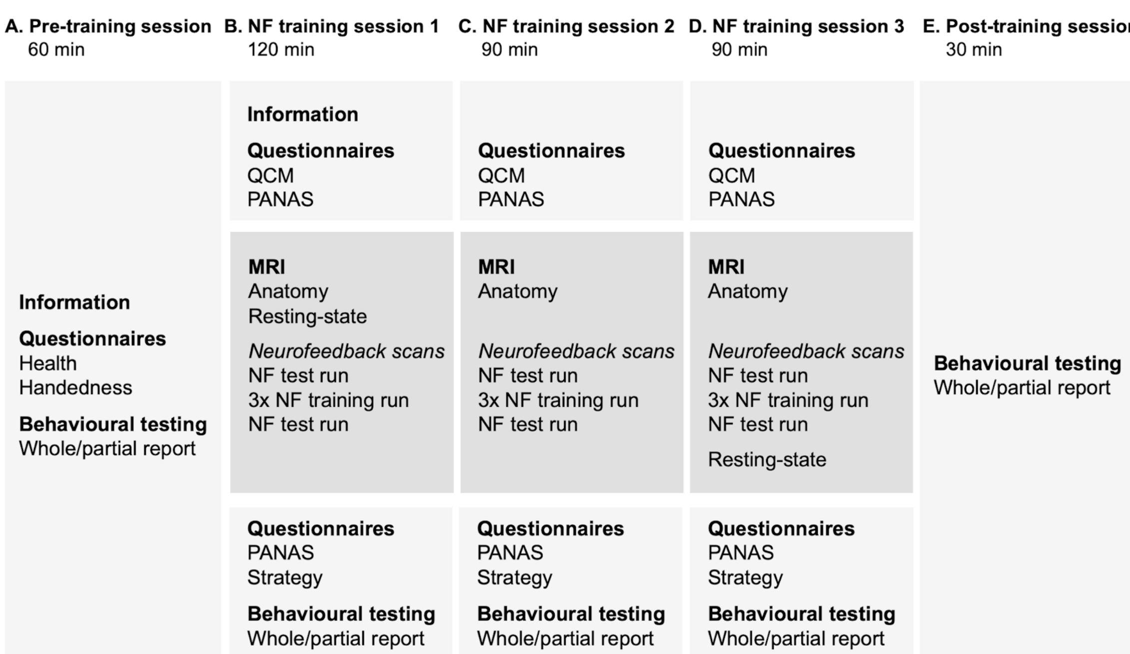

Fig. 1. Experimental procedures. Participants attended five weekly sessions, consisting of three neurofeedback (NF) training sessions and the pre-/post-training assessments. (A) One week prior to the NF training sessions, baseline spatial bias in the distribution of attention was assessed with a whole and partial report task (pre-assessment). (B and D) Then the three weekly training sessions commenced (NF training sessions 1–3). Each NF training session included an anatomical scan and five real-time fMRI neurofeedback scans, comprising two NF transfer runs where no feedback was provided to the participants, and three NF training runs where feedback was presented to the participants regarding their brain activation. A resting-state fMRI scan took place at the beginning of NF training session 1 and at the end of NF training session 3. (E) A week after the last training session, post-assessment of the spatial bias in the distribution of attention was performed. NF: neurofeedback, QCM: Questionnaire of Current Motivation (Vollmeyer and Rheinberg, 2006), PANAS: Positive And Negative Affect Scale (Watson et al., 1988).

2.2.2. Neurofeedback training procedure

Each neurofeedback training session consisted of two neurofeedback transfer runs and three neurofeedback training runs (Fig. 1B–D). Each run lasted 7 min and 20 s, starting with a fixation period of 20 s, followed by 9 rest blocks of 20 s each interleaved with 8 regulate blocks of 30 s each. The feedback display consisted of a white thermometer (2.6° of visual angle wide, 13.3° of visual angle tall) and a fixation cross (0.6° of visual angle) on a uniform grey background (Fig. 2). During the rest blocks, a blue level line appeared in the middle of the thermometer. During the regulate blocks, the level line turned red, instructing participants to use mental strategies as a way to increase the difference in brain activity between IPS_{target} and IPS_{contra}. The feedback display was controlled with the Psychophysics Toolbox (Brainard, 1997; Kleiner et al., 2007; Pelli, 1997) and projected onto a screen visible to the participants through a mirror attached to the head coil.

Participants first performed a neurofeedback transfer run in which no feedback regarding their brain activity was shown to assess their initial self-regulation ability (Fig. 2A). This was followed by three neurofeedback training runs in which they received feedback on the differential activity between IPS_{target} and IPS_{contra} (Fig. 2B). The height of the thermometer level was updated every 2 s. A second neurofeedback transfer run was performed to assess the self-regulation ability after the training. Participants were asked to breathe and blink normally, not to move, and keep looking at the fixation cross in the centre of the thermometer. To minimize head motion, a strip of medical tape was applied across the participants' forehead (Krause et al., 2019). Eye movements were registered using an Eyelink 1000 eye tracking system (SR research Ltd. 2018, Mississauga, Canada) and monitored online to ensure that the participants maintained central fixation. Feedback calculation was performed with custom MATLAB scripts (MATLAB R2016b, The Mathworks, Natick, MA, United States). Real-time feedback calculation and presentation scripts are available on GitHub (https://github.com/wtianlu/rtfMRINF_IPS).

2.2.3. Behavioural assessment

Participants performed a whole and partial report task during the pre-/post-training assessments (Fig. 3A; for a detailed description about the task, see Vangkilde et al., 2011). We estimated individual spatial biases in the distribution of attention weighting with the TVA (Bundesen, 1990). Briefly, this computational theory describes attention as a biased competition between elements in the visual field to enter our awareness, determined by both bottom-up and top-down factors. Attentional weights of elements across the visual field are estimated from the performance on the whole and partial report task, and reflect the behavioural relevance of the element at that location relative to other locations.

During each trial, participants were instructed to fixate on a central fixation cross (1° of visual angle) which was presented for 1000 ms (Fig. 3A). Two or six red or blue letters (2.6° of visual angle in height), chosen from a set of 20 capital alphabet letters (ABDEFGHJKLMNOPRSTVXZ), were presented in an imaginary circle around the fixation cross (7.5° radius) with six possible evenly-spaced stimulus locations, for one of six possible exposure durations (17, 33, 50, 83, 150, 200 ms). The stimulus display was followed by a mask presented for 500 ms, and a black screen without fixation cross indicating that the participants should respond by typing in the target letters that they had seen on a keyboard. Participants were told that they should report as many of the red letters they were "fairly certain" of having seen and that the speed of their response was irrelevant. Stimulus presentation and response registration were performed with Psychopy (version 1.85.3) in Python (version 2.7.14, Anaconda, Inc.). The task was performed on a laptop with a 12.5-inch display (resolution 1366 × 768 pixels, refresh rate 60 Hz). Eye movements were registered using a SensoMotoric Instruments Red-M eye tracker (sampling rate 120 Hz) and stored for subsequent analysis to ensure that participants fixated on the central cross during the stimulus presentation.

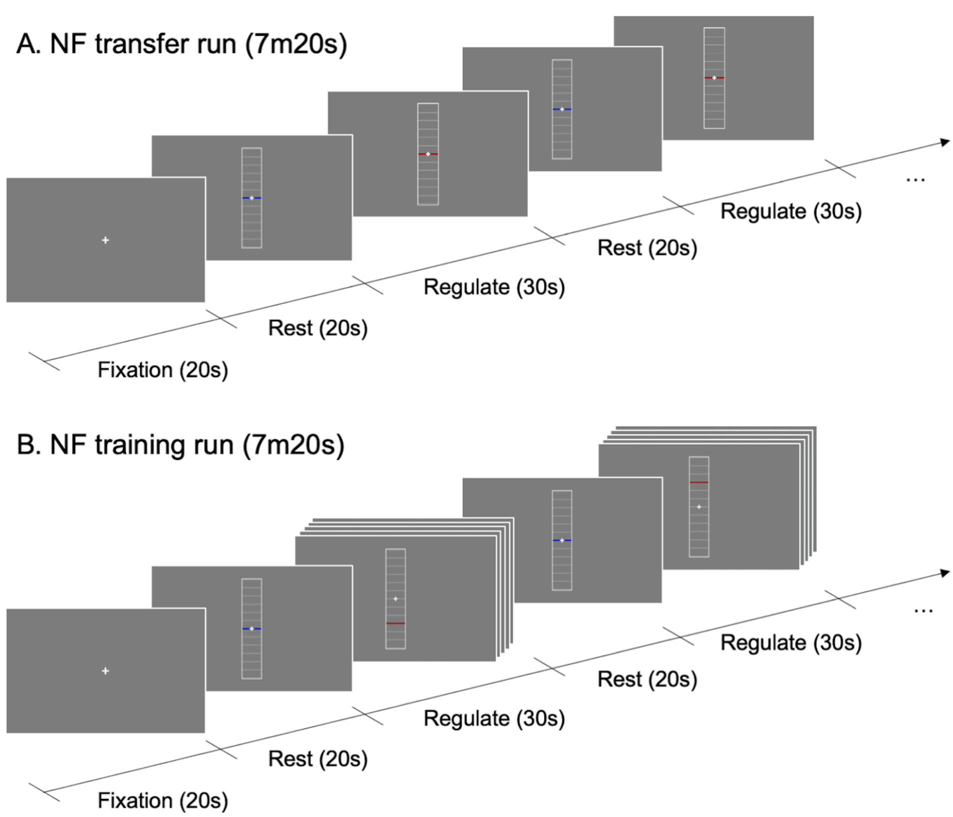

Fig. 2. Neurofeedback display. Participants trained to increase the differential activity between IPS_{target} and IPS_{contra}, represented as the level of a coloured line inside a thermometer. They were cued by a blue line to rest, or by a red line to regulate their own brain activity. The figure shows an example of the feedback display (A) during neurofeedback transfer runs where the participants received no feedback on ongoing brain activity (i.e. the red line remained stationary), and (B) during neurofeedback training runs where feedback was given to the participants (i.e. the red line changed every 2 s according to the interhemispheric IPS activity balance).

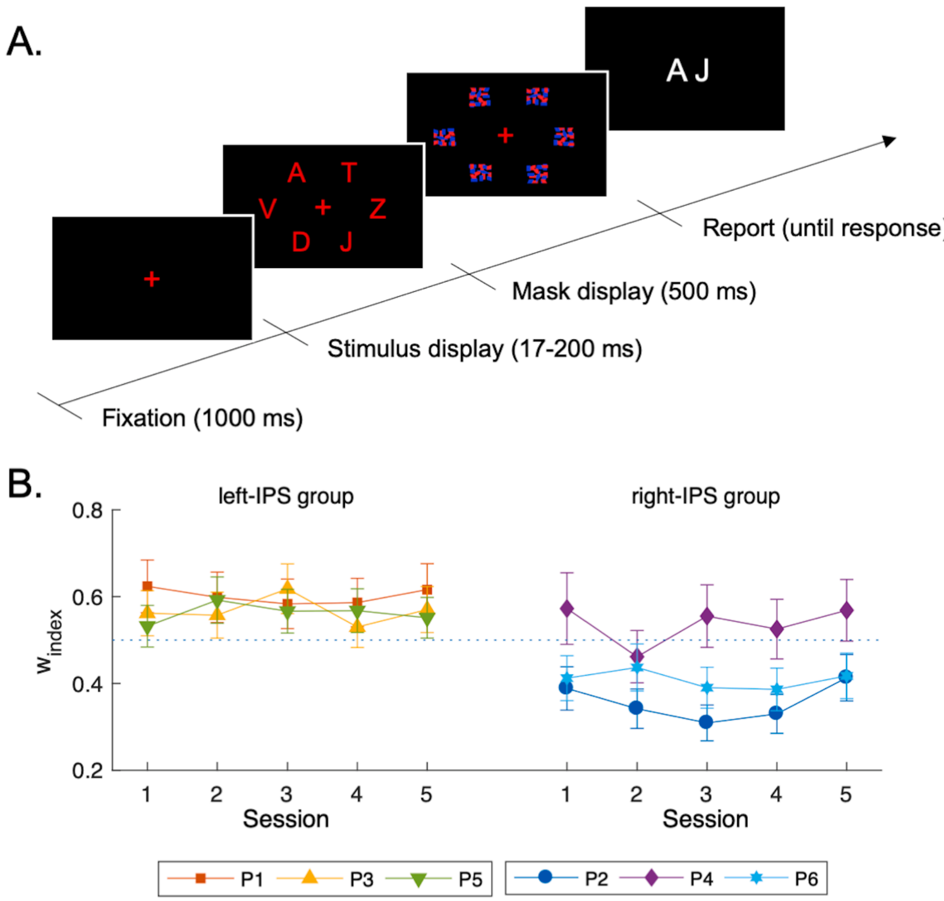

Fig. 3. Assessment of behavioural spatial bias in the distribution of attention. (A) Example of a trial in the whole and partial report task (Vangkilde et al., 2011). (B) Individual estimates of the spatial bias in the distribution of attention (w_{index}) across sessions based on the Theory of Visual Attention (TVA). W_{index} was calculated as $w_{contra}/(w_{contra} + w_{ipsi})$, i.e. w_{index} values above 0.5 indicate a behavioural bias towards the contralateral visual field (rightward for the left-IPS group and leftward for the right-IPS group). Error bars denote the standard error (SE) on w_{index}. The SE on w_{index} was propagated from the SE on the estimate of attentional weight in the left visual field (ω_{left}) according to the error propagation equation for multiplication or division: $S_y/y = \{(S_a/a)^2+(S_b/b)^2\}1/2$ (Ku, 1966). SE (ω_{left}) is used here, as the TVA model estimates ω_{left} with reference to the attentional weight in the right visual field (ω_{right}), which is defined as 1 with no SE (Vangkilde et al., 2011).

2.2.4. Questionnaires

At the start of each neurofeedback session, participants filled in the Positive And Negative Affect Scale (PANAS; Watson et al., 1988), which assesses affect on a 5-point Likert scale, and the Questionnaire for Current Motivation (QCM; Vollmeyer and Rheinberg, 2006), which measures four motivation components (confidence, anxiety, challenge, and interest) on a 7-point Likert scale. After the neurofeedback training, participants filled in the PANAS as well as a questionnaire about their strategies for self-regulation. The latter questionnaire also addressed whether the participants understood and complied to the task, whether they felt they improved their self-regulation ability, their wellbeing during the training, as well as any difficulties they encountered (Fig. 1B–D).

2.3. Acquisition of MR images

Structural and functional MR images were acquired using a 3 T Philips Achieva dStream scanner with a 32 channel receive-only head coil at the University Hospitals Leuven. A T1-weighted anatomical scan was acquired at the beginning of every session (9.6 ms repetition time (TR), 4.6 ms echo time (TE), 256 × 256 acquisition matrix, 1 × 1 mm^2 in-plane resolution, 182 1.2 mm thick coronal slices). The resting-state fMRI scans consisted of gradient-echo T2*-weighted echoplanar images (EPI) acquired in ascending order (420 volumes, 1000 ms TR, 33 ms TE, multiband factor 2, 64 × 64 acquisition matrix, 3.6 × 3.6 mm^2 in-plane resolution, 32 4 mm thick axial slices). The neurofeedback scans consisted of T2* EPI acquired continuously in ascending order (220 volumes, 2000 ms TR, 30 ms TE, multiband factor 2, 96 × 96 acquisition matrix, 2.2 × 2.2 mm^2 in-plane resolution, 52 2.5 mm thick axial slices with 0.2 mm gap). In addition, four volumes of these EPI were acquired at the start of each training session for the anatomical definition of the IPS in native space (see section 2.4.1). Real-time acquisition and transfer of the scan volumes were performed with the Philips direct reconstructor interface data dumper program (version 1.5, Philips Medical Systems, Best, The Netherlands).

2.4. Analysis of MR images

2.4.1. Definition of IPS

We defined the IPS using a probabilistic atlas of visual topography derived from a large number of participants (Wang et al., 2015). A maximum probability map was constructed by comparing the probabilities of all visual topographic areas included in the atlas at each specific voxel, and assigning the voxel to the area with the highest probability (Wang et al., 2015). From this map, we saved the areas IPS0 and IPS1 in Montreal Neurological Institute (MNI) space. These areas correspond to the posterior section of the IPS (Fig. 4), which has been shown to hold the strongest contralateral retinotopic representations (Gillebert et al., 2011; Swisher et al., 2007; Vandenberghe et al., 2005).

At the beginning of every neurofeedback training session, we acquired an anatomical scan. In the first training session, transformation matrices between MNI and native space were obtained via segmentation of the anatomical scan in Statistical Parametric Mapping 12 (SPM12, Wellcome Trust Centre for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm). The left and right IPS masks were warped from MNI to native space, and the resulting images were co-registered to the functional images from the four EPI volumes and binarized. In the second and third neurofeedback sessions, the IPS masks in native space calculated in the first session were adapted to the current head position via co-registration between the anatomical scan from the current session and the anatomical scan from the first session.

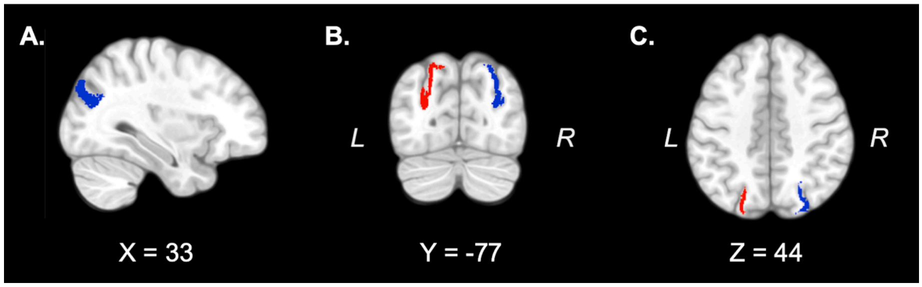

Fig. 4. Regions-of-interest for real-time fMRI neurofeedback and offline fMRI data analyses, presented in Montreal Neurological Institute space. The left IPS (red) and right IPS (blue) are shown on a (A) sagittal (x = 33), (B) coronal (y = -77), and (C) axial (z = 44) slice. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.4.2. Pre-processing

Turbo Brainvoyager 3.2 (Brain Innovation, Maastricht, The Netherlands) was used for online pre-processing and analysis of blood oxygen level-dependent (BOLD) signals. Volumes were motion-corrected using the first volume as reference, smoothed with a 5 mm full width at half maximum (FWHM) kernel, and time courses were detrended to remove temporal drift. The BOLD signals in the voxels of the left and right IPS were averaged and saved to file, to be read and processed with custom MATLAB scripts for online feedback presentation (section 2.4.3) as well as follow-up analyses (section 2.4.4).

2.4.3. Calculation of neurofeedback signal

We calculated a neurofeedback signal reflecting the differential percent signal change (*dPSC*) between IPS_{target} and IPS_{contra} following Eq. (1):

$$dPSC = 100 \times \left(\frac{BOLD_{target}^{regulate} - BOLD_{target}^{rest}}{BOLD_{target}^{rest}} - \frac{BOLD_{contra}^{regulate} - BOLD_{contra}^{rest}}{BOLD_{contra}^{rest}}\right) \quad (1)$$

In Eq. (1), $BOLD_{target}^{regulate}$ and $BOLD_{contra}^{regulate}$ were the mean of three consecutive BOLD values to avoid rapid fluctuations of the feedback display. $BOLD_{target}^{rest}$ and $BOLD_{contra}^{rest}$ were the mean BOLD value of the second half (i.e. last 10 s) of the preceding rest block. A positive *dPSC* value indicates that the BOLD activity in IPS_{target} was higher than the BOLD activity in IPS_{contra} during the regulate block, in comparison to their corresponding BOLD activity levels during the preceding rest block, while the opposite is true for a negative *dPSC* value. The *dPSC* was rounded to the nearest step in a 13-step thermometer, ranging from level −6 to level 6, where the centre level 0 corresponded to a *dPSC* value of zero. The limits of the feedback thermometer were set to −1 and +1 *dPSC* in the first neurofeedback training session. If the highest *dPSC* value exceeded +1, the limit was set to ±150% of this value in the following neurofeedback session.

2.4.4. Analysis of self-regulation performance

Subject-level analyses were performed on the *dPSC* values, which were presented to the participants as feedback during the neurofeedback training runs, to identify whether any improvement in self-regulation performance took place over the course of the training sessions. *DPSC* values were averaged across 12 volumes within each regulate block, excluding the first three volumes to account for the hemodynamic delay, resulting in 8 values per neurofeedback run. Runs were excluded if the maximum framewise displacement was greater than 2 mm. One transfer run from one participant was excluded due to excessive head motion (Supplementary Fig. S2).

A multiple linear regression analysis was performed to estimate the neurofeedback training efficacy, i.e., whether the participants learnt to increase the differential activation between left and right IPS using real-time fMRI neurofeedback. Another multiple linear regression analysis was performed to estimate the transfer success, i.e., whether the ability to self-regulate the interhemispheric IPS activity balance was maintained during the transfer runs in the absence of neurofeedback.

Training efficacy was estimated by comparing the *dPSC* across all training runs using individual multiple linear regression models with categorical factors training run (1, 2, 3) and session (1, 2, 3), as well as their interaction. The reference condition was set to the first training run of the first neurofeedback training session. Increase in self-regulation performance was determined by the presence of a significant positive regression estimate over session and/or run for *dPSC* through comparisons between, on one hand, the performance in the first training run and the performance in the second as well as third training run (averaged over sessions), and, on the other hand, the performance in the first session and the performance in the second as well as third session (averaged over training runs). The statistical threshold was set to $p < .05$, Bonferroni-corrected for the number of estimates for sessions and runs, corresponding to an uncorrected $p < .0125$.

In order to identify whether participants could self-regulate the interhemispheric activity balance in the IPS in the absence of neurofeedback, we calculated average *dPSC* values during the neurofeedback transfer runs in the same way as the training runs. Transfer success was estimated by comparing the *dPSC* of all transfer runs using individual multiple linear regression models with factors transfer run (1, 2) and session (1, 2, 3), as well as their interaction. The reference condition was set to the first transfer run of the first neurofeedback training session. We defined transfer success as a positive regression estimate over session and/or run for *dPSC* through post-hoc tests which compared the performance in the first transfer run to the performance during the second transfer run, averaged over the level of session, as well as post-hoc tests which compared the average performance during transfer runs in the first session to that of the second, as well as the third session. The statistical threshold was set to $p < .05$, Bonferroni-corrected for the number of estimates for session and run, corresponding to an uncorrected $p < .0167$.

The multiple linear regression had two uses in the current study: 1) to identify the strength of the effect of the independent variables (training session and run) on the dependent variable (*dPSC*), and 2) to provide a β-estimate which predicts how much the dependent variable *dPSC* changes when the independent variable is changed. The coding of training session and run into categorical variables allowed us to understand the direction and degree of change in *dPSC* in each of the following sessions and runs with respect to the first run at the start of the neurofeedback training. While neurofeedback studies conventionally compared self-regulation performance during neurofeedback training runs to the performance during transfer runs without neurofeedback to investigate changes over time throughout the training compared to a baseline condition (e.g. Auer et al., 2015), we opted not to use the pre-training transfer run as a baseline to evaluate self-regulation improvement, but compared each training or transfer run to its respective first run instead. Due to the difference in visual stimulation (an empty, stationary thermometer during transfer runs versus a moving thermometer bar during training runs) and cognitive processes (self-regulating the IPS activity balance during transfer runs versus interpreting the presented feedback in addition to self-regulation during training runs), which may both affect the IPS activity (Jeong and Xu, 2016; Luks and Simpson, 2004), comparisons between transfer and training runs may not provide a valid measure of the improvement in self-regulation ability across time.

2.5. Analysis of resting-state data

We conducted individual seed-based functional connectivity analyses between left and right IPS based on the pre- and post-training resting-state fMRI scans to explore whether a decrease in interhemispheric functional connectivity occurred after the neurofeedback training sessions.

Pre-processing steps included realignment to the first volume, normalisation to MNI space, band-pass filtering (0.1–0.01 Hz), and spatial smoothing with a 5 mm^3 FWHM kernel. Outlier detection and scrubbing were performed with a framewise displacement threshold of 0.5 mm (Power et al., 2012). Nuisance signal regression was performed with six motion parameters, white matter and cerebrospinal fluid signals. The IPS ROIs were defined as before (section 2.4.1.). Time series were acquired by averaging the time courses of the voxels within the ROIs, and Pearson's correlation coefficients of the time series were calculated.

2.6. Analysis of behavioural data

2.6.1. Whole and partial report data

The behavioural bias in spatial attention was estimated through TVA-based fitting of the whole and partial report data. We first removed the trials in which participants failed to fixate on the central fixation cross during stimulus presentation, i.e. trials where eye sample x- and y-positions were detected inside a ring-shaped region of 6°–9° of visual angle from the centre, which contained the stimulus letters. On average, 0.3% (SD: 0.6%, range 0–1.4%) of the trials were excluded and the accuracy data were then modelled per participant and per session. We estimated the spatial distribution of attention across the visual field by Bundesen's TVA (Bundesen, 1990) using a maximum-likelihood procedure provided by the LIBTVA toolbox in MATLAB (for a detailed description, see Dyrholm et al., 2011; Kyllingsbæk, 2006; Vangkilde et al., 2011). The behavioural bias in spatial attention, w_{index}, was calculated as in Equation (2):

$$w_{\text{index}} = w_{\text{contra}}/(w_{\text{ipsi}} + w_{\text{contra}}) \tag{2}$$

In this equation, w_{contra} represents the attentional weight assigned to the visual field contralateral to $\text{IPS}_{\text{target}}$, while w_{ipsi} is the weight assigned to the ipsilateral visual field. In the left-IPS group, w_{index} values nearing 0 indicated a bias to the left visual field while values nearing 1 indicate a bias to the right visual field. A w_{index} of 0.5 indicates an equal distribution of attentional weights across the visual field.

2.6.2. Questionnaire data

The questionnaire responses were used as quality control measures. If debriefing suggested that the participants misunderstood the instructions or did not comply with the task, we excluded the data from further analyses.

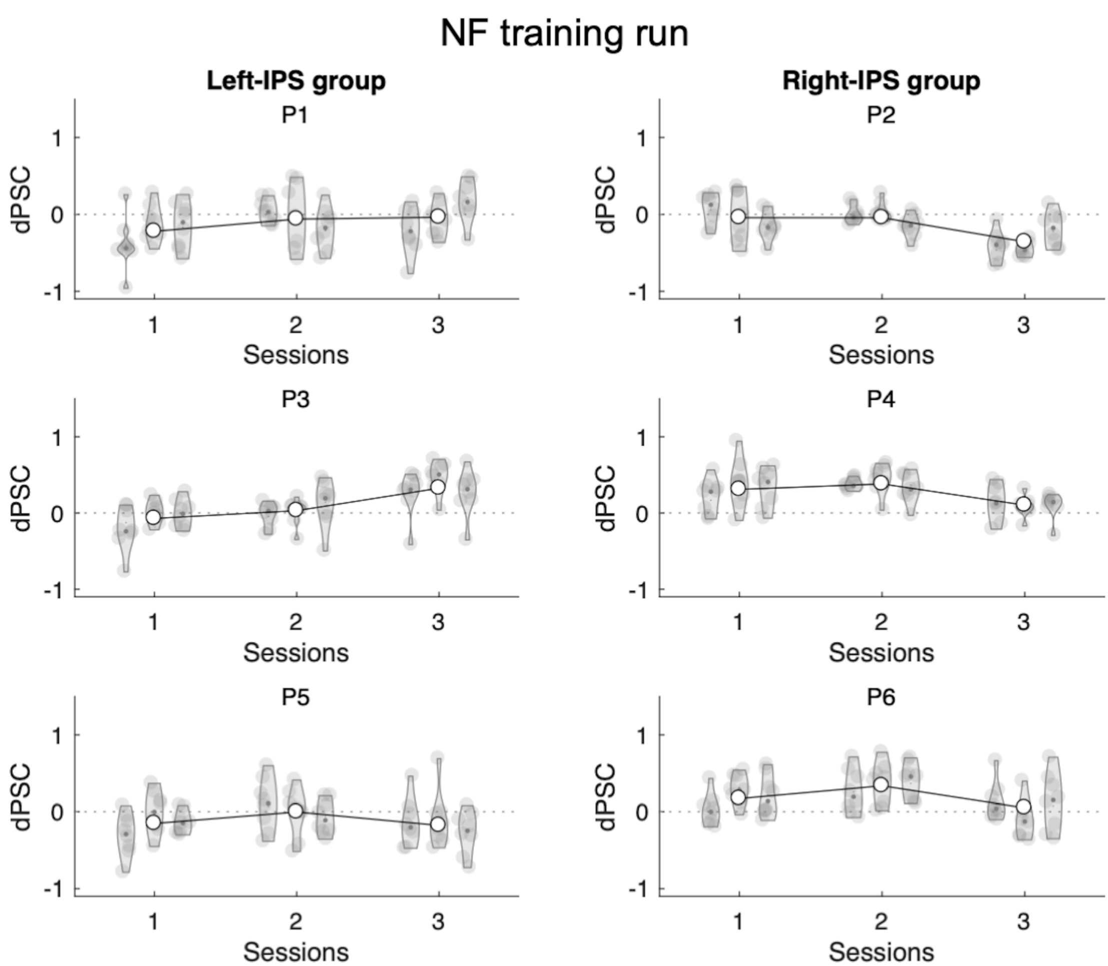

Fig. 5. Results of the neurofeedback training runs in the individual participants. The violin plots represent the observed interhemispheric activity balance, expressed as *dPSC* values, averaged across the volumes of each regulation block. The white dots represent the *dPSC* estimates from the multiple linear regression model, averaged across the three training runs of each session.

3. Results

3.1. Changes in interhemispheric IPS activity balance using real-time fMRI neurofeedback

The individual changes in *dPCS* across the neurofeedback training runs are shown in Fig. 5. A significant multiple linear regression model with factors session (1, 2, 3) and run (1, 2, 3) was found for all participants ($F(8, 63) \geqq 2.5$, $p \leqq .020$, $R^2 \geqq .241$) except for participant P5 in the left-IPS group ($F(8, 63) = 1.5$, $p = .17$, $R^2 = .162$; Supplementary Table S2). The two other participants in the left-IPS group showed positive regression estimates across all sessions and runs with respect to the first training run in the first session. Participant P1 significantly increased the differential percent signal change in the second training session with respect to the first training session ($\beta(\text{session } 2) = 0.43$, $p = .004$). Participant P3 showed a significant increase in session 3 with respect to the first training session ($\beta(\text{session } 3) = 0.46$, $p < .001$). In contrast, none of the participants in the right-IPS group significantly increased the differential IPS activity levels across sessions. Participant P2 even showed a significant decrease ($\beta(\text{session } 3) = -0.49$, $p < .001$; Supplementary Table S2). We did not observe a significant main effect of run after Bonferroni-correction.

The individual changes in *dPSC* during the neurofeedback transfer runs are shown in Fig. 6. Due to excessive head motion, participant P1′s second transfer run from neurofeedback training session 1 was excluded from the analysis (max. displacement = 3.1 mm; Supplementary Fig. S2). A significant multiple linear regression model with factors session (1, 2, 3) and run (1, 2) was found for participant P3 in the left-IPS group ($F(5, 42) = 2.6$, $p = .039$, $R^2 = .236$) and participant P4 in the right-IPS group ($F(5, 42) = 3.4$, $p = .012$, $R^2 = .287$), but not any of the other participants ($F(5, 42) \leqq 1.9$, $p \geqq .125$, $R^2 \leqq .182$; Supplementary Table S2). Participants P3 and P4 showed no significant estimates for either run or session predictors.

3.2. Changes in interhemispheric functional connectivity

Table 2 shows the functional connectivity between the left and right IPS before and after the neurofeedback training for each individual participant.

3.3. Changes in the behavioural bias of spatial attention

Table 2 and Fig. 3B show the behavioural bias in spatial attention, which was assessed using a whole and partial report task.

3.4. Questionnaire responses

Analysis of the questionnaire responses suggested that participants understood the task. The reported mental strategies included focusing on the side of the screen contralateral to the target ROI, imagining writing and solving mathematical equations on the contralateral side of the screen, and imagining pushing a big box to the contralateral side of space. Supplementary Fig. S1 shows the responses of the participants to the QCM and PANAS.

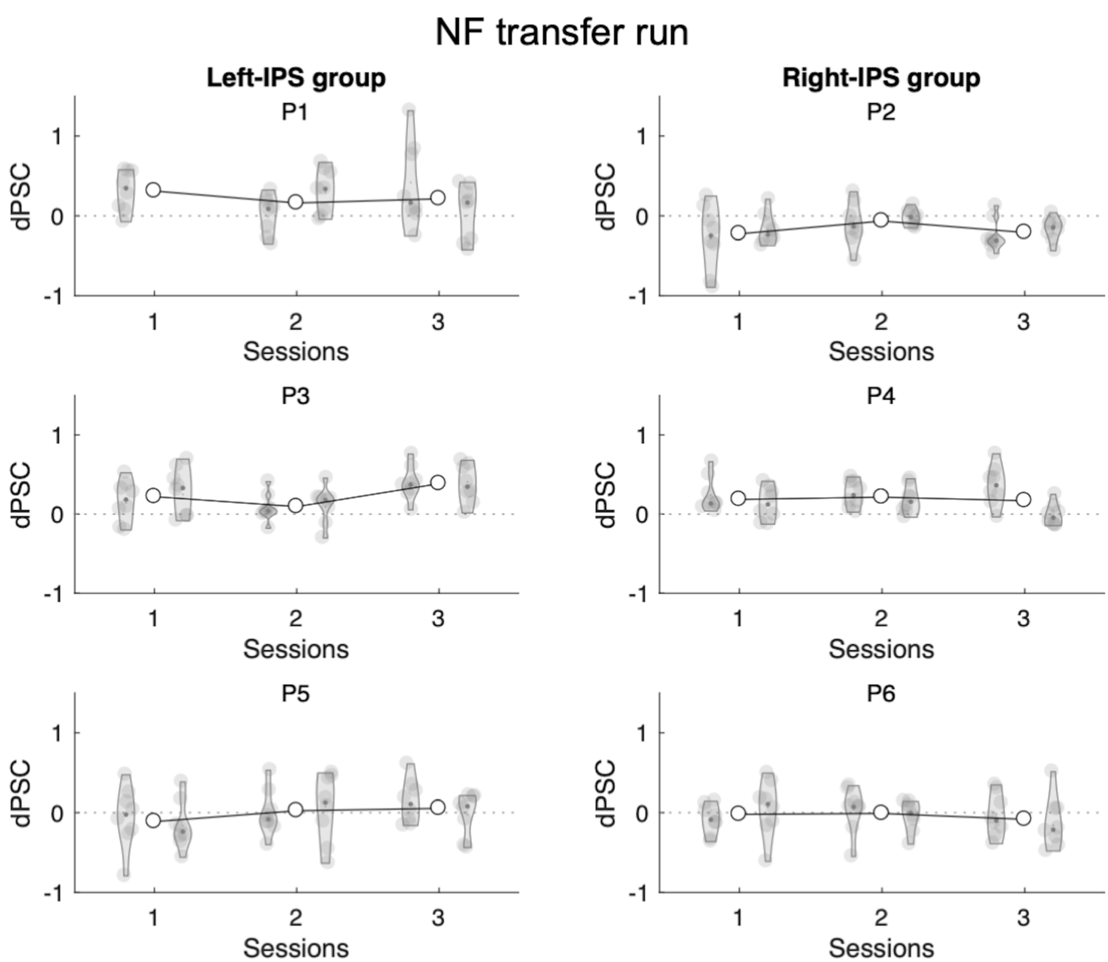

Fig. 6. Results of the neurofeedback transfer runs in the individual participants. The violin plots represent the observed *dPSC* values, averaged across the volumes of each regulation block. The white dots represent the *dPSC* estimates from the multiple linear regression model, averaged across the two transfer runs of each session.

Table 2
Participants' spatial bias in the distribution of attention and IPS functional connectivity before (pre) and after (post) neurofeedback training. The spatial bias in the distribution of attention is expressed as w_{index}, modelled from the responses on a whole and partial report task ($M \pm SE$) before (pre) and after (post) neurofeedback training. The values range between 0 and 1, with a value of 0.5 indicating an even distribution of attention across the visual field. Values nearing 0 indicate a biased distribution of attention towards the side of space ipsilateral to the target IPS, while values nearing 1 indicate a distribution towards the contralateral side of space. Functional connectivity is expressed as temporal correlations as well as Fisher-transformed *Z*-scores (in parentheses) between left and right IPS resting-state time courses before (pre) and after (post) neurofeedback training.

Group	Participant	Spatial bias		Functional connectivity	
		Pre	Post	Pre	Post
Left-IPS	P1	0.62 ± 0.06	0.62 ± 0.06	0.796 (22.2)	0.822 (23.8)
	P3	0.56 ± 0.05	0.57 ± 0.05	0.874 (27.6)	0.856 (26.1)
	P5	0.53 ± 0.05	0.55 ± 0.05	0.773 (21.0)	0.770 (20.8)
Right-IPS	P2	0.39 ± 0.05	0.41 ± 0.05	0.610 (14.5)	0.759 (20.3)
	P4	0.57 ± 0.08	0.57 ± 0.07	0.866 (26.9)	0.813 (23.2)
	P6	0.41 ± 0.05	0.42 ± 0.05	0.872 (27.4)	0.825 (23.9)

4. Discussion

4.1. Main findings

In this study, we assessed whether neurologically healthy participants can use real-time fMRI neurofeedback to modulate the interhemispheric activity balance between left and right IPS at the single-subject level. Our results indicated that two out of three participants in the left-IPS group learnt to increase the activity of the left IPS relative to the right IPS, but this effect did not transfer to the transfer runs without neurofeedback. In contrast, none of the three participants in the right-IPS group was able to modulate the interhemispheric IPS activity balance in the opposite direction. Contrary to our hypotheses, we did not find evidence for a change in functional connectivity between left and right IPS, neither for a change in the behavioural bias in the distribution of attention following the real-time fMRI neurofeedback training. The results indicate that, in line with previous studies (Auer et al., 2015; Chiew et al., 2012; Robineau et al., 2014), healthy individuals may learn to self-regulate the interhemispheric activity balance in homologous brain areas with the help of real-time fMRI neurofeedback. The current study is, to our knowledge, the first to examine the self-regulation of differential BOLD activity in homologous brain areas involved in higher-order cognitive functions. Participants were trained over an extended period and we included a behavioural outcome measure within the framework of a theoretically grounded model of visual attention. The findings add to our understanding of the potential utility of this technique for the rehabilitation of disorders of higher-order cognitive functions such as post-stroke hemispatial neglect.

4.2. Self-regulation of interhemispheric IPS activity balance

Previous real-time fMRI neurofeedback studies targeted the interhemispheric balance in or connectivity between primary motor or primary sensory regions (Chiew et al., 2012; Pereira et al., 2019; Robineau et al., 2014; Sanders et al., 2020). The current study is, to our knowledge, the first to explore the ability of self-regulating interhemispheric activity balance in homologous higher-order areas. The observed changes in IPS activity balance in a subset of the participants were likely to be the result of target-specific neurofeedback rather than global aspecific activations. First, although parietal regions are often co-activated when modulating brain activity using real-time fMRI neurofeedback (Emmert et al., 2016; however, see Skottnik et al., 2019), this would not be expressed as an increase in differential activity across the sessions. Second, as the observed changes in interhemispheric IPS activity balance for participants P1 and P3 did not transfer to the transfer runs, it is likely that our findings are due to neurofeedback-guided self-regulation instead of practice effects due to task repetition. Motivational factors may have been different in the transfer runs compared to the neurofeedback training, however, if the increase in interhemispheric IPS activity balance were due to practice effects and did not depend on the neurofeedback, a similar trend to the one found during the training runs would still be expected during these transfer runs. Third, neurofeedback on differential activity minimizes the risk of non-specific effects from physiological factors such as heart rate and breathing. Finally, we employed a symmetrical feedback display with a vertical thermometer that stayed consistent across regulate and rest blocks. The regulate and rest blocks only differed in the colour and vertical location of the thermometer level. As such, changes in the interhemispheric activity balance could not be attributed to any low-level sensory differences related to the feedback display.

Interestingly, the two participants who successfully increased the differential activity between the left and right IPS in at least one of the two subsequent training sessions both belonged to the left-IPS group, while none of the participants in the right-IPS group succeeded in increasing right relative to left IPS activity over the course of the training. It could be argued that this difference is purely due to chance given the small sample size, and while it is important to exert caution, a large body of evidence exists concerning the functional asymmetries between left- and right IPS that are in accordance with this finding (e.g. Corbetta and Shulman, 2002; Driver and Vuilleumier, 2001; Mesulam, 1999). The questionnaire responses indicated that the group difference was unlikely to be caused by differences in motivation and mood, which are amongst the main predictors of neurofeedback success (Baykara et al., 2016; Kadosh and Staunton, 2019).

While some neurostimulation studies found that stimulating either the left or right posterior parietal cortex produced inhibitory effects in stimulus detection in the contralateral visual field (Szczepanski and Kastner, 2013), others found that the effects were stronger when applied over the right posterior parietal cortex and were dependent on inter-individual differences in the structural organisation of the corpus callosum connecting the hemispheres (Cazzoli et al., 2009; Chechlacz et al., 2015; Dambeck et al., 2006). Interestingly, a recent study used biparietal transcranial direct current stimulation to modulate the interhemispheric interactions between the posterior parietal cortices in neurologically healthy participants (Paladini et al., 2020). The researchers found that excitatory stimulation of the right in combination with inhibitory stimulation of the left posterior parietal cortex alleviated a behavioural rightward attentional bias which was triggered by an increased attentional load, while the opposite, i.e. inhibitory stimulation of the right and excitatory stimulation of the left posterior parietal cortex, did not amplify the rightward attentional bias. Based on these behavioural observations, it was hypothesised that it is easier to counteract an existing interhemispheric activation asymmetry than to exacerbate it (Loftus and Nicholls, 2012; Paladini et al., 2020; for a review, see Reteig et al., 2017). Our findings are in accordance with this hypothesis. More specifically, the estimates for the intercept term in the multiple linear regression analysis, which represent the initial *dPSC* during the first neurofeedback training run, were significantly negative for participants P1 (β = -0.39, $p < .001$) and P3 (β = -0.21, $p = .016$) in the left-IPS group (Supplementary Table S2). In other words, an interhemispheric activation imbalance towards the right IPS was present at baseline, which the participants of the left-IPS group attempted to rebalance. On the other hand, apart from participant P4 in the right-IPS group, no significant estimates were found for the other participants ($|\beta| \leqq 0.07$, $p \geqq .34$). Participant P4 showed a significantly positive estimate for *dPSC* in the first neurofeedback training run ($\beta = 0.21$, $p = .005$), indicating that he was able to self-regulate his interhemispheric activation balance towards the right target IPS at the start of the neurofeedback training, and while he maintained his self-regulation performance, he was not able to increase this further in the following training sessions.

Moreover, as our regulate block duration was 30 s long, this process required sustaining attention to the self-regulation task and maintaining a high level of alertness for an extended period of time (Langner and Eickhoff, 2013). Sustained attention is commonly associated with the ventral attention network (VAN), a frontoparietal network including the inferior parietal lobule, temporoparietal junction, and ventrolateral frontal cortex (Corbetta and Shulman, 2011). The dorsal and ventral attention networks are anatomically connected through a white matter tract and functionally interact to control the allocation of attention (Catani et al., 2017; Corbetta et al., 2008; Leitão et al., 2015; Vossel et al., 2012). Notably, while the DAN is mainly bilateral, the VAN has been suggested to be more lateralised towards the right hemisphere (Corbetta, 2014; Corbetta and Shulman, 2011; Vossel et al., 2012); however, see (Silvetti et al., 2016). It has been proposed that activation levels in the right-lateralised VAN can influence the interhemispheric balance between the left and right DAN (Chandrakumar et al., 2019). Specifically, hemispatial neglect patients following right-hemisphere lesions commonly experience lower levels of alertness compared to patients with corresponding lesions in the left hemisphere, and studies in healthy individuals revealed a rightward bias in attention with declining alertness, and a leftward bias in attention with increasing alertness (Chandrakumar et al., 2019; Corbetta et al., 2008; Corbetta and Shulman, 2011; He et al., 2007; Fimm et al., 2006). Another possible explanation for the absence of neurofeedback training effects in the right-IPS group may thus be related to a decrease in alertness during the regulate blocks. With low alertness, the reduced activity in the VAN may lead to a decrease in the activity in the right DAN, potentially making it more difficult for participants in the right-IPS group to increase the interhemispheric IPS activity balance.

Finally, another possible explanation may be related to the use of lateralised attention strategies, which, according to many, is considered a right hemisphere dominant process (e.g. Heilman and Van Den Abell, 1980; Singh-Curry et al., 2010). Apart from Kinsbourne's interhemispheric competition theory (Kinsbourne, 1977), which most aforementioned neurostimulation studies were based on, another prevailing theory of attention from lesion studies in patients experiencing hemispatial neglect is the hemispatial theory (Mesulam, 1981). Based on the observation that left-sided hemispatial neglect is more common and more severe than right-sided neglect (see for instance Demeyere and Gillebert, 2019), this theory proposes that the left hemisphere controls attention in the right visual field, while the more dominant right hemisphere controls attention in both visual fields (but see Corbetta and Shulman, 2011) for an alternative view). When covertly attending towards the right visual field, a strategy followed by participants in the left-IPS group, the hemispatial theory predicts both left and right hemispheres to be active compared to rest. However, covertly attending towards the left visual field, a strategy followed by participants in the right-IPS group, results in increased activity of the right hemisphere only according to the hemispatial theory. This hemispheric asymmetry suggests that different approaches may be required when training to control the interhemispheric IPS activity balance rightwards versus leftwards.

4.3. Behavioural distribution of attention

The whole and partial report task was selected to probe for any behavioural effects of the neurofeedback training for its sensitivity in identifying small interindividual differences in attentional properties and high test–retest reliability (Chechlacz et al., 2015; Habekost et al., 2014; Vangkilde et al., 2011). For the participants who did not show any significant changes in their self-regulation ability of the interhemispheric IPS balance, we expected w_{index} to remain constant. The two participants who increased their *dPSC* value over the course of the training, however, also did not show changes (Fig. 3B, P1 – orange line, P3 – yellow line). One possible explanation would be that the behavioural changes required more than one week post-training to become visible, since behavioural and neural effects may continue to change weeks or months after the neurofeedback training (for a review, see Rance et al., 2018). Since the participants were healthy and did not show a clinically biased distribution of attention, it is also possible that the behavioural effects of the neurofeedback training were smaller than would be obtained in patients with hemispatial neglect.

4.4. Limitations and recommendations for future research

In our current study design, we opted to perform individual-level analyses rather than group-level analyses as we were interested in the ability of individual participants to learn self-regulation of the interhemispheric IPS activity balance with the help of neurofeedback. However, it is important to note that our interpretation of the results is limited by the small and homogenous sample size.

While repeated neurofeedback training sessions across different days has been recommended due to its consolidation effects (Auer et al., 2015), the break of one week between sessions in our current study is relatively long in comparison to some other real-time fMRI neurofeedback studies (Wang et al., 2018); but see: (Robineau et al., 2014, 2017; Zhang et al., 2013) for studies with a similar training intensity). This time window may be a closer reflection of the clinical practice, where a higher intensity training may not be feasible due to practical constraints. It is however possible that higher training intensities may be beneficial to improve self-regulation ability (Lohse et al., 2014; Sulzer et al., 2013).

Since participants were only trained to self-regulate the interhemispheric IPS balance towards one direction, it is premature to conclude that only leftward shifts of interhemispheric activity balance can be achieved. Future studies may consider bi-directional feedback within the same participant, such that the ability to shift the interhemispheric activity balance leftward and rightward can be compared, and possible differences in difficulty level due to variations in interhemispheric IPS activity imbalance and/or initial behavioural spatial bias in the control of attention can be accounted for (Sorger et al., 2019).

Nonetheless, for stroke patients who exhibit lateralised attention deficits, bi-directional neurofeedback training would not be desirable (Sorger et al., 2019). In this context, it is also important to note the many and often severe non-spatially lateralized deficits associated with neglect, such as deficits in sustained attention, working memory, as well as a lack of awareness or concern about being ill (Husain, 2008; Husain and Rorden, 2003; Malhotra et al., 2005; Van Vleet and DeGutis, 2013). Instead of the neutral, abstract feedback in the form of a vertical thermometer bar in our current study, it would be worthwhile to examine the effect of reinforcing feedback, such as a lateralised feedback display. This could encourage participants when feedback is in the same direction as the regulation target (e.g. Turgut et al., 2018; for a review, see Azouvi et al., 2017), or rather challenge them with feedback in the opposite direction to regulation target (DeBettencourt et al., 2015). Furthermore, given our finding that positive affect significantly dropped after the neurofeedback training, future studies should work toward designing an intuitive, individualised, and more motivational or challenging feedback display in combination with shorter training sessions, which may help to improve training success (Sokunbi et al., 2014).

4.5. Conclusions

Several previous studies have reported that real-time fMRI neurofeedback could be a promising therapeutic intervention to recover abnormal brain functionality after stroke (e.g. Liew et al., 2016; Lioi et al., 2020; Robineau et al., 2017; Sreedharan et al., 2019; for a review, see Wang et al., 2018). While a large part of the neurofeedback literature has focused on the primary motor and sensory regions, the current study investigated the possibility to self-regulate higher-order brain regions involved in complex cognitive processes, such as attention. We included measures to disentangle exogenous effects from effects due to self-regulation, such as a symmetrical feedback display and separate subject-level statistical analyses of the neurofeedback training and transfer runs, as well as a sensitive, quantitative behavioural outcome measure. More specifically, we reported the development and implementation of a real-time fMRI neurofeedback pipeline to train participants to volitionally control brain activity from the bilateral IPS. It provided a first indication of the ability of healthy individuals to self-regulate their interhemispheric IPS activity balance with the help of real-time fMRI neurofeedback. Our study raised the possibility that self-regulation of interhemispheric IPS activity balance may be direction-specific, and underscores the need for research on individualised training protocols.

CRediT authorship contribution statement

Tianlu Wang: Conceptualization, Methodology, Software, Investigation, Writing - original draft. **Ronald Peeters:** Methodology, Resources, Writing - review & editing. **Dante Mantini:** Conceptualization, Methodology, Software, Writing - review & editing. **Céline R. Gillebert:** Conceptualization, Methodology, Writing - review & editing, Supervision.

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Declaration of interest

No potential conflict of interest was reported by the authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2020.102513.

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