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Review

The study of noninvasive brain stimulation using molecular brain imaging: A systematic review

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ABSTRACT

Electromagnetic noninvasive brain stimulation (NIBS) techniques, such as transcranial magnetic stimulation and transcranial electrical stimulation, are widely used in research and represent emerging clinical treatment options for many brain disorders. The brain-wide neurobiological effects of electromagnetic NIBS, however, are not yet fully characterized. The combination of NIBS with molecular brain imaging is a powerful tool for the investigation of these effects. Here, we conducted a systematic review of all published studies investigating the effects of all forms of electromagnetic NIBS using molecular imaging (positron emission tomography, single photon emission computed tomography). A meta-analysis was also conducted when sufficient studies employed similar methodologies. A total of 239 articles were identified, of which 71 were included in the review. Information was extracted about the study design, NIBS parameters, imaging parameters, and observed local and remote effects caused by the stimulation. Regional cerebral blood flow and glucose metabolism were the most common outcome measures, followed by dopamine neurotransmission. While the vast majority of studies obtained remote effects of stimulation in interconnected regions, approximately half of the studies showed local effects at the stimulation site. Our meta-analysis on motor cortex stimulation also showed consistent remote effects. The literature review demonstrates that although the local effects of NIBS as captured by molecular imaging are sometimes modest, there are robust remote changes in brain activity and neurotransmitter function. Finally, we discuss the potential pitfalls and methodological issues and identify gaps in the current knowledge that could be addressed using these techniques.

1. Introduction

Noninvasive brain stimulation (NIBS) is a widely used research tool with rapidly expanding clinical applications (Lefaucheur et al., 2014). The most commonly used methods rely on electromagnetic stimulation and include transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (TES) techniques. These techniques are powerful brain research tools that can be used to explore causal relationships between brain function and behavior (Hallett, 2007; Rossini et al., 2015). The clinical applicability of NIBS relies on its capability to cause long-lasting neuromodulatory effects, i.e. facilitation or inhibition, that outlast the duration of the stimulation (Eldaief et al., 2013).

TMS has been used to study brain functions for over three decades (Barker et al., 1985). TMS interferes with neural function by creating a rapidly changing magnetic field, which penetrates the skull and induces electric currents in the brain capable of neural depolarization. The TMS-induced electric field is maximal in the brain directly beneath the coil when using conventional circular and figure-of-eight coils (Hallett, 2007). Although less focal, newer coil designs, such as the H-coil developed for deep TMS, generate a diffuse electric field that can reach deeper brain

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regions (Deng et al., 2014, 2013; Gomez et al., 2018) and are thought to cause more widespread effects extending to subcortical structures (Zangen et al., 2005). When applied repetitively with specific stimulation patterns (repetitive transcranial magnetic stimulation, rTMS), TMS can be used to either facilitate or inhibit neuronal firing thresholds extending beyond the duration of the stimulation session, which can be verified from changes in muscle evoked potentials in the motor system (Hallett, 2007; Pascual-Leone et al., 1994; Rossini et al., 2015; Wischnewski and Schutter, 2015). Clinically, several rTMS devices and protocols have been cleared by the US Food and Drug Administration (FDA) for the treatment of medication-resistant depression, migraine and obsessive-compulsive disorder (Lefaucheur et al., 2014; Voelker, 2018). The effects of rTMS propagate from the directly targeted cortical region to the connected nodes along neural networks (Eldaief et al., 2013; Shafi et al., 2012). Such distributed effects are considered crucial for the clinical efficacy of rTMS (Fox et al., 2014).

TES techniques change brain function by inducing a weak electric current between two electrode patches placed on the scalp (Nitsche and Paulus, 2000; Paulus, 2003). TES techniques include transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS). The currents created by these techniques are too weak to directly trigger action potentials in cortical neurons, but they cause neuromodulatory effects by changing the membrane potentials by either lowering or increasing the firing thresholds of the neurons (Bikson et al., 2016; Nitsche and Paulus, 2011; Stagg and Nitsche, 2011). Although there are no widely accepted clinical applications yet, tDCS has shown potential for the treatment of several different brain disorders (Moffa et al., 2018). For example, tDCS has been shown to be effective in the treatment of depression when compared to sham stimulation (Brunoni et al., 2017b).

Despite the wide use and clinical potential, the neurobiological mechanisms of action of NIBS methods at the whole-brain level are still relatively poorly known. A vast majority of what we know about these mechanisms is derived from neurophysiological studies focusing on the motor system. The combination of NIBS with neuroimaging is a powerful tool to investigate the effects of stimulation (Ko et al., 2013). Molecular imaging methods, such as positron emission tomography (PET) and single photon emission tomography (SPECT), offer a unique possibility to investigate the neurobiological effects of NIBS at the molecular level with high spatial resolution. PET and SPECT imaging are based on using tracers labelled with short-lived radioisotopes such as ^{15}O, ^{18}F, ^{11}C (PET), or ^{123}I (SPECT) and measuring their kinetics in the brain using a PET or SPECT scanner. PET and SPECT scanners measure the radiation, reflecting the concentration of the tracer in the tissue as a function of time, which can then be mathematically modeled to quantify biologically meaningful properties of the tissue (Zimmer and Luxen, 2012). Commonly used measures include blood flow with ^{15}O-labelled water ($[^{15}O]H_2O$), brain metabolism with ^{18}F-labelled glucose analog ($[^{18}F]$FDG) and dopamine D2 receptor availability with $[^{11}C]$raclopride (Zimmer and Luxen, 2012). Moreover, molecular imaging allows the measurement of specific neurotransmitter release through the use of radiotracers that are sensitive to nanomolar-level changes in the synaptic concentration of endogenous neurotransmitters, such as $[^{11}C]$raclopride and $[^{11}C]$FLB 457 for dopamine and $[^{11}C]$carfentanil for endogenous opioids.

To this date, no systematic review or meta-analysis have been conducted on the combined use of NIBS and molecular imaging to study neural mechanisms in both healthy and clinical populations. Here we systematically review all peer-reviewed published studies investigating the mechanism of NIBS using PET or SPECT in humans. We intend to provide a comprehensive reference material of published studies in this field, discuss methodological issues and identify gaps in the current knowledge.

2. Material and methods

2.1. Literature search

The literature search was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2016). The literature search was conducted in PubMed using the keywords described in Table 1. Original research articles published in English from inception to March 1, 2020, investigating the effects of NIBS using PET or SPECT imaging in healthy volunteers or clinical conditions, were included in this study. The search returned 239 articles, of which 72 were finally included in our study.

Table 1
Keywords for PubMed search (last updated March 1st, 2020).

Category	Keywords	Records identified
rTMS-PET	"repetitive transcranial magnetic stimulation" OR "rTMS" OR "theta burst stimulation" OR "TBS" AND "positron emission tomography" OR "PET"	147 articles
rTMS-SPECT	"repetitive transcranial magnetic stimulation" OR "rTMS" OR "theta burst stimulation" OR "TBS" AND "single photon emission computed tomography" OR "SPECT"	49 articles
TES-PET	"transcranial direct current stimulation" OR "tDCS" OR "transcranial alternating current stimulation" OR "transcranial random noise stimulation" AND "positron emission tomography" OR "PET"	34 articles
TES-SPECT	"transcranial direct current stimulation" OR "tDCS" OR "transcranial alternating current stimulation" OR "transcranial random noise stimulation" AND "single photon emission computed tomography" OR "SPECT"	9 articles

The research article selection is described in the flowchart (Fig. 1). Papers were excluded from the study after reading the titles and abstracts if 1) the study was not relevant to the topic of the review; 2) the research was conducted in animals; 3) the study was not an original research article; 4) PET or SPECT was conducted *only prior* to the application of NIBS (e.g., to select a target region); 5) the paper included only a single case; 6) only single pulse TMS was used; 7) the study reported only qualitative observations (i.e., no statistical analysis); and 8) the study did not report the effects of NIBS alone because the combination of NIBS with a task or clinical intervention can result in very different responses in the brain compared to NIBS alone. Following this, duplicates were excluded, and the same exclusion criteria were used while reading full texts.

From the included studies, we extracted information about the study design (online, offline, mixed), NIBS parameters (target, control condition, rTMS frequency/TES intensity, treatment duration for clinical studies), imaging parameters (tracer, analysis method), and observed local and remote effects caused by the stimulation, as described by the authors of the original study. A full description of the methodology, including additional information on NIBS and imaging parameters, and detailed results in each study are provided in the supplementary materials.

2.2. Illustration of the rTMS stimulation effects

To illustrate the effects of rTMS, we identified the studies that performed whole-brain analyses and reported peak activation coordinates in Talairach or MNI space. Coordinates reported in Talairach space were converted to MNI coordinates using a previously published transformation algorithm (Lacadie et al., 2008). The peak MNI coordinates for each stimulation site and subject population (e.g., healthy volunteers or a patient group) were combined. ALE meta-analyses were performed to identify brain regions consistently activated (increase in blood flow or glucose metabolism) by rTMS in studies using the same rTMS target and subject population.

As the studies were highly heterogeneous (see Table 2), three or more independent studies were identified only for 1) studies investigating left DLPFC high-frequency (HF)-rTMS in healthy volunteers (3 studies, 38 subjects) and in major depressive disorder (3 studies, 53 subjects), and 2) studies investigating M1 low-frequency (LF) rTMS in healthy volunteers

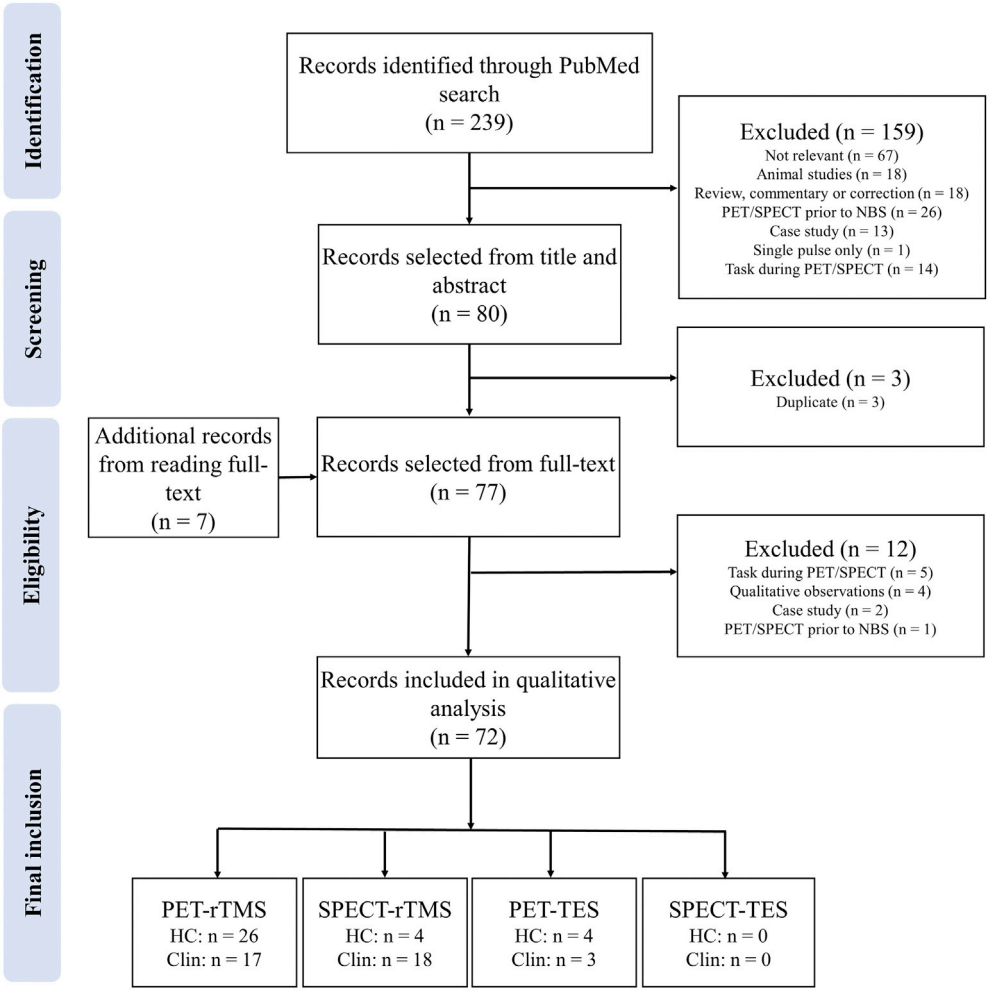

Fig. 1. Systematic review flow diagram of the literature search. Legend: Description of the literature search and study selection process.

(8 studies, 58 subjects). Left DLPFC stimulation effects were analyzed in healthy volunteers and in patients both separately and by combining the groups. ALE meta-analyses were conducted using GingerALE software version 2.3.6 (http://brainmap.org/ale/) (Eickhoff et al., 2009). All analyses were conducted across the whole brain using cluster-level $p = 0.001$ with 1000 permutations and false discovery rate correction (FDR pID) $p < 0.05$.

3. Results

A total of 72 studies were included in this review. As shown in Fig. 1, 64 studies used rTMS: 30 in healthy volunteers and 35 in clinical populations. Only 7 studies used TES (all tDCS): 4 in healthy volunteers and 3 in clinical populations. See Table 2 for a summary of the studies included in the present analyses.

Regional cerebral blood flow (rCBF, n = 34) and glucose metabolism (rCMRglc, n = 22) were the most common outcome measures with rTMS, followed by dopamine neurotransmission (n = 15) and other neurotransmitter systems (n = 3). The large majority of rTMS studies used conventional LF- or HF-rTMS, while only three studies used more recently developed theta burst stimulation (TBS). The dorsolateral prefrontal cortex (DLPFC, n = 29) and primary sensorimotor cortex (M1/S1, n = 17) were by far the most studied cortical stimulation targets with rTMS, with only a few studies targeting other brain regions, such as the cerebellum, insula, and premotor cortex (n < 5 for each of the targets combining all imaging modalities). All seven TES studies used tDCS with a mix of bilateral and unilateral montages, targeting the DLPFC or the M1. The most studied clinical condition overall was major depressive disorder (MDD, n = 20), followed by Parkinson's disease (n = 6).

3.1. rTMS in healthy volunteers

We identified 26 PET and 4 SPECT studies investigating the effects of rTMS in healthy volunteers (Table 3, full details in Table S1). One of the studies used more than one tracer and is listed twice in Table 3.rCBF was investigated in 16 studies using either [^{15}O]H_2O PET or [^{99m}Tc]ECD SPECT, glucose metabolism in 7 studies using [^{18}F]FDG PET, dopamine neurotransmission in 6 studies, and serotonin and opioid neurotransmission in one study each.

3.1.1. Blood flow

The motor system. In a pioneering proof-of-principle study, Fox et al. (1997) stimulated the left M1 with LF-rTMS in 3 healthy volunteers and showed an increase in blood flow at the stimulation site. Subsequently, a series of studies showed dose-dependent blood flow changes in local and remote brain regions as a function of the number of pulse trains when stimulating either the left frontal eye field (Paus et al., 1997) or the left M1 (Paus et al., 1998) with HF-rTMS. Similar linear changes were further demonstrated by showing that increasing the frequency of left M1 stimulation from 1 to 5 Hz led to a greater increase in local blood flow (Siebner et al., 2001b). In addition, increasing the stimulation intensity of LF-rTMS to the left M1 increased changes in blood flow both locally and in connected brain regions, such as the basal ganglia, cerebellum, insula and temporal cortex (Speer et al., 2003a). A similar pattern of local

Table 2
Experimental details of the included studies

Population	**Tracer**											
	rCBF			rCMRglc	Dopamine						Serotonin	u-opioid
	^{15}O-H_2O	Tc-99m-ECD	^{99m}Tc-HMPAO	^{18}FDG	[^{11}C]raclopride	[^{11}C]FLB 457	PHNO	L-[β-^{11}C] DOPA	^{123}I-FP-CIT	[^{123}I] IBZM	^{11}C-αMtrp	[^{11}C] carfentanil
Healthy	12	4	-	7	5	1	2	-	-	-	1	2
Clinical	2	11	5	14	4	-	-	1	1	1	-	-
Total	**14**	**15**	**5**	**21**	**9**	**1**	**2**	**1**	**1**	**1**	**1**	**2**
Grand total	**34**			**21**	**15**						**1**	**2**

Population	**rTMS protocols**			
	HF	LF	iTBS	cTBS
Healthy	12	22	-	-
Clinical	22	17	1	2
Total	**34**	**39**	**1**	**2**

Population	**rTMS Targets**											
	DLPFC	MDLPFC	MePFC/OFC	PFC/ frontal	Cerebellum	Insula	M1/ SM1	S1	PMC	FEF/ occipital	Temporal/ sLT	Temporo-parietal
Healthy	7	3	1	1	1	1	13	1	2	1	1	1
Clinical	22	-	1	3	1	-	4	1	-	1	1	3
Total	**29**	**3**	**2**	**4**	**2**	**1**	**17**	**1**	**2**	**2**	**2**	**4**

Population	**tDCS protocol**		**tDCS target**	
	Bilateral	Unilateral	DLPFC	M1
Healthy	3	1	2	1
Clinical	2	1	2	1
Total	**5**	**2**	**4**	**2**

Clinical population	MDD	SCZ	OCD	Congenital blindness	Fibromyalgia	Tinnitus	PD	Alcohol use disorder	MCI/Alzheimer's disease	Pain
	20	2	1	1	1	3	6	1	2	1
Total	38									

Legend: ^{11}C-αMtrp: [^{11}C]-alpha-methyl-tryptophan; [^{11}C]FLB 457: 11Ccyclopropyl-FLB; DLPFC: dorsolateral prefrontal cortex; [^{123}I] IBZM: [123I] iodoben-zamide; ^{123}I-FP-CIT: 123I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodo-phenyl) nortropane; ^{18}FDG; 18-fluorodeoxyglucose; FEF: frontal eye field; HF: high-frequency; LF: low-frequency; L-[β-^{11}C]DOPA: L-3,4-dihydroxyphenylalanine (L-DOPA) labelled with 11C; M1: primary motor cortex; MCI: mild cognitive impairment; MDD: major depressive disorder; MDLPFC: medial-lateral prefrontal cortex; MePFC: medial prefrontal cortex; OCD: obsessive-compulsive disorder; OFC: orbitofrontal cortex; ^{15}O-H_2O: ^{15}O-labelled water; PHNO-PET: [11c}-(+)-propyl-hexahydro-naphto-oxazin; PD: Parkinson's disease; PFC: prefrontal cortex; PMC: premotor cortex; SCZ: schizophrenia; sLT: superior lateral temporal cortex; SM1: primary sensorimotor cortex; ^{99m}-Tc HMPAO: 99m-Tc hexamethylpropylene amine oxime; Tc-99m-ECD: tech- netium-99 bicisate.
Note: some studies are represented more than once in the table as some included more than one tracer or target.

Table 3
rTMS combined with PET/SPECT in healthy volunteers.

Authors	*N*	Study design	rTMS parameters			Imaging parameters			Effects	
			Target(s)	Control(s)	Freq.	Method	Tracer	Imaging Analysis	Local	Remote
rCBF										
Fox et al. (1997)	3	Mixed	L M1	Baseline	1Hz	PET	$[^{15}O]H_2O$	Voxelwise	↑	NA
Paus et al. (1997)	6	Online	L FEF	Variation of pulse trains	10Hz	PET	$[^{15}O]H_2O$	Voxelwise	↑	↑ superior parietal, L cuneus, R SEF
Paus et al. (1998)	6	Online	L SM1	Variation of pulse trains	10Hz	PET	$[^{15}O]H_2O$	Voxelwise	↓	↓ R M1, premotor and SMA, medial parietal
George et al. (1999)	8	Mixed	L DLPFC	Baseline	10Hz	SPECT	$[^{99}mTc]$ ECD	Voxelwise	↔	Widespread ↑ and ↓
					20Hz				↔	Widespread ↑ and ↓
Paus et al. (2000)	8	Offline	L MDLPFC	Control group no rTMS	1Hz	PET	$[^{15}O]H_2O$	Voxelwise	↑	↑ ACC, posterior cingulate, frontopolar ↓ inferior parietal
Okabe et al. (2003)	5	Online (injection)	L M1	Sham rTMS	1Hz	SPECT	$[^{99}mTc]$ ECD	Voxelwise	↓	↑ R cerebellum↓ R cortical motor regions, parietal ctx
Siebner et al. (2001b)	6	Online	L SM1	Sham rTMS Variation of frequency	1–5 Hz	PET	$[^{15}O]H_2O$	Voxelwise	↑	↔
Speer et al. (2003a)	10	Mixed	L M1	Baseline Variation of intensity	1Hz	PET	$[^{15}O]H_2O$	Voxelwise	↑	↑ sub-cortical (putamen, red nucleus, cerebellum), insula, primary auditory ctx ↓ frontal, occipital and cingulate
Speer et al. (2003b)	10	Mixed	L PFC	Baseline	1Hz	PET	$[^{15}O]H_2O$	Voxelwise	↓	↑ R A1, insula and S1; L ACC and cerebellum
				Variation of intensity						↓ R PFC and occipital ctx, L temporal, parrahippocampus
Barrett at al. 2004	8	Online	L MDLPFC	Baseline	1Hz	PET	$[^{15}O]H_2O$	Seed-voxel PLS	↑	NA
					10Hz				↔	NA
Ohnishi et al. (2004)	7	Mixed	R DLPFC	Sham rTMS pre and post	1Hz	PET	$[^{15}O]H_2O$	Voxelwise	↔	↑ *during*: R ACC, medial PFC;↑ *post:* R medial and L ventral PFC, L ventral striatum
Takano et al. (2004)	6	Mixed	L M1	Post-rTMS	5Hz	PET	$[^{15}O]H_2O$	Voxelwise	↑ (early) ↓ (late)	↑ temporal ctx and insula ↓ medial frontal, occipital, cuneus
Knoch et al. (2006)	16	Offline	L DLPFC	Baseline	1Hz	PET	$[^{15}O]H_2O$	Voxelwise	↑	↑ frontal, cingulate and caudate regions, R cortical motor regions ↓ parrahippocampus, L OFC
			R DLPFC		1Hz				↔	↑ cortical motor regions, R cingulate ↓ L posterior cingulate
			L DLPFC		10Hz				↑	↑ R inferior frontal ↓ L parrahippocampus, R medial frontal
			R DLPFC		10Hz				↑	↑ L uncus, R caudate ↓ medial and superior frontal regions
Urushihara at al. 2006	9	Offline	L PMC	Baseline	0.2Hz	SPECT	$[^{99}mTc]$ ECD	Voxelwise	↑	↑ L middle frontal, R limbic lobe and cingulate gyrus
Eisenegger et al. (2008)	12	Offline	R DLPFC	Baseline	1Hz	PET	$[^{15}O]H_2O$	Voxelwise	↔	↑ frontal (L DLPFC, R VLPFC and inferior frontal)
Hosono et al. (2008)	7	Offline	L PMC	Baseline	0.2Hz	SPECT	$[^{99}mTc]$ ECD	Voxelwise	↔	↑ L thalamus, frontal gyrus
					1Hz					↑ L occipital, R parietal
rCMRglc										
Siebner et al. (1998)	6	Offline	L SM1	Baseline	2Hz	PET	$[^{18}F]FDG$	Voxelwise VOI	↑	↑ bilateral SMA
Siebner et al. (1999)	12	Offline	L SM1	Baseline	2Hz	PET	$[^{18}F]FDG$	Voxelwise VOI	↑	↑ bilateral A1
Siebner et al. (2000)	8	Offline	L M1	Baseline	5Hz	PET	$[^{18}F]FDG$	ROI/VOI	↑	↑ R M1, SMA ↔ A1
Siebner et al. (2001a)	12	Online (injection)	L SM1	Baseline	2Hz	PET	$[^{18}F]FDG$	ROI/VOI	↑	↑ R M1, ACC, mesial frontal, SMA
Kimbrell et al. (2002)	14	Online (injection)	L DLPFC	Baseline	1Hz	PET	$[^{18}F]FDG$	Voxelwise	↔	↑ ACC, subcortical regions (basal ganglia), cerebellum, R superior frontal ↓ occipital ctx, L cuneus, R insula, L parietal
				Sham rTMS					↔	↑ cuneus ↓ L superior frontal
Cho et al. (2012)	12	Offline	L lateral cerebellum	Sham rTMS	1Hz	PET	$[^{18}F]FDG$	Voxelwise	↓	↑ L middle/inferior frontal, temporal ctx, L pons, L dentate nucleus ↓ R SMA, R PPC, R tonsil, L frontal (OFC, medial) and ACC, L semilunar lobule
Lee et al. (2013)	12	Offline	R temporal	Baseline Sham rTMS	1Hz	PET	$[^{18}F]FDG$	Voxelwise	↓	↑ R temporal, R frontal and ACC, motor cortical regions

(*continued on next page*)

Table 3 (*continued*)

Authors	*N*	Study design	rTMS parameters			Imaging parameters			Effects	
			Target(s)	Control(s)	Freq.	Method	Tracer	Imaging Analysis	Local	Remote
Dopamine										
Strafella et al. (2001)	8	Offline	L MDLPFC	Control region	10Hz	PET	[^{11}C] raclopride	Voxelwise ROI	NA	↓ L dorsal caudate
Strafella et al. (2003)	6	Offline	L M1	Control region	1Hz	PET	[^{11}C] raclopride	Voxelwise ROI	NA	↓ L putamen
Cho and Strafella (2009)	7	Offline	L DLPFC	Ipsilateral region	10Hz	PET	[^{11}C]FLB 457	ROI	NA	↓ L subgenual and pregenual ACC, L medial OFC
			R DLPFC							↔
Cho et al. (2015)	11	Offline	MePFC	Control region	10Hz	PET	[^{11}C]-(+)-PHNO	ROI	NA	↓ dorsal putamen, dorsal/ventral globus pallidus
Lamusuo et al. (2017)	10	Offline	R M1/S1	Sham rTMS	10Hz	PET	[^{11}C] raclopride	ROI	NA	↔
Malik et al. (2017)	8	Offline	Insula	Sham rTMS	1Hz	PET	[^{11}C]-(+)-PHNO	ROI	NA	↔
					10Hz					↑ sensorimotor and associative striatum, substantia nigra
Serotonin										
Sibon et al. (2007)	10	Offline	L DLPFC	Control region	10Hz	PET	[^{11}C]-αMtrp	Voxelwise	↔	↑ R cingulate and cuneus ↓ L parahyppocampus, R insula
u-opioid										
Lamusuo et al. (2017)	10	Offline	R MS1	Sham rTMS	10Hz	PET	[^{11}C] carfentanil	Voxelwise	↔	↓ R ACC, MPFC, OFC and ventral striatum; L insula, DLPFC, precentral ctx and superior temporal

Legend: A1: primary auditory cortex; ACC: anterior cingulate cortex; AMT: active motor threshold; [^{11}C]αMtrp: [^{11}C]-alpha-methyl-tryptophan; [^{11}C]FLB 457; [^{11}C]-cyclopropyl-FLB; ctx: cortex; DLPFC: dorsolateral prefrontal cortex; [^{18}F]FDG; [^{18}F]-fluorodeoxyglucose; FEF: frontal eye field; L: left; M1: primary motor cortex; MPFC: medial prefrontal cortex; neuronav.: neuronavigation; OFC: orbitofrontal cortex; [^{15}O]H_2O: [^{15}O]-labelled water; [^{11}C]-(+)-PHNO: [^{11}C]-(+)-propyl-hexahydro-naphto-oxazin; PFC: prefrontal cortex; PLS: partial-least squares; PMC: premotor cortex; PPC: posterior parietal cortex; R: right; RMT: resting motor threshold; ROI: region of interest; SM1: primary sensorimotor cortex; SMA: supplementary motor area; SEF: supplemental eye field; [^{99}mTc]ECD: [^{99}mTc]-ethyl cysteinate dimer; VLPFC: ventrolateral prefrontal cortex; VMPFC: ventromedial prefrontal cortex; VOI: voxel of interest.
Note: More details in **Supplementary Table 3**. Voxelwise analyses conducted across the whole brain unless stated otherwise.

and distal changes was observed *during* LF-rTMS to the left M1 (Okabe et al., 2003). However, the time course of blood flow changes does not seem to be linear, as left M1 LF-rTMS was associated with early increases but late decreases in blood flow in the stimulated regions and connected brain regions (Takano et al., 2004). The premotor cortex (PMC) was also targeted with LF-rTMS in a series of SPECT studies that revealed changes in motor frontal networks (Hosono et al., 2008; Urushihara et al., 2006).

Prefrontal cortex (PFC). As with M1 rTMS, targeting the left DLPFC with LF-rTMS wasshown to be associated with remote effects outside the stimulated brain regions (George et al., 1999; Knoch et al., 2006; Speer et al., 2003b) and greater changes in blood flow with increasing stimulation intensity (Speer et al., 2003b). However, the activated remote brain regions vary from study to study, with studies showing effects that are widespread (George et al., 1999; Speer et al., 2003b) or restricted to fronto-cingulate networks (Knoch et al., 2006). In contrast to M1 stimulation, only some studies have reported changes in local blood flow in response to DLPFC stimulation (Knoch et al., 2006), while most did not observe any change (Eisenegger et al., 2008; George et al., 1999). In an elegant study by Knoch et al. (2006), the authors investigated differences in left/right DLPFC and low-/high-frequency rTMS. The study demonstrated a clear effect of laterality, as the left versus right dorsolateral PFC activated different networks, in support of prefrontal hemispheric asymmetry. Notably, both LF left and HF right stimulation induced the most important changes in the fronto-limbic network. Finally, two studies investigating left medial-dorsolateral prefrontal cortex (MDLPFC) stimulation reported both local and remote changes in regional blood flow (Barrett et al., 2004; Paus et al., 2000).

3.1.2. Glucose metabolism

Interestingly, all studies that assessed changes in glucose metabolism in healthy volunteers employed a LF-rTMS paradigm. In a large series of early studies, Siebner and colleagues investigated the effect of LF-rTMS on the left sensorimotor cortex (Siebner et al., 2001a, 2000, 1999, 1998). A local increase in glucose uptake was consistently reported, as well as increases in glucose metabolism in other cortical motor regions, such as the SMA and right sensorimotor cortex. Consistent with most results from blood flow studies, the only study that targeted the left DLPFC with LF-rTMS did not report local changes, but widespread remote changes in fronto-limbic networks (Kimbrell et al., 2002). The unique study targeting the cerebellum reported a decrease in local glucose metabolism and widespread changes in frontal, parietal and temporal brain regions following LF-rTMS (Cho et al. (2012). Similarly, the only study targeting the right temporal cortex using LF-rTMS showed decreased glucose metabolism locally but increased metabolism in the contralateral temporal and frontal brain regions (Lee et al., 2013).

3.1.3. Dopamine

The investigation of rTMS-induced modulations of the dopaminergic system mostly showed ipsilateral changes in the basal ganglia. Two studies targeted the motor cortex, three studies examined different parts of the prefrontal cortex (i.e., dorsolateral, medial and medial-dorsolateral) and one study examined the insula. What is particular to dopamine studies is not only the wide range of regions that were targeted but also the different tracers that were employed in healthy controls, making it more difficult to draw conclusions or to use the data for our ALE analysis. As such, the results from the studies will be discussed in relation to the specific tracer that was employed.

[^{11}C]Raclopride is a D2/D3 dopamine receptor antagonist that competes for binding sites with extracellular dopamine in the striatum (Laruelle, 2000). In a seminal paper, Strafella et al. (2001) were the first to show that rTMS could induce neurotransmitter release in the living human brain. In this study, left DLPFC 10 Hz rTMS resulted in an ipsilateral decrease in [^{11}C]raclopride binding potential in the dorsal caudate nucleus, indicative of dopamine release. In a subsequent study

Table 4
rTMS combined with PET/SPECT in clinical populations.

Authors	*N*	Study design	rTMS parameters				Imaging parameters			Effects	
			Target(s)	Control(s)	Freq.	Treatment duration	Method	Tracer	Imaging Analysis	Local	Remote
ALCOHOL USE DISORDER											
Dopamine											
Addolorato et al. (2017)	11	Pre/post treatment	Bilat. DLPFC	Baseline Sham rTMS	10Hz	12 sessions 4 weeks	SPECT	[^{123}I]FP-CIT	ROI	NA	↓ R caudate (statistical trend)
CONGENITAL BLINDNESS											
rCBF											
Wittenberg et al. (2004)	20	Pre/post 1 session	L S1	Sham Early vs. late blindness	10Hz	1 session	PET	[^{15}O]H_2O	Voxelwise ROI	↔	↑ (early blind) frontal, parietal, occipital, anterior insula ↑ (late blind) R temporal, L anterior cingulate, cerebellum, L basal ganglia
FIBROMYALGIA											
rCMRglc											
Boyer et al. (2014)	38	Pre/post treatment	L M1	Baseline Sham rTMS	10Hz	14 sessions 10 weeks	PET	[^{18}F]FDG	Voxelwise	↔	↑ R medial temporal
MAJOR DEPRESSIVE DISORDER											
rCBF											
Teneback et al. (1999)	22	Pre/post treatment	L DLPFC	Baseline	5Hz or 20Hz	10 sessions 2 weeks	SPECT	[^{99}mTc] HMPAO	Voxelwise	↔	↑ cingulate, bilat cerebellum ↓ R cerebellum, L SM, occipital ctx, L parietal
Speer at al. 2000	10	Pre/post treatment	LDLPFC	Baseline Sham rTMS	10 Hz 1Hz	10 sessions 2 weeks	PET	[^{15}O]H_2O	Voxelwise	↑ ↔	↑ R PFC, ACC, L amygdala, insula, uncus, basal ganglia, thalamus, hippocampus, parahippocampus, cerebellum ↓ R PFC, L medial temporal, L basal ganglia, L amygdala
Catafau et al. (2001)	7	Pre/during/ post treatment	L DLPFC	Baseline	20Hz	10 sessions 2 weeks	SPECT	[^{99}mTc] ECD	ROI	↑	↔
Nahas et al. (2001)	23	Pre/during treatment	LDLPFC	Baseline Sham rTMS	5Hz or 20Hz	10 sessions 2 weeks	SPECT	[^{99}mTc] ECD	Voxelwise	↑	↑ parietal ctx, R medial frontal ↓ R cerebellum, L cingulate, insula and unicate fasciculus
Peschina et al. (2001)	4	Pre/post 1 session	Bilat frontal	Baseline	0.25 Hz	10 sessions 2 weeks	SPECT	[^{99}mTc] HMPAO	ROI	↑	↑ Bilat temporal, Bilat frontal superior ↓ Bilat occipital inferior
Shajahan et al. (2002)	15	Pre/post 1 session	L DLPFC	Baseline	5Hz, 10Hz or 20Hz	10 sessions 2 weeks	SPECT	[^{99}mTc] HMPAO	Voxelwise	↔	↑ ACC, medial prefrontal
Mottaghy et al. (2002)	9	Pre/post treatment	L DLPFC	Baseline	10Hz	10 sessions 2 weeks	SPECT	[^{99}mTc] HMPAO	ROI	↔	↓ R DLPFC
Loo et al. (2003)	18	Online (injection during rTMS)	L DLPFC	Sham rTMS	15Hz	10 sessions 2 weeks	SPECT	[^{99}mTc] HMPAO	Voxelwise ROI (DLPFC)	↑	↑ inferior and superior frontal, posterior cingulate, PHC ↓ R OFC, R subcallosal, L uncus
					1Hz					↓	↑ R ACC, bilateral parietal, insula, L cerebellum
Kito et al. (2008a)	12	Pre/post treatment	L DLPFC	Baseline	10Hz	10 sessions 2 weeks	SPECT	[^{99}mTc] ECD	Voxelwise	↑	↑ L premotor
Kito et al. (2008b)	14	Pre/post treatment	R DLPFC	Baseline	1Hz	10 sessions 2 weeks	SPECT	[^{99}mTc] ECD	Voxelwise	↓	↓ premotor, L DLPFC, OFC, medial PFC, L ACC, R sgACC, insula, L SM, L inferior parietal
Kito et al. (2011)	26	Pre/post treatment	R DLPFC	Baseline	1Hz	10 sessions 2 weeks	SPECT	[^{99}mTc] ECD	Voxelwise	↓	↓ R VLPFC, OFC, sgACC, globus pallidus, thalamus, insula and midbrain
Richieri et al. (2012)	61	Pre/post treatment	LDLPFC or R DLPFC	Baseline	10Hz 1Hz	20 sessions 4 weeks	SPECT	[^{99}mTc] ECD	Voxelwise	↔ ↔	↓ L perirhinal cortex ↓ L perirhinal cortex
Richieri et al. (2017)	58	Pre/post treatment	L DLPFC	Baseline	10Hz	20 sessions 4 weeks	SPECT	[^{99}mTc] ECD	Voxelwise	↔	↓ L lateral temporal, R medial temporal
CMRglc											
Peschina et al. (2001)	4	Pre/post 1 session	Bilat frontal	Baseline	0.25 Hz	10 sessions 2 weeks	SPECT	[^{18}F]FDG	ROI	↓	↑ R central ↓ L frontal inferior
Baeken et al. (2009)	21	Pre/post treatment	L DLPFC	Baseline	10 Hz	10 sessions 2 weeks	PET	[^{18}F]FDG	ROI	↔	↑ ACC
Li et al. (2010)	20	Pre/post treatment	L DLPFC	Baseline	10 Hz	10 sessions 2 weeks	PET	[^{18}F]FDG	Voxelwise	↔	↑ cingulate, somatosensory ctx and precuneus ↓ L fusiform gyrus and middle temporal

(*continued on next page*)

Table 4 (*continued*)

Authors	*N*	Study design	rTMS parameters				Imaging parameters			Effects	
			Target(s)	Control(s)	Freq.	Treatment duration	Method	Tracer	Imaging Analysis	Local	Remote
Baeken et al. (2015)	15	Pre/post treatment	L DLPFC	Baseline Sham rTMS	10 Hz	20 sessions 4 days	PET	[^{18}F]FDG	Voxelwise ROI	↔	↑ R PFC ↓ sgACC
Li et al. (2018)	56	Pre/post treatment	L DLPFC	Baseline Sham TBS	iTBS	10 sessions 2 weeks	PET	[^{18}F]FDG	Voxelwise ROI	↔	↑ bilat. temporal ↓ ACC, mPFC, R PFC
			R DLPFC		cTBS						↑ ACC, mPFC, PCC, precuneus ↓ R temporal
			L and R DLPFC		iTBS + cTBS						↑ bilat. temporal, parietal, precuneus ↓ cerebellum
Dopamine											
Kuroda et al. (2006)	9	Pre/1day post treatment	L DLPFC	Baseline	10 Hz	10 sessions 2 weeks	PET	[^{11}C] raclopride	ROI	NA	↔ (putamen, caudate)
Pogarell et al. (2006)	5	Pre/post 1 session	L DLPFC	Baseline	10Hz	1 session	SPECT	[^{123}I] IBZM	ROI	NA	↓ Bilat striatum
Kuroda et al. (2010)	8	Pre/1day post treatment	L DLPFC	Baseline	10 Hz	10 sessions 2 weeks	PET	L-[β-^{11}C] DOPA	ROI	NA	↔ (putamen, caudate)
OBSESSIVE-COMPULSIVE DISORDER											
CMRglc											
Nauczyciel et al. (2014)	10	Post treatment	R OFC	Sham rTMS	1 Hz	10 sessions 1 week	PET	[^{18}F]FDG	Voxelwise	↓	↓ R frontal, L putamen, L cingulate
PARKINSON'S DISEASE											
rCBF											
Ikeguchi et al. (2003)	12	Pre/post treatment	Bilat frontal	Baseline	0.2Hz	6 sessions 2 weeks	SPECT	[^{99}mTc] ECD	Voxelwise	↓	↓ L middle frontal, R inferior frontal
			Bilat occiptal							↔	↓ L lingual, R cerebellum
Fregni et al. (2006)	26	Pre/post treatment	L DLPFC	Baseline	15Hz	10 sessions 2 weeks	SPECT	[^{99}mTc] ECD	Voxelwise	↔	↑ ACC, posterior cingulate ↓ medial frontal
CMRglc											
Brusa et al. (2012)	8	Pre/post treatment	Bilat. CRBL	Baseline Sham rTMS	50 Hz-cTBS	5 sessions 1 week	PET	[^{18}F]FDG	Voxelwise	↓	↓ Inferior vermis, semilunar lobule, dentate nucleus
Dopamine											
Strafella et al. (2005)	7	Pre/post 1 session	Bilat. M1	Baseline 2 regions	10 Hz	1 session per region	PET	[^{11}C] raclopride	Voxelwise ROI	NA	↓ Ipsi. putamen
Strafella et al. (2006)	7	Pre/post 1 session	R M1	Baseline Sham rTMS	5 Hz	1 session per region	PET	[^{11}C] raclopride	Voxelwise ROI	NA	↓ Dorsal and ventral striatum
Kim et al. (2008)	9	Pre/post 2 sessions	L or R M1	Baseline Sham rTMS	5 Hz	2 sessions	PET	[^{11}C] raclopride	Voxelwise ROI	NA	↓ Contra. caudate
SCHIZOPHRENIA											
rCBF											
Hajak et al. (2004)	20	Pre/post treatment	L DLPFC	Baseline Sham rTMS	10Hz	10 sessions 2 weeks	SPECT	[^{99}mTc] ECD	Voxelwise	↔	↔
CMRglc											
Horacek et al. (2007)	12	Pre/post treatment	L TP ctx	Baseline	0.9 Hz	10 sessions 2 weeks	PET	[^{18}F]FDG	Voxelwise	↓	↑ Middle frontal, sup. temporal, precuneus, supramarginal gyrus ↓ Temporal, cerebellum, insula, cuneus, uncus, hippocampus
TINNITUS											
rCBF											
Marcondes et al. (2010)	20	Pre/post treatment	L TP	Baseline Sham rTMS	1Hz	5 sessions 1 week	SPECT	[^{99}mTc] ECD	Voxelwise	↓	↑ R uncus and cingulate ↓ Bilat temporal
CMRglc											
Mennemeier et al. (2011)	14	Pre/post treatment	L or R sLT	Baseline Sham rTMS	1 Hz	5 sessions 1 week	PET	[^{18}F]FDG	ROI	↓	↑ posterior visual ctx ↓ ipsi. Sensorimotor ctx
Kan et al. (2019)	11	Pre/post treatment	L TP	Baseline	1 Hz	10 sessions 10 days	PET	[^{18}F]FDG	ROI	↓	↑ Bilat insula, R parahippocampus, temporal and frontal, L parietal and precentral ↓ L postcentral and inferior temporal

Legend: ACC: anterior cingulate cortex; ctx: cortex; contra.: contralateral; DLPFC: dorsolateral prefrontal cortex; [^{18}F]FDG; [^{18}F]-fluorodeoxyglucose; [^{123}I]IBZM: [^{123}I]-iodoben-zamide; [^{123}I]-FP-CIT: [^{123}I]–N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodo-phenyl) nortropane; ispi.: ipsilateral; L-[β-^{11}C]DOPA: L-3,4-dihydrox-yphenylalanine (L-DOPA) labelled with [^{11}C] in the beta position; M1: primary motor cortex; MSO: maximum stimulator output; NA: not assessed; OFC: orbitofrontal cortex; [^{15}O]H_2O: [^{15}O]-labelled water; PFC: prefrontal cortex; RMT: resting motor threshold; ROI: region of interest; sLT: superior lateral temporal cortex;; SM: sensorimotor cortex; [^{99}mTc]HMPAO: [^{99}mTc]-hexamethylpropylene amine oxime; [^{99}mTc]ECD: [^{99}mTc]-ethyl cysteinate dimer; TP: temporo-parietal; VLPFC: ventrolateral prefrontal cortex.

Note: More details in **Supplementary Table 4**. Voxelwise analyses conducted across the whole brain unless stated otherwise.

from the same group, targeting the left M1 with 1 Hz rTMS induced dopamine release in the ipsilateral putamen, i.e., reduced [^{11}C]raclopride binding potential (Strafella et al., 2003). It should be noted that Lamusuo et al. (2017) failed to replicate the findings using M1 HF-rTMS, but this study had a substantially longer delay between the stimulation and the beginning of the PET scan, which could lead to missing the peak activation of the changes in dopamine levels induced by rTMS.

[^{11}C]FLB 457 is a high-affinity DA D2-receptor antagonist, making it suitable for the measurement of dopamine release outside the striatum (Farde et al., 1997). Left DLPFC 10 Hz rTMS resulted in decreased [^{11}C]FLB 457 binding potential in the ipsilateral subgenual/pregenual ACC and medial orbitofrontal cortex, but no local effect was found directly beneath the stimulation coil (Cho and Strafella, 2009). Surprisingly, 10 Hz rTMS applied to the right DLPFC did not induce any significant changes in [^{11}C]FLB 457 binding.

[^{11}C]-(+)-PHNO is another high-affinity D2/D3 agonist radiotracer that is sensitive to the functional release of dopamine (Willeit et al., 2006). In contrast to [^{11}C]FLB 457 and [^{11}C]raclopride, [^{11}C]-(+)-PHNO has a preference for D3 over D2 receptors. This preference allows the measurement of dopamine release in predominantly D3 regions, such as the substantia nigra. Using this tracer, Cho et al. (2015) applied 10 Hz rTMS to the left medial PFC, inducing bilateral dopamine release (reduction in [^{11}C]-(+)-PHNO binding) bilaterally in the basal ganglia. When targeting the insula using a specifically designed H-coil, 10 Hz rTMS increased the binding potential in the striatum and substantia nigra, suggesting a decrease in synaptic dopamine concentration. (Malik et al., 2017). In contrast, 1 Hz rTMS did not have an effect on [^{11}C]-(+)-PHNO in any of the studied brain regions. It should be noted, however, that the relationship between changes in the binding of either of the high-affinity tracers ([^{11}C]FLB 457 or [^{11}C]-(+)-PHNO) and synaptic dopamine levels is not as extensively validated as with [^{11}C]raclopride. Thus, changes in synaptic dopamine levels may not be the only mechanism behind the observed changes in tracer binding following stimulation.

3.1.4. Serotonin

The only study investigating serotonin neurotransmission applied 10 Hz rTMS to the left DLPFC and measured serotonin function using [^{11}C]-αMtrp PET imaging (Sibon et al., 2007). [^{11}C]-αMtrp is analogous to the amino acid precursor to 5-HT and thus provides an index of 5-HT synthesis capacity (Diksic and Young, 2001). The investigation of the serotoninergic system is particularly relevant considering the known effect of DLPFC rTMS on mood. The results from this study showed no local effects but demonstrated both increases and decreases in serotoninergic activity in remote regions involved in emotion regulation, including the cingulate and insula.

3.1.5. μ-Opioid receptor

Lamusuo et al. (2017) investigated the ability to activate the endogenous opioid system using 10 Hz rTMS to the motor cortex, which has shown efficacy for the treatment of pain (Lefaucheur et al., 2014). The responses in the opioid system were measured using PET with [^{11}C]carfentanil, which is a μ-opioid receptor antagonist. The stimulation resulted in a decrease in [^{11}C]carfentanil binding in several brain regions, including the prefrontal cortex, insula and cingulate. Although the relationship between changes in [^{11}C]carfentanil binding and synaptic endogenous opioid concentrations is not fully understood, the finding suggests that M1 10 Hz rTMS can be used to increase opioidergic neurotransmission, which could underlie the analgesic effects of rTMS.

3.2. rTMS in clinical populations

We found 17 PET and 18 SPECT (Table 4, Table S2) studies on rTMS effects in different clinical populations. Studies investigated regional blood flow (n = 18), glucose metabolism (n = 14) or dopamine neurotransmission (n = 8). The vast majority of clinical rTMS-PET or rTMS-SPECT studies investigated major depressive disorder (n = 20), and only a few other conditions, such as Parkinson's disease (n = 6), schizophrenia (n = 2), tinnitus (n = 3), and a handful of other disorders (n = 1 each), were investigated. In contrast with studies in healthy volunteers, the majority of the clinical studies investigated metabolic changes after a treatment course of rTMS and compared them with baseline brain activity and not the effects of a single rTMS session.

3.2.1. Major depressive disorder

Left DLPFC HF-rTMS. In the treatment of major depressive disorder (MDD), HF-rTMS is typically applied to the left DLPFC. Several studies have investigated the effects of this protocol on blood flow, glucose metabolism and the dopaminergic system. Ten studies explored the metabolic changes before and after a treatment course of 10 daily rTMS sessions over two weeks. The results are inconsistent across studies with regard to metabolic changes at the stimulation site: five studies showed a local increase in cerebral blood flow (Catafau et al., 2001; Kito et al., 2008a; Loo et al., 2003; Nahas et al., 2001; Speer et al., 2000), while five studies did not find any local change in cerebral blood flow (Mottaghy et al., 2002; Shajahan et al., 2002; Teneback et al., 1999) or glucose metabolism (Baeken et al., 2015, 2009; Li et al., 2010). However, all studies reported remote widespread changes in blood flow or glucose metabolism in the brain, including frontal cortical regions and the anterior cingulate cortex (see Table 4 and Table S2 for details).

More recent studies have investigated different durations or protocols of stimulation. Richieri et al. (2017, 2012) investigated the effect of 4 weeks of daily HF-rTMS on cerebral blood flow. Although no local effect was found, remote reductions in the temporal cortex, including the perirhinal cortex, were observed. A new accelerated treatment protocol that involves 20 sessions of HF-rTMS applied over 4 days resulted in similar results to conventional protocols, showing only remote effects in slightly different brain regions (PFC, subgenual cingulate) (Baeken et al., 2015).

The newer type of facilitatory stimulation, intermittent TBS, also showed comparable effects: no local changes but decreased glucose metabolism in the cingulate and prefrontal cortex and increases in the temporal lobes (Li et al., 2018). Therefore, it seems that HF-rTMS is associated with widespread remote changes in brain metabolism independent of the exact protocol used. However, remote effects are reported in heterogeneous brain regions. The reason for the heterogeneity is not yet clear, but challenges in defining the exact target in the DLPFC could play a role.

A SPECT study assessing the effect of a *single* session of left DLPFC HF-rTMS reported decreased binding of [^{123}I]IBZM in the bilateral striatum, suggesting that a single session would be sufficient to increase brain dopamine levels (Pogarell et al., 2006). However, studies investigating striatal dopamine neurotransmission using two different PET tracers following two weeks of rTMS treatment failed to find any changes when compared to baseline imaging, leaving the dopaminergic effect uncertain (Kuroda et al., 2010, 2006).

Right DLPFC LF-rTMS. LF-rTMS applied to the right DLPFC is an alternative treatment option for MDD with comparable clinical efficacy as with left DLPFC HF-rTMS (Brunoni et al., 2017a). Two weeks of daily right DLPFC LF-rTMS resulted in local and remote reductions in cerebral blood flow (Kito et al., 2011, 2008b). The remote changes were primarily located in the ACC and frontal regions. However, cTBS to the right DLPFC increased glucose metabolism in remote regions, including the ACC, suggesting clearly distinct neurobiological effects between 1 Hz rTMS and cTBS stimulation (Li et al., 2018). However, direct comparisons between conventional rTMS and TBS are missing, precluding definite conclusions.

Bilateral DLPFC rTMS. Using a nonfocal round coil, Peschina et al. (2001) stimulated both frontal hemispheres with LF-rTMS and compared the effect of a single treatment session on glucose metabolism and cerebral blood flow using SPECT in a small sample of patients (n = 4). Interestingly, they found a discrepancy between cerebral blood flow and

Table 5
tDCS combined with PET/SPECT in healthy volunteers.

Authors	*N*	Study design	tDCS parameters			Method	Imaging parameters		Effects	
			Target(s)	Control(s)	Intensity (duration)		Tracer	Imaging Analysis	Local	Remote
Dopamine										
Fonteneau et al. (2018)	32	Mixed	L DLPFC (a) R DLPFC (c)	Sham tDCS	2 mA (20min)	PET	[^{11}C] raclopride	ROI	NA	↓ R caudate nucleus
Fukai et al. (2019)	20	Offline	L DLPFC (a) R DLPFC (c)	Sham tDCS	2 mA (26min)	PET	[^{11}C] raclopride	ROI	NA	↓ R ventral striatum
u-opioid										
DosSantos et al. (2014)	9	Online	R M1 (a) L SO (c)	Baseline Sham tDCS	2 mA (20min)	PET	[^{11}C] carfentanil	Voxelwise	↔	↑ (sham) R precuneus, PAG, L thalamus ↑ (active) L precuneus, L prefrontal
Glucose										
Kraus et al. (2020)	15	Online	L DLPFC (a) R DLPFC (c)	Sham tDCS	0.5mA (10min) 1mA (10min) 2mA (10min)	PET	[^{18}F]FDG	Voxelwise	↔	↔

Legend: DLPFC: dorsolateral prefrontal cortex; [^{18}F]FDG: [^{18}F]fluorodeoxyglucose; L: left; mA: milliamp; NA: not assessed; PAG: periaqueductal grey matter; R: right; SO: supraorbital. (a) = anode; (c) = cathode.
Note: More details in **Supplementary Table 3**. Voxelwise analyses conducted across the whole brain unless stated otherwise.

metabolism beneath the stimulation sites: increased blood flow decreased glucose metabolism. This finding could be related to the different time scales of the imaging and suggest an early increase (reflected in blood flow measurement) and a late decrease in activity (reflected in glucose metabolism measurement); however, the finding needs to be interpreted with caution due to the small sample size. Finally, sequential stimulation with left DLPFC iTBS and right DLPFC cTBS showed widespread changes in glucose metabolism in the temporal, parietal and cerebellar regions, possibly extending further the finding with unilateral TBS paradigms (Li et al., 2018).

3.2.2. Parkinson's disease

Six studies have investigated the effect of rTMS using PET/SPECT in Parkinson's disease. The frontal cortex was used as a target with the hypothesis that it can release dopamine in the striatal regions and improve symptoms. Ikeguchi et al. (2003) assessed the effect of 2 weeks of LF-rTMS applied to the frontal cortex or occipital cortex. Along with clinical improvements, they showed widespread rCBF decreases in frontal regions following frontal rTMS. Fregni et al. (2006) showed changes in rCBF uptake in the cingulate gyrus and medial frontal regions following 2 weeks of HF-rTMS applied to the left DLPFC, which was also accompanied by clinical improvements. A separate group targeted the cerebellum for 1 week with cTBS and showed widespread decreases in glucose uptake within the cerebellar region (Brusa et al., 2012). Finally, three studies showed that one or two sessions of M1 HF-rTMS can act on the dopaminergic system in the basal ganglia. Specifically, the results showed increases in dopaminergic activity in the ipsilateral putamen (Strafella et al., 2005), dorsal and ventral striatum (Strafella et al., 2006) and contralateral caudate nucleus (Kim et al., 2008).

3.2.3. Schizophrenia

The left DLPFC was targeted with HF-rTMS over 2 weeks in patients with schizophrenia. Although significant clinical effects were reported on levels of negative symptoms, no change was seen in brain regional blood flow (Hajak et al., 2004). Targeting auditory hallucinations with 2 weeks of LF-rTMS to the left temporoparietal cortex decreased glucose metabolism at the stimulation site, extending to the temporal cortex and contralateral hemisphere (Horacek et al., 2007).

3.2.4. Tinnitus

The temporal and parietal regions have been targeted with LF-rTMS for the treatment of tinnitus. When the temporal-parietal junction was targeted for one week (Marcondes et al., 2010) or ten consecutive days (Kan et al., 2019), a decrease in local rCBF and glucose was obtained. A reduction in rCBF and glucose was also induced in temporal regions, while glucose metabolism showed a more widespread pattern of increase in activity. Mennemeier et al. (2011) targeted the superior lateral temporal cortex and showed a local reduction in blood flow that was not correlated with symptom improvement.

3.2.5. Other clinical populations

In alcohol use disorder, HF-rTMS applied to the bilateral DLPFC over 4 weeks induced a reduction in ^{123}I-FP-CIT dopamine binding in the right caudate nucleus (Addolorato et al., 2017). In congenital blindness, one session of HF-rTMS applied to the sensory cortex induced remote changes in rCBF that were distinct for early vs. late blindness, indicating differential cross-modal plasticity (Wittenberg et al., 2004). In fibromyalgia, 10 weeks of HF-rTMS applied to the left M1 induced an increase in glucose metabolism in the right limbic structures (i.e., medial temporal cortex), which correlated with an improvement in quality of life (Boyer et al., 2014). In obsessive-compulsive disorder, the right orbitofrontal cortex was targeted with HF-rTMS with 10 sessions over 1 week (Nauczyciel et al., 2014). The results showed a significant decrease in glucose metabolism at the stimulation site and in remote regions functionally related to the OFC, such as the putamen and cingulate.

3.3. TES in healthy volunteers

Only four studies were found that have investigated the effects of a single session of tDCS on dopamine and μ-opioid receptor function, as well as glucose metabolism in healthy volunteers using PET (Table 5, Table S3). No published studies investigating the effects of tACS or tRNS with PET or SPECT in healthy volunteers were found.

Bilateral DLPFC tDCS (anode left, cathode right) has been shown to reduce [^{11}C]raclopride binding in the right caudate nucleus (Fonteneau et al., 2018) and right ventral striatum (Fukai et al., 2019), indicating increased dopamine release in the striatum in the cathodal stimulation hemisphere. Another study employed a novel functional PET technique

Table 6
tDCS combined with PET/SPECT in clinical populations.

Authors	*N*	Study design	tDCS parameters				Method	Imaging parameters		Effects	
			Target(s)	Control(s)	Intensity (duration)	Treatment duration		Tracer	Imaging Analysis	Local	Remote
MILD COGNITIVE IMPAIRMENT/ALZHEIMER'S DISEASE											
CMRglc											
Yun et al. (2016)	16	Pre/post treatment	L DLPFC (a) R DLPFC (c)	Sham tDCS	2 mA (20min)	9 sessions 3 weeks	PET	[^{18}F] FDG	Voxelwise	↑	↑ Precuneus, mid-temporal, ACC
Im et al. (2019)	18	Pre/post treatment	L DLPFC (a) R DLPFC (c)	Sham tDCS	2 mA (30min)	182 sessions 6 months	PET	[^{18}F] FDG	Voxelwise	↔	↑ L middle/inferior temporal
PAIN											
CMRglc											
Yoon et al. (2014)	16	Pre/post treatment	L M1 (a) R SO (c)	Baseline Sham tDCS	2 mA (20min)	20 sessions 2 weeks	PET	[^{18}F] FDG	Voxelwise	↑	↑ R caudate, medulla ↓ L angular, posterior cingulate, and middle and superior frontal

Legend: ACC: anterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex; [^{18}F]FDG; [^{18}F]-fluorodeoxyglucose; L: left; mA: milliamp; R: right; SO: supra-orbital.
Note: More details in **Supplementary table 4**. Voxelwise analyses conducted across the whole brain unless stated otherwise.

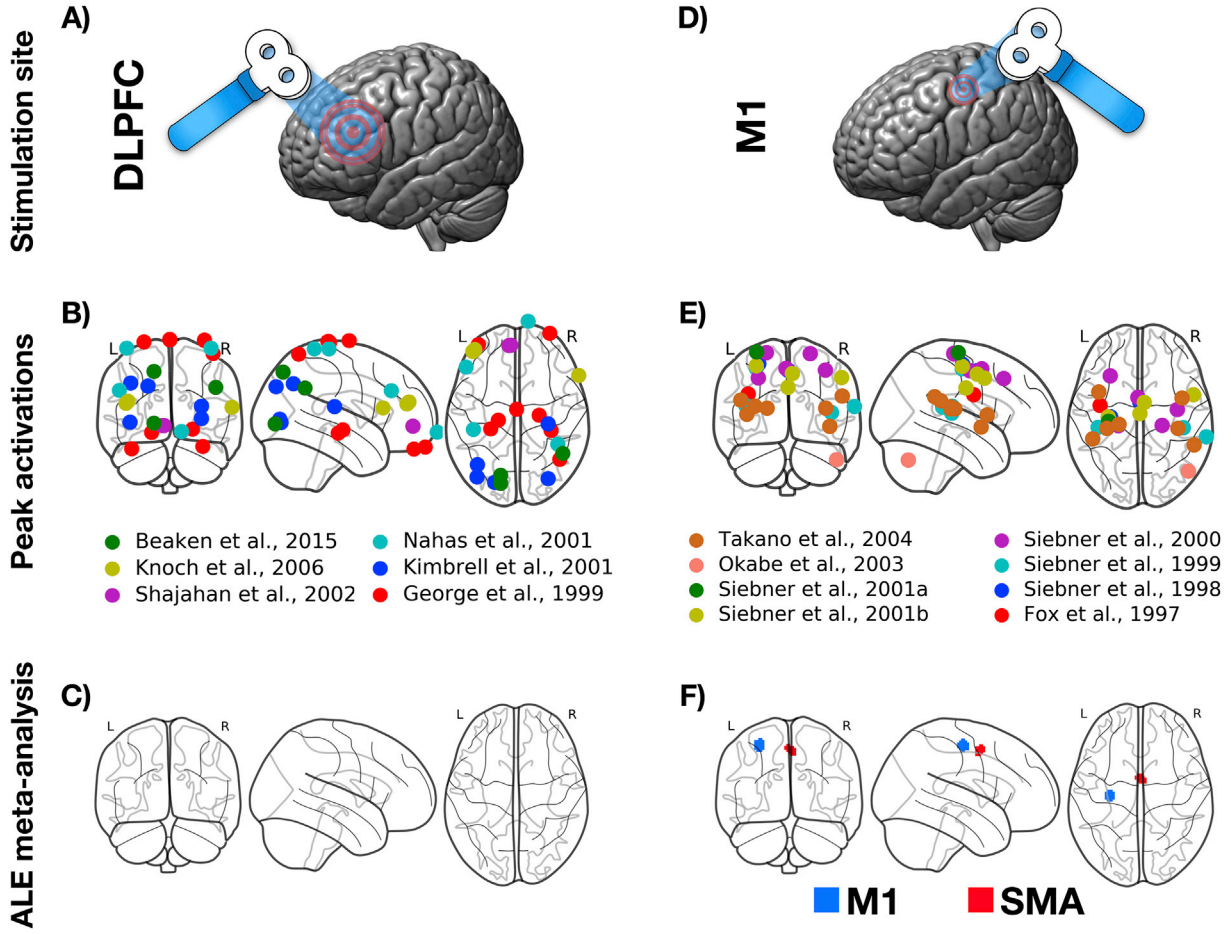

Fig. 2. Illustration of the rTMS stimulation effects. Legend: A) Target site for DLPFC stimulation. The size of the target reflects the heterogeneity in targeting the left DLPFC across studies. B) Visualization of peak activations from each study included in the ALE meta-analysis that targeted the left DLPFC with HF-rTMS. Widespread heterogeneous activations are observed. C) Results of the ALE meta-analysis for left DLPFC HF-rTMS. No significant clusters were obtained. D) Target site for left M1 stimulation. The size of the target reflects small variability in the location of the target. E) Visualization of peak activations from each study included in the ALE meta-analysis that targeted the left M1 with LF-rTMS. Peak activations are mainly focused on bilateral sensorimotor regions. F) Results of the ALE meta-analysis for left M1 LF-rTMS. Significant clusters are obtained at the target site and the supplementary motor area.

using a continuous infusion of [^{18}F]FDG during bilateral DLPFC tDCS applied at three intensities, allowing to detect dynamic changes in glucose consumption (Kraus et al., 2020). No significant results were observed, suggesting a potential lack of immediate effects on glucose uptake and highlighting the need for studies investigating after-effects.

Finally, one study investigated the online effects of tDCS on the motor

system. Anodal tDCS was applied to the left M1 (cathode right supraorbital) and μ-opioid receptor availability was assessed using [^{11}C]carfentanil (DosSantos et al., 2014). Active tDCS increased [^{11}C]carfentanil binding in the left prefrontal cortex. Interestingly, they showed that both active and sham tDCS increased [^{11}C]carfentanil binding in the precuneus and periaqueductal grey matter, which the authors interpreted as a potential mechanism underlying the placebo experience.

3.4. TES in clinical populations

Three studies have investigated the effects of tDCS using [^{18}F]FDG (Table 6, Table S4). Interestingly, they involved two clinical populations that have not been investigated using rTMS, i.e., mild cognitive impairment/Alzheimer's disease and chronic pain. As with healthy volunteers, there are no published studies investigating the effects of tACS or tRNS with PET or SPECT in clinical populations.

In mild cognitive impairment, there was increased glucose metabolism following 3 weeks of bilateral DLPFC tDCS (left anodal and right cathodal) in local and remote brain regions involved in memory processing, such as the mid-temporal cortex (Yun et al., 2016). In early Alzheimer's disease, 6 months of daily at-home bilateral DLPFC tDCS also increased glucose metabolism in the mid-temporal regions (Im et al., 2019). In individuals with chronic pain following spinal cord injury, 2 weeks of M1 tDCS (left anode, right supraorbital cathode) increased glucose metabolism locally as well as in the contralateral caudate and medulla (Yoon et al., 2014).

3.5. Illustration of the rTMS stimulation effects

A visualization of the neuroimaging cluster coordinates illustrates that the effects of left DLPFC stimulation are scattered, whereas the effects of left M1 stimulation are more concentrated on brain regions involved in motor control (Fig. 2). This observation was confirmed by the ALE meta-analyses, showing that M1 LF-rTMS in healthy volunteers showed significant clusters in the ipsilateral M1 and supplementary motor area (SMA) (Fig. 2C) but no significant clusters after left DLPFC HF-rTMS in healthy volunteers or in those with major depressive disorder (Fig. 2F).

4. Discussion

The current paper provides a comprehensive and up-to-date systematic review of studies investigating the effects of NIBS using molecular imaging in humans. Our results show that molecular imaging studies investigating the mechanisms of NIBS methods have focused on rTMS, with only a very limited number of studies on tDCS. These studies have demonstrated changes in regional blood flow and metabolism in both local and remote brain regions. Studies focusing on the dopamine system have provided proof of concept that noninvasive brain stimulation can be used to modify brain neurotransmitter function. However, there are only single studies investigating other neurotransmitter systems, such as the μ-opioid receptor system, preventing any firm conclusions in neurotransmitters other than dopamine. Overall, the findings corroborate and complement the studies using other neuroimaging modalities, such as fMRI and EEG, demonstrating the propagation of the stimulation effects to connected brain regions (Bergmann et al., 2016; Hallett et al., 2017). However, there are some limitations in the currently available evidence, which are discussed below in detail with suggestions and recommendations for future studies.

4.1. Repetitive transcranial magnetic stimulation (rTMS)

4.1.1. Local and remote effects of rTMS

The vast majority of rTMS studies have investigated cerebral blood flow or metabolism. Approximately half of the studies were able to demonstrate local effects directly beneath the stimulation coil. Interestingly, both low- and high-frequency stimulation have resulted in increased local blood flow or brain metabolism, although there is some variation between studies. The left motor cortex was the most studied stimulation target using low-frequency rTMS followed by high-frequency stimulation to the left DLPFC. Motor cortex stimulation resulted in relatively consistent increases in tracer uptake in the motor circuit, particularly in the motor cortex and SMA. Left DLPFC stimulation also resulted in remote effects, but the locations of the peak effects showed very little consistency, which is reflected in the negative results in the ALE meta-analysis. The more heterogeneous remote effects after DLPFC stimulation are likely to be explained by the increased variability of the stimulation targets between studies, which is discussed in more depth in the next paragraph. Studies investigating other stimulation targets are still scarce, and the available data are mostly based on single studies.

4.1.2. Targeting

In the motor system, the stimulation site is defined based on motor evoked potentials, which can be considered an accurate and replicable method to define the optimal stimulation site even without neuronavigation (Rossini et al., 2015). The motor cortex is unique in the sense that both functional and anatomical targeting result in essentially the same localization (the hand knob in the precentral gyrus). In nonmotor targets, such as the DLPFC, targeting the stimulation is more difficult because there are no good anatomical landmarks or physiological measurements that can be used to guide stimulation. This leads to differences in target coordinates between studies and to high interindividual variance within a study (Peleman et al., 2010), when no neuronavigation is employed (e.g., using the 5-cm rule) (Ahdab et al., 2010; Herwig et al., 2001; Peleman et al., 2010; Pommier et al., 2017). The variability in coil placement can have a huge impact on the biological effects, as demonstrated by stimulation site connectivity and clinical efficacy of rTMS in major depression (Fox et al., 2012). Accordingly, we failed to identify any consistent changes after DLPFC stimulation in healthy volunteers or patients with major depression. Some studies report the group-level Talairach or MNI coordinates, but the methods used to warp individual data to the standard space vary from study to study, which is known to increase variance in the final coordinates of the target (Laird et al., 2010).

Although rTMS is generally targeted to a specific location in the brain, the induced field is not focal. The induced magnetic field is maximal directly beneath the coil and is inversely proportional to the distance squared. However, the electric fields responsible for the modulation of neuronal function are more complex and greatly affected by intracranial anatomy and axonal orientation in the cortex (Nummenmaa et al., 2014). None of the published NIBS molecular imaging studies used electric field modeling apart from defining the field peak. The combination of anatomically realistic models of the induced electric fields can allow better understanding of the local and remote effects of NIBS. It should also be noted that there may be differences in the functional organization of the brain across individuals, especially in brain networks involved in higher cortical functions (Kashyap et al., 2019; Mueller et al., 2013). In this context, the use of functional (connectivity) imaging to define and individualize targets could lead to more robust effects on brain networks (Fox et al., 2014).

4.1.3. Neurotransmitter function

The dopamine system is the only neurotransmitter system that has been studied in detail using combined NIBS and molecular imaging. Early studies on dopamine function investigated endogenous neurotransmitter release to either M1 or left DLPFC stimulation, showing dopamine release in the striatum (Strafella et al., 2003, 2001). Importantly, dopamine responses were seen in anatomically meaningful subregions of the striatum, i.e., DLPFC and M1 stimulation resulted in dopamine release in the caudate (Strafella et al., 2001) and putamen (Strafella et al., 2003), respectively. These findings are in agreement with the known topography of anatomical and functional corticostriatal circuits (Alexander, 1986; Di Martino et al., 2008; Haber, 2003; Leh et al., 2007). Similarly,

studies using other tracers targeting the dopamine system have demonstrated changes in remote brain regions, corresponding to the stimulation site and tracer binding profile (Cho et al., 2015; Cho and Strafella, 2009; Malik et al., 2017). Overall, these studies indicate that the dopamine system can be modified via rTMS in a regionally specific manner.

4.1.4. Stimulation frequencies

The most common stimulation frequencies in rTMS-PET/SPECT studies are 1 Hz and 10 Hz following the most widely used clinical protocol with well-established effects on MEP amplitudes (McClintock et al., 2018; Rossini et al., 2015). In general, high-frequency (10–20 Hz) and low-frequency ($\leq$1 Hz) stimulation both resulted in an increase in brain metabolism directly beneath the coil. However, the remote effects are much more variable, with most of the studies reporting both activation and deactivation. This finding is consistent with the fact that the remote effects are complex and will depend on both the local physiological effect in the target region (i.e., net inhibition versus facilitation) and the nature of connections with remote regions (i.e., predominantly inhibitory versus facilitatory) (Fecteau et al., 2006; Valero-Cabré et al., 2007, 2005). The characterization of interconnected regions using functional and anatomical brain connectivity measures in conjunction with molecular imaging may help better predict and interpret the remote effects of NIBS.

There are only two clinical studies investigating the effects of newer types of protocols, such as intermittent or continuous TBS. In healthy controls, TBS has been used in molecular imaging studies only in combination with a behavioral task, and the "pure" neurobiological effects of these newer stimulation paradigms on the healthy brain remain to be characterized. Although TBS can be used to increase or decrease cortical excitability, the hypothesized mechanism of action differs from conventional rTMS; therefore, the generalization of any findings from conventional rTMS to TBS should be made with caution. Given the recent findings validating the use of intermittent TBS for the treatment of major depression (Blumberger et al., 2018), a more detailed investigation of the effects of TBS would be important to move the field forward.

4.2. Transcranial electrical stimulation (TES)

The only TES method investigated with PET or SPECT imaging to date is tDCS, and only a handful of studies have been published, which prevented the use of an ALE meta-analysis. The mechanism of action of tDCS differs from rTMS. For instance, the direct electrical current produced by tDCS is thought to modulate cortical excitability via a subthreshold modification, i.e., depolarization or hyperpolarization, of membrane potentials (Lefaucheur et al., 2017; Nitsche et al., 2008). Nevertheless, similar to rTMS, tDCS applied to the DLPFC in healthy volunteers was shown to modulate the dopamine and μ-opioid receptor systems in anatomically relevant interconnected regions. It is important to note that so far, there have been no attempts to replicate any of these findings; thus, the results need to be interpreted with caution.

4.3. Methodological issues

4.3.1. Multimodal nature of NIBS

rTMS, and to a lesser degree TES, have multimodal effects on brain function, extending beyond the direct effects of induced electric currents modulating neuronal function. The multimodal effects are intrinsic to these methods and highly important to consider when interpreting results from molecular imaging. TMS is associated with substantial acoustic noise, a tapping scalp sensation and possibly even pain, which can all lead to significant activation of brain networks involved in these functions (Siebner et al., 1999). These activations invariably modulate the rTMS-induced effects on brain networks. In addition, TMS applied to the motor cortex results in spinal activation and MEP with a potential long-loop reflex (Kofler et al., 2008), which can also impact motor cortex activations. Conversely, TES is not associated with auditory stimulation and produces only a slight tingling sensation, which is significantly weaker and more diffuse than the sensory effect of TMS. Thus, the secondary impact of TES on sensory networks is expected to be smaller. Developing control conditions that allow us to account for these activations is not only difficult but also may not be entirely desirable, as these sensory/acoustic activations most likely interact with the "direct" effect of rTMS and TES. Currently, there are new sham coil designs that provide a realistic auditory and sensory stimulus closely mimicking real rTMS. The use of these new sham coils may provide an important advancement towards better control conditions and improve our understanding of the interaction between sensory/auditory/motor activations and the "direct" effect and connectivity-mediated effect of rTMS and TES.

Moreover, rTMS and TES can have powerful placebo (or nocebo) effects (Burke et al., 2019; Fiorio, 2018; Razza et al., 2018), again evoking additional brain responses. TES studies have consistently used a sham condition, with the standard ramping up and down of the electrical current. However, as shown in Table 3, the choice of the control conditions in rTMS-PET/SPECT studies is highly variable, likely adding heterogeneity to the results. Some studies used stimulation to another brain region, sham stimulation by tilting the coil, or a specific sham coil that does not result in high enough magnetic field intensity in the cortex to modify neuronal function. Some of the studies merely compared pre- and post-stimulation tracer uptake without any control stimulation. However, the issue of reliable control conditions affects all rTMS studies and is not specific for molecular imaging studies. Future study designs should account for both the placebo and multimodal nature of NIBS.

4.3.2. Timing of scanning

Although high-frequency and low-frequency stimulation are generally considered excitatory and inhibitory, respectively, both stimulation types seem to result in local increases in regional blood flow and metabolism during stimulation (e.g., (Paus et al., 1998, 1997; Siebner et al., 2001b). As the effects of rTMS extend beyond the duration of the stimulation and low-frequency protocols have inhibitory aftereffects, the time window when brain activity is measured is important for the interpretation of the results. For instance, changes in opposite directions in regional brain activity during the accumulation of [^{18}F]FDG could cancel out, resulting in false-negative findings (e.g., if an increase was followed by a decrease, resulting in no change on average). The large majority of PET/SPECT measurements were performed almost immediately after the stimulation had ended (offline). The only exception is the study by Lamusuo et al. (2017), who had a delay up to several hours between the end of the stimulation and tracer injection/scanning. The long delay may have contributed to the lack of significant changes in [^{11}C]raclopride, which would otherwise seem contradictory to the earlier findings (Cho et al., 2015; Cho and Strafella, 2009; Strafella et al., 2003, 2001). Nevertheless, Lamusuo et al. (2017) reported a change in μ-opioid receptor binding 3–4 h after stimulation, suggesting that the molecular-level effects may persist much longer than what would be expected based on MEP measurements after contralateral motor cortex stimulation (Rossini et al., 2015). This finding is intriguing but needs replication.

4.3.3. Interindividual variability

One important factor to consider when combining NIBS with molecular imaging studies is the inherent interindividual variability of the excitability changes induced by rTMS and TES, which is well characterized using electromyography (Hordacre et al., 2017; López-Alonso et al., 2014; Maeda et al., 2000; Wiethoff et al., 2014). This variability may partially underlie the lack of consistent findings across studies, as the modulatory effects would be predicted to vary from one individual to another. In this context, including larger samples that allow the exploration of different pattern of responses in the sample may be a good strategy to better account for this variability. The use of individualized targets may help reduce this variability by targeting a specific network rather than an anatomical region.

4.4. Differences between healthy volunteers and clinical conditions

An important question is whether the neurobiological effects of NIBS in healthy volunteers can be generalized to individuals with neurological and psychiatric disorders. Notably, all studies were conducted in either healthy volunteers or clinical populations, and there is not even a single study to date combining both clinical and healthy volunteer populations to investigate the potential differential mechanism of action of NIBS on brain regional blood flow, metabolism or neurotransmitter function. In addition, clinical studies mostly involved a pre- and post-treatment design (often involving 15–30 sessions), whereas healthy volunteer studies typically involve a before and after one-session design. This fundamental discrepancy in study designs makes it very difficult to reconcile and compare results from both types of studies. To better understand the molecular effect of NIBS, clinical studies should include control groups and use study designs that allow a comparison with previous literature.

4.5. Insights from preclinical studies

Although the current review of the literature focused on human studies, it is important to highlight that animal experiments can provide complementary information about the neural mechanisms of action of NIBS. For example, the effects of rTMS on the dopaminergic system have been studied in rodents using *in vivo* microdialysis (see Moretti et al., 2020 for review), in which HF-rTMS applied to the frontal regions induced dopamine release in subcortical regions, i.e. striatum (Ben-Shachar et al., 1997; Kanno et al., 2004), nucleus accumbens (Erhardt et al., 2004) and hippocampus (Ben-Shachar et al., 1997; Keck et al., 2000). The effects of rTMS over M1 was also studied using [^{11}C] raclopride PET in anesthesized monkeys, showing dopamine release in the ventral striatum and putamen (Ohnishi et al., 2004), consistent with human studies in clinical populations and healthy individuals (Strafella et al., 2006, 2005, 2003). Together, these studies provide strong evidence that the dopaminergic system can be modulated with rTMS.

Preclinical studies have also investigated prefrontal rTMS effects on glucose metabolism using [^{18}F]FDG micro-PET in rodents (Parthoens et al., 2016, 2014). Notably, these studies have shown that local effects do not follow the expected LF-decrease and HF-increase in glucose metabolism, corresponding to human studies, as highlighted in this review. For instance, stimulation of prefrontal areas using 1, 10 and 50 Hz rTMS induced a local decrease in glucose metabolism in all conditions (Parthoens et al., 2016). As for human studies, widespread remote effects on glucose metabolism was seen with both high and low frequency rTMS (Parthoens et al., 2016, 2014). Similarly, high and low frequency rTMS induced widespread rCBF changes in rodents in a study using ^{99m}Tc-HMPAO micro-SPECT (Wyckhuys et al., 2013). However, it should be noted that the stimulation in small animals is less focal and some of the effects may be caused by extended local stimulation rather than true remote effects.

In line with what has been reported in motor cortex rTMS human studies, PET studies in non-human primates have shown that high-frequency rTMS applied to M1 changes rCBF in motor areas, including the SMA as well as the premotor cortex, thalamus, caudate and cerebellum (Salinas et al., 2013, 2016). These studies also suggested that specific stimulation frequencies target different networks in the motor system, possibly by activating distinct neuronal populations (Salinas et al., 2013). Similar frequency-specific network modulations have been observed in humans following prefrontal rTMS (Knoch et al., 2006), but remains to be investigated for the motor cortex.

Altogether, preclinical studies increase our understanding of the neural determinants of NIBS effects but more work is needed to determine how well these findings translate to humans. In addition, animal models can also provide a framework for the study of alternative neurotransmitters systems, such as GABA and glutamate, which have been shown to be central to the effect of electromagnetic stimulation in rodents but have not yet been studied in humans (Lenz and Vlachos, 2016; Moretti et al., 2020).

Table 7
Recommendations for future molecular imaging studies.

R1	Use of MRI-based neuronavigation systems and targets consistent across studies
R2	Use of anatomically realistic models of induced electrical fields
R3	Use of better control condition, such as realistic rTMS sham coils, and taking into consideration the multimodal nature of NIBS
R4	Replication of previous findings and larger sample sizes
R5	Investigation of the effects of timing of scanning and duration of the after-effects
R6	Investigation of newer rTMS protocols, such as TBS, and TES
R7	Use of novel radiotracers that allow to investigate other relevant neurotransmitter systems such as glutamate, GABA and serotonin
R8	Conducting studies including both clinical and healthy populations, allowing direct comparisons between the groups
R9	Standardized reporting (including whole brain analyses with MNI coordinates) and open-data sharing to allow for replication and meta-analyses
R10	Use of functional or connectivity imaging to identify or control individual differences in optimal target location and to predict remote effects of NIBS

5. Conclusions and recommendations

Molecular imaging studies have confirmed and extended the knowledge on the brain-wide network effects of NIBS. Compared with other functional neuroimaging tools, such as fMRI and EEG, PET/SPECT allows the assessment of specific molecular events and neurotransmitter systems with nanomolar-level sensitivity and relatively good spatial resolution. Despite these advantages, the review of the literature identified several limitations of the currently available data, including small sample sizes; a lack of independent replication of most of the findings; and variable targeting methods, control conditions and reporting of the results. In addition, a surprisingly small number of studies have investigated molecular systems other than glucose metabolism, blood flow and dopamine neurotransmission. Using novel PET tracers that may be sensitive to endogenous neurotransmitter release, such as [^{11}C]ABP688 for glutamate (Smart et al., 2018), [^{11}C]CIMBI-36 for serotonin (Ettrup et al., 2014), and [^{11}C]Ro15-4513 for GABA (Møller et al., 2019), or measuring synaptic density using tracers such as [^{11}C]UCB-J (Finnema et al., 2016) could provide further insights into the molecular mechanisms of NIBS.

In light of the limitations and results of the current review, we have developed a series of recommendations for future NIBS molecular brain imaging studies, which are listed in Table 7. These include methodological issues (e.g. the use of MRI-based neuronavigation and improved experimental control conditions), investigation of new NIBS paradigms and use of novel radiotracers, new study designs (e.g. combined PET and MRI, direct comparison of clinical and healthy controls), and standardized reporting of findings. We hope that these recommendations will allow us to further the field of molecular neuroimaging and NIBS, and lead to important advances in our understanding of NIBS mechanisms of action, potentially leading to the development of more reliable therapeutic applications.

Author contributions

ST, LT and JJ conceptualized the study. ST and VZ conducted the literature search and designed the tables. LT and JJ analyzed the data. All authors interpreted the data. AP provided additional critical feedback on data interpretation. ST and JJ wrote the manuscript. LT and ST designed the figures. All authors critically reviewed and approved the manuscript.

Data and code availability

The data and/or code used in the meta-analysis section of this review are available from the corresponding author upon reasonable request.

Declaration of competing interest

Dr. Joutsa has participated in sponsored academic meetings and seminars. Dr. A. Pascual-Leone serves on the scientific advisory boards for Neosync, Starlab Neuroscience, Neuroelectrics, Magstim Inc., Constant Therapy, Nexstim, and Cognito and is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation with electroencephalography and magnetic resonance imaging. Dr. Tremblay and Dr. Tuominen do not have any competing interest to disclose.

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Appendix A. Supplementary data

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