OPINION

Rehabilitating the addicted brain with transcranial magnetic stimulation

Marco Diana, Tommi Raij, Miriam Melis, Aapo Nummenmaa, Lorenzo Leggio and Antonello Bonci

Abstract | Substance use disorders (SUDs) are one of the leading causes of morbidity and mortality worldwide. In spite of considerable advances in understanding the neural underpinnings of SUDs, therapeutic options remain limited. Recent studies have highlighted the potential of transcranial magnetic stimulation (TMS) as an innovative, safe and cost-effective treatment for some SUDs. Repetitive TMS (rTMS) influences neural activity in the short and long term by mechanisms involving neuroplasticity both locally, under the stimulating coil, and at the network level, throughout the brain. The long-term neurophysiological changes induced by rTMS have the potential to affect behaviours relating to drug craving, intake and relapse. Here, we review TMS mechanisms and evidence that rTMS is opening new avenues in addiction treatments.

Addiction is a chronic relapsing brain disorder characterized by seeking a drug (or engaging in an activity) where use becomes compulsive or difficult to control despite harmful consequences (according to DSM-V). Neuronal circuits involved in reward and fear processing adapt as a result of chronic drug use and abuse[1]. As this adaptation is fundamentally a learning and conditioning process, brain stimulation applied to these circuits at suitable parameters could potentially reverse some of the associated neuronal processes and, hopefully, reduce addictive behaviours. Indeed, basic science studies support this potential. On the one hand, localized activation of infralimbic brain regions such as the prefrontal cortex (PFC) via either electrical or optogenetic stimulation results in reduced cocaine intake in rats[2,3]. On the other hand, dopaminergic (DAergic) activity is tonically reduced in rodent models and in people with addictions (REF. 4 for review), and brain stimulation has been shown to 'boost' DA signalling in the human brain[5], thereby providing a path for restoring neural homeostasis.

Transcranial magnetic stimulation (TMS) is a noninvasive method for delivering electric field (E-field) pulses into the brain[6–8]. Magnetic fields, generated with a coil placed over the scalp, efficiently pass through the electrically insulating skull, allowing magnetic stimuli to induce strong and moderately spatially focal intracranial currents in the underlying brain tissue. Delivering many TMS pulses in sequences can cause long-term changes that facilitate or impede neuronal excitability and specific behaviours, depending on the stimulation site, sequence parameters and other factors.

In this Review, we describe the fundamentals of TMS and its putative mechanisms of action. We also detail and discuss the pros and cons of TMS and argue that plasticity and connectivity changes may underlie some of the long-term effects of TMS. Finally, we link optogenetic observations in rodents to imaging and human pilot studies describing effects of rTMS on drug craving and intake, pinpointing new advances and highlighting conceptual gaps to be filled by future controlled studies.

TMS physiology

TMS is a flexible tool with which different stimulation parameters engage different neuronal mechanisms (TABLE 1). Depending on the anatomical loci and parameters, TMS may induce different short- or long-term, facilitative or suppressive, neuronal and/or behavioural effects. Note that the terms 'facilitation' and 'suppression' here refer to whether the TMS sequence increases or reduces motor-evoked potentials (MEPs) during stimulation of the primary motor cortex; the effects outside the motor cortex are less studied. The neuronal mechanisms of both facilitation and suppression may include excitatory and/or inhibitory processes, but the mechanisms underlying TMS activations and rTMS-induced plasticity are complex and not yet completely understood. Below, we review what is currently known and suggest some possible mechanisms.

A TMS pulse lasts only ~0.2–0.3 ms, which enables targeting of timing-dependent neuronal processes with single-pulse TMS (spTMS) and paired-pulse TMS (ppTMS); these techniques induce neuronal effects lasting only a fraction of a second. By contrast, longer repetitive TMS (rTMS) pulse sequences may induce long-term neuroplastic changes, thereby offering enduring alterations that carry therapeutic potential. For this purpose, TMS pulses have usually been delivered in trains (for example, conventional 1 Hz or 20 Hz rTMS) or, more recently, in more complex patterns (for example, theta burst stimulation, TBS; quadripulse stimulation, QPS; and repetitive paired-pulse TMS, rppTMS) (REF. 9 for review). As current therapeutic trials on SUDs mainly use conventional rTMS, we focus on it here, with brief notes on TBS, QPS and rppTMS[10,11].

For all TMS pulse sequences, their long-term effects on cortical excitability depend on stimulation parameters (TABLE 1). For example, high-frequency rTMS (5–25 Hz) typically has a facilitative effect[12], whereas low-frequency rTMS (~1 Hz) usually reduces excitability[13], reminiscent of long-term potentiation (LTP) and long-term depression (LTD), respectively. However, frequency is clearly not the only factor. For example, the baseline cortical activation state

Table 1 | **Examples of transcranial magnetic stimulation pulse sequences and putative mechanisms**

Family	Technique	Persisting effects	Timing of pulses	Effects on MEPs and/or neurons	Refs
spTMS	–	No	Individual pulses >5 seconds apart	Depolarization of brain cells	6,159–164
ppTMS	SICI	No	Two pulses 1–5 ms apart	Suppression via axonal refractoriness and inhibitory interneuron $GABA_A$ receptors	168–170
ppTMS	ICF	No	Two pulses 5–15 ms apart	Facilitation via excitatory interneuron NMDA	168–170
ppTMS	SICF	No	Two pulses ~1.5, 3.0 or 4.5 ms apart (at I-wave periodicity)	Facilitation via axonal activation of excitatory interneurons	171–174
ppTMS	LICI	No	Two pulses 50–200 ms apart	Suppression via $GABA_B$ receptors	48,49,175
rTMS	Low frequency	Yes	Steady train of pulses at ~1 Hz	Suppression	13
rTMS	High frequency	Yes	Several trains of pulses at ~5–25 Hz	Facilitation	12
TBS	cTBS	Yes	Three pulses at 50 Hz repeated at 5 Hz, continuous	Suppression of MEPs and reduced SICI	10
TBS	iTBS	Yes	Three pulses at 50 Hz repeated at 5 Hz, intermittent	Facilitation of MEPs and increased SICI	10
QPS	_	Yes	Four pulses several ms apart (off I-wave periodicity, long intervals 30–100 ms)	Suppression	11,176
QPS	_	Yes	Four pulses ~1.5, 5 or 10 ms apart	Facilitation	11,176
rppTMS	_	Yes	Two pulses ~3.0 ms apart at subthreshold intensity, repetitive ~0.6 Hz	Suppression via strengthening of synapses from inhibitory interneurons to pyramidal neurons	177
rppTMS	_	Yes	Two pulses ~1.5 ms apart at suprathreshold intensity, repetitive ~0.2 Hz	Facilitation	178–180

This list is not intended to be comprehensive, as more sequences and techniques exist, and yet more are being developed. Moreover, the physiology underlying the immediate and long-term neuroplastic effects of many sequences is incompletely understood. cTBS, continuous TBS; ICF, intracortical facilitation; iTBS, intermittent TBS; LICI, long-interval intracortical facilitation; MEP, motor-evoked potential; ppTMS, paired-pulse TMS; QPS, quadripulse stimulation; rppTMS, repetitive paired-pulse TMS; rTMS, repetitive TMS; SICF, short-interval intracortical facilitation; SICI, short-interval intracortical inhibition; spTMS, single-pulse TMS; TBS, theta burst stimulation; TMS, transcranial magnetic stimulation.

influences the effects of TMS[14] because the impact of any external stimulus on neural function represents an interaction with the ongoing brain activity at the time of stimulation. Accordingly, the behavioural effects of TMS may also be partially state-dependent, that is, cortical activity before or during TMS may influence whether TMS facilitates or impedes behaviour[15].

In the human brain, the effects of TMS on brain physiology have been studied mainly in the primary motor cortex (M1) while simultaneously recording MEPs from peripheral muscles. TMS-evoked brain activity can also be more directly recorded with electroencephalography (EEG)[16], positron emission tomography (PET)[17], or functional MRI (fMRI)[18,19]. Additional details have been revealed through *in vitro*[20,21] and *in vivo* animal studies[22,23] with computational modelling of the E-fields and their interaction with brain cells[24–33] and through TMS–pharmacological studies[34–36]. As the neuronal activations are driven by TMS-induced E-field pulses driving intracranial electric currents, much of the prior research on (pulsed) electrical stimulation of neuronal tissue also applies.

TMS causes primary activations of brain tissue directly under the coil, as well as secondary activations of remote cortical and subcortical areas anatomically connected (directly or indirectly) to the primary activation site[16,17,19,37] (FIG. 1a). To illustrate their differences, we organize the text below in terms of primary and secondary activations.

Effects at primary activation sites

Short-term spTMS-induced effects at the primary activation site. The key factors determining spTMS-induced neuronal activity, as well as which cell types and parts are stimulated, are the TMS E-field intensity, orientation of the E-field relative to the neuronal elements and the effective gradient of the E-field across the neuronal structures, as well as axonal thickness and myelination (REFS 7,8,38 for reviews). The TMS pulse shape also has a role[39,40]. Many of the relevant properties differ between cell types. These factors are discussed in FIG. 1a-d and in the text below.

The intensity of the E-field is the most relevant factor, as insufficient intensities will have no effect, whereas very high intensities will force all types of neurons to fire irrespective of their background activity. Here, it should be noted that the activation thresholds for different cells may vary; when TMS intensity is gradually increased, different neuronal types become active. Some smaller interneurons may have lower activation thresholds than the larger pyramidal cells[21]. Consequently, TMS at relatively low intensities may activate such intracortical interneurons without generating action potentials in pyramidal neurons. When TMS intensity is increased, interneuron and layer II (input) pyramidal activations become strong enough to trigger layer V (output) pyramidal neurons

trans-synaptically, that is, through the indirect mechanism (I-mechanism). At even higher intensities, pyramidal neurons are activated through the direct mechanism (D-mechanism) at the axon hillock and/or axon[21]. The orientation of the E-field relative to the cortical folds also has a major role in determining thresholds and which cell types are activated, particularly in sulci (FIG. 1b). An effective E-field gradient is created where the axon curves, resulting in the different parts of the axon being exposed to different axial currents, making axonal bends prone to stimulation[25,33,41–44] (FIG. 1b–d). Effective depolarization also occurs at synaptic terminals, or axon terminals where the axial current is hindered by the high-impedance membrane termination[25,45]. Finally, thick axons are easier to activate than thin ones, which may be related to differences in their experimentally measured time constants[46]. Correspondingly, in primates, the thresholds for direct cortical stimulation are over twofold higher in PFC than in motor cortex[47], which would be expected to lead to interregional differences in TMS and rTMS thresholds.

rTMS-induced long-term plasticity at the primary activation site. In addition to acute effects, TMS can result in long-term plasticity. The TMS pulse sequence frequency and pattern are some of the major determinants of whether the long-term plastic effects are facilitatory or suppressive[12,13,48,49] (TABLE 1). In addition, all the factors already discussed above for single-pulse TMS physiology influence rTMS-induced long-term plasticity. While most clinical rTMS trials use relatively strong intensities (~100–120% of the motor threshold), even relatively weak rTMS intensities that do not result in pyramidal cell action potentials (APs) can modulate cortical excitability, possibly by changing synaptic strengths between interneurons and pyramidal cells[50].

Several studies have reported major inter-individual differences in the magnitude and direction of plastic effects of both rTMS[51,52] and TBS[53,54]. These differences could partially reflect the

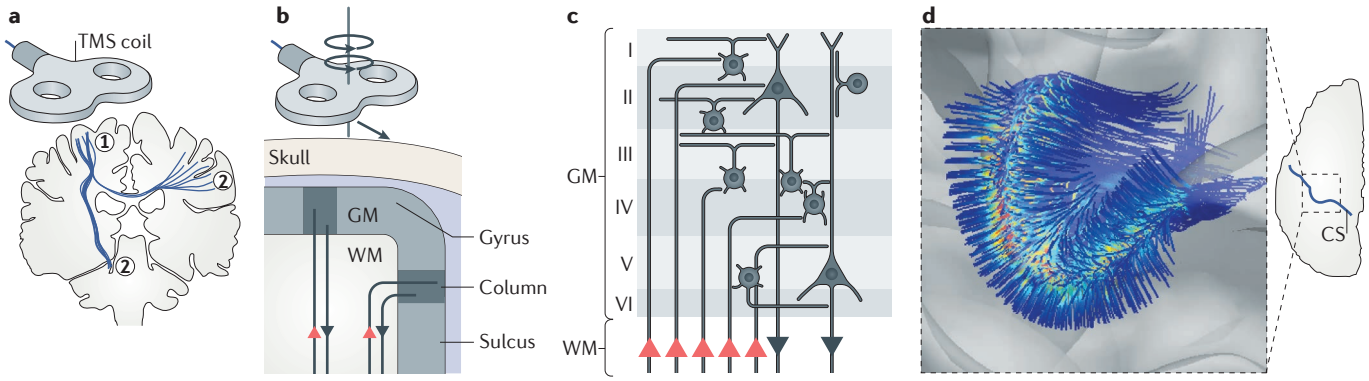

Figure 1 | **TMS physiology. a** | Primary and secondary transcranial magnetic stimulation (TMS) activations. TMS is administered using a coil, here shown above the brain (left motor cortex). According to the Maxwell–Faraday equation, the time-varying magnetic field induces an electric field. This E-field generates electric currents that depolarize transmembrane potentials and activate neurons at the primary activation site (**1**) directly under the TMS coil. The shape of the intracranial E-field, and therefore the primary activation area, depends on the coil geometry and the conductivity properties of the head[24,26,28,32,150–153]. Some coil geometries (such as the figure-of-eight coil, shown here) project focal, quite superficial E-fields, whereas larger coils (circular, double-cone and H-coils) can offer modest increases in depth penetration at the cost of reduced focality[126,154]. Regardless of coil type, the maximal E-fields occur closest to the coil. As a result, TMS primary E-fields are strongest on the brain's surface and rapidly attenuate with depth[126]. The primary activations may spread to secondary activation sites (**2**) (brainstem and contralateral hemisphere) via long-range axonal connections that may be monosynaptic or polysynaptic[5,16,17,19,37]. Note that the strong E-fields are the driving force for primary activations, whereas the connectivity-based secondary activations depend mainly on neurotransmitter release at the secondary activation sites (the E-field amplitudes are very weak far away from the coil). **b** | TMS E-fields and cortical columns in gyri versus sulci: the effects of E-field orientation and coil rotation. The TMS-induced intracranial currents flow predominantly tangential to the skull, regardless of coil type, orientation or tilt[155]. Rotating a figure-of-eight coil around the radial axis of the head (round arrows) correspondingly rotates the E-field orientation (straight arrow). The cortical columns in gyri and sulci are oriented at 90 degrees relative to each other. Therefore, sulcal activations are sensitive to whether the currents flow at right angles to the sulcal wall (parallel to the columns) or parallel to the sulcus (perpendicular to the columns). In gyri, the primary currents always flow parallel to the cortical surface (perpendicular to the columns). Consequently, rotating the coil, and therefore the E-field, strongly influences sulcal activations but has little effect in gyri. For sulcal activations, the lowest thresholds for pyramidal cell activation are typically found when the E-field is perpendicular to the sulcus[156–158]. **c** | Effect of TMS E-fields on cellular components of the cortical column in grey matter. A column is an assembly of cells containing pyramidal cells (triangular cell bodies), many inhibitory interneurons and a few excitatory interneurons (round cell bodies) distributed across cortical layers I–VI. Only pyramidal cells send outputs to white matter. Layer II (input) pyramidal neurons and interneurons may have lower TMS activation thresholds than layer V (output) pyramidal neurons. Therefore, when TMS intensity is increased above threshold, the layer V pyramidal neurons are first activated trans-synaptically, that is, indirectly (I-waves), and, with sufficiently strong intensities, directly (D-waves)[47,159–164]. Axons are the preferred activation sites for TMS, particularly at the initial segment[21], synaptic terminals and where they curve. Note that both afferent (red arrows) and efferent (black arrows) axons may be activated, leading to antidromic and orthodromic propagation to secondary activation sites, respectively. **d** | Effect of TMS E-fields on axons in white matter. The figure shows high-resolution MRI tractography results from a block in the left hemisphere motor cortex (area delineated in the insert). The tracts were exposed to a TMS E-field (figure-of-eight coil centred above and rotated perpendicular to the central sulcus, CS). The activation likelihood was computed for each axonal segment (yellow and red show the most likely activations). TMS E-fields along the cell axis have a strong effective spatial gradient where the axons bend, which occurs particularly at the grey matter–white matter border of sulcal walls, making them preferred activation sites[41–44] (see also panel **b**). GM, grey matter; WM, white matter. Panel **a**, Raij and Nummenmaa, unpublished; panel **c** is adapted with permission from REF. 165, Palgrave Macmillan; panel **d** is adapted with permission from REF. 33, Elsevier.

influence of TMS E-field intensity, location or orientation relative to the individual anatomy. Additional factors likely include individual differences in the brain's response to particular TMS sequence parameters. The origins of the inter-individual variability are still largely unknown but likely include, for example, genetic polymorphisms (see below).

Effects at secondary activation sites

Secondary activations rely on neurotransmitter release (FIG. 1) and require the triggering of efferent pyramidal cell APs at the primary site. Another mechanism for secondary activations is backpropagating (antidromic) APs from the primary activation site. Hence, rTMS of frontal cortex can lead to acute subcortical release of a wide variety of neurotransmitters[5,55–57]. The secondary activations, such as connectivity-based spread from dorsolateral PFC (DLPFC) to mesolimbic areas in major depressive disorder, are likely to be therapeutically relevant (REF. 58 for review).

Secondary areas often show long-term plastic changes[59–62], although these effects may not have the same direction of modulation as the primary area. The direction of modulation may depend on whether the physiological (pre-TMS) tonic influence from the primary to the secondary area is excitatory or inhibitory. For example, rTMS- or TBS-induced suppression of M1 will increase excitability in the contralateral M1 (REFS 51,53,54) and vice versa[63]. Additionally, both presynaptic and postsynaptic neurons at the primary site are exposed to stimulating E-fields, whereas neurons at secondary sites are influenced mainly by neurotransmitter release. Therefore, the plasticity-inducing mechanisms could differ between the primary and secondary targets.

Cellular-level mechanisms of rTMS

Studies on rTMS in cell culture and slices, while not reflecting the exact reality in the living human brain, have offered insight into the possible cellular-level events. For example, these studies have identified mechanisms that require simultaneous activation of presynaptic and postsynaptic compartments, reminiscent of the direct mechanism[64–66] and similar to classical NMDAR-dependent Hebbian plasticity. Further, rTMS promotes spine formation in entorhino–hippocampal slice culture, and the effects of a magnetic field-induced electric current on spine size is predominantly seen in small spines, thus suggesting differential effects on specific subpopulations of spines[64]. These experiments indicate a direct and enduring action on spines, even *in vitro* when their afferents are removed surgically.

As intracortical interneurons can be activated even at low intensities (FIG. 1), modulation of GABAergic input to pyramidal neurons is likely to play a role in rTMS plasticity[67–69]. However, it is likely that multiple mechanisms, which differ in the requirement for postsynaptic activation and its timing, coexist[70,71] (for additional reviews, see REFS 72–78).

As suppressive (1 Hz) and facilitatory (20 Hz) rTMS have opposing effects, despite the fact that the individual TMS pulses are identical, the pulses must also interact across time. While the detailed mechanisms are poorly understood, it is tempting to hypothesize that Ca^{2+} plays a key role. rTMS at 20 Hz results in Ca^{2+} accumulation in postsynaptic dendrites[79], thereby increasing the likelihood that the presynaptic axon and the postsynaptic dendrite are simultaneously active, which would be expected to potentiate the synapse. Further, brief, strong increases in postsynaptic Ca^{2+} induce LTP, whereas prolonged, modest postsynaptic Ca^{2+} increases induce LTD[80]. Moreover, spTMS causes a Ca^{2+}-mediated inhibition of pyramidal cell dendritic activity lasting approximately 500 ms (REF. 81). While these observations could partially explain the difference between high- and low-frequency rTMS effects, the underlying downstream cascade is still poorly understood and likely more complex[82].

The acute synaptic events discussed above may lead to long-term changes via dendritic spine growth and receptor or neurotransmitter regulation, with possible contributions from presynaptic axonal sprouting and re-uptake modulation. In addition, nonsynaptic mechanisms may also be involved, such as metabotropic receptor activation, brain-derived neurotrophic factor upregulation, genetic polymorphism[83,84], glial cell modulation[85,86] and epigenetic changes[87] (for reviews, see REFS 74,76).

Neuroplasticity underlying addiction

Compelling evidence from preclinical and clinical studies indicates that rTMS of frontal brain regions produces adaptations of specific subcortical neural circuits, resulting in substantial behavioural changes[56,88–91]. This effect may be mediated by modifications in the release of neurotransmitters and neuromodulators with effects on synaptic gain, signalling pathways and gene transcription.

Neurobiology of addiction

Chronic exposure to drugs of abuse typically induces reward-related behaviours by producing neurobiological adaptations of the mesocorticolimbic dopamine system[92,93] (FIG. 2), which is also involved in the aversive effects of drug consumption[94,95] and represents negative motivation underlying the occurrence of relapses.

Hence, the dopamine hypothesis of drug addiction, key in the brain disease model of addiction, has mainly focused attention on the dopamine pathway as a neural substrate of SUDs and drug action[1,4,94,96,97]. Seminal preclinical studies have shown that increased AMPAR (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor)-mediated synaptic responses have been associated with LTP of glutamatergic synapses onto ventral tegmental area (VTA) DA neurons after both acute and chronic drug exposure[98–104]. This form of synaptic plasticity, pivotal in memory and learning mechanisms, is represented as a portion of a 'drug engram' (or drug memory trace), which precedes subsequent specific and long-lasting neurocircuitry modifications resulting from chronic drug use in individuals who are addicted[2,105–108].

Clinical data support the hypothesis that brain DAergic neurotransmission is 'blunted' in drug addiction, with drug consumption and lowered DA receptors triggering much smaller increases in DA levels in people with addiction than in control subjects[109–111]. This state, which is characterized by anhedonia and is associated with hypoactivity of the mesocorticolimbic DAergic circuit, increases the risk of drug use escalation and relapse, thus perpetuating the addiction cycle[110,112,113]. Neural changes associated with the addicted state are embedded within the mesocorticolimbic system and spread to the circuit of the extended amygdala and the 'anti-reward' system'[114,115], involving corticotropin-releasing factor and glutamate (GLU), among other neurotransmitters. In particular, GLU transmission has been shown to be tightly time-locked with DA signalling to promote spine enlargements[116], thus favouring Hebbian learning mechanisms through spike-timing-dependent plasticity[117]. In line with a close interdependence between DA and GLU transmission, alcohol-dependent rats show impaired NMDAR-dependent LTD, with a loss of long, thin dendritic spines[118]. As these spines are fundamental learning sites[119], in which DA and GLU converge to form the ventral striatal 'synaptic triad'[120], their

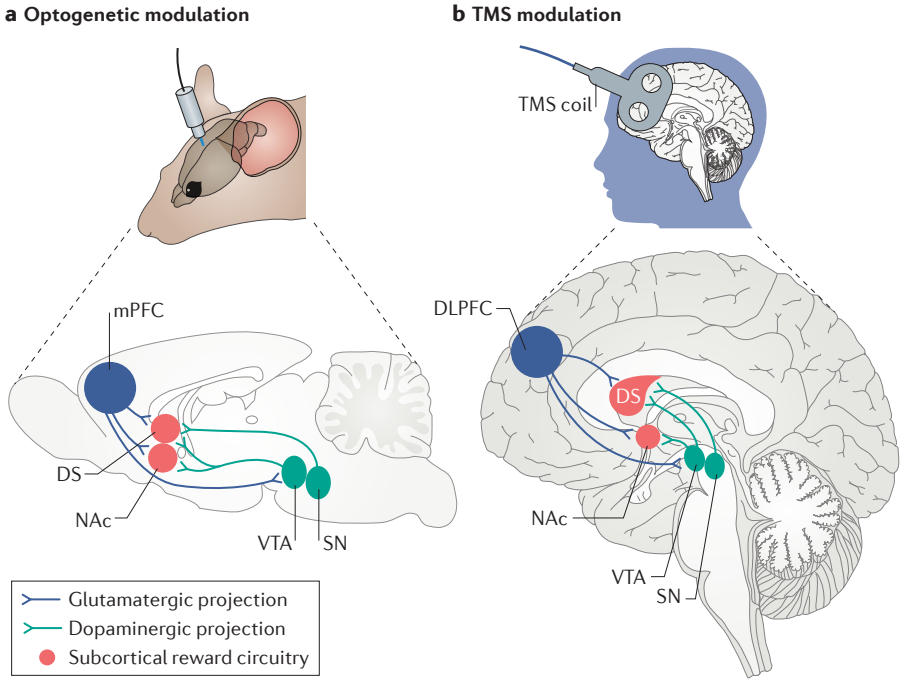

Figure 2 | **Brain stimulation mechanisms in animal and human models of addiction.** The figure emphasizes similarities between optogenetic stimulation of the medial prefrontal cortex (mPFC), which suppresses compulsive cocaine seeking in rats[4], and the hypothetical mechanism of the transcranial magnetic stimulation (TMS)-induced dorsolateral PFC (DLPFC) stimulation yielding a reduction in cocaine use and relapse in people addicted to cocaine. The mechanism of this therapeutic effect may include modulated activity in subcortical reward circuitry involving the dopaminergic midbrain ventral tegmental area (VTA) and nucleus accumbens (NAc) through glutamatergic PFC efferents. Strengthening the hypofunctional PFC[166] (primary mechanism) — which, through pyramidal efferent neurons, directly projects to the spiny neuron of the NAc[2] — and strengthening the PFC→VTA pathway should 'boost' dopamine release in the NAc (secondary mechanism). DS, dorsal striatum; SN, substantia nigra. Note that, for illustrative purposes, DLPFC is here shown at the brain midline (where the relevant subcortical nuclei are), but it is in fact situated on the lateral frontal cortex. Figure adapted with permission from REF. 167, Macmillan Publishers Limited.

low DA tone-dependent loss may underlie learning deficits typical of individuals with alcohol and SUDs.

Neuroplastic effects of rTMS on addiction circuitry

In vivo optogenetic stimulation of rat prelimbic cortex prevented compulsive cocaine seeking, whereas optogenetic inhibition of the same brain area increased cocaine seeking[2]. In addition, the strengthening of the accumbal indirect pathway, as indexed by a potentiation of synapses onto DA D2 receptor (D2)-containing spiny neurons (SNs) of the nucleus accumbens (NAc), was associated with resilience towards compulsive cocaine seeking[105]. Conversely, the weakening of the accumbal indirect pathway might be a synaptic marker required for the expression of compulsive behaviour towards drugs such as cocaine and alcohol[100,105]. These findings provide the neurobiological underpinnings for a therapeutic role of rTMS-driven PFC stimulation in treating cocaine dependence. Hence, an optogenetic study of compulsive cocaine self-administration[100] in rats inspired a pilot open-label clinical study, in which high-frequency rTMS of the left DLPFC reduced cocaine use and craving in patients with cocaine use disorder[121]. Additional clinical pilot studies, albeit preliminary, provide further support for the potential role of rTMS in cocaine craving[122,123] and intake[124]. Further clinical work in larger samples and with rigid, controlled trial designs is needed to further investigate the potential role of rTMS in addictions.

That high-frequency rTMS of DLPFC is potentially useful in treating cocaine addiction might be explained by its effects on neurotransmitters and neuromodulators. Given the abovementioned roles of GLU and DA (among others) in the addicted state, we mainly focus on the effects of high-frequency rTMS on the levels of these two neurochemicals in cortical and subcortical regions. Accordingly, rTMS of frontal brain regions produces a selective stimulation of hippocampal DA release, with no changes in serotonin or noradrenaline efflux[125], thereby positioning DA as a key candidate neurotransmitter system directly and selectively modulated by rTMS.

Indeed, imaging studies have shown that high-frequency rTMS of DLPFC induces a sustained increase of DA levels in the human ventral striatal complex[5,55] and in cortical areas[56]. Accordingly, microdialysate DA efflux studies in rodent NAc have provided similar results[89,90]. Direct stimulation of NAc by the induced E-field appears to be unlikely because the intensity of stimulation sharply decays with distance from the coil[126]. Thus, indirect secondary effects (see above) from PFC stimulation, occurring in the NAc through NAc-projecting DA neurons (for more details, see REF. 96), are more likely. Remarkably, only low-frequency rTMS modifies GLU levels in the rat NAc[91]. This effect is consistent with the notion that differences in rTMS frequency and pattern result in discrete short- and long-term effects on neural plasticity. In any case, the translational studies mentioned above suggest that the mechanism of action of rTMS involves neuromodulation of subcortical areas, such as the NAc and the VTA, via its broader action on cortical areas such as DLPFC. In the field of addiction, two sham-controlled and double-blind controlled studies support this hypothesis: these studies indicate that 'deep' rTMS results in a substantial reduction in number of drinks per day in patients with alcoholism[88,127] and in cigarette use and level of nicotine dependence in cigarette smokers[128]. Factors such as the history of synaptic activity and intrinsic plasticity not only contribute to the addicted state but also may be crucial in shaping neurochemical outcomes of rTMS. Therefore, it would be interesting to assess whether, and how, high-frequency rTMS affects the levels of other neuromodulators that are key in synaptic plasticity, such as endogenous cannabinoids[129,130]. Indeed, these lipid signalling molecules are essential mediators of diverse forms of synaptic plasticity, as well as regulators of homosynaptic and heterosynaptic metaplasticity[131,132].

Another issue related to clinical applications of rTMS in SUDs is whether rTMS should be applied to the left or right hemisphere. Some studies targeted the left DLPFC, while a smaller number of studies targeted the right DLPFC. Only three studies

have compared left versus right DLPFC: one indicated reduced spontaneous craving for cocaine after rTMS targeting the left side[122], another for the right side[133], whereas the third showed reduced spontaneous craving for alcohol after targeting either the right or the left side[134]. Notably, two of the studies discussed above applied 'deep' rTMS by use of an H-coil, capable of bilaterally stimulating DLPFC. In summary, the clinical studies carried out so far do not provide a clear-cut answer on whether left, right or bilateral stimulation may be the best therapeutic approach. Nonetheless, the possibility of laterality raises intriguing translational questions. In fact, converging evidence supports hemispheric differences in anatomical and neurochemical circuits, as well as network modulation of behaviour and cognition[135]. The role of DA in experience-dependent plasticity, which can be dynamically affected by both short- and long-term activity-dependent forms of plasticity, is well known. Nonetheless, whether this asymmetry takes part in the control of neuronal (for example, D2-SN) activity, whose re-wiring might contribute to the reduction of drug craving and taking in humans, awaits confirmation.

High-frequency rTMS increases DA levels not only in the NAc, ACC and PFC but also in the hippocampus, where activation of specific ensemble neurons is sufficient for engram retrieval[106,136]. Accordingly, a small portion of neurons in the amygdala are recruited to be part of the 'cocaine engram'. This finding is particularly relevant because the amygdala is involved in those processes through which a neutral cue acquires conditioned rewarding properties when paired to a rewarding stimulus such as cocaine. Moreover, one might speculate that high-frequency rTMS of left DLPFC could strengthen synaptic plasticity at excitatory synapses onto D2-SNs. As such, D2-SNs may be a critical component of a large, compulsive drug-taking memory engram. In fact, the weakening of excitatory synapses onto D2-SNs is associated with the expression of habitual and compulsive drug seeking[137]. In this regard, it is worth mentioning that an engram-erasing capacity of TMS was anticipated almost three decades ago, when it was shown that 50 TMS pulses may cause retrograde memory disruption[138].

Future outlook

The initial rTMS results from SUD trials appear promising. Double-blind studies are both warranted and necessary to examine how efficient the therapies are and how they could be further improved.

At the same time, for any clinical indication, rTMS therapies that strongly reduce symptoms are currently scarce. There are multiple possible reasons for their rarity. Mechanistic insight into the neurobiological effects of TMS remains limited. The lack of detailed knowledge on cellular and molecular mechanisms of rTMS-mediated neural plasticity and inter-individual variability interferes with the ability to deliver clinical rTMS therapies that would work in all patients. For example, future research could be aimed at understanding the interactions between rTMS frequency, pattern of stimulation and coil orientation relative to the anatomy. Further, achieving cumulative long-term effects with conventional rTMS seems to require weeks of stimulation sessions[139]. Developing novel TMS protocols that result in stronger and more persistent long-term plasticity, with fewer treatment visits than in conventional rTMS, would improve the clinical utility of the method. It also remains a future possibility that TMS sequence parameters could be customized to match the individual physiology of the patient (for example, REFS 140,141). Other possible future directions could capitalize on state dependency by combining rTMS with addiction-related behavioural tasks and/or closed-loop rTMS–EEG (see REF. 142 for a review). More research in all these areas is warranted.

In addition to developing TMS, it will also be necessary to better understand the disease-specific brain pathophysiology of addiction in order to select optimal cortical and network-level targets and other parameters for TMS. Neuroimaging tools could be useful in predicting which patients will benefit from rTMS and which are likely to relapse, as well as in guiding target selection[143–145]). As all TMS activations critically depend on the relation between the E-fields and anatomy, and as experimental rTMS effects may be improved by using TMS neuronavigation[59], future clinical trials would likely benefit from using individual MRIs and TMS navigator devices[146]. Estimating the E-field intensity, orientation and gradients using individual anatomy[32,33] can be used during planning to target the intended cortical areas[147] and networks[143,148] in order to maximize the physiological and therapeutic effects.

In conclusion, TMS appears ready to be subjected to rigorous, hypothesis-driven experimental scrutiny and to be tested as a promising therapeutic aid for a brain disease, that is, addiction[149]. Its mechanisms of action, which tap into the brain's strong potential for functional reorganization, offer new hope for creating enduring changes to enable the rewiring of a brain system gone awry.

Marco Diana is at the 'G. Minardi' Laboratory for Cognitive Neuroscience, Department of Chemistry and Pharmacy, University of Sassari, 07100 Sassari, Italy.

Tommi Raij is at the Shirley Ryan AbilityLab, Center for Brain Stimulation, the Department of Physical Medicine and Rehabilitation and the Department of Neurobiology, Northwestern University, Chicago, Illinois 60611, USA.

Glossary

Conventional rTMS
A form of TMS sequences where the pulses are given at regular intervals (for example, 1 Hz or 20 Hz).

Direct mechanism
(D-mechanism). A mechanism in TMS in which the pyramidal neurons are directly activated by the TMS-induced E-fields.

Electric field
(E-field). The field induced by the TMS coil. When the E-field interacts with a conducting medium, this drives electric currents.

Indirect mechanism
(I-mechanism). A mechanism in TMS in which the pyramidal neurons are activated trans-synaptically, that is, indirectly.

Motor threshold
(MT). The minimum TMS intensity that must be applied to the motor cortex to induce a peripheral muscle contraction.

Quadripulse stimulation
(QPS). A form of patterned TMS where the TMS pulses are arranged in more complex patterns than in conventional rTMS.

Repetitive paired-pulse TMS
(rppTMS). A form of patterned TMS where the TMS pulses are arranged in more complex patterns than in conventional rTMS.

Repetitive TMS
(rTMS). A form of TMS in which individual TMS pulses are presented at regular time intervals (for example, 1 Hz, 20 Hz). Also known as 'conventional rTMS'.

Theta burst stimulation
(TBS). A form of patterned TMS where the TMS pulses are arranged in more complex patterns than in conventional rTMS.

TMS navigator
A device that enables accurate tracking of the TMS coil position relative to the subject's head. Often integrated with MRI of the subject's head.

Miriam Melis is at the Department of Biomedical Sciences, Division of Neuroscience and Clinical Pharmacology, University of Cagliari, 09042 Monserrato, Italy.

Aapo Nummenmaa is at the Massachusetts General Hospital (MGH)/Massachusetts Institute of Technology (MIT)/Harvard Medical School (HMS) Athinoula A. Martinos Center for Biomedical Imaging, Harvard Medical School, Boston, Massachusetts 02129, USA.

Lorenzo Leggio is at the Section on Clinical Psychoneuroendocrinology and Neuropsychopharmacology, US National Institute on Alcohol Abuse and Alcoholism Division of Intramural Clinical and Biological Research (NIAAA DICBR) and US National Institute on Drug Abuse Intramural Research Program (NIDA IRP), NIH (National Institutes of Health), Bethesda, Maryland 20892, USA; and at the Center for Alcohol and Addiction Studies, Brown University, Providence, Rhode Island 02912, USA.

Antonello Bonci is at the US National Institute on Drug Abuse Intramural Research Program (NIDA IRP); and at the Departments of Neuroscience and Psychiatry, Johns Hopkins University, Baltimore, Maryland 21224, USA.

Correspondence to A.B
antonello.bonci@nih.gov

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