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Neuroimaging Outcomes of Brain Training Trials

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1. Introduction

The brain remains plastic throughout the human lifespan. This unique property holds great promise for the better treatment of cognitive disorders, and forms the basis for behavioural interventions aimed at promoting mental function that may help delay and prevent the onset of dementia. Brain training (BT) is a direct method for targeting brain plasticity that employs repetitive cognitive exercises. Over the past decade increasing evidence has accumulated that BT can lead to clinical and cognitive benefits in psychiatric samples (McGurk et al., 2005, 2007), as well as in healthy older individuals (Valenzuela & Sachdev, 2009). However, the neurobiological mechanisms underlying these clinical benefits are not well understood. Advances in neuroimaging therefore has potential for revealing the complex *in vivo* structural, functional and metabolic brain changes that accompany BT. The aim of this systematic review was to compare and integrate results of several recent clinical trials of BT that have employed Magnetic Resonance Imaging (MRI), with a particular emphasis on design and technical issues. These studies are beginning to provide fascinating insights into the nature of BT effects on the human brain.

2. Definition of brain training

The wider cognitive intervention field abounds with multiple ill-defined terms that have hampered their development and validation, and can also explain mixed findings to date (Gates & Valenzuela, 2010). Clare and Woods divide this general area into 'cognitive rehabilitation', 'cognitive stimulation', or 'cognitive training' (CT) (Clare & Woods, 2004). We have proposed a specific operational definition for cognitive training (CT) to include cognitive interventions that meet the following four criteria: 1) involves repeated practice, 2) on tasks with an inherent problem, 3) using standardized exercises, and 4) that specifically target a cognitive domain (Gates & Valenzuela, 2010) . Here, the terms BT and CT are identical and are used interchangeably.

3. Method

3.1 Search strategy

The Medline (1996 – 04/2011) database was searched for original research articles in English that met the following criteria. (a) 'brain training', 'cognitive training', 'cognitive

intervention', 'cognitive exercise', 'mental exercise', 'cognitive activity' or 'cognitive stimulation', and (b) 'individuals', 'adults', 'persons', 'subjects', but no 'children' or 'teenagers', and (c) 'Magnetic Resonance Image', 'MRI' or 'brain scans'. Combined intervention, subject, and method terms were searched across all fields and produced 144 studies. The title and abstract of these studies were reviewed to identify potentially relevant trials, and these were supplemented by manual checking through reference lists of published reports.

3.2 Inclusion criteria & study quality

Studies were selected for review if they met the following criteria: i) comprised a longitudinal clinical trial with either a randomized controlled trial (RCT) design or uncontrolled clinical trial design (UCT), ii) sample included only healthy individuals not selected against clinical psychiatric criteria, iii) had MRI assessment at least at baseline (before training) and at post-training, and iv) the nature of the intervention met our definition for cognitive training (described above). The qualities of included studies were assessed against CONSORT 2001 criteria for clinical trials (www.consort-statement.org).

4. Results

4.1 Search results

After reviewing the 144 abstracts returned by our search, nine studies containing ten trials met our criteria. These included 7 RCT and 3 UCT. Details are provided in **Table 1**.

4.2 Study quality

Quality of studies varied between 13.5 and 19.5 (out of a maximum of 24). The main limiting factors were unspecified sample size calculations, or details about method of randomizing and blinding. CONSORT criteria scores for RCTs are provided in **Table 1** (maximum = 25).

4.3 Subjects

There were a total of 309 subjects included in the ten identified trials, split between training (N=168) and control groups (N=138). Sample size varied from 10 (Dahlin et al., 2008; Takeuchi et al., 2010) to 58 (Mozolic et al., 2010). Studies divided into three main groups based on age of participants: five studies of young adults with average age of 20-30 years (Dahlin et al., 2008; Erickson et al., 2007a; Olesen et al., 2004; Takeuchi et al., 2010), three studies of elderly subjects with mean age over 60 years (Engvig et al., 2010; Mozolic et al., 2010; Valenzuela et al., 2003), and two studies that combined both elderly and young adult age groups (Erickson et al., 2007b; Lovden et al., 2010). Recruitment source was also variable: young adult subjects were mainly university students, while elderly subjects were from the community based on newspaper advertisements (Dahlin et al., 2008; Engvig et al., 2010; Lovden et al., 2010). All subjects were cognitively-intact.

4.4 Nature of brain training

Because two studies used the same BT protocols (Erickson et al., 2007a, 2007b), a total of nine protocols were reviewed. These could be distinguished on the basis of implementation, either computer-based exercises (Dahlin et al., 2008; Erickson et al., 2007a, 2007b; Lovden et al., 2010; Olesen et al., 2004; Takeuchi et al., 2010), or non-computerized 'paper-and-pencil' exercises (Engvig et al., 2010; Valenzuela et al., 2003). Computerized BT most commonly

Citation	Intervention Summary	Targeted Cognitive Domain	Difficulty Level	Delivery	Time per Session	Frequency	Training Period	CONSORT Scores
Erickson 2007a Erickson 2007b	Pure or combined colour discrimination or letter discrimination tasks	Memory and decision	RT feedback	Computer	60 mins	Five sessions in total across 2-3 weeks		17.5 17.5
Lovden 2010	Three working memory tasks, three episodic memory tasks, and six perceptual speed tasks	Memory and perceptual speed	Adjusted automatically by performance	Computer	60 mins	Average of 101 sessions in 6 months		18
Olesen 2004 (Experiment I)	Three working memory tasks: visuo-spatial working memory task, a backwards digit span task and a letter span task	Memory	adjusted automatically by performance	Computer	35-45mins	Daily	5 weeks	N/A
Olesen 2004 (Experiment II)	Three spatial memory tasks only: Grid, Grid rotation and 3D Grid (Cogmed cognitive medical systems)	Memory	adjusted automatically by performance	Computer	35-45mins	Daily	5 weeks	N/A
Takeuchi 2010	Computer based working memory training	Memory	adjusted automatically by performance	Computer	25 mins	Daily	2 months	N/A
Mozolic 2010	Visual and auditory tasks with visual and auditory distracters	Detecting classifying and sequencing	adjusted automatically by performance	Computer	60 mins	Once per week	2 months	15.5
Dahlin 2008	One letter memory criterion task and five other updating tasks	Memory and updating	adjusted automatically by performance	Computer	45 mins	3 sessions per week	5 weeks	13.5
Engvig 2010	MOL(method of loci) verbal recollection memory task	Memory strategy	lengthen the word list	Group session +homework	60 mins	5 sessions per week	2 months	19.5
Valenzuela 2003	MOL, remember a list of unrelated concrete nouns	Memory strategy	lengthen the word list	Group session	15-20 mins	Once per week	5 weeks	16

Table 1. Summary of brain training interventions with MRI outcomes.

consisted of different memory-based exercises (i.e., unidomain) (Dahlin et al., 2008; Erickson et al., 2007a, 2007b; Lovden et al., 2010; Olesen et al., 2004; Takeuchi et al., 2010). BT exercises were generally custom-designed by the research group, although one study investigated a multi-domain commercial program which included detecting, classifying, and/or sequencing with audio and visual distracters (Mozolic et al., 2010). Non-computerized BT studies used a specific mnemonic strategy known as the Method of Loci (MoL) (Engvig et al., 2010; Valenzuela et al., 2003). Further BT details are available in **Table 1**.

For most of the computerized BT interventions, difficulty level was automatically adjusted based on performance on previous tasks, whereas the Erickson group utilized continuous real-time feedback (response time) to help motivate and challenge subjects (Erickson et al., 2007a). Across all studies, training was session-based, varying form 20 minutes to 60 minutes per session. Frequencies of BT also varied from one session per week to daily. The duration of interventions were generally around two months) (Dahlin et al., 2008; Engvig et al., 2010; Mozolic et al., 2010; Olesen et al., 2004; Takeuchi et al., 2010; Valenzuela et al., 2003), except for one 6 month training study (Lovden et al., 2010) and two 2-week training studies (Erickson et al., 2007a, 2007b).

Definition of control training in RCTs was predominantly a no-intervention wait-and-see condition in 6 studies, whilst one study used an active control training condition, which comprised an educational lecture program and quizzes (Mozolic et al., 2010).

4.5 Types of MRI

Five studies used an event-related fMRI approach, employing in-scanner tasks either identical or highly similar to the offline training exercises (Erickson et al., 2007a, 2007b; Olesen et al., 2004). One fMRI study is unique for investigating functional BT-related changes related to both the trained task as well as to non-trained tasks within the scanner (Dahlin et al., 2008). Two studies investigated BT-induced changes to white matter fractional anisotropy (FA) and mean diffusivity (MD) using DTI (Lovden et al., 2010; Takeuchi et al., 2010). Another study used perfusion MRI (pMRI) to investigate BT effects on whole-brain cerebral blood flow (Mozolic et al., 2010). Finally, one study employed MR spectroscopy (MRS) to explore biochemical change before and after BT in several cortical and subcortical areas (Valenzuela et al., 2003).

Whilst all studies were selected for employing a baseline and post-training scan, one study conducted dual baseline scans in one experiment, and 5 serial scans over 5 weeks during BT in another experiment (Olesen et al., 2004). T1 structural MRI (sMRI) were common to all studies, however only two studies have specifically reported structural BT outcomes (Engvig et al., 2010; Lovden et al., 2010). Three out of ten studies used a 3 Tesla scanner, remaining studies used 1.5 Tesla field strength. No study specifically reported the presence or absence of hardware scanner changes or upgrades during the follow-up period.

4.6 Approaches to MRI pre-processing

Three main software platforms were used to perform MRI preprocessing: Four papers used different versions (SPM99, SPM2, SPM5) of Statistical Parametric Mapping (SPM, http://www.fil.ion.ucl.ac.uk/spm/) (Dahlin et al., 2008; Mozolic et al., 2010; Olesen et al., 2004; Takeuchi et al., 2010), two studies used FSL (FMRIB Software Library http://www.fmrib.ox.ac.uk/fsl/) (Erickson et al., 2007a, 2007b), and one study was based on Freesurfer (http://surfer.nmr.mgh.harvard.edu/) (Engvig et al., 2010). Further MRI pre-processing information is summarized in **Table 2**.

Citation	MRI	MRI assessment point	Main MRI protocol	Scanner info	Pre-processing platform	Pre-processing steps
Erickson 2007a	2	Pre- and Post training	fMRI (training tasks)	3T	FSL	Slice timing, motion-corrected, temporally filtered (1.5s-50s) and smoothing (7mm)
Erickson 2007 b	2	Pre- and Post training				
Lovden 2010	2	Pre- and Post training	DTI	1.5T	Semi-auto algorithm	Motion correction, generating MD and FA maps and semi-auto corpus callosum (CC) segmentation
Olesen 2004 (Experiment I)	3	twice at Pre- and once at Post training	fMRI (lowload working memory task and control task)	1.5T	SPM99	Motion correction, normalized by using T1 localizer and smoothing (6mm)
Olesen 2004 (Experiment II)	5	5 scans during 5 weeks (day 0, 2,4,8 23)	fMRI(highload and lowload memory tasks and control tasks)			
Takeuchi 2010	2	Pre- and Post training	DTI	3T	SPM5	Optimised VBM, intra-subject coregistration and smoothing (10mm)
Mozolic 2010	2	Pre- and Post training	perfusion MRI and structural MRI	1.5T	SPM5	Optimised VBM and smoothing (8mm)
Dahlin 2008	2	Pre- and Post training	fMRI (letter memory, n-back and Stroop)	1.5T	SPM2	Slice timing, realigned and unwarped, normalized and smoothing (8mm)
Engvig 2010	2	Pre- and Post training	Structural MRI	1.5T	Freesufer	Tissue segmentation, cortical thickness measures, subtraction of pre BT from post BT after coregistration to mid point and smoothing (30mm)
Valenzuela 2003	2	Pre- and Post training	MRS at right hippocampus, left frontal lobe and occipital-parietal	1.5T	Not applicable	N-acetylaspartate, choline and phosphocreatine relative to internal water peak corrected by cerebral spinal fluid percentage using voxel segmentation and white matter hyper-intensity volume

Table 2. Hardware and preprocessing information of reviewed studies.

Irrespective of MRI modality or research interest, the goal of preprocessing should be to prepare data so that further analytical assumptions are valid (Klein et al., 2009). For example, motion correction and spatial normalization maximizes the likelihood that a particular voxel property comes from same location across subjects. In the ten studies reviewed, fMRI preprocessing procedures were similar, including slice timing, motion correction, normalization, and smoothing. pMRI, DTI and sMRI studies created sample-specific template for coregistration and normalization purpose. Two studies (Mozolic et al., 2010; Takeuchi et al., 2010) followed the Optimized VBM (Good et al., 2001) approach, and one study created subject-specific templates by averaging image pairs across pre- and post-sessions (Engvig et al., 2010). Finally, the Lovden group used a semi-automatic algorithm for analysis of the corpus callosum (Niogi et al., 2007).

MRS studies require no geometric preprocessing. Rather, quantitative MRS assessment of neurometabolites may be influenced by scanning parameters such as shimming and receiver gain. MRS studies generally report relative metabolic signal intensity against a reference signal, and creatine is by far the most common reference signal. However, because subclinical degenerative disease and the intervention itself could hypothetically alter resting state phosphocreatine-creatine turnover (Valenzuela & Sachdev, 2001), we have used tissue-water as a more reliable reference signal in studies of ageing and BT (Valenzuela et al., 2003).

4.7 Approaches to MRI statistical inference

The General Linear Model (GLM) assumes an individual's MRI signal of interest is a function of a 'ground truth' signal modified by one or more experimental conditions and affected by error. The strengths (Friston et al., 2007) and weaknesses (Haynes, 2011) of the GLM approach therefore apply generally to the present set of fMRI, sMRI and DTI studies. In the context of longitudinal BT studies, statistical inference was mainly geared at testing Group (BT vs control) × Time (Pre vs Post-BT) interactions. In addition, one study carried out a regression analysis when analyzing DTI, using total BT amount (completed sessions) as the covariate of interest (Takeuchi et al., 2010).

When testing the null hypothesis, BT MRI studies have generally adopted a 'mass univariate' voxel-by-voxel test, either across the whole-brain or restricted to some ROI defined by prior knowledge. This approach assumes each voxel (or larger cluster of voxels) is necessarily an independent observation, an assumption that contradicts brain biology and introduces a significant multiple-comparison problem (Nichols & Hayasaka, 2003). Four studies used cluster-level correction (Dahlin et al., 2008; Erickson et al., 2007a, 2007b; Mozolic et al., 2010; Olesen et al., 2004), and one study voxel-level correction (Engvig et al., 2010). Some studies designed an initial experiment, and such first-level results were consequently used as an explicit mask for the next experiment (Dahlin et al., 2008; Erickson et al., 2007a, 2007b; Mozolic et al., 2010; Olesen et al., 2004). In this case, close attention is required to avoid non-independence errors (Kriegeskorte et al., 2009; Vul et al., 2009). Interestingly, one study used a split-half validation approach that uses a more relaxed multiple-correction threshold in one half of the sample to generate hypotheses for rigorous (but more constrained) testing in the other half of the sample (Engvig et al., 2010). Notably, alternative network approaches that consider covariance patterns across and between ensembles of brain locations (Haynes 2011), including Partial Least Squares analysis (Krishnan et al., 2011), Independent Components Analysis (Biswal & Ulmer, 1999; Calhoun et al., 2001), or graph-based analysis (Bullmore & Sporns, 2009), have not yet been applied to BT studies. Further details are available in **Table 3**.

Table 3. Post-processing and statistical correction details.

Citation	Post-processing steps	Multiple Correction Approach
Erickson 2007a	1. Extract the mean signal from first level task-contrast activation and test interaction with time × group 2. Whole brain voxel wise interaction analysis 3. Test correlation between activity change and performance improvement.	1. Threshold cluster at z<2.33 (p<0.01) uncorrected, then use p(corrected)<0.01 to define ROI 2. Threshold cluster at z<3.1 (p<0.001) uncorrected, then p(corrected)<0.01
Erickson 2007 b	1. Extract the mean signal from first level task-contrast activation and test interaction with time × group 2. Whole brain time × group analysis 3. Test other interaction (time × group × condition × age) on these regions from step2	To define ROI: z>3.1(p<0.001)uncorrected=>cluster level correction at p=0.01
Lovden 2010	1. Time × Group × Age interaction test of the FA and MD of 5 segments of Corpus Callosum (CC) 2. Test correlation of performances and DTI result 3. Structure change of voxel for each segmented CC	Not involved
Olesen 2004 (Experiment I)	Whole brain time × group analysis	Threshold at z<2.33(p<0.01) uncorrected, then threshold at p<0.01 cluster level correction
Olesen 2004 (Experiment II)	1. First level analysis (task-control task) 2. Regression analysis on the level one contrast with individual working memory capacities	Threshold at t>2.44 (p<0.022) uncorrected, then threshold at p<0.01 cluster level correction
Takeuchi 2010	1. Pre- and post-training groups paired-t analysis 2. Regression analysis between different fractional anisotropy (FA) map and the total amount of BT within step 1 regions 3. Test correlation between total BT and mean FA changes within step 1 regions	Threshold at p<0.005 uncorrected, then threshold at p<0.05 cluster level correction
Mozolic 2010	1. Whole brain time × group interaction test on cerebral blood flow (CBF) map 2. GM time × group interaction test within ROI from step1 3. Test correlation on changes of CBF and performance improvements	1. p(uncorrected)<0.001, then extent p(corrected)<0.05; 2. Biological Parametric Mapping toolbox to correct
Dahlin 2008	1. First level pre-training scans for three tasks 2. Second level time × group interaction analysis for each tasks 3. A conjunction analysis of letter memory task and 3-back tasks	1. p(FDR)<0.01 for two tasks, p(uncorrected)<0.005 for Stroop task; 2, p(uncorrected)>0.05
Engvig 2010	1. Time × group interaction whole brain 2. Split-half validation 3. Memory improvement correlates with the mean ROI GM thickness change	1. p(FWE)<0.05 peak level; 2. p(uncorrected)<0.05 and overlap the two split-half results
Valenzuela 2003	Regression analysis in SPSS	Not involved

MRI	Citation	Regions	Main Results
fMRI	Erickson 2007a	Bilateral dorsolateral prefrontal cortex (DLPFC)	↑ activation
		Right inferior frontal gyrus, right superior parietal lobule, right dorsal inferior frontal gyrus and left superior parietal lobule (trend)	↓ activation
	Erickson2007 b	Left ventral prefrontal cortex, bilateral DLPFC	↑ activation
		Right ventral prefrontal cortex	↓ activation
	Olesen 2004 (Experiment I)	Right middle frontal gyrus, right inferior parietal cortex, and bilateral intraparietal cortex	↑ activation
		Cingulate sulcus	↓ activation
	Olesen 2004 (Experiment II)	Left middle frontal gyrus; bilateral superior parietal cortex, bilateral inferior parietal cortex, left intraparietal cortex, thalamus, and right caudate head	↑ activation
		Cingulate suclus; right inferior frontal sulcus and left postcentral gyrus	↓ activation
	Dahlin 2008	Bilateral putamen, right temporal lobe, and right occipital lobe	↑ activation
		Right frontal lobe, right parietal lobe	↓ activation
		Left frontal lobe, left parietal lobe, left temporal lobe and left putamen	↑ activation
DTI	Takeuchi 2010	WM adjacent to the inferior parietal sulcus; the border between the frontal lobe and parietal lob; adjacent to the intraparietal suclus; anterior part of the corpus callosum	↑ fractional anisotropy
	Lovden 2010	Segment 1 (anterior) of corpus callosum	↑ fractional anisotropy and voxels
pMRI	Mozolic 2010	Right inferior prefrontal cortex	↑ cerebral blood flow
sMRI	Engvig 2010	Right insular, right lateral orbitofrontal cortex, right fusiform cortex, and left lateral orbitofrontal cortex	↑cortical thickness
		Global	↑ right hemisphere thickness
MRS	Valenzuela 2003	Hippocampus (right)	↑ creatine and choline

Table 4. Summary of MRI results of brain training in healthy adults.

4.8 Neuroimaging outcomes in BT trials

All MRI studies have to date revealed significant training-induced brain changes. Moreover, there is some overlap between studies in terms of topographical distribution. Training-related adaptation in the frontal lobe is most common. In fact, frontal lobe functional changes were reported in all fMRI studies, although the direction of changes was not consistent, and the precise localization of differences also varied (see **Table 4**). Even in the same experiments, there was evidence of both increased and reduced activation in distinct frontal lobe areas (Erickson et al., 2007a, 2007b). These functional changes are also supported by BT-related increments to cerebral blood flow (Mozolic et al., 2010), and in one study, increased cortical thickness (Engvig et al., 2010). Since all BT (either explicitly or implicitly) requires repetitive high-load engagement of working memory, it is not altogether surprising that frontal lobe plasticity is consistently implicated. Differences in BT design may help explain regional heterogeneity in these fMRI studies.

Another working-memory related area is the parietal lobe (Osaka et al., 2007), also implicated in multimodal integration (Fogassi et al., 2005), and hence potentially relevant to BT. Greater superior or inferior parietal lobe activity was detected in five fMRi studies after training compared with the untrained groups (Dahlin et al., 2008; Erickson et al., 2007a, 2007b; Olesen et al., 2004), with the exception of one study which found reduced activation in the right superior parietal lobe (Dahlin et al., 2008). Furthermore, a DTI study found increased fractional anisotropy (FA) in white matter regions adjacent to the inferior parietal sulcus, as well as at the border between the frontal and parietal lobe (Takeuchi et al., 2010).

Two studies have investigated the corpus callosum (CC) using DTI, and both revealed increased FA of the anterior CC after BT (Lovden et al., 2010; Takeuchi et al., 2010). Finally, only one study has focused on BT-related changes in the hippocampus, arguably the brain's most plastic area (Burke & Barnes, 2006; Gage et al., 2008), using MRS after a five-week Method of Loci trial (Valenzuela et al., 2003). Increased phosphocreatine was found in the hippocampus, but not other grey and white matter areas, suggestive of an activity-dependent upregulation of cellular-energy resting state, potentially of neuroprotective benefit (Brustovetky et al., 2001) in an area highly susceptible to degeneration.

There were also several differences in outcomes between studies, and so it is important to consider possible moderating factors. Session number or frequencies are unlikely to have had a major impact as they were relatively consistent between studies. Age, however, may be salient to BT outcomes. For example, in Erickson and colleagues' study (Erickson et al., 2007b), whilst a significant group × time interaction was for both elderly and young subjects at the dorsal prefrontal cortex bilaterally, the direction of the effects were opposite: in the older subjects there was reduced activation after BT, and increased activation amongst young subjects. Age differences have also been observed in a DTI study, whereby FA increased after BT only in the older group (Lovden et al., 2010).

5. Discussion

5.1 A biological insight into the trained brain

One of the major unresolved challenges for the BT field is to adequately demonstrate transfer or generalizability of outcomes (Gates & Valenzuela, 2010; Valenzuela & Sachdev, 2009). Individuals will predictably improve on almost any trained task – in clinical terms this is rather trivial unless gains can also be demonstrated in non-trained tasks. Neuroimaging studies are only beginning to address this issue. For example, one study

found that the effect of training in one task translates to functional brain changes in non-trained tasks (Dahlin et al., 2008). Brain imaging studies can therefore provide independent biological evidence about the impact of BT on brain structure, function and biochemistry.

So far, BT studies have been universally positive, each study reporting at least one significant brain imaging outcome. It is of course impossible to assess the role of publication bias, as null studies may have been self-censored by authors, or rejected by editors and reviewers. The field is also manifestly young, only 10 studies were found following a systematic search, across a mix of BT designs, approaches, MRI modalities and subjects. Nevertheless, a number of studies point to the key role of frontal lobe plasticity in potentially mediating BT benefits. All fMRI studies have so far found changes in this region, and as mentioned, this may reflect the heavy working memory demands of BT itself. Interestingly, repetitive practice of working memory problems does not necessarily lead to straightforward increases (in terms of signal change or spread of suprathreshold voxels) in task-related functional activity. Rather, a complex series of increases and decreases in brain activity have been observed. BT may therefore lead to two major types of functional adaptations including (Lustig et al., 2009): i) task-related hyperactivation, where the network of brain regions that normally subserves a given task becomes primed to activate, and ii) efficiency gains, where for a less extensive brain response, the same (or increased) cognitive proficiency is possible.

The cellular and molecular mechanisms that underlie BT-related frontal lobe plasticity are currently not known. Environmental enrichment, (in part) a model for BT in animals, is known to produce a wide range of neurobiological changes, including enhanced synaptic plasticity, neurogenesis and angiogenesis, as well as macroscopic structural changes including increased brain volume (Nithianantharajah & Hannan, 2006; Valenzuela et al., 2007). Interestingly, one sMRI has found that extensive memory training (2 months, 5 days a week) can translate into increased cortical thickness in the frontal lobe (Engvig et al., 2010), and two DTI studies further suggest frontal lobe structural plasticity in the form of increased FA in the anterior corpus callosum (Lovden et al., 2010; Takeuchi et al., 2010). The temporal dynamics of such structural BT changes are not understood, but studies of mental activity outside of our BT definition do provide some clues. Knowledge acquisition amongst college students led to persistent hippocampal volumetric increases even 3 month after the end of study (Draganski et al., 2006), whilst motor training studies suggest gray matter volume reaches a zenith after just 7 days of training and gains are reversed three months later (Boyke et al,. 2008; Driemeyer et al., 2008). With sufficient practice, functional BT effects may transform into detectable structural brain changes. From a practical viewpoint, sMRI plasticity may take longer to develop, or simply produce subtle changes, and hence studies with this outcome in mind need to pay attention to adequate BT dosage, power and sample size.

5.2 Limitations and challenges for the field

Whilst BT research has so far employed the full range of MR modalities, the field conspicuously lacks multi-modal studies. Each modality has its strengths and weaknesses, and so combining MR approaches will allow the clearest insight into putative neurobiological mechanisms. Use of network-based analyses will also help integrate findings across modalities, as well as recognize the interconnected and dynamic nature of human brain plasticity (Bullmore & Sporns, 2009). However, of more fundamental concern is the absence of any active control group in almost all reviewed RCTs. Since BT typically involves participants coming into a centre for some level of person-to-person instruction, as

well as often undertaking training in group sessions, receiving personalized feedback, and a host of other non-specific stimulatory factors, it is altogether unclear whether results so far reflect the benefits of BT specifically, or the neural manifestation of social contact, motivation, generic mental activity, and other Hawthorne effects. Future studies must employ active control conditions to ensure that valid neurobiological inferences are possible. Similarly, whilst BT often implicates working memory-related brain regions such as the prefrontal lobe, few studies have demonstrated a clear correlation between MRI-changes and BT-induced cognitive benefits (Engvig et al., 2010; Erickson et al., 2007a, 2007b). Of course, when testing for such links there are numerous technical MR processing pitfalls that could lead to spurious results. This has been graphically illustrated by Thomas et al., 2009, who found that a period of mirror-reading training led, alternatively, to either nil, modest, or widespread structural brain changes depending on which Voxel-Base-Morphometry assumptions were made, or even which software package was chosen. Recently, a systematic comparison of different sMRI software platforms found each had strengths and weaknesses, depending on the nature of the question (de Bresser et al., 2011). Clearly, for the field to advance on solid ground, claims of BT-related plasticity should not be pipeline-dependent (Valenzuela, et al., *in press*), and the strongest results will be those with some level of cross-validation, either though the use of multiple imaging modalities, verification by manual methods, or parameter-based sensitivity testing.

Finally, a technical factor that is often overlooked is the role of hardware MRI upgrades during the intervention period (Ridgway et al., 2008). These routinely occur, often outside the control of the investigator, and become increasingly relevant in longitudinal studies. Reporting of any hardware changes during a BT trial should be standard, and if this change selectively affects some subjects but not others, at a bare minimum this information should be added to analyses as a nuisance covariate.

6. Conclusions

Neuroimaging studies of BT emphasize the brain's potential to adapt and change during the whole of life. Functional BT changes are most frequently implicated, with consistent findings of altered activity patterns in frontal and parietal lobe areas. Cross-validation of these results is also emerging with MR studies reporting BT-induced structural, blood flow and biochemical adaptation. Multimodal imaging investigation of BT is needed, recognizing that structural BT-related plasticity may be subtle and have a different time course to functional BT-related plasticity. A major challenge for the field is to start to draw connections between BT-related changes in brain structure and function to the cognitive benefits increasingly evident in clinical studies. Future studies should also take care to design active control conditions, as well as ensure that results are not overly influenced by arbitrary processing decisions.

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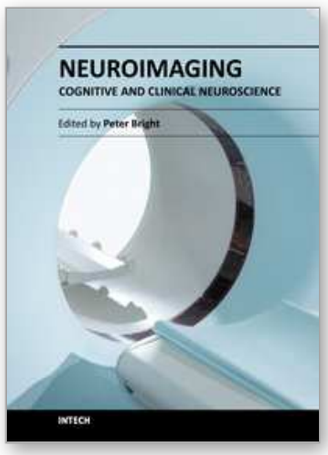

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The rate of technological progress is encouraging increasingly sophisticated lines of enquiry in cognitive neuroscience and shows no sign of slowing down in the foreseeable future. Nevertheless, it is unlikely that even the strongest advocates of the cognitive neuroscience approach would maintain that advances in cognitive theory have kept in step with methods-based developments. There are several candidate reasons for the failure of neuroimaging studies to convincingly resolve many of the most important theoretical debates in the literature. For example, a significant proportion of published functional magnetic resonance imaging (fMRI) studies are not well grounded in cognitive theory, and this represents a step away from the traditional approach in experimental psychology of methodically and systematically building on (or chipping away at) existing theoretical models using tried and tested methods. Unless the experimental study design is set up within a clearly defined theoretical framework, any inferences that are drawn are unlikely to be accepted as anything other than speculative. A second, more fundamental issue is whether neuroimaging data alone can address how cognitive functions operate (far more interesting to the cognitive scientist than establishing the neuroanatomical coordinates of a given function - the where question).

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