A systematic review of the neurobiological effects of theta-burst stimulation (TBS) as measured using functional magnetic resonance imaging (fMRI)

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Abstract

Theta burst stimulation (TBS) is associated with a range of clinical, cognitive, and behavioural outcomes, but specific neurobiological effects remain somewhat unclear. This systematic literature review investigated resting-state and task-based functional magnetic resonance imaging (fMRI) outcomes post TBS in healthy human adults. Forty-two studies that applied either continuous- or intermittent- (c/i) TBS, and adopted a pretest-posttest and/or sham-controlled design, were included. For resting-state outcomes following stimulation applied to motor, temporal, parietal, occipital, or cerebellar regions, functional connectivity generally decreased in response to cTBS and increased in response to iTBS, though there were some exceptions to this pattern of response. This is mostly consistent with the assumed long-term depression (LTD)/long-term potentiation (LTP)-like plasticity effects of cTBS and iTBS, respectively. Task-related outcomes following TBS were more variable. TBS applied to the frontal cortex, irrespective of task or state, also produced more variable responses, with no consistent patterns emerging. Individual participant and methodological factors are likely to contribute to the variability in responses to TBS. Future studies assessing the effects of TBS via fMRI must account for factors known to affect the response to TBS, both at the level of individual participants and of research methodology.

Keywords: transcranial magnetic stimulation (TMS); repetitive transcranial magnetic stimulation (rTMS); theta burst stimulation (TBS); functional magnetic resonance imaging (fMRI); non-invasive brain stimulation (NIBS); inter-individual variability.

Highlights

- Resting-state fMRI studies generally show that cTBS to motor, parietal, temporal, occipital, and cerebellar sites reduce functional connectivity
- By contrast, resting-state fMRI studies involving iTBS to these regions show increased functional connectivity
- Outcomes are more variable when TBS is applied to the prefrontal cortex, or where outcomes pertain to task-related paradigms
- It is critical to consider methodological and participant factors when using fMRI to determine effects of TBS

Abbreviations

AI/FO: anterior insula/frontal operculum

AMT: active motor threshold

APB: abductor pollicis brevis

BOLD: blood oxygen level dependant

CBF: cerebral blood flow

cTBS: continuous theta burst stimulation

DAN: dorsal attention network

DC: degree centrality

DLPFC: dorsolateral prefrontal cortex

DMN: default mode network

EMG: electromyography

FEF: frontal eye field

fMRI: functional magnetic resonance imaging

GABA: gamma amino-butyrlic acid

HCN: hippocampal-cortical network

HGal: anterolateral Heschl's gyrus

IFG: inferior frontal gyrus

IPL: inferior parietal lobe

iTBS: intermittent theta burst stimulation

LTD: long-term depression

LTP: long-term potentiation

M1: primary motor cortex

MEP: motor evoked potential

MRS: magnetic resonance spectroscopy

MSO: maximum stimulator output

NIBS: non-invasive brain stimulation

NMDA: N-methyl-D-aspartate

OFC: orbitofrontal cortex

PFC: prefrontal cortex

PMv: ventral premotor cortex

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analysis

pSTS: posterior superior temporal sulcus

RMT: resting motor threshold

ROI: region of interest

rsFC: resting-state functional connectivity

rTMS: repetitive transcranial magnetic stimulation

S1: primary somatosensory cortex

S2: secondary somatosensory cortex

SMA: supplementary motor area

SFG: superior frontal gyrus

SPL: superior parietal lobe

STG: superior temporal gyrus

TBS: theta burst stimulation

V1: primary visual cortex (medial striate area)

V2: visual area 2

V3: visual area 3

1. Introduction

Theta burst stimulation (TBS) is a [repetitive] transcranial magnetic stimulation ([r]TMS) protocol that was first developed for human application by Huang and colleagues (2005). TBS protocols can be delivered over a shorter period and at lower stimulation intensities than conventional rTMS protocols (Chung, Hill, Rogasch, Hoy, & Fitzgerald, 2016; Chung, Hoy, & Fitzgerald, 2015; Huang et al., 2005) while yielding comparable, if not enhanced, neuroplastic effects (Chung et al., 2015). TBS also has a well-established safety and tolerability profile in both adult and paediatric samples (Hong et al., 2015; Oberman, Edwards, Eldaief, & Pascual-Leone, 2011; Rossi et al., 2009). Consequently, TBS is now increasingly utilised to probe brain-behaviour relationships (Demeter, 2016), is considered a viable alternative to conventional rTMS as a biomedical intervention for major depressive disorder (Chung et al., 2015), and has been trialled for anxiety-related disorders, psychotic symptoms, and dependence disorders (see Rachid, 2017 for a review). From a clinical perspective, patterned rTMS protocols such as TBS, which take 1-3 minutes to administer compared to 20-45 minutes for conventional rTMS protocols, would also allow for many more sessions/treatments to be delivered daily within clinics, allowing greater access for patients (Chung et al., 2015). This also has benefits in terms of the feasibility of delivering accelerated treatment protocols, whereby multiple treatments are delivered daily, over a shorter time-course (Cole et al., 2020; Sonmez et al., 2019; Xiao et al., 2019).

The standard TBS paradigm involves administering TMS in three-pulse 50 Hz “bursts” of stimulation repeated every 200 milliseconds (5 Hz, “theta” burst frequency) (Huang et al., 2005). Continuous TBS (cTBS) involves uninterrupted TBS delivery, typically across 40 seconds (600 pulses). When administered over the primary motor cortex (M1), cTBS has often been considered or expected to suppress motor evoked potential (MEP) amplitudes (Chung et al., 2016; Huang et al., 2005). In contrast, intermittent TBS (iTBS) involves delivering 2 second TBS trains (10 bursts) followed by 8 second inter-train intervals, typically for 190 seconds (600 pulses). When applied over M1, iTBS is generally expected to facilitate MEP amplitudes (Chung et al., 2016; Huang et al., 2005). Although the neurological mechanisms underpinning cTBS and iTBS are not fully characterised (Di Lazzaro et al., 2008; Di Lazzaro et al., 2005), TBS neuromodulation is likely underpinned by long-term depression (LTD)- and long-term potentiation (LTP)- like mechanisms (Huang, Rothwell, Chen, Lu, & Chuang, 2011). Studies have shown that TBS effects originate in the cortex (Di Lazzaro et al., 2008; Di Lazzaro et al., 2005) and are *N*-methyl-D-aspartate (NMDA) receptor dependent (Huang, Chen, Rothwell, & Wen, 2007). Notably, however, there is great variability with respect to both the behavioural and neurophysiological after-effects of TBS (Chung et al., 2016; Corp et al., 2020; Do et al., 2018; Hamada, Murase, Hasan, Balaratnam, & Rothwell, 2013; Jannati, Block, Oberman,

Rotenberg, & Pascual-Leone, 2017), and while the factors surrounding this observed variability remain largely unknown (Ridding & Ziemann, 2010), important work is being conducted to elucidate this (Corp et al., 2020).

Much of what is known regarding the neurobiological and mechanistic effects of TBS, and TMS more broadly, is derived from research investigating the motor cortex, primarily due to the relative accessibility of measurable outcomes, such as MEPs recorded via electromyography (EMG) in peripheral muscles (Chung et al., 2016; Di Lazzaro et al., 2008; Di Lazzaro et al., 2005; Huang et al., 2005). As with all TMS protocols, the extent to which this knowledge translates to applications outside of the motor cortex is unclear. Despite this, the past decade has seen rapid growth in research implementing TBS protocols outside of the motor cortex, both experimentally and clinically. It is well established that the cytoarchitecture of different brain regions, however, varies widely, which consequently affects signal transmission (van den Heuvel, Scholtens, Barrett, Hilgetag, & de Reus, 2015), and is therefore likely to have implications for the response to TBS.

Functional neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), can be immensely beneficial in elucidating the neurobiological effects of TBS. Such protocols can provide indications of TBS induced alterations in regional excitability and network connectivity/reactivity, beyond the motor cortex, and with strong spatial resolution. In this review, we sought to describe and synthesise the literature investigating these neurobiological aftereffects, as measured via fMRI, of a single session of TBS in non-clinical adult populations.

2. Methods

The review protocol was registered with PROSPERO (PROSPERO 2020 CRD42020150589) and was conducted in alignment with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Moher et al., 2009; Moher et al., 2015).

2.1. Search strategy

We searched for research papers (peer-reviewed [published or in press], pre-print, or thesis) published in English, and did not impose limits on year of publication. Scopus, Ovid Medline, and Google Scholar were initially searched on 16th September, 2019 using the following search terms: ("theta burst stimulation" or "TBS" or "continuous theta burst stimulation" or "cTBS" or "intermittent theta burst stimulation" or "iTBS") and ("magnetic resonance imaging" or "MRI" or "functional magnetic resonance imaging" or "fMRI" or "functional MRI" or "magnetic resonance spectroscopy" or "MRS" or "neuroimaging"). Searches were completed by one reviewer (MK) and compiled into the Rayyan database (Ouzzani, Hammady, Fedorowicz, & Elmagarmid, 2016). Searches

were repeated and updated on 25th March, 2020, with the year of publication restricted to 2019 – 2020, and again on 10th August, 2020, restricting the year of publication to 2020 only.

2.2. Eligibility criteria

Research was considered eligible for review if either cTBS or iTBS was applied to any part of the human cortex, with the MRI outcomes listed above presented. Studies were required to have adopted a pretest-posttest and/or sham-controlled design.

Only data for neurotypical (i.e., non-clinical) adults, aged 18 and above, were reviewed. Research was not excluded if clinical (i.e., neuropsychiatric, neurological, or neurodevelopmental disorders) or paediatric data were also presented, however, these data are not reported on in the present review. This decision was made to avoid confounds associated with the presence of neuropathophysiology and/or neurodevelopmental factors.

2.3. Screening

Title and abstract screening was completed by two of the authors (MK and PHD) via Rayyan (Ouzzani et al., 2016). The reviewers were blind to each other's decisions. In instances where the title and abstract did not provide sufficient information to determine eligibility, the full text (methods section) of the manuscript was reviewed. Upon completion of the initial screening, results were unblinded and any discrepancies were resolved via discussion between the two reviewers. Where consensus could not be reached, a third reviewer (PGE) was consulted.

2.4. Analysis

A systematic/narrative approach was adopted for this review, as there is a pressing need for a clear evaluation and summary of the relevant literature in the field. This consolidation of the available literature will provide brain stimulation researchers with much needed direction when planning future TBS studies that involve a neuroimaging component. It was decided that a meta-analytic approach would not be appropriate for this review given the multiple sources of heterogeneity associated with this data in terms of study design, stimulation site, and outcomes measures.

3. Results

Results of the search and screening process are presented in Figure 1. Our searches initially identified a total of 894 manuscripts, and one additional manuscript (Gratton, Lee, Nomura, & D'Esposito, 2014) which was identified via the references presented within the reviewed manuscripts. 613 remained following the removal of duplicates, and these were then screened according to the criteria described above, resulting in 59 manuscripts that were full text screened for

eligibility. Of these, 17 were excluded for the following reasons: not meeting eligibility criteria (n = 10), full text published in a language other than English (n = 1), and duplication of results (i.e., peer-reviewed manuscript from within a thesis [n = 4 theses excluded]). Additionally, two manuscripts employed magnetic resonance spectroscopy (MRS) as an outcome measures, and one reported both MRS and fMRI outcomes. Therefore, at this point it was decided that MRS outcomes (n = 2 manuscripts) would be excluded from this review as the limited research in this area would limit our ability to make any informed interpretations about the effects of TBS on MRS outcomes. This resulted in a total of 42 manuscripts being included in this review. Relevant sample, protocol details, and a general indication of the results from included studies are presented in Table 1.

Figure 1. PRISMA flow diagram for search, screening, and manuscript selection. Adapted from (Moher et al., 2009).

Table 1. Summary of reviewed studies and indication of results

Reference	Sample size, sex ratio (M:F), age (years)	Study design	TBS protocol, parameters ^a , Stimulation Intensity	Method for locating target site [active control]	Outcome Protocol [Time to return to scanner] Paradigm Summary of results
Abellana-Pérez et al. (2019)	Younger: n = 24 (5:19) 23.4 ± 1.6 Older: n = 28 (6:22) 68.2 ± 4.6	Pretest-posttest, between subjects, sham controlled	iTBS Younger = 80% AMT Older = 90% AMT	Neuronavigation (functional connectivity) - (L) inferior parietal lobule	<i>Resting-state fMRI</i> [Younger: 33 ± 3 minutes, Older: 34 ± minutes] Functional Connectivity ↑ rsFC between target and anterior (medial frontal) default mode network seeds in younger adults. ↑ rsFC between (L) inferior parietal lobe and posterior cingulate cortex in older adults who received active, but not sham iTBS. ↑ pre-iTBS rsFC predicted "younger" or "younger like" response to iTBS.
Agnew et al. (2018)	N = 16 23-49 years ^b	Pretest-posttest, within-subjects, active control	cTBS; Total pulses: 300 40% MSO	Neuronavigation (anatomical/coordinate) - (R) ventral premotor cortex (MNI = 54, -2, 44) - [vertex]: middle of nasion andinion	<i>Task (auditory emotion)-based fMRI</i> [fMRI 5 minutes post cTBS] BOLD No effects at target site or contralateral homologue ↑ at a (R) post- and pre-central gyri. ↑ inferior frontal gyrus (pars opercularis and triangularis), left supplementary motor area, cerebellar vermis, right parahippocampal gyrus, bilateral, inferior parietal lobe (angular gyrus), bilateral superior and right middle frontal gyri and right postcentral gyrus. ↓ left hippocampus, right middle cingulate cortex, right precuneus, left supramarginal gyrus, right supplementary motor area, right inferior frontal gyrus (pars triangularis) and right rolandic operculum.
Alkhasli et al. (2019)	N = 16 (8:8) 27.6 ± 7.0	Pretest-posttest, within-subjects	iTBS 90% RMT 120% RMT	Neuronavigation (anatomical/coordinate) - (L) dorsolateral prefrontal cortex: (Tal = -45, 45, 35)	<i>Resting-state fMRI</i> [7 minutes] Functional Connectivity Sub threshold stimulation: ↑ rsFC between (L) dorsolateral prefrontal cortex and the striatum, (L) and (R) caudate. Supra-threshold stimulation: ↑ rsFC between (L) caudate and the (L) and (R) amygdala.

Anderkova et al. (2018)	N = 20 (7:13) 25.2 ± 2.7	Pretest- posttest, within subjects, cross-over	cTBS iTBS 80% AMT	Neuronavigation (anatomical/coordinate) - (R) inferior frontal gyrus (MNI = 46, 14, 32), - (L) superior parietal lobule (MNI = -24, -68, 48)	<i>Resting-state fMRI</i> [immediate] Functional connectivity iTBS to (L) superior parietal lobule: ↑ rsFC between (L) superior parietal lobule and (L) cerebellar nodule, and overall ↑ in rsFC within the dorsal attention network. No effects of cTBS. No reported effects of (R) inferior frontal gyrus stimulation.
Andoh et al. (2013)	N = 13 (6:7) 23.3 ± 5.9	Pretest- posttest, within- subjects, cross- over, active control	cTBS 41% MSO	Neuronavigation (functional activation): - (L) anterolateral Heschl's gyrus - (R) anterolateral Heschl's gyrus Neuronavigation (anatomical) - [vertex]	<i>Task (melody)-based fMRI</i> [immediate: 2.8 min ± 0.4 minutes] BOLD and Functional Connectivity (R) anterolateral Heschl's gyrus: ↑ BOLD at (R) anterolateral Heschl's gyrus, inferior and superior temporal cortices, and middle frontal gyrus. (R) anterolateral Heschl's gyrus: ↑ FC between (L)/(R) auditory cortices, (L) anterolateral Heschl's gyrus and (R) pre- & post- central gyri and insula.
Andoh et al. (2015)	N = 17 (8:9) 23.1 ± 4.9	Pretest- posttest, within subjects	cTBS 41% MSO	Neuronavigation (Anatomical/coordinate) - (L) anterolateral Heschl's gyrus (MNI = -51.4, -17.2, 2.6) - (R) anterolateral Heschl's gyrus (MNI = 54.6, -10.8, 0.3) - [vertex (anatomically defined)]	<i>Resting-state fMRI</i> [immediate: day 1 = 2.8 ± 0.5 minutes, day 2 = 2.5 ± 0.3 minutes, day 3 = 2.4 ± 0.1 minute] Functional Connectivity (R) anterolateral Heschl's gyrus: ↓ in ipsilateral and contralateral auditory regions, and bilateral motor (including motor, premotor, and primary and secondary somatosensory cortices) regions. (L) anterolateral Heschl's gyrus: ↓ rsFC with (R) anterolateral Heschl's gyrus.
Annak et al. (2019)	N = 16 (6:10) 23.8 ± 2.3	Pretest- posttest, within subjects, cross- over, sham controlled	cTBS 80% AMT	Neuronavigation (functional activation): - (L) primary motor cortex; FDI representation - (L) secondary somatosensory cortex	<i>Task (nociceptive stimulation; chemosensory pain model)-based fMRI</i> [time to return to scanner not clear/reported] BOLD (L) primary motor cortex: ↓ BOLD at rolandic operculum, insula and postcentral gyrus. Strength or relationship between BOLD signal and stimulus strength reduced post cTBS to (L) primary motor cortex. No effects of stimulation to (L) secondary somatosensory cortex.

Cárdenas-Morales et al. (2011)	N = 17 (17:0) 27.3 ± 2.6	Pretest-posttest, within subjects	iTBS 90% AMT	Hot-spot - (L) primary motor cortex; APB representation	<i>Task (choice reaction)-based and resting-state fMRI</i> [immediate] BOLD and CBF Task: ↓ BOLD at left (L) primary motor cortex, and (R) primary motor cortex, primary somatosensory cortex, rostral parts of (R) superior and inferior parietal gyrus, and the (R) premotor area. No effects at rest.
Cocchi et al. (2015)	N = 23 (11:12) 23.0 ± 3.0	Pretest-posttest, within subjects	cTBS iTBS 80% AMT	Hot-spot - (R) primary motor cortex; APB	<i>Resting-state fMRI</i> [5 minutes] Functional Connectivity cTBS: ↓ participation index (PI) and ↑ within module degree (WMD) at motor and somatosensory cortices, ↑ PI and ↓ WMD at insula, striatum, and (L) temporal cortex. iTBS: No effects of iTBS on PI or WMD.
Gratton, et al (2013)	N = 27 (16:11) 18 – 31 years ^b	Pretest-posttest, within-subjects, cross-over	cTBS 80% AMT	Neuronavigation (anatomical and functional) - (L) dorsolateral prefrontal cortex - (L) anterior insula/frontal operculum - [(L) primary somatosensory cortex]	<i>Resting-state fMRI</i> [~ 10 minutes] BOLD and Functional Connectivity Non-significant trend towards increased rsFC of the fronto-parietal network following TBS to both the (L) dorsolateral prefrontal cortex and (L) anterior insula/frontal operculum compared to active control. Strongest ~ 20 minutes post TBS. No whole brain effects immediately following TBS to either test site. Widespread frontal, parietal and cingulate effects 20 minutes post stimulation. (L) anterior insula/frontal operculum: ↑ FC between (L) anterior insula/frontal operculum and bilateral regions of lateral inferior and middle frontal gyrus and a the (R) intraparietal sulcus, (R) superior frontal gyrus, orbito frontal cortex, posterior temporal lobe, and (L) anterior temporal lobe. ↑ FC between (L) dorsolateral prefrontal cortex and anterior and posterior cingulate cortex, bilateral, supramarginal/angular gyrus, bilateral superior frontal gyrus, (L) precentral gyrus, (R) inferior anterior insula, and the midcingulate ↑rsFC between (L) dorsolateral prefrontal cortex and default mode network regions

					<p>(L) dorsolateral prefrontal cortex: ↑ rsFC between (L) dorsolateral prefrontal cortex and bilateral areas of the anterior insula/frontal operculum, anterior cingulate, medial superior frontal gyrus, (R) middle frontal gyrus and anterior superior frontal gyrus</p> <p>↑ rsFC between anterior insula/frontal operculum and (L) dorsal premotor cortex, middle and superior frontal gyrus, angular gyrus, (L) middle and superior temporal gyri and the right supramarginal gyrus.</p> <p>No changes after cTBS to primary somatosensory cortex</p>
Gratton, et al (2014)	N = 27 (16:11) 18 – 31 years ^b	Pretest-posttest, within-subjects, cross-over	cTBS 80% AMT	<p>Neuronavigation (anatomical and functional)</p> <p>- (L) dorsolateral prefrontal cortex</p> <p>- (L) anterior insula/frontal operculum</p> <p>- [(L) primary somatosensory cortex]</p>	<p><i>Resting-state fMRI</i> [~ 10 minutes]</p> <p>CBF</p> <p>Trend level ↑ in CBF at site of stim following cTBS, variability in direction and magnitude of CBF change following cTBS (increased and decreased) at all sites.</p> <p>↑CBF related to decreased FC of cingulo-opercular or fronto-parietal networks following cTBS to (L) anterior insula/frontal operculum or (L) dorsolateral prefrontal cortex respectively (not due to underlying baseline relationship).</p> <p>When stratified based on directionality of perfusion, group with ↑ perfusion showed reduced network connectivity, and ↓ perfusion showed increased network connectivity.</p>
Halko et al (2014)	N = 9 (5:4) ^b	Pretest-posttest, within subjects, sham controlled	iTBS 100% AMT	<p>Neuronavigation (functional)</p> <p>- (R) lateral cerebellum; Crus I or Crus II (mean MNI = 41, 72, 39)</p> <p>Neuronavigation (anatomical)</p> <p>- midline cerebellum; lobule VII (MNI = 1, 73, 33)</p>	<p><i>Resting-state fMRI</i> [immediate]</p> <p>Functional Connectivity</p> <p>(R) lateral cerebellum: ↑ default mode network functional connectivity.</p> <p>Medial cerebellum: ↑ dorsal attention network connectivity.</p>

Hartwigsen et al (2013)	N = 17 (7:10) 23.8 ± 2.2	Within-subjects, repeated measures, sham controlled	cTBS 80% AMT	Neuronavigation (anatomical/coordinate) - (L) anterior inferior frontal gyrus (MNI = -52, 34, -6) - (L) posterior inferior frontal gyrus (MNI = -52, 13, 8)	<i>Task (speech production)-based fMRI</i> [immediate] BOLD and Functional Connectivity (L) posterior inferior frontal gyrus: ↓ BOLD at (L) posterior inferior frontal gyrus and ↑ BOLD at (R) posterior inferior frontal gyrus during pseudo word repetition. (L) posterior inferior frontal gyrus: ↑FC between (R) and (L) posterior inferior frontal gyri.
Heinen et al (2017)	N = 16 (10:6) 19-34 years ^b	Pretest-posttest (1 st session only), within subjects, sham controlled	cTBS 80% AMT	Neuronavigation (anatomical/visual) - (R) frontal eye field (mean MNI = 27, 3, 57)	<i>Task (visuospatial attention shifting)-based fMRI</i> [immediate: 5-10 minutes] BOLD and Functional Connectivity ↓ BOLD bilateral frontal eye field, bilateral supramarginal gyri, (R) inferior parietal lobule, (R) and superior parietal lobule. ↓FC between (R) frontal eye field and (R) supramarginal gyrus, and putamen.
Hermiller et al. (2019)	N = 24 (10:14) 23.5 ± 2.6	Within-subjects, repeated measures, sham controlled	cTBS iTBS 80% RMT	Neuronavigation (functional connectivity) - (L) parietal cortex	<i>Resting-state fMRI</i> [~6 minutes] Functional Connectivity No effects of cTBS or iTBS on hippocampal-cortical network (target network), dorsal attention network (control), or primary visual network (control). Relationship between behavioural performance on an episodic memory task and hippocampal-cortical network connectivity.
Howard et al. (2020)	TBS n = 28 (12:16) 24.0 ± 3.5 SHAM n = 28 (12:16) 24.0 ± 4.5	Between subjects, sham controlled	cTBS 80% RMT	Neuronavigation (anatomical/coordinate) - (R) ventrolateral prefrontal cortex (MNI = 48, 38, 20)	<i>Resting-state fMRI</i> [immediate] Functional Connectivity ↓ in (R) central/lateral orbitofrontal cortex related global connectivity with cingulate cortex, lateral prefrontal cortex, posterior parietal cortex, ventro-temporal cortex, and left orbitofrontal cortex.

Hu et al. (2017)	N = 36 (17:19) 20-34 years ^b	Pretest- posttest, within subjects	cTBS 70% RMT	Hot-Spot - (R) primary motor cortex; FDI	<i>Resting-state fMRI</i> [30 minutes] Functional connectivity Bilaterally ↓ ALFF and fALFF and ReHO along the postcentral gyrus at sites controlling the (L) face and limbs and (L) and (R) trunk.
Iwabuchi et al. (2017)	N = 28 ^b 25.1 ± 7.1	Within subjects, repeated measures, sham- controlled, cross-over	iTBS ^c : 3 runs, 5 minutes apart 80% RMT	Neuronavigation (functional) - (L) dorsolateral prefrontal cortex	<i>Resting-state fMRI</i> [immediate] Functional connectivity ↓ between (L) dorsolateral prefrontal cortex and anterior cingulate cortex.
Ji et al. (2017)	N = 19 (6:13) 22.7 ± 2.1	Pretest- posttest, cross- over, within subjects	cTBS (3 runs, 15 minutes apart) 70% RMT	Neuronavigation (anatomical/coordinate) - (L) supplementary motor area (MNI = -6, -6, 77)	<i>Resting-state fMRI</i> [Immediate] BOLD and Functional Connectivity No local effects. ↓ rsFC at the (L) inferior frontal gyrus, and (L) supplementary motor area/middle cingulate cortex, maintained for 6.1 min in the (L) inferior frontal gyrus and 6.6 min in the (L) supplementary motor area/middle cingulate cortex.
Mastropasqua et al. (2014)	TBS: n = 18 (9:9) 26.7 ± 3.8 SHAM: n = 14 (6:8) 27.07 ± 3.6	Pretest- posttest, between subjects, sham controlled	cTBS 80% AMT	10-20 system - (R) dorsolateral prefrontal cortex (F4)	<i>Resting-state fMRI</i> [immediate] Functional Connectivity ↓ rsFC between (L) dorsolateral prefrontal cortex and (R) posterior parietal cortex.
Nettekoven et al. (2014)	N = 16 (7:9) 27.0 ± 3.0	Pretest- posttest, sham controlled, within subjects, repeated measured crossover	iTBS: 3 runs, 15 minutes apart 70% RMT	Hot-spot - (L) primary motor cortex; APB	<i>Resting-state fMRI</i> [time to return to scanner after each TBS run unclear/not reported] Functional connectivity ↑ rsFC between primary motor cortex and various sensorimotor regions, with local maxima consistently at bilateral supplementary motor area and dorsal premotor cortex (superior frontal sulcus) across blocks, and less consistently in parts of the somatosensory and superior parietal cortices. No effects in a control (visual) network.

					<p>Dose dependency: primary motor cortex-dorsal premotor cortex connectivity was significantly higher after iTBS₁₈₀₀ compared with iTBS₆₀₀ and iTBS₁₂₀₀, but not between iTBS₆₀₀ and iTBS₁₂₀₀, and sham.</p> <p>Supplementary control experiment: iTBS₁₈₀₀ = ↑rsFC between primary motor cortex and bilateral supplementary motor area, dorsal premotor cortex, and parts of the somatosensory and superior parietal cortex when compared to iTBS₆₀₀ followed by 2 sham runs, supporting the notion of a cumulative (dosage) effect, rather than delayed effect of a single dose of iTBS.</p>
Nettekoven et al. (2015)	N = 16 (7:9) 27.0 ± 3.0	Pretest-posttest, sham controlled, within subjects, repeated measures, crossover	iTBS: 3 runs, 15 minutes apart 70% RMT	Hot-spot - (L) primary motor cortex; APB	<p><i>Resting-state fMRI</i></p> <p>[time to return to scanner after each TBS run unclear/not reported]</p> <p>Functional connectivity</p> <p>In responders, ↑ FC between primary motor cortex and bilateral supplementary motor area and dorsal premotor cortex, as well as the contralateral primary motor cortex.</p> <p>rsFC ↑ with each dose of iTBS in responder group, but not for non-responders. i.e. multiple doses of iTBS did not change responsiveness to iTBS (non-responders did not become responders).</p>
Odorfer et al. (2019)	N = 8 ^b	Pretest-posttest, between subjects, sham controlled	cTBS 80% AMT	<p>Measurement (3 cm lateral and 1 cm inferior to theinion)</p> <p>- (L) cerebellum (lobule VIII) followed by (R) cerebellum (60 second break between sites)</p>	<p><i>Task (finger-tapping)- related fMRI</i></p> <p>BOLD</p> <p>[immediate]</p> <p>Cerebellar cTBS had no effects on brain activation in healthy controls.</p>
Orosz et al. (2012)	N = 12 (7:5) 23.9± 2.1	Pretest-posttest, within subjects, sham controlled, cross over	cTBS 80% RMT	<p>Hot-spot</p> <p>- (R) primary motor cortex; small hand muscles</p>	<p><i>Task (finger tapping)-based and resting-state fMRI</i></p> <p>[immediate]</p> <p>CBF</p> <p>CBF ↑ at (R) primary motor cortex during finger tapping (left hand) compared to rest.</p> <p>CBF ↑ at (R) primary motor cortex, and more voxels were implicated compared to baseline.</p>

Pitcher et al. (2014)	N = 15 ^b	Pretest-posttest, within subjects, cross-over	cTBS; Total pulses: 900 80% AMT or 30% MSO (whichever was higher)	Neuronavigation (functional) - (R) posterior superior temporal sulcus - (R) occipital face area	Task (<i>face/emotion processing</i>)-based fMRI [time to return to scanner not clear/reported] BOLD (R) posterior superior temporal sulcus: ↓ (R) posterior superior temporal sulcus (dynamic faces). (R) occipital face area: ↓ (R) posterior superior temporal sulcus (static faces).
Pitcher et al. (2017)	N = 23 (10:13) ^b	Pretest-posttest, within subjects, active control	cTBS; Total pulses: 900 80% AMT or 30% MSO (whichever was higher)	Neuronavigation (functional) - (R) posterior superior temporal sulcus - [vertex]; top of the head halfway between nasion/inion	Task (<i>face/emotion processing</i>)-based fMRI [immediate] BOLD ↓ BOLD in response to faces at (R) posterior superior temporal sulcus, (R) anterior posterior superior temporal sulcus, and amygdala.
Rahnev et al. (2013)	N = 4(2:2) 23-32 years ^b	Pretest-posttest, within subjects, active control	cTBS 80% phosphene threshold	Hot-spot “hunting procedure” - (L) occipital cortex - [vertex]	Resting-state fMRI [time to return to scanner unclear/not reported] Functional connectivity ↓ between V1-2, V1-3, V2-3. ↓ between L-R V1, V2, V3.
Rastogi et al. (2017)	N = 12 (7:5) 29.7 ± 9.4	Pretest-posttest, within subjects, sham controlled	cTBS 80% AMT	Measurement - (R) cerebellum; crus 1 (1 cm inferior and 3 cm to the right of the inion)	Resting-state fMRI [immediate] Functional Connectivity ↓ rsFC in active compared to sham cTBS in non-motor (cognitive) network: (L) inferior parietal lobe, posterior medial frontal cortex, lateral prefrontal cortex, and the right medial posterior parietal cortex (precuneus). No effect on motor network.
Ruan et al. (2017)	N = 60 (30:30) 23.5 ± 4.4	Pretest-posttest, within and between subjects	iTBS cTBS cTBS _{left} + iTBS _{right}	- (L) primary motor cortex; suprahyoid muscle	Resting-state fMRI [immediate] Functional Connectivity cTBS ↓ ALFF in anterior cingulate gyrus. iTBS ↑ ALFF to bilateral precuneus. cTBS+iTBS ↓ ALFF in brainstem and ↑ ALFF in middle cingulate cortex and (L) precentral gyrus.

Ruan et al. (2019)	N = 60 (30:30) 23.5 ± 4.4	Pretest- posttest, within and between subjects	iTBS cTBS cTBS _{left} + iTBS _{right}	- (L) primary motor cortex; suprahyoid muscle	<p><i>Resting-state fMRI</i> [immediate] Functional Connectivity cTBS ↑ ReHo in the (R) lingual gyrus and (R) precuneus, and ↓ ReHo in the posterior cingulate gyrus.</p> <p>iTBS ↑ in ReHo in the bilateral precentral gyrus, (L) postcentral gyrus, and cuneus, and ↓ ReHo in the (L) cerebellum, brainstem, (L) temporal gyrus, (R) insula, and (L) middle frontal gyrus.</p> <p>cTBS+iTBS ↑ ReHo in the precuneus and ↓ ReHo in the (R) cerebellum posterior lobe, (L) cerebellum anterior lobe, and (R) inferior frontal gyrus.</p>
Shang et al. (2019)	N = 36 (15:21) 22.9 ± 3.3	Pretest- posttest, within and between subjects, sham controlled crossover	cTBS 80% RMT	<p>Neuronavigation (anatomical/coordinate)</p> <p>- (L) dorsolateral prefrontal cortex (MNI = -40, 26, 37)</p>	<p><i>Resting-state fMRI</i> [immediate] Functional Connectivity and CBF ↓ rsFC between (L) dorsolateral prefrontal cortex and (R) parahippocampal gyrus, (L) lingual gyrus and posterior cingulate cortex/precuneus. No effects of sham. No local effects on dorsolateral prefrontal cortex activity. ↑ CBF to (L) parahippocampal gyrus, (L) hippocampus, (L) amygdala, (L) inferior temporal cortex, (L) inferior parietal cortex and (L) precuneus - this did not survive statistical controls.</p>
Steel et al. (2016)	N = 22 (10:12) 26.0 ± 4.2	Within subjects, crossover, sham controlled	cTBS 80% AMT	<p>Hot-spot</p> <p>- (L) primary motor cortex; FDI</p>	<p><i>Task (motor procedural learning)- based fMRI</i> [330 ± 80 seconds for the TBS and 450 ± 28 seconds for sham] BOLD and functional connectivity No effects of cTBS on BOLD response at any brain region. ↓ global connectivity at (L) primary visual cortex and dorsal premotor area. ↑ global connectivity at middle cingulate gyrus, dorsal anterior cingulate, and superior frontal gyrus. ↓ FC between (L) inferior occipital gyrus and dorsal premotor area, supplementary motor area, and primary motor cortex. ↓ FC between superior occipital gyrus and primary motor cortex and supplementary motor area. ↑ FC between the middle temporal and dorsal anterior cingulate. ↑ FC between the superior and inferior frontal gyri.</p>

Tang et al. (2019)	N = 10 (6:4) 25.5 ± 2.8	pretest- posttest, within subjects	iTBS 80% RMT	Neuronavigation (anatomical/coordinate) - (L) dorsolateral prefrontal cortex (MNI = -44, 36, 20)	<i>Resting-state fMRI</i> [immediate, and repeated at 15 minutes] Functional Connectivity Immediately following TBS: rsFC ↑ between (L) dorsolateral superior frontal gyrus and left dorsal inferior frontal gyrus, and ↑ between the left rostral inferior frontal gyrus and (R) middle frontal gyrus. rsFC ↓ within orbital gyrus regions. Effects were attenuated ~15 minutes post TBS. 15 minutes post TBS: rsFC ↓ between caudal inferior frontal gyrus and (R) medial amygdala. rsFC ↓ between (L) left caudal inferior frontal gyrus and (R) medial orbital gyrus. rsFC ↓ between the (R) opercular inferior frontal gyrus and (L) medial orbital gyrus. rsFC ↑ between middle frontal gyrus and (L) orbital gyrus. fALFF ↑ at (L) medial superior frontal gyrus, (L) dorsal middle frontal gyrus, (L) ventral cingulate gyrus, and (L) opercular inferior frontal gyrus.
Valchev et al. (2015)	N = 17 (11:6) 20.9 ± 2.0	Within subjects, sham controlled	cTBS 80% RMT	Neuronavigation (functional) - (L) primary somatosensory cortex (mean MNI: -43 -35 57)	<i>Resting-state fMRI</i> [within 6 minutes] Functional connectivity ↓ rsFC between (L) primary somatosensory cortex and dorsal premotor cortex, and premotor cortex/supplementary motor area.
Valchev et al. (2016)	N = 17 (11:6) 20.9 ± 2.0	Within subjects, sham controlled	cTBS 80% RMT	Neuronavigation (functional) - (L) primary somatosensory cortex (mean MNI: -43 -35 57)	<i>Task (action/observation)- based fMRI</i> [within 6 minutes] BOLD No group effects at target site. Individual results indicate reduction of signal for some participants, and an increase for others.
Van Holstein et al. (2018)	N = 27 (14:13) 21.7 ± 2.0	Within subjects, crossover, no TMS baseline (either pretest, or	cTBS 80% AMT	Neuronavigation (anatomical/coordinate) - (L) anterior prefrontal cortex (MNI = -30, 60, 8)	<i>Task (task-switching reward manipulation)-based fMRI</i> [immediate] BOLD (L) anterior prefrontal cortex: non-significant trend towards ↓ reward- related processing in the caudate nucleus. No effects at other sites.

		30 minutes post)		<ul style="list-style-type: none"> – (L) dorsolateral prefrontal cortex (MNI = -36,36, 20) – (L) premotor cortex (MNI = -28, 10, 66) 	
Van Nuenun et al. (2012)	N = 11 (11:0) 27.0 ± 6.5	Within subjects, sham controlled	cTBS 80% AMT	Measurement - (L) dorsal premotor cortex (2 cm anterior and 1 cm medial to hot-spot (FDI)	<i>Task (cued grip and lift)-based fMRI</i> [15 minutes] BOLD cTBS did not modulate preparatory activity at L) dorsal premotor cortex.
Vidal-Piñeiro et al. (2014)	N = 24 (12:12) 71.8 ± 6.8	Between subjects, sham controlled	iTBS 80% AMT	Neuronavigation (anatomical/coordinate) - (L) inferior frontal gyrus (MNI = -42,14,30)	<i>Task (encoding memory-based and resting-state fMRI</i> [immediate] BOLD and functional connectivity iTBS did not have any effects on rsFC during deep encoding. BOLD increased at primary visual areas, lateral occipital cortex, ventral occipitotemporal areas and the cerebellum. Frontal and posterior (cerebellum-occipital) connectivity was greater during deep encoding post iTBS
Wawrzyniak et al. (2017)	N = 20 (10:10) 25.1 ± 2.5	Between subjects, cross-over, sham controlled	cTBS 80% AMT	Neuronavigation (anatomical/coordinate) - (L) anterior inferior frontal gyrus (MNI = -54, 26, 4) - (L) posterior middle temporal gyrus (MNI = -51, -31, 4)	<i>Resting-state fMRI</i> [8.9 ± 0.4 minutes] Functional Connectivity No effects on rsFC.
Welniarz et al. (2018)	N = 22 ^c	Pretest-posttest, within subjects, sham controlled	cTBS 90% AMT	Neuronavigation (anatomical) - (R) supplementary motor area	<i>Task (delayed response cued-movement go-no-go)-based fMRI</i> [within 30 minutes of TBS] BOLD and Functional Connectivity cTBS did not affect BOLD. Bimanual preparation: FC between (L) supplementary motor area and primary motor cortex was negative before cTBS and positive afterward.

					FC between (L) and (R) supplementary motor area was positive pre cTBS and reinforced post. (L) and (R) primary motor cortex FC was positive post cTBS.
Zhang et al. (2019)	N = 20 (10:10) 23.5 ± 4 .4	Pretest- posttest, within subjects	cTBS _{left} followed immediately by iTBS _{right} 80% AMT	Hot-spot - bilateral primary motor cortex; suprahyoid muscle	<i>Resting-state fMRI</i> [immediately] Functional Connectivity Static FC: ↑ rsFC in the precuneus, (L) fusiform gyrus, and (R) pre/postcentral gyrus. ↓ FC in the posterior cingulate gyrus and (L) inferior parietal lobule. Dynamic FC: earlier time windows showed decreased FC, later showed increased.
Zhang et al. (2020)	N = 40 (20:20) 23.7 ± 2.6 cTBS: n = 20 (10:10) 23.6 ± 2.2 iTBS: n = 20 (10:10) 23.0 ± 2.7	Pretest- posttest, between subjects	cTBS iTBS 80% AMT	Hot-spot - (L) primary motor cortex; suprahyoid muscle	<i>Resting-state fMRI</i> [within 30 minutes] Functional Connectivity cTBS: ↑ degree centrality in (L) inferior frontal gyrus compared to baseline. iTBS: ↓ degree centrality in the (L) cerebellum and medial frontal gyrus. ↑ degree centrality in the (R) superior temporal gyrus, superior frontal gyrus, and postcentral gyrus, as well as the (L) paracentral lobule compared to baseline.

Note: ^a parameter detail only provided when divergent from those reported by Huang et al. (2005). Where detail is not provided, it has been assumed that the protocol is comparable to that reported by Huang et al. (2005), ^b demographic information unclear, incomplete or not provided, ^c Authors (Iwabuchi et al., 2017) report iTBS, however parameters are consistent with cTBS. ↑ increased, ↓: decreased, (L): left, (R): right, ALFF: amplitude of low-frequency fluctuation, AMT: active motor threshold, APB: abductor pollicis brevis, BOLD: blood oxygen level dependant, CBF: cerebral blood flow, cTBS: continuous theta burst stimulation, DMN: default mode network, fALFF: functional amplitude of low-frequency fluctuation, FDI: first dorsal interosseous, iTBS: intermittent theta burst stimulation, MSO: maximum stimulator output, ReHo: regional homogeneity, RMT: resting motor threshold, rsFC: resting-state functional connectivity, TBS: theta burst stimulation

4. Discussion

This review sought to systematically synthesise and evaluate the fMRI literature investigating the functional neurobiological aftereffects of TBS applied to the human brain in neurotypical adults. TBS-induced alterations in offline brain activity and connectivity are summarised. In all studies, TBS was applied at rest. Specific details regarding the regions implicated are provided in Table 1. Here, we consolidate these findings and discuss the broad directionalities of the neurobiological response to TBS at various sites, as well as factors that contribute to the neurobiological responses induced by TBS. As shown in Table 1, while it is possible to detect neurobiological effects of a single session of TBS using fMRI, the response to both TBS protocols, as measured by fMRI, is extremely variable. Given this variability, we will not summarise the effects of either TBS protocol in terms of the generally “expected” response, as proposed by Huang et al. (2005). Rather, the relevant literature will first be summarised with respect to the region stimulated, and results will be considered with respect to the observed neurobiological responses, at both local and network levels. Findings will be considered separately at rest (i.e., in the absence of any cognitively or behaviourally demanding stimuli) and during offline task performance, as these contextual factors are likely to have implications for neural processing and responses. Any relevant behavioural influences will be discussed where appropriate. Following this, themes and patterns emerging from this summary, which elucidate some factors that contribute to the variability in the brain’s response to TBS will also be considered.

4.1. Functional neurobiological responses to TBS across the cortex

4.1.1. TBS to the motor cortex

Given that the vast majority of the wider TMS literature broadly targets motor regions, we first provide a summary of studies reporting fMRI outcomes of TBS when applied to this region. In total, 16 of the identified studies targeted various motor regions broadly.

In terms of the general directionality of the response to TBS applied to the motor cortex at rest, and therefore in the absence of physical and cognitive confounds associated with motor preparation and execution, neither cTBS to left supplementary motor area (SMA) (Ji, Yu, Liao, & Wang, 2017) or iTBS to the left M1 (Cárdenas-Morales, Grön, & Kammer, 2011) induced any measurable effects on blood oxygen level dependant (BOLD) response or cerebral blood flow (CBF), respectively. At a network level, however, the majority of the reviewed literature indicates resting-state functional connectivity (rsFC) reductions in response to cTBS to M1 hand (Hu et al., 2017) and the suprahyoid muscle cortex (Ruan et al., 2017; Ruan et al., 2019; Zhang et al., 2019) representations, and also the SMA (Ji et al., 2017). In contrast, rsFC increases were reported in response to iTBS when applied to M1 hand

(Nettekoven et al., 2014; Nettekoven et al., 2015) or the suprahyoid muscle cortex (Ruan et al., 2017; Ruan et al., 2019) representations, though some conflicting findings were also noted (Cárdenas-Morales et al., 2011; Zhang et al., 2020). These studies used a combination of seed- (Ji et al., 2017; Nettekoven et al., 2014; Nettekoven et al., 2015) and voxel- (Hu et al., 2017; Ruan et al., 2017; Ruan et al., 2019; Zhang et al., 2019) based connectivity analyses. A more recent study (Zhang et al., 2020), however, which employed a novel, graph-based approach to investigating rsFC, known as degree centrality (DC), reported conflicting results. Zhang et al. (2020) reported increased DC, and therefore functional connectivity, in the left inferior frontal gyrus (IFG) following cTBS to the left suprahyoid M1 representation. In contrast, iTBS to this site resulted in both increased (at the superior temporal gyrus [STG], right superior frontal gyrus [SFG], right postcentral gyrus, and left paracentral lobule) and decreased (at the left cerebellum and left medial frontal gyrus) DC. Finally, one study reported no effects of iTBS to M1 on rsFC outcomes (Cárdenas-Morales et al., 2011).

When complexities associated with tasks and behavioural performance are introduced, however, the response to TBS becomes less clear. Indeed, the neurobiological effects of TBS applied to various motor regions appear to be task- and state-dependant. Despite no observable effects of iTBS to the left M1 hand representation at rest, during a choice reaction task Cárdenas-Morales et al. (2011) reported decreased BOLD responses at numerous motor and parietal sites. cTBS to various regions of the motor cortex has been reported to have no effect on BOLD response during components of tasks/behaviours related aspects of motor performance that might be considered to have cognitive underpinnings, such as motor procedural learning (M1 hand representation; Steel et al., 2016), preparatory phases of a motor action (dorsal premotor cortex; van Nuenen, Kuhtz-Buschbeck, Schulz, Bloem, & Siebner, 2012), and response delays (SMA; Welniarz et al., 2019). Conversely, yet still relevant to cognitive processes, following cTBS to the ventral premotor cortex (PMv) Agnew, Banissy, McGettigan, Walsh, and Scott (2018) report both increases and decreases in BOLD response at distal frontal, motor, parietal, and sub-cortical regions during emotion processing. This study reported no local effects of stimulation (Agnew et al., 2018). Additionally, when accompanied by nociceptive (via gaseous CO₂) stimulation, cTBS to the M1 was associated with reduced activity at the rolandic operculum, insula and postcentral gyrus, and the strength of the relationship between BOLD signal and stimulus strength was also reduced (Annak et al., 2019).

During motor execution, however, Orosz et al. (2012) report increased CBF in response to cTBS at the targeted right M1 during a left handed finger tapping task. The authors also reported activation of a larger area of M1 compared to baseline. In line with these findings, Cocchi et al. (2015) also reported facilitatory effects of cTBS applied to the right M1. Even at rest, the authors found increased responsiveness of non-motor regions involved in the production of left thumb

movements, which was a function of specialisation for the targeted right abductor pollicis brevis (APB) motor cortex representation (i.e. “hot-spot”), including the insula, striatum, and left temporal cortex.

In sum, with regard to TBS targeted to motor regions broadly, irrespective of the exact stimulation location, the available literature indicates a more consistent pattern of neurobiological effects in response to TBS at rest. Specifically, network wide increases in rsFC were observed in response to iTBS to motor regions, while network wide reductions in rsFC were observed in response to cTBS, though some inconsistency was noted. The introduction of cognitively or physically demanding tasks yields more inconsistent results, and the specific task, or target behaviour, also appears to mediate responses. We speculate that this might, at least in part, reflect the complexity of networks involved in particular tasks and behaviours. Another important consideration, however, is that while most studies investigating resting-state outcomes targeted M1 regions, the exact location/motor representation varied. Regarding task-related outcomes, less literature was available, and there was even greater variability in the motor regions targeted.

4.1.2. TBS to the prefrontal cortex

Outside of the motor cortex, various regions of the prefrontal cortex (PFC) are commonly investigated using TMS protocols. In this review we identified 12 studies targeting various prefrontal brain regions. Given the diversity of prefrontal regions targeted in the studies identified within this review, where possible, we attempted to synthesize these as focally as practicable.

The dorsolateral prefrontal cortex (DLPFC) is perhaps the most commonly targeted frontal region for TMS research. This is due to its critical involvement in numerous cognitive processes (Balconi, 2013; Brunoni & Vanderhasselt, 2014), its well established role as an efficacious clinical target for major depressive disorder (Perera et al., 2016), having been trialled as a potential target for numerous conditions and disorders with neurobiological underpinnings (Doruk Camsari, Kirkovski, & Croarkin, 2018), and ease of access. The effects of TBS to the DLPFC as measured by fMRI, however, are inconsistent. At rest, network wide increases (Gratton, Lee, Nomura, & D'Esposito, 2013; Gratton et al., 2014; Shang et al., 2019) and decreases (Iwabuchi et al., 2017; Mastropasqua et al., 2014; Shang et al., 2019) in rsFC and CBF have been noted in response to cTBS. While less research has investigated the neurobiological effects of iTBS to the DLPFC, again, at rest, both network wide increases (Alkhasli, Sakreida, Mottaghy, & Binkofski, 2019; Tang et al., 2019) and decreases (Tang et al., 2019) have been observed. While not targeting the DLPFC specifically, Howard et al. (2020) applied TBS to a ventral region of the right lateral PFC, with the intention of indirectly modulating

activity at the orbitofrontal cortex (OFC). At rest, cTBS to this region resulted in widespread reductions in global connectivity of the right central/lateral OFC network (Howard et al., 2020).

One identified study investigated the effects of cTBS to the left DLPFC on neurobiological responses to an offline task (switching protocol with a reward manipulation to investigate reward anticipation [motivation], and task [cognitive] or response [action] switching performance) (Van Holstein, Froböse, O'Shea, Aarts, & Cools, 2018). The authors reported no significant effect of stimulation on BOLD responses at the target, or distal brain regions using both a whole brain and small-volume approach (Van Holstein et al., 2018).

The IFG has also been a target of interest for the TBS research identified in this review. While some authors report no effects of iTBS (Anderkova et al., 2018) or cTBS (Anderkova et al., 2018; Wawrzyniak et al., 2017) to the IFG on rsFC, during task performance, the effects of both TBS protocols have been observed. Specifically, iTBS to the left IFG resulted in widespread increased network wide activity and connectivity at frontal, occipital and cerebellar regions during phases of encoding in older adults (Vidal-Piñeiro et al., 2014). During pseudo word repetition, task related BOLD activity was reduced at the target left IFG following cTBS, and increased at the contralateral homologue (Hartwigsen et al., 2013).

cTBS has also been shown to increase rsFC and CBF when applied to the anterior insula/frontal operculum (AI/FO) (Gratton et al., 2013, 2014), and decrease network wide BOLD response and connectivity during an attention shifting paradigm when applied to the frontal eye field (FEF) region (Heinen, Feredoes, Ruff, & Driver, 2017). As only single studies have targeted these regions, no interpretations can be made.

The breadth and variation of target regions across these studies renders it difficult to draw strong conclusions about the effects of TBS when applied to the prefrontal cortex. Unlike the pattern of results described regarding stimulation to the motor cortex, frontal stimulation yields widely inconsistent findings. There is evidence of both facilitatory and inhibitory effects of both protocols at rest, and during various tasks. This clear inconsistency in response to TBS effects, therefore, appears to go beyond task- or state-dependence when the prefrontal cortex is targeted. There are several factors that may contribute to this variability. For example, different approaches to targeting, specifically DLPFC, localisation (Rusjan et al., 2010) and coil position/angle (Tsuyama et al., 2009), can affect stimulation outcomes in this region. Other possible considerations regarding these findings are the role that the complexity of neural organisation of the frontal cortex has in producing these effects (Kolb et al., 2012), and/or the complexity of cognitive and behavioural demands associated with the tasks performed.

4.1.3. TBS to the parietal cortex

iTBS to the left inferior parietal lobe (IPL) (Abellana-Pérez et al., 2019) and superior parietal lobe (SPL) (Anderkova et al., 2018) has been demonstrated to increase network wide rsFC (Abellana-Pérez et al., 2019; Anderkova et al., 2018). Conversely, cTBS to these regions has not produced any significant effects on neurobiological function at rest (Anderkova et al., 2018), though Valchev et al. (2015) do report reduced rsFC following cTBS to the left somatosensory cortex. When using an alternative approach to determining the target site, by way of individually identifying areas of the left parietal cortex based on hippocampal-cortical network (HCN) connectivity, Hermiller, VanHaerents, Raij, and Voss (2019) reported no effects of either TBS protocol on the target HCN, nor the control dorsal attention network (DAN) or primary visual network. Theoretically, this approach should more focally target the network of interest.

The effects of cTBS to parietal regions of the brain on the neural basis of offline task performance has only been investigated by one study reviewed here. cTBS to the left somatosensory cortex appeared to have no neurobiological effects on action/observation task performance (Valchev, Gazzola, Avenanti, & Keysers, 2016).

Based on the available literature it appears that the neurobiological effects of parietal iTBS are more readily observable than the neurobiological effects in response to parietal cTBS. As only one study investigated task-related outcomes of TBS, no conclusions can be drawn in this regard.

4.1.4. TBS to the temporal cortex

Andoh and colleagues (2015; 2013) demonstrated that the right, compared to the left, auditory cortex, specifically anterolateral Heschl's gyrus (HGal), may be more susceptible to cTBS-induced neuromodulation when using both resting-state (Andoh et al., 2015) and task-related (Andoh & Zatorre, 2013) fMRI paradigms. In response to right hemisphere stimulation, reduced rsFC was identified in ipsilateral and contralateral auditory regions, and in bilateral motor (including motor, premotor), and primary (S1) and secondary somatosensory (S2) regions. cTBS to the left HGal resulted in reduced rsFC between the target region and contralateral homologue (Andoh et al., 2015). A different neurobiological response to cTBS, however, has been observed in a task-state (Andoh & Zatorre, 2013). During a melody discrimination task, cTBS to the right HGal increased BOLD responses at the contralateral homologue, as well as inferior and superior temporal cortices, and the middle frontal gyrus. rsFC between the left HGal, right pre- and post-central gyri, and the insula also increased. Stimulation to the left HGal elicited no such effects (Andoh & Zatorre, 2013).

Two further studies demonstrate that cTBS to the right posterior superior temporal sulcus (pSTS) induced reductions in BOLD response at the target and proximal temporal regions, as well as the amygdala during face emotion processing (Pitcher, Duchaine, & Walsh, 2014; Pitcher, Japee, Rauth, & Ungerleider, 2017).

Limited conclusions can be drawn regarding TBS to the temporal cortices, as only a small number of studies, and from the same groups, have been reviewed here. The patterns of network wide effects on rsFC following cTBS are consistent with what was observed in response to stimulation to the motor cortex (see Section 4.1.1) and the literature more broadly (Huang et al., 2005). Again, increased variability was observed when task-related outcomes were assessed. The mechanisms that drive the observed right hemisphere susceptibility to TBS-induced modulation, as reported by (Andoh et al., 2015; Andoh & Zatorre, 2013), remains unclear and cannot be answered by the available literature.

4.1.5. TBS to the occipital cortex

cTBS to the left occipital cortex has been shown to reduce rsFC between the primary, secondary, and third visual cortices (V1-V2, V1-V3, and V2-V3) bilaterally (Rahnev et al., 2013), and also to reduce BOLD response to the presentation of static faces at the right pSTS (Pitcher et al., 2014). Given that only two studies stimulated the occipital lobe using cTBS (and none with iTBS), both measuring different outcomes, it is difficult to draw any meaningful conclusions regarding the effects of TBS to this region. Further research investigating the neurobiological effects of TBS to the occipital cortex is needed.

4.1.6. TBS to the cerebellum

Cerebellar stimulation with TBS has demonstrated effects on non-motor cortical regions and networks, depending on the cerebellar region targeted. Specifically, cTBS to the right lateral cerebellum (Crus I) decreases rsFC between core default mode network (DMN) regions (Rastogi et al., 2017), whereas iTBS targeting an overlapping region (Crus I/II) increased rsFC within DMN regions (Halko et al., 2014). iTBS to the medial cerebellum, increased DAN rsFC (Halko et al., 2014). During a finger tapping paradigm, however, cerebellar cTBS was not shown to have effects on brain regions implicated in motor performance during such tasks in healthy populations (Odorfer, 2019).

A pertinent consideration regarding cerebellar stimulation, given the location of the cerebellum within the skull and its cellular organisation, is whether the magnetic field created by the TMS coil can adequately and focally stimulate the target site (van Dun, Bodranghien, Manto, & Mariën, 2017). Double-coned coils might be more effective for cerebellar stimulation (Fernandez, Major, Teo,

Byrne, & Enticott, 2018; Fernandez et al., 2020; van Dun et al., 2017), though none of the studies reviewed here used these coils. The studies which reported using standard figure-of-eight coils, however, all demonstrated effects of cerebellar TBS (Halko, Farzan, Eldaief, Schmahmann, & Pascual-Leone, 2014; Rastogi et al., 2017), while Odorfer (2019), who used a figure-of-eight coil with a slight bend for curved scalp locations (MagVenture, Inc., Georgia, USA) which may improve the depth of penetration to a target site, reported no effects of stimulation.

4.1.7. Consolidation of findings

A major pattern to emerge across the literature is that the response to TBS, as measured with fMRI, appears to be largely state- and task-dependent. At rest, the observed neurobiological response to both cTBS and iTBS is largely consistent across target regions, and is also akin to the electrophysiological outcomes described in Section 1: Introduction (see also: Huang et al., 2005). That is, cTBS appears to inhibit, or reduce, rsFC, while iTBS appears to facilitate, or increase, rsFC. A clear and important exception to this observed pattern of neurobiological responses is when stimulation has been applied to the prefrontal cortex, where considerable variability was observed across all neurobiological outcome measures, irrespective of state or task.

The introduction of external stimuli, however, by means of cognitive or behavioural tasks, greatly affects the neurobiological response to TBS, and vastly increases variability, across all target regions. Furthermore, offline behavioural performance on tasks relevant to the stimulated region/network was also observed to be a factor related to the neurobiological response to TBS (e.g. Annak et al., 2019; Hermiller et al., 2019), suggesting that the effects of TBS are also dependent on external conditions. Experimentally, it might be suggested that a combination of both resting-state and task-based measures would be most informative. Importantly, regarding studies showing no effects, while the majority of these studies implicated cTBS, this must be considered with extreme caution as it could likely be attributable to the fact that vastly more studies investigated the effects of cTBS, rather than iTBS.

4.2. Limitations and directions for future research

4.2.1. Regarding the observed outcomes

While tasks and/or state were identified as key factors influencing the response to TBS as measured using fMRI, future research needs to specifically characterise these effects. Generally, increased variability in the response to TBS was observed during the completion of offline tasks following stimulation. A greater understanding of the influence of particular types of tasks, or task demands, on neurobiological responses is needed in order to aid the selection of the most appropriate TBS

protocol for future studies. Regarding resting-state protocols, increased consistency in terms of participant actions during, and even immediately prior to this period, would be beneficial. For example, standardised protocols surrounding having eyes open/closed, focusing on a fixation cross versus a dark screen, or being instructed to “mind-wonder” might be implemented. In a similar vein, such parameters *during* stimulation also need to be more precisely controlled and clearly reported. Where possible, both resting-state and task-related data should be collected within the same study.

4.2.2. Participant factors

In the broad non-invasive brain stimulation (NIBS) literature, several individual/participant factors have been identified as being likely, at least to some degree, to affect the observed response to stimulation. Most commonly, age, biological sex, and genetic/epigenetic factors are known to affect the response to NIBS (Pellegrini, Zoghi, & Jaberzadeh, 2018; Ridding & Ziemann, 2010), though there are likely many unknown sources of variability also. Such relevant factors, however, were seldom investigated or appropriately controlled for in the reviewed literature. Indeed, only one study reviewed here systematically investigated the effects of age (Abellaneda-Pérez et al., 2019), and while Hu et al. (2017) reported data stratified by biological sex, statistical comparisons were not presented. Regarding age, it is also important to note that while most studies reported here include young-middle aged adults, two studies (Abellaneda-Pérez et al., 2019; Vidal-Piñeiro et al., 2014) report samples >65 years. These studies must be considered with caution as neurodevelopmental factors associated with this population might confound results. None of the reviewed literature investigated, or accounted for, genetic or epigenetic effects.

More broadly, despite studies often reporting group effects, and the response to TBS being described as having effects in a particular direction, there is evidence from the literature investigating the effects of TBS on MEPs, that demonstrates a great deal of individual variability to TBS response. That is, there are reports of some participants showing facilitatory effects, others inhibitory, and others classified as “non-responders” within the same study/protocol (Corp et al., 2020; Do et al., 2018; Goldsworthy, Müller-Dahlhaus, Ridding, & Ziemann, 2014; Hamada et al., 2013; Jannati et al., 2017; Vallence et al., 2015). Although it is not commonplace for studies to report or present individual data, of the studies reviewed here who have reported such data, similar patterns of individual participant variability in responses have been observed (Abellaneda-Pérez et al., 2019; Nettekoven et al., 2015; Rahnev et al., 2013).

The factors that contribute to this variability in response, of which those listed above are likely contributors, at least in part, needs further investigation. Of the studies reviewed here, there is

additional evidence pointing towards the underlying anatomical structures (Abellana-Pérez et al., 2019; Agnew et al., 2018) and behavioural effects (Annak et al., 2019; Hermiller et al., 2019) contributing to an individual's response to TBS, and these too, should be further investigated.

4.2.3. Methodological factors

4.2.3.1. Protocol

There were several sources of methodological variability across studies including: intensity of TBS delivery, target site variability, methods for determining the target site (i.e. neuronavigation [functional, visual, or coordinate based], using the international 10-20 coordinate system, functionally based on M1 response measured via EMG, or by measurement from another location [e.g. from the hot-spot]), outcome measures, modalities and analysis approaches, TMS and scanner equipment, and time to return participants to the scanner. Similar to the participant characteristics described above, such factors are likely to affect TBS outcomes, though of the studies reviewed here, again, these factors were seldom systematically investigated regarding fMRI outcomes.

Perhaps one of the most common sources of variability in the TBS literature more broadly is the stimulation threshold. In their seminal TBS paper, Huang et al. (2005) apply TBS at 80% of active motor threshold (AMT). Of the studies reviewed here, stimulation intensity ranged between 80-100% of AMT, 70-120% of resting motor threshold (RMT), or 30-40 % of maximum stimulator output (MSO). The effects of (sub- versus supra-threshold) stimulation intensity, however, were only investigated by one study (Alkhasli et al., 2019), and while their results are not readily generalisable to the broader TBS literature, as the vast majority of studies administer sub-threshold stimulation, the authors do provide evidence demonstrating altered effects at different threshold intensities.

Similarly, a number of the studies reviewed here modulated TBS dose, either by manipulating the protocol parameters, and therefore the number of pulses delivered (Agnew et al., 2018; Pitcher et al., 2014; Pitcher et al., 2017), or by delivering multiple runs of TBS to the same site 15 minutes apart (Ji et al., 2017; Nettekoven et al., 2014; Nettekoven et al., 2015), which may induce metaplastic-like effects (Karabanov et al., 2015). Such effects were only systematically investigated in one study (Nettekoven et al., 2014), in which support is provided for the notion of cumulative effects of iTBS. Specifically, while even a single run of iTBS (iTBS600) increased rsFC within a predefined motor network, effects were stronger following 3 runs of iTBS (iTBS1800) compared to just one, or two runs (iTBS1200). The authors also confirmed that the observed effects are indeed dose-related, and reflective of a cumulative effects of iTBS, rather than a delayed response to a single run of iTBS (Nettekoven et al., 2014). Thorough and systematic investigation of alternative stimulation intensities or doses on fMRI-based outcome measures has not been performed. Our own review

does not elucidate any clear, consistent, or differentiating effects on outcomes based on the threshold type/intensity used, and therefore, no speculations will be made in this regard. It is important to clarify, however, that we by no means imply that these are not important contributors to the observed variability in TBS outcomes. Rather, we emphasize that more thorough and systematic investigation of these factors is imperative.

While thorough and systematic investigation across studies is still lacking, consolidation of the reviewed literature might provide some insight regarding temporal effects of TBS on fMRI outcomes. The vast majority of studies reported returning participants to the scanner “immediately” following TBS, however many did not record, or failed to report, the actual time taken to commence the scan. For those who did report this information, time to return to the scanner ranged between ~2 and 30 minutes across studies for a single block of outcome recording. Some report a strengthening of the TBS effects over time (Gratton et al., 2013; Tang et al., 2019), while others report shifts in the direction of response (Heinen et al., 2017; Hu et al., 2017; Zhang et al., 2019). The duration of time that the effects of TBS are held might also be site/network dependant. Ji et al. (2017), for example, report that dynamic functional connectivity effects at the target site (left SMA) might outlast similar effects observed at other regions (specifically, the IFG). This lack of consistency in time to return to the scanner and/or record outcomes, as well as variability in methodologies, outcome measures, and analysis protocols, makes it difficult to elucidate any clear temporal effects or to draw reliable conclusions regarding the optimal time post TBS administration for outcomes to be observed. More systematic reporting and investigation of temporal effects on TBS response is needed.

4.2.3.2. Non-specific effects of TBS

While many of the limitations that characterise the NIBS literature were unable to be addressed by the present review, such as those described above, we were able to give some consideration to the methodological approaches taken when attempting to account for non-specific effects of TBS.

Several studies reviewed here targeted the vertex as an active (Agnew et al., 2018; Andoh et al., 2015; Andoh & Zatorre, 2013; Pitcher et al., 2017; Rahnev et al., 2013) or sham (Nettekoven et al., 2014; Nettekoven et al., 2015) control site, while others performed statistical comparisons between the target and a non-target network (Halko et al., 2014; Hermiller et al., 2019; Nettekoven et al., 2014; Rastogi et al., 2017; Wawrzyniak et al., 2017).

Regarding the former approach, the vertex is commonly considered an appropriate control site in TMS research, being referred to by some as an “empty quarter” unlikely to play a role in the target (often behavioural) mechanisms (Davis, Gold, Pascual-Leone, & Bracewell, 2013; Jung, Bungert,

Bowtell, & Jackson, 2016). While for the most part this seems like an appropriate comparison, Agnew et al. (2018) reported numerous and widespread changes in BOLD response following cTBS to the their target region, the right PMv, but also reported that this was no different to BOLD activity within the same region of interest (ROI) following active-control cTBS applied to the vertex, demonstrating non-specific effects of stimulation. Additionally, a caveat of active-control stimulation is, depending on the location of the target site, control stimulation to the vertex can feel and sound different to the target region (Davis et al., 2013), which might reduce its effectiveness as a comparable control. Furthermore, such stimulation might only be appropriate when testing certain outcome measures. Jung et al. (2016) investigated the effects of 1 Hz rTMS to the vertex, and despite reduced activity in DMN regions being observed, the authors support its use as an active control for task-related outcomes. As many DMN regions are also involved in other processes, however, careful consideration must be taken when selecting the vertex as an active control site. Active control stimulation should be targeting a region unrelated to, or less implicated in, the tasks and mechanisms of interest, e.g. targeting the opposite hemisphere (Andoh et al., 2015; Andoh & Zatorre, 2013), or a region implicated in a control, or unrelated, neural network.

As an alternative to stimulating an active control site, studies comparing effects at target and non-target networks provide evidence in support for the notion that the effects of TBS are not global (i.e., brain wide), but instead specifically act on the target network. This has been demonstrated by studies showing TBS induced modulation of cortical networks involved in cognition, but not cortical motor networks, following stimulation to “cognitive” cerebellar regions (Halko et al., 2014; Rastogi et al., 2017). Similarly, functional connectivity within the visual network, acting as a control network, was not shown to be influenced by iTBS over M1 or the vertex, rather, stimulation effects remained within the stimulated motor network (Nettekoven et al., 2014). In contrast, others who have taken this approach report no significant TBS effects to either the target or control networks (Hermiller et al., 2019; Wawrzyniak et al., 2017). Hermiller et al. (2019), however, reported a positive relationship between cTBS induced improvements in an offline behavioural memory task and increases in functional connectivity between the hippocampus and the target HCN, whereas a similar pattern of results was identified between the hippocampus and non-HCN regions for iTBS. No such relationships were identified for control networks, namely the DAN and the primary visual network (Hermiller et al., 2019). Together, these findings provide some support for the use of a non-target control network for statistical comparisons, however, caution must be taken. It is crucial to note that many studies reviewed here report widespread effects of TBS which might go beyond the intended/target network of interest. A recent review of resting-state fMRI outcomes of several rTMS

protocols, including TBS, also indicates that the effects are not network-specific (Beynel, Powers, & Appelbaum, 2020).

While there is limited research investigating the effects of active control stimulation versus comparisons to a non-target network on MRI outcomes, based on the literature reviewed here, it appears that either comparison approach might only be appropriate in certain situations, selection of which requires careful consideration. Task- and state- based factors related to outcome measures are likely to affect the networks and regions modulated by TBS, and therefore must be considered when selecting the most appropriate comparison.

4.3. Broad statement on directions for future research

The limited research available regarding the variability in participant and methodological factors identified in this review, as well as other likely factors not identified here, make it difficult to draw strong or clear conclusions about the effects of these factors on fMRI outcomes post-TBS. More thorough and systematic research in this domain is clearly imperative for the field.

Age and biological sex are factors that could be accounted for in future research with relative ease, and cost effectively, and hence should be considered more consistently. Where possible, genetic underpinnings should also be considered. Also, regarding individual variability, future research should take a systematic approach to understanding the role of structural neurobiology on TBS related outcomes, by including, where possible, structural imaging (e.g. diffusion weighted imaging) outcomes. Throughout this review we also emphasize the importance of task and state on TBS outcomes. Clearer and more detailed reporting of the conditions surrounding recording of outcome measures is of utmost importance, however, so too are such conditions immediately prior to, and during, stimulation.

Methodologically, while we concede that more challenges are likely to arise and some inconsistencies would be more difficult to overcome, such as variability in apparatus and equipment type and availability, there remains some room for improved consistency across studies. Despite this not being identified by the present review as being a clear contributor to the variability in outcomes, as mentioned in Section 4.1.2 for example, variability in target localisation is likely to affect outcomes. While stereotaxic neuronavigation is considered the “gold-standard” method, variability remains. Future research needs to work towards understanding the effects of various approaches for target identification, depending on the stimulation location, network of interest, and outcomes task/state.

One limitation of this present review, by nature of the available research, is that given the inconsistency across study methodologies and outcomes, a meta-analytic approach was not feasible. By developing protocols with as much consistency as possible, we as a field have the opportunity to overcome another large hurdle frequently observed in the literature, i.e. small sample sizes. Small sample size is often considered unavoidable in neuroimaging research due to high costs associated with conducting such research, as well as access to participants and time constraints. Consequently, insufficient power reduces the likelihood of detecting true effects and impacts upon reproducibility (Button et al., 2013). Growing acceptance of this problem in the field of neuroimaging has led towards numerous data sharing initiatives, now widely accessed across many areas. Similar initiatives have already been implemented regarding electrophysiological outcomes of TBS (Corp et al., 2020), and similar practices regarding neuroimaging outcomes in response to TBS, and other NIBS protocols, would be of immense benefit to the field. For such an initiative to be fruitful, however, greater consistency across protocol is imperative.

4.4. Summary and conclusion

The present review has summarised and synthesized the literature investigating fMRI-based outcomes of TBS to the cortex of healthy human adults. Although outcomes are often variable, some consistencies emerged when examining resting-state outcomes of TBS applied at motor, parietal, temporal, occipital and cerebellar regions. Specifically, cTBS appeared to induce inhibitory effects, most consistently by way of reduced rsFC, while iTBS produced the opposite (i.e., facilitatory) effect, increasing rsFC. Results of TBS delivered to the prefrontal cortex were more variable. This was apparent irrespective of task, state, or specific location. Factors contributing to this increased variability observed in response to frontal stimulation, however, are unclear.

There are numerous methodological inconsistencies across studies, as well as individual factors known to affect the response to NIBS, which must be addressed. Future research should aim to thoroughly and systematically investigate the role of individual factors such as age, biological sex, anatomical structure and genetic/epigenetic factors on TBS outcomes. Methodologically, more consistency is needed across studies in order to facilitate greater integration of findings and data sharing initiatives. Where possible, resting-state, and task-based outcomes should be measured, as well as both structural and functional imaging protocols. Care should be taken when determining appropriate comparisons and control targets. Such efforts will be of great benefit to the enhancement of the field, improving outcomes for experimental research studies, and therefore translation into clinical programs.

In conclusion, factors such as task and state cannot be overlooked when developing future studies and should be considered when determining the most appropriate TBS protocol. More research investigating the effects of known, as well as identifying currently unknown, sources of variability regarding the response to TBS is critical.

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