Combining non-invasive transcranial brain stimulation with neuroimaging and electrophysiology: Current approaches and future perspectives

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ABSTRACT

Non-invasive transcranial brain stimulation (NTBS) techniques such as transcranial magnetic stimulation (TMS) and transcranial current stimulation (TCS) are important tools in human systems and cognitive neuroscience because they are able to reveal the relevance of certain brain structures or neuronal activity patterns for a given brain function. It is nowadays feasible to combine NTBS, either consecutively or concurrently, with a variety of neuroimaging and electrophysiological techniques. Here we discuss what kind of information can be gained from combined approaches, which often are technically demanding. We argue that the benefit from this combination is twofold. Firstly, neuroimaging and electrophysiology can inform subsequent NTBS, providing the required information to optimize where, when, and how to stimulate the brain. Information can be achieved both before and during the NTBS experiment, requiring consecutive and concurrent applications, respectively. Secondly, neuroimaging and electrophysiology can provide the readout for neural changes induced by NTBS. Again, using either concurrent or consecutive applications, both "online" NTBS effects immediately following the stimulation and "offline" NTBS effects outlasting plasticity-inducing NTBS protocols can be assessed. Finally, both strategies can be combined to close the loop between measuring and modulating brain activity by means of closed-loop brain state-dependent NTBS. In this paper, we will provide a conceptual framework, emphasizing principal strategies and highlighting promising future directions to exploit the benefits of combining NTBS with neuroimaging or electrophysiology.

Introduction

Non-invasive transcranial brain stimulation (NTBS) plays a pivotal role in human systems and cognitive neuroscience as it can reveal the relevance of certain brain structures or neuronal activity patterns for a given cognitive or motor function, especially when used in conjunction with neuroimaging and electrophysiology. Brain mapping techniques are correlational in nature. They can associate specific temporo-spatial activity patterns with certain cognitive functions, but cannot demonstrate their actual relevance. In contrast, NTBS can be used to interfere with or enhance a specific neuronal pattern (e.g. entrain an oscillation) to show that it is necessary (though may be not sufficient) for a certain brain function, rather than being a mere epiphenomenon.

Classical transcranial electric stimulation (TES) uses brief high-voltage currents which are applied via local bipolar scalp electrode montages (Merton and Morton, 1980). TES is a very painful stimulation technique and hardly used in modern cognitive neuroscience research (Rossini et al., 2015). Since 1985, TES has been replaced by painless NTBS techniques (section "A primer on non-invasive transcranial brain stimulation (NTBS)"): first transcranial magnetic stimulation (TMS) (Barker et al., 1985), then later transcranial direct current stimulation (TDCS) (Nitsche and Paulus, 2000) and transcranial alternating current stimulation (TACS) (Antal et al., 2008), together referred to as transcranial current stimulation (TCS). Both TMS and TCS nowadays can be combined with a variety of neuroimaging and

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electrophysiological techniques, either consecutively or concurrently (section "Combining NTBS with neuroimaging and electrophysiology"). The benefit for NTBS is twofold. Firstly, neuroimaging and electrophysiology can inform subsequent NTBS (section "Neuroimaging and electrophysiological approaches to inform NTBS"), providing information about where (section "Where to stimulate?"), when (section "When to stimulate"), and how (section "How to stimulate?") the brain should be stimulated. Secondly, neuroimaging and electrophysiology can provide readouts (i.e. indices or measurements) of neuronal activity, which allow to assess the changes caused by NTBS (section "Neuroimaging and electrophysiology as readout for NTBS effects"). "Online" brain mapping offers an immediate readout of acute NTBS effects that arise during or seconds after the application of NTBS (section "Concurrent application to read out immediate effects of online NTBS"). "Offline" brain mapping is performed after a plasticity-inducing NTBS protocol to capture neuromodulatory after-effects that outlast NTBS for minutes to hours (section "Consecutive application to read out after-effects induced by offline NTBS"). Both strategies can be combined to close the loop between measuring and modulating brain activity by means of closed-loop brain state-dependent brain stimulation (section "Closing the loop with brain-state dependent NTBS"). Here we present a conceptual framework for combining NTBS with neuroimaging and electrophysiology, emphasizing principal strategies and highlighting promising future directions. Importantly, TCS and TMS are not discussed in isolation, but rather contrasted and compared in each of the sections. Due to space restrictions, we do not provide an exhaustive technical review of the state-of-the-art for combining NTBS and neuroimaging/electrophysiology (Siebner et al., 2009a).

A primer on non-invasive transcranial brain stimulation (NTBS)

NTBS can be given "offline" or "online" with respect to a task or brain mapping (Fig. 1): (1) The "Offline" approach applies conditioning NTBS protocols that can induce long-term potentiation (LTP)-like or long-term depression (LTD)-like plasticity and hereby facilitate or inhibit a certain brain region before a task or brain mapping. Task performance and brain activity measurements after NTBS are used as readouts to uncover the consequences of NTBS-induced plasticity on human brain function (Siebner et al., 2009a). (2) The "Online" approach applies NTBS during a task or neuroimaging to measure its immediate impact on brain function or activity. Depending on the applied NTBS technique and the very stimulation parameters chosen, online NTBS can be used (a) to quantify local network properties by applying stimuli that are strong enough to evoke direct neural output (i.e., synaptic activity), (b) to interfere with ongoing spontaneous neural activity or task-related neuronal processing, or (c) to modulate the level or timing of spontaneous or task-related neuronal activity.

Fig. 1. Principal experimental approaches using NTBS. The "Online" NTBS approach applies NTBS during a task or neuroimaging to measure its immediate consequences for behavior, perception, or brain activity. Depending on the applied NTBS technique and the very stimulation parameters chosen, online NTBS can be used (a) to quantify local network properties by applying stimuli that are strong enough to evoke direct neural output (i.e., synaptic activity), (b) to interfere with ongoing spontaneous neural activity or task-related neuronal processing, or (c) to modulate the leve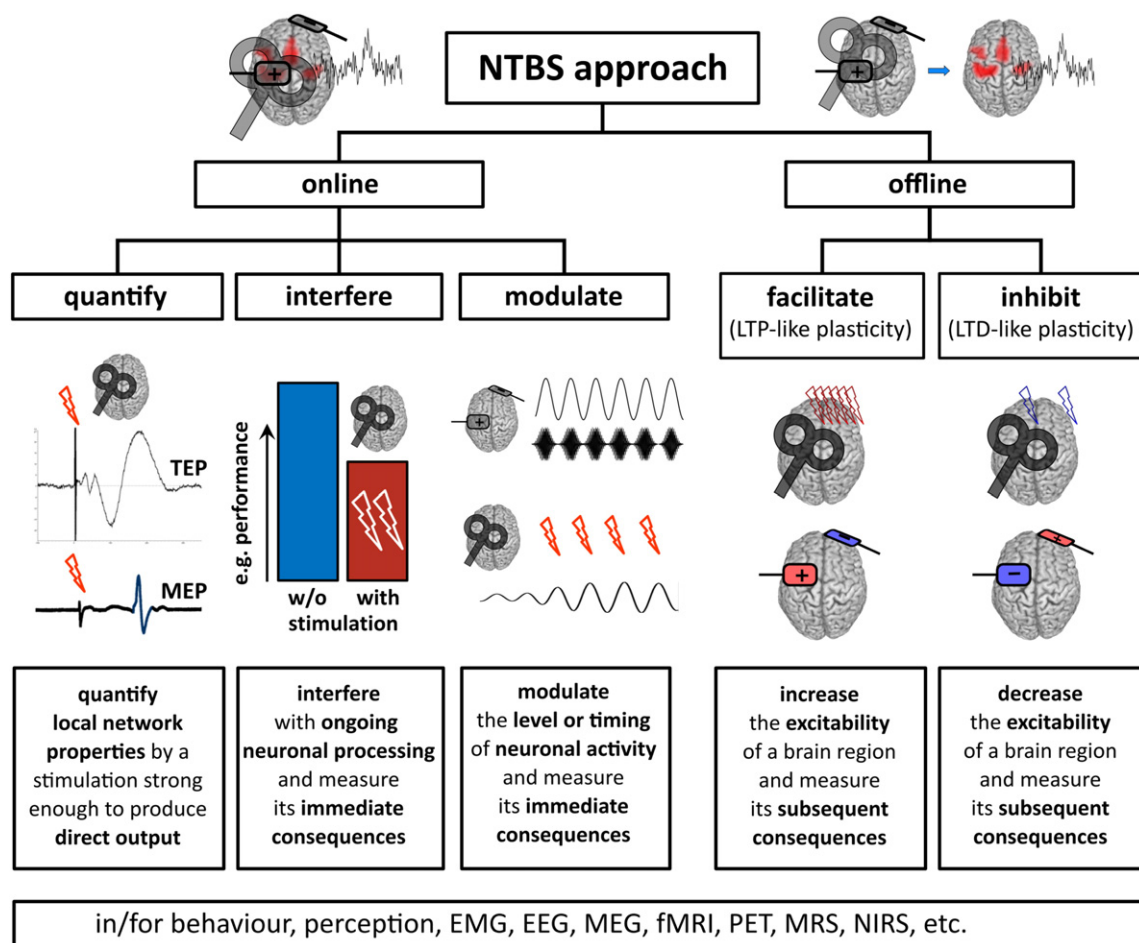l or timing of spontaneous or task-related neuronal activity (see section "A primer on non-invasive transcranial brain stimulation (NTBS)" for details). The "Offline" NTBS approach applies conditioning protocols that can induce long-term potentiation (LTP)-like or long-term depression (LTD)-like plasticity and hereby facilitate or inhibit a certain brain region before a task or brain mapping (e.g. fMRI). Task performance and brain activity measurements are used as readouts to uncover the consequences of NTBS-induced plasticity on human brain function.

All NTBS techniques produce electrical stimulation of neurons in the brain, yet these techniques rely on different mechanisms of action. This has strong conceptual implications with regard to their use in cognitive neuroscience: TCS passes the electric current directly through scalp and skull whereas TMS "bypasses" these electric obstacles by producing a magnetic field that induces an electric current in the brain tissue. TMS and TCS also differ in their neurophysiological mechanism of action: The steep, high-amplitude currents induced by TMS (and TES) are able to fully depolarize the axonal membrane of cortical neurons and thereby trigger action potentials. In contrast, the comparably weak currents of TCS affect the neurons' membrane potential more subtly. TCS is thought to shift the membrane potential causing a slight depolarization or hyperpolarization. The TCS-induced shift in membrane potential increases or decreases the likelihood of spontaneous neuronal firing (Bindman et al., 1964; Paulus et al., 2013). TMS and TCS also differ substantially in terms of the effectively stimulated brain volume, with relevant implications for their spatial selectivity (Opitz et al., 2015; Thielscher et al., 2011) and the specific information needed to configure an effective stimulation protocol.

TDCS (Nitsche and Paulus, 2000), TACS (Antal et al., 2008), and TMS (Barker et al., 1985; Walsh and Cowey, 2000) complement each other, as these techniques have different strengths and weaknesses. While either technique can induce bidirectional plasticity using the offline approach, they do substantially differ regarding their online application. Because TMS can excite neurons in a suprathreshold fashion, it is well suited to actually evoke neuronal activity, allowing to quantify network properties such as excitability and connectivity or to interfere with ongoing spontaneous or task-related neuronal activity (Siebner et al., 2009b). In contrast, TCS is primarily suited to modulate both the level and timing of spontaneous or task-related neuronal activity (Reato et al., 2013). The disruptive effect of TMS on neuronal information processing, which is key to the "interference" approach, is not fully understood but probably involves a combination of the following mechanisms: (i) degradation of the signal-to-noise ratio by evoking random neuronal excitation, (ii) aligned GABAergic inhibition via feedback inhibition or direct stimulation of inhibitory interneurons, (iii) decrease of entropy and thereby information capacity due to the resulting neuronal synchronization (Siebner et al., 2009b; Walsh and Cowey, 2000). In any case, the goal of the interference approach is to transiently induce a so-called "virtual lesion". Here TMS-induced neurostimulation causes a functional perturbation of the stimulated region affecting ongoing neural processing for a few tens to hundreds of milliseconds (Pascual-Leone et al., 2000). In contrast, the "modulation" approach aims not to acutely disrupt but rather to gently shape the neuronal activity profile, gently biasing the stimulated brain region towards a specific working mode while leaving it principally intact. The goal of this approach is to increase or decrease either the level (e.g. with TDCS) or the timing (e.g. with TACS) of internally generated excitatory or inhibitory activity patterns. TMS and TCS therefore often require different neuroimaging or electrophysiological readouts to have their effects adequately assessed (section "Neuroimaging and electrophysiology as readout for NTBS effects") and their combination with different neuroimaging and electrophysiological techniques poses specific technical challenges (Siebner et al., 2009a).

Combining NTBS with neuroimaging and electrophysiology

Many non-invasive neuroimaging and electrophysiological techniques are available to map different aspects of brain structure and function at varying levels of spatial and temporal resolution (Bandettini, 2009). These techniques can be combined with NTBS in a consecutive fashion to assess the offline effects of NTBS after stimulation. Given the limited time of the induced after-effects, recordings should start as soon as possible after the end of the plasticity inducing NTBS protocol. This requires a swift transfer of the participants from the NTBS laboratory to the imaging facility. At the same time, it might be important not to unintentionally interfere with the induced NTBS effects during this

interval, avoiding unnecessary activation of targeted brain regions of interest, e.g., muscle activation (Siebner et al., 2003), speech production/comprehension (Hartwigsen et al., 2013), or visuospatial attention (Marshall et al., 2015b). Therefore, NTBS is often applied within or close to the MR scanner room or wheelchairs are used for the transfer while the experimenter tries to maintain a relaxed atmosphere and avoid overly strong effort or excitement of the participant.

In contrast, the concurrent application of NTBS during the recording of neuroimaging or electrophysiological data is complicated by a variety of NTBS-related artefacts. The nature and severity of these artefacts differs markedly between the various NTBS-Imaging combinations. A detailed description is beyond the scope of this paper. Comprehensive reviews on these issues can be found elsewhere (Siebner et al., 2009a) and specific advice is available on how to prevent or remove those artefacts for TMS–EEG (Herring et al., 2015; Ilmoniemi and Kicic, 2010; Korhonen et al., 2011; Mäki and Ilmoniemi, 2011; Mutanen et al., 2013; Rogasch et al., 2014), TMS–fMRI (Bestmann et al., 2008a), TMS–EEG–fMRI (Peters et al., 2013), TMS–NIRS (Parks, 2013), TCS–fMRI (Saiote et al., 2013), or TCS–MEG (Marshall et al., 2015a; Neuling et al., 2015; Soekadar et al., 2013).

While we will mainly discuss the manifold benefits neuroimaging and electrophysiology provide for both optimizing and assessing NTBS, there are cases where NTBS results inform neuroimaging analysis. For example, pre-surgical neuronavigated TMS mapping has been successfully used to provide seed points for fibre tracking based on diffusion weighted imaging (DWI) data when reconstructing the corticospinal tract (Frey et al., 2012) as well as language-relevant pathways (Sollmann et al., 2015). Future scenarios may even extend to the combination of DWI with dual-coil TMS approaches, informing measures of structural by those of effective connectivity.

Neuroimaging and electrophysiological approaches to inform NTBS

Neuroimaging and electrophysiological measures can guide NTBS, providing information about where, when and how to apply the stimulation (Fig. 2). This information can be exploited to improve the precision and efficacy of NTBS protocols. The delay between extraction of the required information from neuroimaging or electrophysiology and application of NTBS can vary considerably. Information with high inter- but low intra-subject variability, for instance about brain structure, can be acquired before the start of the NTBS experiment, sometimes even in a separate session, allowing recordings and NTBS to be conducted in a consecutive fashion. However, information with high intra-subject variability, for instance about the functional brain state, need to be determined immediately before stimulation onset or even traced continuously for repeated stimulation trials. The latter requires a concurrent mapping approach during which functional brain mapping and the application of NTBS are interleaved.

Where to stimulate?

Which information is required to optimize the spatial accuracy of NTBS? A certain degree of spatial information is always necessary to apply NTBS to the brain region of interest, no matter whether NTBS is used in an offline or online approach. For TMS, not only the position of the TMS coil relative to the target site (precision of a few millimetres) but also its orientation relative to the orientation of the cortical gyri (precision of a few degrees) is of crucial importance to induce a current of appropriate strength and orientation in the targeted brain tissue, while leaving regions of no interest as unaffected as possible. For TCS, the placement of the electrodes on the scalp and the orientation of the induced current flow determine the optimal electrode montage. Two steps are necessary for spatial optimization of NTBS. First, the precise location of the target site needs to be localized within the brain of each subject. Thereafter, the position and orientation of the stimulation
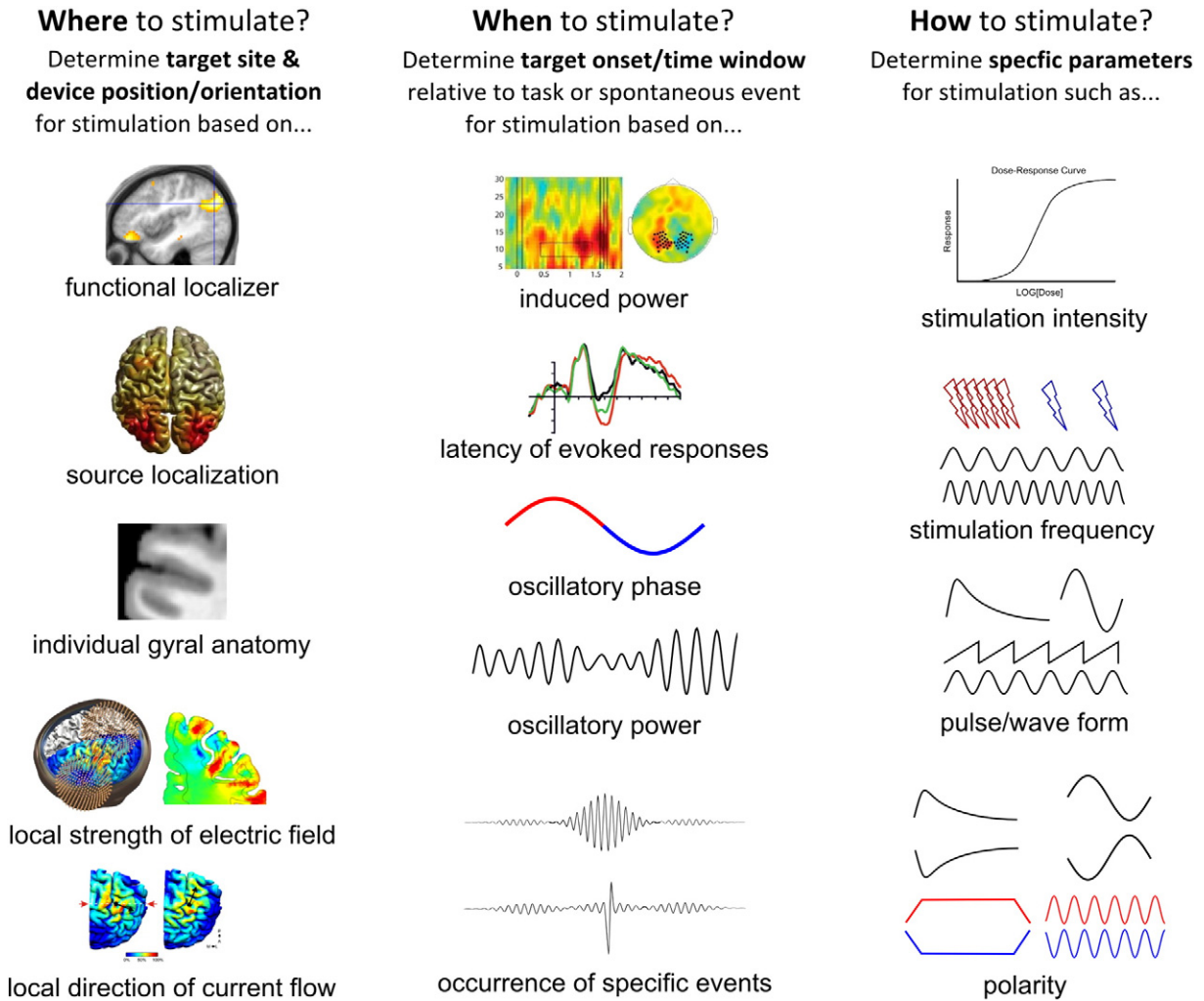
Where to stimulate?
Determine **target site & device position/orientation** for stimulation based on…

functional localizer

source localization

individual gyral anatomy

local strength of electric field

local direction of current flow

When to stimulate?
Determine **target onset/time window** relative to task or spontaneous event for stimulation based on…

induced power

latency of evoked responses

oscillatory phase

oscillatory power

occurrence of specific events

How to stimulate?
Determine **specfic parameters** for stimulation such as…

stimulation intensity

stimulation frequency

pulse/wave form

polarity

Fig. 2. Neuroimaging and electrophysiological measures may inform NTBS about where, when, and how to stimulate. This information can be exploited to improve the precision and efficacy of NTBS protocols and to enable the investigation of NTBS effects in a brain state-dependent manner by relating the NTBS effects to the spontaneous or task-related neuronal activity at the time of stimulation.

devices, the TMS coil or the TCS electrode montage needs to be determined to apply a current of optimal intensity and orientation to the target site.

Consecutive application to derive spatial information

The target site and optimal position of the NTBS device are relatively stable entities. Therefore, neuroimaging or electrophysiological mapping can be performed before starting an NTBS experiment to derive the necessary spatial information. The choice to target a certain region is primarily motivated by the research question and commonly based on the existing literature. Yet the precise location of the target site in an individual brain still remains to be determined due to substantial inter-subject anatomical variability. Several approaches are listed here in the order of increasing precision and experimental power (Sack et al., 2009; Sparing et al., 2008).

(1) Skull anatomy-based site selection relies on skull anatomy alone and does not require any information from neuroimaging but is also relatively inaccurate. This approach uses cranial landmarks to determine the approximate location of a brain region, e.g. a certain distance lateral and anterior of the vertex or inion for the primary motor hand area ($M1_{HAND}$) and the early visual cortex, respectively; often also positions of the 10–20 EEG system are used, such as C3/C4 for $M1_{HAND}$, O1/O2 for visual cortex, or F3/F4 for the dorsolateral prefrontal cortex (DLPFC).

(2) Brain anatomy-based site selection relies on neuroanatomical landmarks and is based on information derived from (e.g. T1-weighted) structural MRI. Some brain regions can be roughly determined based on the spatial pattern of cortical gyri and sulci and their respective location or shape. For instance, the $M1_{HAND}$ can be identified as omega-/epsilon-shaped "hand-knob" in the central sulcus (Boroojerdi et al., 1999; Yousry et al., 1997), and the frontal eye field (FEF) is often assumed anterolateral to the intersection of superior frontal sulcus and precentral sulcus (but see Vernet et al., 2014).

(3) Functionally defined site selection relies on the functional involvement of a specific brain region and requires structural (MRI) as well as functional imaging data (e.g. fMRI or MEG/EEG) to derive the coordinates for which neuronal activity is maximally associated with a certain task condition or experimental contrast. Either (a) the coordinates are identified in previous group studies and denormalized to estimate the location in the specific subject's brain, for instance for the left posterior inferior frontal gyrus (Hartwigsen et al., 2013), or (b) individual functional localizers (independent functional imaging experiments) are conducted to identify the coordinates for each subject. This kind of spatial information can be derived from fMRI, for instance to localize the FEF (Marshall et al., 2015b)), but also high-density MEG or EEG can be used for this purpose, especially if one is interested in the spatial localization of a certain

time-resolved process like an ERP or oscillation such as the parietal alpha oscillation generator (Thut et al., 2011b). This approach provides maximal precision and is feasible for all potential target sites.

(4) Stimulation-based site selection relies on the causal demonstration of a certain brain region being involved in a specific function and requires an NTBS technique like TMS, which can be used to either quantify the output of the target brain structure or to interfere with the function of the target brain structure. When using the quantification approach, the coil position and orientation causing the maximal (or most consistent) output of the target structure, e.g. the amplitude of the motor evoked potential (MEP) for M1$_{HAND}$ or phosphene perception for the visual cortex, is considered the optimal spatial configuration. Following the interference approach, the coil position and orientation producing the maximally disruptive effects is considered optimal, e.g. when functionally localizing Broca's area by inducing speech arrest (Rogic et al., 2014) or to localize the FEF by saccade delay (Ro et al., 2002). In fact, stimulation-based localization is the only approach providing proof that the NTBS application actually reaches the neuron populations of interest. It is therefore the approach of choice for quantification or interference, whenever a reliable behavioral readout is available. However, this is only the case for very few brain regions.

After determining the target site, the NTBS device has yet to be positioned correctly to effectively stimulate neurons at the target site, which is particularly critical for TMS. MR-based frameless stereotactic neuronavigation enables precise positioning of the TMS coils relative to any desired stereotactic coordinate of interest. Another major advantage is that frameless neuronavigation secures the maintenance of a constant coil position and orientation within and across experimental sessions (Schonfeldt-Lecuona et al., 2005), particularly important for concurrent TMS–EEG approaches (Lioumis et al., 2009). However, to navigate the stimulation coil into an optimal position, additional information is needed regarding the optimal direction of the induced current flow in the target region. For TMS, the main direction of induced current flow in the brain tissue is roughly opposite to the direction of current flow in the coil (Kammer et al., 2001b), making the orientation (incl. rotation and tilt) of the coil the major variable to be controlled by neuronavigation. For TCS, the direction of current flow in the brain tissue has to be controlled by the specific location of the two or more stimulation electrodes.

For a few brain regions, the optimal direction of current flow has been determined by systematic experimental variation: for M1$_{HAND}$, a posterolateral-to-anteromedial direction at an angle of approximately 45° relative to the mid-sagittal line and thus perpendicular to the central sulcus most effectively evokes MEPs (Mills et al., 1992), whereas for the visual cortex on average an anterior-to-posterior direction (Kammer, 1999) or lateral-to-medial direction (Kammer et al., 2001a) most effectively evokes phosphenes (with optimal direction depending on individual gyral orientation (Kammer et al., 2007)). Notably, these directions correspond roughly to the current flow induced by the now "classical" TCS montages for M1$_{HAND}$ (C3 or C4 vs. contralateral forehead) (Nitsche and Paulus, 2000) and visual cortex (Cz–Oz) for both TDCS (Antal et al., 2004a, 2006) and 10 Hz TACS (Neuling et al., 2013). Also lateral-to-medial currents seem to be effective for both TMS (Kammer et al., 2001a) and 10 Hz TACS in O1–O2 montage (Zaehle et al., 2010). For most other brain regions, however, robust outcome measures for quantification and systematic investigations are lacking. Attempts to systematically determine the optimal current direction in a specific brain region to maximally interfere with a specific cognitive task, e.g. posteromedial-to-anterolateral for the right PFC to interfere with memory-guided saccades (Hill et al., 2000), are rare but of critical importance to reveal consistent effects. Instead, coil positions are often

arbitrarily chosen or based on previously published successful attempts, resulting in very different coil orientations for the same target sites. To improve the effectiveness and precision of TMS and TCS, a more detailed knowledge is needed both with respect to the actual current distribution in the brain and the relation between current direction and the relevant neuronal elements.

For both TMS and TCS, the distribution of the electric field in the brain tissue crucially depends on the specific spatial distribution of brain tissue classes with different conductivity values, such as grey matter, white matter and corticospinal fluid (Windhoff et al., 2013). However, while TMS induces the effective electric current directly in the brain tissue bypassing scalp and skull (Opitz et al., 2011), TCS has to pass the current through these structures, rendering them crucial for the current distribution in the brain (Opitz et al., 2015). Moreover, TMS induces a comparably focal electric field for which mainly the local gyral geometry has to be considered (Kammer et al., 2007; Thielscher et al., 2011), whereas TCS produces a widespread electric field extending in varying degrees throughout the entire head (Opitz et al., 2015). The use of individually computed and empirically validated head models would thus markedly improve the spatial precision of both TMS and TCS. While neuronavigated small high-precision TMS coils (Groppa et al., 2012b) and high-definition TCS (Edwards et al., 2013), MR-informed customized TCS electrode shapes (Cancelli et al., 2015), and a more informed selection of the electrode properties (Saturnino et al., 2015) may increase the reliability and spatial resolution of NTBS, a valid estimation of the effective electric field is necessary to ensure stimulation of the desired brain region while leaving adjacent structures as unaffected as possible.

Concurrent application to derive spatial information

Currently, spatial information is obtained before starting NTBS and not up-dated over the course of NTBS. Brain networks are dynamic and task-related neuronal activity pattern may slowly change in the aftermath of an intervention or during the course of a learning paradigm. In these cases, spatial shifts in neuronal activity patterns should be tracked continuously (e.g. using fMRI or EEG) to be able to spatially adjust NTBS to the currently relevant brain site. For TMS, this has become possible by the use of a robotic arm, which is constantly controlled by a neuronavigation system (Ginhoux et al., 2013; Richter et al., 2010; Todd et al., 2014). While robotic neuronavigation is currently not MRI-compatible (due to ferromagnetic parts and severe space constraints in the MRI head coil), it is well feasible for concurrent TMS–EEG. Here, it may even automatically track and target the local occurrence of spontaneous events like sleep spindles, slow oscillations or epileptic activity patterns. For TCS, a fast relocation of stimulation electrodes is not possible, but multi-channel devices to rapidly switch for each electrode between EEG recording and TCS application mode are available (Ruffini et al., 2014). Given that stimulators with a high number of channels or a switch-matrix are offered in the future, it might become feasible to target multiple sites in a single experimental session by switching between different TCS electrode montages while still retaining the spatial focality that has been demonstrated for multi-channel TCS. Such a setup is also a prerequisite for future attempts to automatically configure completely new stimulation montages based on the current brain-state.

When to stimulate?

Timing is essential for neuronal communication, emphasizing the need for "temporal neuronavigation" which is as important as spatial neuronavigation for NTBS. For online NTBS, the temporal properties of neural processing need to be characterized and extracted to determine the onset and duration of NTBS accordingly. Indeed, the timing of NTBS determines its ability to successfully (i) quantify network properties in a brain state-dependent manner, (ii) interfere with ongoing neuronal processes, and (iii) modulate neuronal activity in a temporally specific manner (cf. section "A primer on non-invasive transcranial

brain stimulation (NTBS)" and Fig. 1). In addition to the temporal properties of neural processing, the temporal precision of the NTBS technique needs to be taken into account. Since TMS has a higher temporal resolution than TCS, the onset of stimulation relative to a task or assessment of brain activity needs to be defined more precisely for TMS. Single TMS pulses themselves last for a few hundred microseconds only and paired-pulse conditioning-test TMS paradigms can reveal functional interactions between subsequent pulses with sub-millisecond precision (Reis et al., 2008). At the same time, some of the evoked neurophysiological effects may last for several hundred milliseconds, as do the associated online effects at the behavioral level (Pascual-Leone et al., 2000; Siebner et al., 2009b; Walsh and Cowey, 2000). In contrast, the earliest effects reported for TCS so far start at 4–5 s after stimulation onset for both TDCS (Nitsche and Paulus, 2000) and TACS (Joundi et al., 2012), which may restrict its temporal resolution. A notable exception is TACS where the internal temporal structure of TACS with respect to its oscillatory phase may actually require high levels of precision as well to be optimally aligned to ongoing intrinsic brain activity (Brittain et al., 2013).

At first glance, one might assume that the timing of NTBS is less relevant for offline NTBS. However, there is converging evidence showing that the state of the brain is a critical factor determining the efficacy of NTBS to induce plastic changes in the brain (Karabanov et al., 2015). This implies that the temporal structure of offline NTBS should be tuned to the brain state that is most susceptible to the plasticity inducing effects of the NTBS protocol (see below).

Consecutive application to derive temporal information

MEG/EEG can be performed before NIBS to reveal when task-related neuronal processes emerge and disappear in a given subject. Since the temporal properties of neural processing can vary substantially across individuals, such experiments provide valuable information to individually determine the optimal time point (e.g., for single-pulse TMS) or time window (e.g., for burst-TMS or brief TCS blocks) of stimulation. The onset or latency of an evoked cortical potential (Thut et al., 2003) or the time course of induced oscillatory power changes may guide the timing of NTBS. For instance, the lateralized readiness potential (LRP) has been successfully used to determine the timing of stimulation in a single-pulse TMS study. The LRP is a negative scalp potential preceding lateralized hand movements. By varying the timing of TMS relative to the latency of the peak LRP, the time course of cortico-spinal excitability changes can be traced preceding lateralized motor responses (Verleger et al., 2009, 2010). Moreover, the individual frequency of an oscillation of interest (e.g., the alpha band) has been assessed to facilitate the efficacy of NTBS to entrain intrinsic cortical oscillations (Klimesch et al., 2003; Thut et al., 2011b; Zaehle et al., 2010).

Concurrent application to derive temporal information

Concurrent brain mapping and stimulation allow to trace the dynamic expression of the brain state of interest and to time NTBS based on ongoing intrinsically generated brain activity. Temporal neuronavigation of NTBS allows to characterize the causal impact of specific brain states on a specific brain function. Both TMS and TCS can be performed concurrently with fMRI to study cortical excitability and connectivity as a function of spontaneous BOLD fluctuations, yet MEG and EEG have a much higher temporal resolution than fMRI. Therefore, electrophysiological techniques are better suited to inform the timing of NTBS.

Online triggering of NTBS based on the ongoing MEG or EEG is only feasible when the signal-to-noise ratio is sufficiently high and the automated analysis pipeline sufficiently fast. This often applies to ongoing neuronal oscillations or other highly synchronized neural events where power and even instantaneous amplitude and phase can be determined online (Bergmann et al., 2012; Hartmann et al., 2011). For instance, EEG-triggered TMS of the primary motor cortex has been successfully used during deep sleep to target the up- vs. down-state of

the ongoing sleep slow oscillation (<1 Hz) and investigate rapid shifts in cortical excitability as indexed by MEP and TMS-evoked EEG potential (TEP) amplitude (Bergmann et al., 2012). In principle, the high temporal resolution of EEG and MEG should allow for targeting sporadic and very transient spontaneous neural events, such as epileptic spikes or task-evoked cortical potentials. The problem is that these neural events have rarely sufficient SNR and averaging across trials is usually necessary. However, spatial filters may increase the timing precision for single trials (De Vos et al., 2012; Salajegheh et al., 2004). A fully or semi-random application of NTBS together with post-hoc trial sorting may sometimes offer a valid alternative when NTBS triggering based on the ongoing EEG is not possible. The stimulation procedure itself is easy to perform and results in a good, though random, coverage of different brain states during the recording session. Using this approach, visual alpha power and phase preceding the TMS pulse have been shown to predict the probability of occipital TMS to evoke phosphenes (Dugue et al., 2011; Romei et al., 2008). Likewise, the pericentral power of the mu-rhythm has been shown to predict the size of the MEP amplitude evoked with TMS over the motor cortex (Sauseng et al., 2009). A clear disadvantage of the post-hoc trial sorting approach is that a relative large fraction of NTBS is applied during periods of no interest. Further, the random application of NTBS precludes the possibility to repetitively and exclusively target a specific brain state. This option is required if the aim is to systematically address the state-dependency of offline NTBS effects, for instance the impact of alpha power or phase expressed at the time of NTBS on the ability of NTBS to induce LTP- and LTD-like plasticity.

How to stimulate?

Stimulation variables such as intensity, frequency and duration have an influence on the neurobiological effects of NTBS. For TMS, the physiological impact additionally depends on the pulse form (e.g. monophasic or bi-phasic) and the direction of the electrical current induced in the brain tissue (Pascual-Leone et al., 2000; Walsh and Cowey, 2000) and, in case of repetitive TMS (rTMS), the precise temporal pattern of pulses (Fitzgerald et al., 2006; Ziemann et al., 2008). When using TCS, electrode design, size and placement, as well as the electrode-skin resistance and its spatial homogeneity across the electrode surface are additional contributing factors, (Nitsche et al., 2008; Saturnino et al., 2015), whereas frequency, waveform and DC offset are stimulation variables of interest for TACS (Antal and Paulus, 2013; Herrmann et al., 2013). Theoretically, many of the above-mentioned stimulation settings may benefit from information derived from neuroimaging or electrophysiological measurements. Due to space restrictions, we will only focus on how neuroimaging and electrophysiology can be used to optimize stimulation intensity and frequency.

Consecutive application to derive stimulation parameter information

Stimulation intensity is certainly among the most essential parameters to be adjusted, as it impacts not only the effectiveness but also the safety of a certain NTBS protocol (Miranda, 2013; Nitsche et al., 2008; Rossi et al., 2009). Online TMS, for example, may have beneficial or disruptive effects on a cognitive task depending on stimulation intensity, whereas for offline TMS protocols it may determine whether it is facilitatory or inhibitory (Miniussi et al., 2013). Therefore, proper adjustment of stimulation intensity to accommodate for individual brain anatomy may reduce the large inter-session and inter-subject variability observed for offline NTBS protocols (Karabanov et al., 2015; Li et al., 2015; Ziemann and Siebner, 2015). For TMS, it is currently common practice to adjust stimulation intensity relative to the individual resting or active motor threshold (RMT, AMT), determined as the minimal intensity required to induce an MEP with 50% probability in the relaxed or pre-contracted muscle, respectively (Groppa et al., 2012a; Rossini et al., 1994), or the phosphene threshold, determined as minimal intensity to evoke a phosphene with 50% probability (Kammer et al., 2001a;

Lou et al., 2011). Given that the correlation between MEP and phosphene threshold is moderate at best (Antal et al., 2004b; Boroojerdi, 2002; Deblieck et al., 2008; Gerwig et al., 2003; Stewart et al., 2001), it is questionable whether effective stimulation intensities of one brain region can be generalized to other brain regions. It would be favorable to adjust TMS intensity based on the local responsiveness of the target region for the specific coil position/orientation actually used in the experiment. When focal online TMS disrupts task performance, one can determine the individual intensity threshold for inducing a perturbation (Hartwigsen et al., 2010). However, TMS-induced behavioral effects are often subtle and might require a large number of trials or uncomfortably high stimulation intensities.

The magnetic field rapidly decays with distance, and the distance between the scalp region where NTBS is applied and the targeted cortex varies considerably across individuals and cortical sites. Scalp-cortex distance can be derived from structural MRI data and stimulation intensity can be adjusted accordingly (Janssen et al., 2014; Stokes et al., 2005). Anatomically precise head models may allow the inclusion of additional indices to estimate the required stimulation intensity for individual participants, target sites and coil positions. Some commercially available TMS neuronavigation systems feature an estimation of the induced electric field, but the underlying models are crude and do not sufficiently take into account individual neuroanatomy to actually base decisions for stimulation intensity on these values. Other anatomical indices that have been related to inter-individual variations in responsiveness to NTBS are local grey matter density, derived from voxel-based morphometry (Granert et al., 2011), or white matter fractional anisotropy, derived from diffusion tensor imaging (DTI) (Kloppel et al., 2008). Regional fractional anisotropy has shown to predict RMT (Kloppel et al., 2008), but see Hubers et al. (2012), as well as intra-hemispheric cortico-cortical facilitation (Groppa et al., 2012c).

Since TMS-evoked EEG potentials (TEP) (section "Concurrent application to read out immediate effects of online NTBS") capture the direct cortical response to TMS, TEP recordings may offer a more generally applicable means to establish a threshold for any cortical region accessible by TMS without the need for motor or perceptual output. However, no valid TEP threshold estimation has been established for the following reasons. First, SNR is too low on single trial level requiring the averaging of several tens of evoked responses per intensity step to obtain a reliable estimate. Second, TEPs are strongly confounded by co-evoked auditory and somatosensory potentials caused by the TMS click sound and the stimulation of cranial muscles and peripheral nerves, respectively (Herring et al., 2015; Nikouline et al., 1999), both modulated by intensity as well. This renders an appropriate sham condition mandatory, again doubling the number of trials required. Third, TMS-related electrical, mechanical, and biological non-cortical artefacts (like cranial muscle twitches and electrode-electrolyte polarization) often require cumbersome post-processing of the data (Herring et al., 2015; Ilmoniemi and Kicic, 2010; Korhonen et al., 2011; Rogasch et al., 2014). In summary, establishing a valid TEP threshold would require a sophisticated experimental and post-processing setup. Further a considerably large number of pulses (e.g. 200 pulses, resulting from 100 trials × 2 conditions) need to be acquired at each intensity during a staircasing procedure. Advances in data processing algorithms and spatial filter techniques may allow online artefact correction and a reliable estimation of TEP waveform and amplitude from a lower number of trials, paving the way towards making TEP threshold estimation a feasible instrument in the near future.

Stimulation intensity is even more coarsely determined for TCS, because stimulation intensity is usually not individually adjusted like it is the case for TMS. Given the fundamental impact of stimulation intensity on the size and nature of physiological effects, it is surprising that TCS is still applied in a one-intensity-fits-all manner without individual adjustment of stimulation intensity. This may explain why no simple linear relationship seems to exist between stimulation intensity and the size or direction of TCS effects (Bastani and Jaberzadeh, 2012, 2013;

Batsikadze et al., 2013; Moliadze et al., 2012). Up till now, a coarse estimation of the current density (mA/cm^2) at the scalp level is assumed to determine the effectiveness of TCS (Nitsche et al., 2007; Nitsche and Paulus, 2000). The same default current densities of 0.029 to 0.08 mA/cm^2 (corresponding to 1 mA intensity with 35 cm^2 to 12 cm^2 electrodes) are commonly used uniformly across participants and target sites, because they were demonstrated to be effective for TCS of $M1_{HAND}$ on the group level (Nitsche et al., 2008). However, since current density distribution within the brain is largely determined by individual and local anatomical parameters like bone thickness etc. (Opitz et al., 2015), it is questionable whether current density directly under the electrode is of any predictive value for the effective current density in target regions outside M1, or whether it is merely relevant as safety parameter to avoid skin irritation (Nitsche et al., 2008; Palm et al., 2008). In addition, the current density is not homogeneously across the electrode-skin interface and is likely also affected by the electrode and gel properties, making the stated values a very coarse estimate (Miranda et al., 2006; Saturnino et al., 2015). As for TMS, algorithms estimating the induced electric field in the brain based on individual anatomy are promising avenues to improve proper dosage determination (Windhoff et al., 2013).

Unlike TMS, TCS does not directly evoke action potentials and no response thresholds can be obtained. However, TDCS may induce shifts in neural excitability of corticospinal neurons in the primary motor cortex, which can be assessed online and offline by TMS (Nitsche et al., 2008; Nitsche and Paulus, 2000; Stagg and Nitsche, 2011). A potential solution at least for the primary motor cortex would thus be to use concurrent TCS–TMS to determine the intensity at which online TCS causes an immediate increase or decrease in MEP amplitude. For TDCS of $M1_{HAND}$, online effects are observed already after approximately 4 s of stimulation, as indexed by increased and decreased MEP amplitude measured 50 ms before the end of 4 s of anodal and cathodal TDCS blocks (relative to sham), respectively (Nitsche and Paulus, 2000). Notably, online increases in MEP amplitude measured 10, 20 and 30 s after the beginning of the first dozen blocks of 30 s anodal TDCS robustly predicted subsequent offline TDCS effects measured immediately after a total of 20 and 40 min of stimulation (Bergmann et al., 2009). Even if the use of a "TMS probe" to determine a TDCS threshold for inducing shifts in cortical excitability might work for the motor cortex, this approach cannot be blindly transferred to other brain regions, where no objective online measures of cortical excitability (like the MEP) are available. Phosphene thresholds yet provide a well-established readout for visual cortex excitability, and facilitatory online effects of 20 Hz TACS have been described (Kanai et al., 2010). However, while online TDCS effects on cognitive functions associated with other non-motor cortical areas have been reported in numerous studies (Shin et al., 2015), the reliability of these effects appears to be very low (Horvath et al., 2015), and none of them appear to be robust enough to provide a behavioral threshold criterion. Like for TMS, the use of individually computed and empirically validated head models based on structural neuroimaging data may allow an estimation of individually effective TDCS intensity. This may improve the reliability of TDCS effects (Datta et al., 2012), which has recently been challenged (Horvath et al., 2014, 2015). For TACS, the minimal effective current density remains to be examined systematically. TACS studies report either peak-to-peak or absolute current amplitudes of the oscillatory current, and intensity effects appear to be frequency-dependent (Antal and Paulus, 2013).

Stimulation frequency is another crucial variable, which is highly relevant for the safety and efficacy of TMS (Rossi et al., 2009) or TACS (Antal and Paulus, 2013; Fertonani et al., 2015; Herrmann et al., 2013). In many online TMS experiments, burst of 3–5 pulses at frequencies of 10–20 Hz are used, with 5-pulse 10 Hz bursts being the most common configuration (Hamidi et al., 2009). Compared to single-pulse TMS at the same intensity, burst-like online TMS increases and prolongs the interference effect, interfering with ongoing neuronal processes for about 500 ms. It is worth noting that 10 Hz corresponds to the

frequency of spontaneous alpha oscillations (Hamidi et al., 2009), proposed to gate information processing by means of pulsed inhibition (Jensen and Mazaheri, 2010; Klimesch et al., 2007). Indeed there is evidence suggesting that 10 Hz bursts may actually entrain alpha oscillations (Romei et al., 2010; Thut et al., 2011a, 2011b). Also for continuous offline rTMS, stimulation frequency is crucial as it determines whether a protocol produces LTD-like inhibition with 1–2 Hz or LTP-like facilitation with >5 Hz, at least in M1$_{HAND}$ (Fitzgerald et al., 2006; Karabanov et al., 2015; Siebner and Rothwell, 2003). For patterned rTMS protocols, such as theta burst stimulation (TBS) or quadro-pulse stimulation (QPS) (Hamada et al., 2007), both the within- and the between-burst interval are important, and the neuronal effects evoked at the two frequencies may interact (Goldsworthy et al., 2012; Huang et al., 2005). Again, all these frequencies are reminiscent of corresponding spontaneous neuronal oscillations. Slow frequencies around 1 Hz correspond to delta waves and slow oscillations are associated with synaptic downscaling during sleep (Tononi and Cirelli, 2006), whereas 5 Hz matches the frequency of theta oscillations, and 30–50 Hz bursts at 5 Hz have a temporal pattern that mimics theta–gamma coupling. Both, theta oscillations and theta–gamma coupling, are tightly associated with memory processes in hippocampus and neocortex (Jensen and Lisman, 2005).

Given the analogies between the temporal profiles of NTBS protocols and intrinsic oscillatory patterns, one might hypothesize that rTMS is capable of recruiting the same mechanisms that spontaneous neuronal oscillations are based on (Herring et al., 2015; Thut et al., 2011a). As the frequency profile differs both across individuals and brain regions, it may be beneficial to individually tailor plasticity inducing protocols based on the local EEG frequency profile at the target site (Rosanova et al., 2009) and, importantly, also during the targeted brain state (Bergmann et al., 2012; Massimini et al., 2007). For both offline and online TACS, the individual adjustment of stimulation frequency based on frequency information derived from preceding EEG sessions is already common practice (Cecere et al., 2015; Neuling et al., 2013; Zaehle et al., 2010). This is not surprising as this method was initially inspired by the mimicking or entrainment of neuronal oscillations. Studies following the same rationale of trying to entrain brain oscillations with rTMS bursts sometimes adjust their simulation frequencies as well (Klimesch et al., 2003; Thut et al., 2011b). This might, however, not always be critical as the transcranial frequency of TMS or TACS tends to "capture" the endogenous one, even if the transcranial frequency deviates to some degree from the endogenous one (Helfrich et al., 2014).

Concurrent application to derive stimulation parameter information

New opportunities may arise when NTBS parameters are adjusted during the experiment based on concurrent recordings of brain activity or connectivity. This approach would allow to compensate for fluctuations in cortical excitability associated with different brain-states, such as the power and phase of certain neuronal oscillations (Bergmann et al., 2012; Dugue et al., 2011; Sauseng et al., 2009), to make standard NTBS protocols more effective. For example, the intensity of individual TMS pulses during rTMS may be adjusted based on the current power of the ongoing sensorimotor mu-rhythm, known to influence MEP amplitude (Sauseng et al., 2009). For low frequency rTMS (e.g. 1 Hz) or paired associative stimulation (PAS) there is sufficient time between subsequent pulses to assess ongoing oscillatory power. However, this is challenging during high frequency rTMS (e.g. 5 Hz) or theta burst stimulation; here, advanced online correction methods (e.g. based on moving average template subtraction or spatial filtering) remain to be developed to gather sufficient TMS artefact-free EEG signal between consecutive TMS pulses or bursts. While it is yet unknown whether and how neuronal oscillations modulate the effects of TDCS, instantaneous adjustment of current intensity based on concurrent EEG recording is feasible (Mangia et al., 2014) as long as DC corrections prevent saturation. Also the after-effects of 10 Hz TACS on subsequent alpha power (Neuling et al., 2013; Zaehle et al., 2010) may benefit from

concurrent adjustment of stimulation intensity to overcome decreased efficacy of the stimulation during periods of high spontaneous alpha power (Neuling et al., 2013). As also the frequency of e.g. induced gamma oscillations depends on specific stimulus characteristics (Ray and Maunsell, 2010; van Pelt and Fries, 2013), the stimulation frequency of rTMS or TACS targeting these oscillations could be adjusted accordingly continuously or in a trial-wise fashion to remain maximally effective. Importantly, a novel approach using amplitude-modulated TACS (Witkowski et al., 2015) enables online removal of TACS artefacts and thus allows for continuous assessment of oscillatory power (see section "Concurrent application to read out immediate effects of online NTBS" for details).

Neuroimaging and electrophysiology as readout for NTBS effects

Neuroimaging and electrophysiological measures can also be used to capture either the changes in neuronal activity related to the after-effects following plasticity-inducing NTBS protocols (offline approach) or the neuronal activity (facilitation versus inhibition) immediately evoked or induced by NTBS (online approach). When combining NTBS with neuroimaging and electrophysiology, it is of critical importance to carefully select the most appropriate readout for the neuronal effect of the specific NTBS protocol at hand. However, given the limited knowledge of the very mechanisms underlying some of the observed NTBS effects, this may first require a series of methodological studies to empirically determine appropriate readouts (Table 1).

Two different rationales motivate combined NTBS-neuroimaging or NTBS-electrophysiology studies. (i) Neuroimaging or electrophysiology can reveal how NTBS impacts on task-related or spontaneous brain activity and hereby causes online interference or offline effects, such as facilitation or inhibition of a brain region. Here, the NTBS effect is already taken for granted and brain mapping serves as a tool to study the brain's responsiveness during a specific state. (ii) Neuroimaging or electrophysiology in conjunction with NTBS can also be exploited to advance the understanding regarding a specific NTBS technique itself. In this case, the very nature of NTBS effects itself is the object of investigation. Here, brain mapping is employed to disclose the underlying neuronal mechanisms of a given NTBS technique, its effects on neural activity and functional connectivity, or the relevance of certain stimulation parameters.

Once brain mapping readouts have been identified and validated, they may qualify as functional probe to test new NTBS protocols. This would be particularly useful when spatial information about the appropriate TMS coil orientation or TCS electrode montage is lacking. Indeed there is a high demand for such brain mapping readouts when NTBS is targeting less established cortical sites or when other stimulation parameters such as intensity or frequency have to be optimized. Unfortunately, robust imaging and electrophysiological readouts for NTBS effects are scarce. Moreover, measures of cortical excitability such as the MEP amplitude and NTBS-induced changes in the BOLD signal do not necessarily reveal congruent results (Turi et al., 2012). Hence, online as well as offline NTBS effects are often investigated in a purely exploratory fashion, giving rise to post-hoc interpretation of the wide-spread activation patterns observed in fMRI studies, or the effects extending across channel, time, and frequency dimensions in MEG or EEG studies.

Combined NTBS-fMRI studies often reveal widespread stimulation effects, involving interconnected brain regions (Hartwigsen et al., 2013; Turi et al., 2012; Volman et al., 2011). These "remote" NTBS effects may occur in neighbouring cortical regions close to the targeted cortex as well as in distant cortical and subcortical areas via intra- or interhemispheric connections (Bestmann et al., 2003; Polania et al., 2012). While it is plausible that remote regions are affected as a result from activation spread via axonal projections from the stimulated cortex (so called network effects), sometimes only remote effects can be observed but no immediate effects at the target site itself (Antal et al., 2011). Not only are these findings difficult to interpret, they also challenge the

Table 1
Examples for successful readouts of NTBS effects on neuronal activity sorted by imaging modality (rows), as well as NTBS technique, and research approach (columns).

	TMS		TCS	
	Offline	Online	Offline	Online
fMRI	• cTBS of left IFG ➔ Task-related BOLD response (Hartwigsen et al., 2013) • cTBS to left anterior PFC ➔ task-related BOLD repsonse (Volman et al., 2011)	• 2 Hz and 10 Hz rTMS of M1 ➔ rCBF during blocks with CASL (Moisa et al., 2008) • 9 Hz rTMS bursts of FEF ➔ TMS-related BOLD-response (Ruff et al., 2006)	• Anodal TDCS of M1➔ functional connectivity (graph theoretical analysis) in resting state BOLD (Polania et al., 2011)	• Anodal/cathodal TDCS of M1 ➔ BOLD-signal change during 20s TDCS blocks with or without fingertapping (Antal et al., 2011)
PET	• 1 Hz rTMS of M1 ➔ rCBF H$_2^{15}$O (Siebner et al., 2003) • 10 Hz rTMS trains of DLPFC ➔ dopamine [^{11}C]raclopride (Strafella et al., 2001)	• 1–5 Hz rTMS of M1 ➔ rCBF H$_2^{15}$O (Siebner et al., 2001) • Burst-TMS FEF ➔ rCBF H$_2^{15}$O (Paus et al., 1997)	• Anodal/cathodal TDCS of M1 ➔ rCBF H$_2^{15}$O (Lang et al., 2005)	• Anodal/cathodal TDCS of M1 ➔ task-releated change in rCBF H$_2^{15}$O (Paquette et al., 2011)
MRS	• Anodal/cathodal/sham TDCS of M1 ➔ GABA (Kim et al., 2014)	Limited sensitivity of MRS necessitates temporal averaging which complicates the assessment of online effects.	• anodal/cathodal TDCS of M1➔ GABA &Glx (Stagg et al., 2009)	Limited sensitivity of MRS necessitates temporal averaging which complicates the assessment of online effects.
NIRS	• 1 Hz rTMS of M1 ➔ HbO$_2$/HHb at contralateral M1 (Chiang et al., 2007)	• Single-pulse TMS at M1 ➔ HbO$_2$ directly under the TMS coil (Noguchi et al., 2003)	• Anodal/sham TDCS of prefrontal cortex ➔ HbO$_2$ at the stimulation site (Merzagora et al., 2010)	• TRNS of left DLPFC ➔ HbO$_2$/HHb/HbT at LPFC directly under the TCS elctrodes (Snowball et al., 2013)
EEG	• PAS of M1➔ spindle density and SWA during subsequent NREM sleep (Bergmann et al., 2008) • 1 Hz rTMS to V1 ➔ VEP amplitude (Bohotin et al., 2002)	• EEG-triggered single-pulse TMS of M1 during sleep slow oscillation up- vs. down-states ➔ TEP (Bergmann et al., 2012) • Single- and paired-pulse TMS after pharmacological intervention ➔TEP (Premoli et al., 2014a, 2014b)	• TACS at IAF of occipital cortex ➔ posterior alpha power (Neuling et al., 2013; Zaehle et al., 2010)	• 10 Hz TACS of occipital cortex➔ alpha power, frequency and phase (Helfrich et al., 2014)
MEG	• cTBS of FEF ➔ attentional parieto-occipital alpha and gamma power modulation (Marshall et al., 2015b)	Technically not feasible because (i) TMS coil does not fit into MEG helmet and (ii) TMS pulse would probably destroy MEG sensors	• Anodal/sham TDCS to M1 ➔ swallowing-related oscillatroy power changes (Suntrup et al., 2013) • TACS at 10 Hz of primary sensorimotor cortex ➔ cortico-muscular coherence (Wach et al., 2013)	• Anodal TDCS of M1 ➔ motor task-related beta power desynchronization[(n.s.)] (Soekadar et al., 2013) • Anodal/cathodal TDCS of occipital cortex ➔ visual stimulus-induced gamma power synchronization and alpha power desynchronization (Marshall et al., 2015a)

<NTBS> ➔ <readout> indicates the NTBS technique used and the imaging readout assessed after (offline) or during (online) NTBS. (n.s.) indicates that while technically sound, no significant effect of NTBS was observed in the used readout measure.

Abbreviations in alphabetical order: BOLD = blood oxygenation level dependent; CASL = continuous arterial spin labelling; cTBS = continuous theta burst stimulation; DLPFC = dorsolateral prefrontal cortex; EEG = electroencephalography; FEF = frontal eye field; fMRI = functional magnetic resonance imaging; GABA = gamma aminobutyric acid; Glx = unresolved glutamate and glutamine; HbO$_2$ = oxyhemoglobin; HHb = deoxyhemoglogin; HbT = total hemoglobin; IAF = individual alpha frequency; IFG = inferior frontal gyrus; M1 = primary motor cortex; MEG = magnetoencephalography; MRS = magnetic resonance spectroscopy; NIRS = near-infrared spectroscopy; NREM = non rapid eye movement sleep; PAS = paired associative stimulation; PET = position emission tomography; rCBF = regional cerebral blood flow; rTMS = repetitive TMS; SWA = slow wave activity (EEG power at 0.5–4 Hz during sleep); TCS = transcranial current stimulation; TEP = TMS-evoked potential; TMS = transcranial magnetic stimulation; TRNS = transcranial random noise stimulation; VEP = visual evoked potential.

assumed origin of remote effects in general. At closer inspection, a lack of NTBS effects at the target site itself can have two potential reasons. First, the site has been effectively stimulated but the readout is either not sensitive in general for the induced neuronal effects or it is lacking the statistical power to detect them (e.g. due to method-specific inhomogeneity of SNR across brain regions). This can either be unfortunate and result from an inappropriately chosen readout, or even expected a priori when deliberately selecting a readout that is specifically sensitive to the remote effects under investigation. The latter approach has for example been taken in TMS-MEG or TMS–EEG studies. TMS was used to target nodes of the dorsal fronto-parietal attention network (i.e., frontal eye fields and intraparietal sulcus), while EEG and MEG were employed to assess the altered top-down impact on oscillatory neural activity in the occipital cortex, i.e. attentional modulation of alpha power during stimulus anticipation and gamma band power during stimulus processing (Capotosto et al., 2009; Marshall et al., 2015b). The second potential reason for a lack of direct NTBS effects at the target site is obviously that the target site has indeed not been effectively stimulated. If effects at distant brain sites are observed nonetheless, they cannot be attributed to network projections from the target site but rather result from stimulation of the remote brain regions themselves. For TMS (with a focal figure-of-eight coil) the direct effects of

stimulation are relatively local and confined to the vicinity of the target site (Opitz et al., 2011; Thielscher et al., 2011). Here, distant sites are mainly activated via true network effects, although accidental (co)stimulation of directly adjacent brain region is principally possible, which in turn can cause remote network effects. For TCS, however, not only brain areas in the vicinity of the electrodes (importantly, both the "target" and the "return" electrode) may be affected but also more distant sites may effectively be stimulated by the widespread electric field. At least standard montages with two electrodes generate a rather cluttered stimulation pattern with several field peaks between the electrodes (Opitz et al., 2015). In the future, individualized electric field calculations and more precise high-definition TCS (Edwards et al., 2013) may help to resolve this ambiguity.

Consecutive application to read out after-effects induced by offline NTBS

Offline effects of NTBS (both TMS and TCS) presumably involve the lasting potentiation or depression of neuronal synapses (Siebner and Rothwell, 2003; Stagg and Nitsche, 2011), while modulatory online effects of TCS are likely based on shifts in neuronal membrane potential (Stagg and Nitsche, 2011). Both approaches, however, primarily affect the level of cortical excitability, which in turn affects spontaneous

neuronal excitation. This implies that the neural responsiveness to spontaneous or task-related neuronal input to these neurons will be modified, causing a facilitation or attenuation of input-driven neural activity. Likewise, the outgoing activity will be modified, resulting in increased or decreased output levels.

Some neuroimaging readouts may be particularly suited for the assessment of NTBS offline effects, as they are sensitive to the functional consequences in terms of neural integration at the network level following the induction of synaptic plasticity. They indicate either changed metabolic demands by means of regional cerebral blood flow (rCBF) via position emission tomography (PET) (Siebner et al., 2003), near-infrared spectroscopy (NIRS) (Chiang et al., 2007) and continuous arterial spin labelling (CASL) (Orosz et al., 2012), altered neurotransmitter synthesis and binding via PET (Strafella et al., 2001), and relative concentrations of neurotransmitters such as glutamate and GABA via magnetic resonance spectroscopy (MRS) (Kim et al., 2014). Other readouts require some kind of input to actively drive and challenge the modulated neuronal system in order to reliably capture the functional changes induced by NTBS. This input may be generated experimentally by means of exogenous sensory stimuli that trigger task-related BOLD-responses (Hartwigsen et al., 2013; Volman et al., 2011), ERPs (Bohotin et al., 2002) or oscillatory power modulations (Marshall et al., 2015b). Alternatively, this input may be spontaneously generated within the modulated network or connected regions, as reflected in BOLD network connectivity (Polania et al., 2011) or spontaneous EEG oscillations (Bergmann et al., 2008; Huber et al., 2007; Neuling et al., 2013; Vossen et al., 2015; Zaehle et al., 2010). In fact, MEG, EEG and fMRI provide a large variety of readouts to assess the after-effects of rTMS protocols, which indicate facilitatory and suppressive effects on neural excitability, activity, or connectivity (Thut and Pascual-Leone, 2010). In principle, these readouts should be equally sensitive to detect after-effects induced by TMS and TCS, as both NTBS techniques are assumed to rely on LTP- and LTD-like synaptic plasticity (Paulus et al., 2013).

As noted above, the plastic changes in neural activity induced by different NTBS protocols may not be restricted to the stimulated area itself. In this context, measures of functional connectivity, defined as the temporal covariance between remote neurophysiological events or effective connectivity, defined as the causal influence one remote neuronal event exerts over another (Friston, 2002), are particularly suited to capture rapid NTBS-induced functional reorganization and adaptive plasticity on the network level by investigating the interaction between different network nodes at rest or during a specific task (for a recent review see Hartwigsen et al., 2015). Changes in effective connectivity following offline TMS have been studied during speech production using dynamic causal modelling (DCM) (e.g. Hartwigsen et al., 2013) and during action selection using psychophysiological interactions (PPI) (e.g. Ward et al., 2010). Changes in functional connectivity following offline TDCS have been demonstrated using a graph theoretical approach, showing that the after-effects of TDCS over M1 during subsequent resting-state fMRI mimicked training-induced changes in the motor network (Polania et al., 2011). Particularly, anodal TDCS increased the functional connectivity between left sensorimotor and motor-related cortical areas but decreased functional coupling between sensorimotor and contralateral motor regions.

Moreover, NTBS-induced changes in task-related neural activity may also be related to the observed modulation in task performance (e.g., Andoh and Paus, 2011; Andoh and Zatorre, 2013; Hartwigsen et al., 2013; Ward et al., 2010). However, in some cases, it remains unclear whether the behavioral changes induced by different NTBS protocols are related to the modulation of neural activity in the targeted brain region or in remote connected areas (Hartwigsen, 2014). Indeed, studies employing effective connectivity analyses of fMRI data after TMS-induced perturbation over a key region within a specific network revealed changes in the functional drive between different network nodes (Hartwigsen et al., 2013; Herz et al., 2014). These findings suggest

that distributed network effects rather than the modulation of the neural activity at the stimulated cortical area itself might mediate the NTBS-induced changes on the behavioral level during some tasks.

Concurrent application to read out immediate effects of online NTBS

Online single-pulse or burst-TMS triggers action potentials and consequently trans-synaptic neuronal excitation, making it possible to directly assess the neuronal response to the stimulation itself. For online TMS–fMRI, this can mainly be achieved by measuring the immediate BOLD-response to TMS (Bestmann et al., 2005; Ruff et al., 2006). Typically, short bursts of high-frequency TMS are given which allows neural excitation to sum up and facilitate the detection of neural activation with interleaved fMRI. Technical advances in online TMS–fMRI might render it possible to reliably assess hemodynamic responses evoked by single TMS pulses in future studies (Navarro de Lara et al., 2014). Experimental manipulations of stimulus intensity and the brain state (e.g. level of attention or task complexity) have been successfully used to map the online effects of TMS on effective connectivity between the stimulated cortex and other brain regions (Bestmann et al., 2008b; Moisa et al., 2012; Ruff et al., 2006).

For online TMS–EEG, one needs to select the appropriate readout depending on the effects of interest at the neuronal level. EEG readouts of the brain response to TMS are commonly derived in one or the other way from the TMS-evoked potential (TEP), i.e. the EEG potential time-locked to the TMS-pulse (Bonato et al., 2006; Ilmoniemi et al., 1997; Paus et al., 2001). After TMS-artefact correction and averaging, the TEP can be analyzed like an ordinary sensory ERP, e.g. by quantifying amplitude and latency of specific components. For instance, the N45 and N100 of the TEP evoked in $M1_{HAND}$ have been related to GABA-A- and GABA-B-receptor specific activation, respectively (Premoli et al., 2014a, 2014b). Moreover, frequency and power of TMS-evoked oscillations can be assessed by means of wavelet or moving window Fourier analyses, transforming the average TEP into a time-frequency representation (TFR) (Rosanova et al., 2009). Note that this should not be confused with the averaging of single-trial TFRs, which captures a mixture of both phase-locked (i.e. evoked) and non-phase-locked (i.e. induced) oscillatory power. Additionally, more complex and integrated readouts can be derived, reflecting the state of the thalamo-cortical system (as well as the level of consciousness). Examples for such readouts are global mean field power (Esser et al., 2006), significant current density phase locking, and significant current scattering (Casali et al., 2010).

Online effects of TCS are much harder to quantify as they do not directly evoke action potentials but rather modulate the level (TDCS) or timing (TACS) of cortical excitability. Polarization induced changes in neural excitability may well affect the level of ongoing postsynaptic neural activity. If these changes alter the summed neural activity in a brain region, this might be mapped by fMRI. However, some TCS applications might not modify the summed neural activity and therefore fail to show concurrent changes in the BOLD signal. Online TDCS of $M1_{HAND}$ for example does not induce any concurrent changes in BOLD-signal during 20 s stimulation blocks (Antal et al., 2011), and 10 s blocks of TACS of the visual cortex at individual alpha frequency did not result in a TACS-related BOLD decrease (Vosskuhl et al., 2015) as expected from previous concurrent EEG–fMRI work on alpha oscillations (e.g. Moosmann et al., 2003; Scheeringa et al., 2011). Task-free BOLD-fMRI may thus not be the measure of choice to directly assess the neuronal online effects of TDCS, unless specific resting-state connectivity measures are applied (Polania et al., 2011). However, the TDCS induced change in neural excitability may acutely change the input–output curves of neurons in the stimulated brain regions. By shifting the neurons' resting membrane potential towards depolarization and thus closer to firing threshold, TDCS increases the likelihood that spontaneous synaptic input will cause neuronal firing. Conversely, shifting the resting

membrane potential towards hyperpolarization has the opposite effect. This may result in a corresponding change of regional activity and inter-regional connectivity during concurrent fMRI. For instance, TDCS of sensorimotor cortex acutely modulated the cortical responsiveness to tactile stimulation (Wang et al., 2015), TDCS of $M1_{HAND}$ modulated task-related BOLD-responses evoked by finger tapping in the supplementary motor area (SMA) (Antal et al., 2011), and TACS at individual alpha frequency reduced the BOLD response in the occipital cortex to visual targets in a vigilance task (Vosskuhl et al., 2015). However, it should be noted that an inadvertent effect of TCS on attention, e.g. via stimulation-related sensory or visual input or via incidental stimulation of attention control networks, may provide an alternative explanation for augmented responses to sensory stimuli. Experimental designs need to appropriately control for these alternative mechanisms, for instance by introducing a TCS condition over a "control" site.

To assess the immediate effects of online TACS on neuronal activity by MEG or EEG, TACS artefacts need to be removed completely while ensuring that neither residual artefacts are left nor true brain activity is removed. On the one hand, full recovery of the true brain signal at TACS frequency from EEG (Helfrich et al., 2014) and MEG (Neuling et al., 2015) may in fact be impossible due to its temporal and spatial co-variation with the TACS signal at the target site (in the case of successful entrainment). On the other hand, oscillations of other frequencies or evoked responses may be recovered from both TACS and TDCS (Helfrich et al., 2014; Marshall et al., 2015a; Neuling et al., 2015; Soekadar et al., 2014). A promising strategy is amplitude-modulated TACS which uses a carrier frequency well beyond the frequencies of interest (e.g. 220 Hz) and modulates the amplitude of the carrier frequency at the frequency of interest (e.g., 23 Hz). It has been recently shown that amplitude-modulated high-frequency TACS enables the artefact-free assessment of the
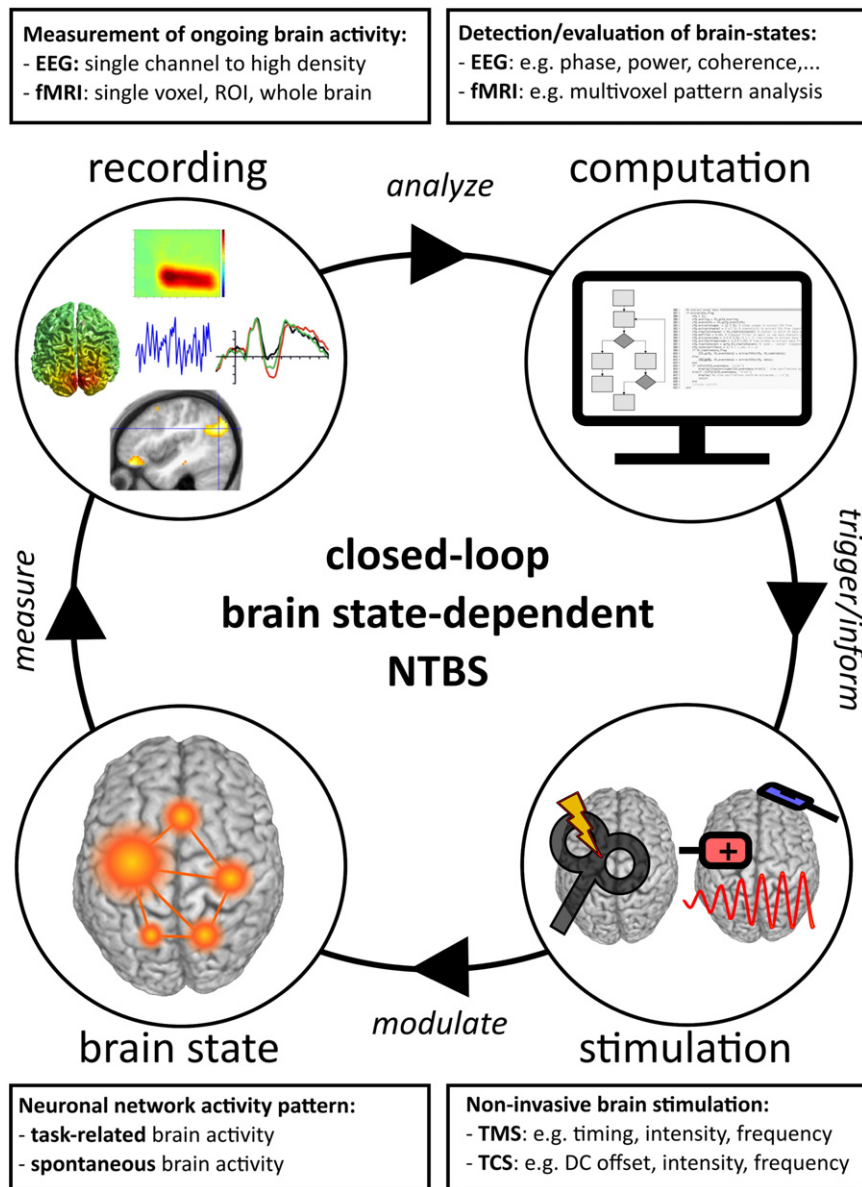

Fig. 3. Closed-loop brain-state dependent non-invasive transcranial brain stimulation. Brain states can be defined based on specific neuronal activity patterns within a region or network, which emerge either spontaneously at rest or related to a certain task. Indices of these neuronal profiles are continuously recorded at rest or during a task by an electrophysiological (e.g. EEG) or neuroimaging (e.g., fMRI) technique. Raw data are then processed and analyzed online by computational algorithms in order to detect brain states of interest and extract relevant information. Based on the computational outcome, brain stimulation parameters (e.g. target site, timing, intensity or frequency) are set and the stimulation is triggered. Closing the loop, non-invasive transcranial brain stimulation then affects neuronal activity and alters the brain state in the desired direction.

lower frequency of interest (Witkowski et al., 2015). Although the feasibility of concurrent TCS–MEG or TCS–EEG has been demonstrated, the immediate online effects of TACS on spontaneous or task-related brain activity still have to be unravelled.

Closing the loop with brain-state dependent NTBS

Neuroimaging and electrophysiology can be employed to provide spatial, temporal and parameter-specific information for adjusting and optimizing NTBS application (section "Neuroimaging and electrophysiology approaches to inform NTBS") or to capture the neural effects that are induced by NTBS at the regional and systems level (section "Neuroimaging and electrophysiology as readout for NTBS effects"). These approaches can be merged into a brain–NTBS interface approach. When NTBS and neuroimaging or electrophysiology is applied concurrently and both strategies are iteratively combined within the same experimental setup, the stage is set for closed-loop brain state-dependent NTBS (Fig. 3). A closed-loop system in the strict sense iteratively controls a certain parameter of a system via a control signal to reach and maintain a predefined set-point of that parameter while trying to reduce errors (i.e. deviations from that set-point) by monitoring the parameter (feedback) and adjusting the control signal accordingly. Applied to online NTBS, concurrent neuroimaging or electrophysiology traces a certain brain state and the dynamic expression of that brain state is used to iteratively adjust spatial, temporal or other variables (such as intensity or frequency) of NTBS in order to suppress, facilitate, or maintain that brain state with NTBS.

What defines a brain state? In the context of brain state-dependent NTBS, we use the term in its broadest sense. Extending the definition by Zagha and McCormick (2014), we define brain state as a recurring set of neuronal conditions, also referred to as dynamic circuit motif (Womelsdorf et al., 2014), which is stable for a behaviorally (or neuro-computationally) significant period of time. These brain states can be described along multiple spatial and temporal scales and can be indexed by a variety of both physiological and behavioral measures. Although the general term brain state suggests a global (i.e. brain-wide) condition, it does in practice often refer to anything ranging from the state of specific neuron populations and local excitatory/inhibitory circuits over large-scale brain networks to the entire thalamocortical system (although in the former cases, neuronal state or network state would be more appropriate terms). Along the temporal dimension, these states can change slowly over days or even years (e.g. in the context of brain maturation or post-stroke cortical reorganization), vary across minutes to hours (e.g. related to certain sleep stages or vigilance states (Gervasoni et al., 2004), or the recent history of learning-related plasticity (Karabanov et al., 2015) or sensory adaptation (Silvanto et al., 2008)), or even fluctuate in the range of seconds to milliseconds. Rapidly fluctuating brain states reflect the momentary degree of neuronal (de)synchronization in a network (Zagha and McCormick, 2014) or the phase of a single oscillatory cycle comprising excitatory and inhibitory periods (Destexhe et al., 2007). Importantly, brain states are under control of both subcortical ascending neuromodulatory systems as well as thalamo-cortical and cortico-cortical projections, giving rise to modulations at various levels of spatial and temporal specificity (Harris, 2013; Harris and Thiele, 2011; Lee and Dan, 2012; Zagha and McCormick, 2014). Especially the level of neuronal synchronization, reflected in the power of network-specific neuronal oscillations (e.g. the 8–12 Hz alpha band), has proven as useful indicator, if not constituting element, of the level of vigilance or selective attention which fluctuates spontaneously but is also modulated in a task-related manner (Harris and Thiele, 2011; Jensen et al., 2011; Ros et al., 2014).

Brain states can be indexed non-invasively by a plethora of different measures, either indirectly via associated changes in behavioral (e.g. accuracy and reaction time on attention, vigilance, or working memory tasks) and peripheral electrophysiological readouts (e.g. muscle

activity, heart rate, or skin conductance), or more directly via metabolic indices (e.g. perfusion or neurotransmitter turnover) and readouts of ongoing neuronal activity in the brain via MEG, EEG (e.g. oscillatory power or phase) or fMRI (e.g. resting state connectivity). Most demanding, but may be also most promising for closed-loop NTBS are the very transient functional brain states that fluctuate at the rate of milliseconds to minutes and can only be monitored electrophysiologically with methods that offer very high temporal resolution such as EEG and MEG. They may be defined based on topographical EEG microstates (Khanna et al., 2015), certain rule-based classification schemes (e.g. sleep stages in polysomnography (Iber et al., 2007)), oscillatory power of specified frequency bands (e.g. 8–12 Hz alpha power), the occurrence of certain neuroelectric events (e.g. sleep spindles or epileptic spikes), or the phase of ongoing oscillations (e.g. sleep slow oscillations).

Closed-loop applications that use invasive brain stimulation techniques for clinical treatment purposes are already in use (Berenyi et al., 2012; Cagnan et al., 2013; Rosin et al., 2011; Sun and Morrell, 2014), whereas closed-loop NTBS protocols in the strict sense, based on direct readout of brain activity are currently under development. When extending the readout to peripheral measures, the most elegant example for closed-loop NTBS so far is the application of TACS to $M1_{HAND}$ at the individual tremor frequency in patients with Parkinson's disease to suppress tremor amplitude, presumably by means of phase-cancellation between spontaneous and induced oscillatory neuronal activity (Brittain et al., 2013): Informed by the ongoing tremor activity, the phase of TACS was constantly adjusted to maintain the optimal phase-delay between TACS and the ongoing tremor rhythm as determined from simultaneous actigraphy measures.

Closed-loop paradigms for concurrent TMS–fMRI setups may become relevant if the dynamics of the brain-state of interest have a slow time constant such as slow fluctuations in resting-state connectivity, because they are matching the slow temporal properties of the BOLD-signal. Potential advantages of fMRI-based readouts are the high spatial resolution and the higher sensitivity to subcortical structures due to a more uniform spatial sensitivity profile and point-spread function) as compared to MEG or EEG. Conversely, MEG or EEG is required to readout more transient brain states, dynamically fluctuating at higher frequencies. So far no actual closed-loop but only informed open-loop NTBS-M/EEG paradigms have been published. Informed open-loop NTBS-M/EEG exploits knowledge about the current expression of a given brain state to inform NTBS in a feed-forward manner, but does not require rapid online feed-back and iterative evaluation of immediate NTBS effects (like the TEP) but merely inform NTBS in a feed-forward manner. For example, EEG-triggered TMS to the up- and down-states of the sleep slow oscillation was temporally informed by the ongoing EEG, while a refractory period of about 3 s was deliberately used to avoid continuous triggering of TMS by the previous slow-oscillation like TEP (Bergmann et al., 2012). In contrast, continuous triggering was actively employed in a slow oscillation up-state-triggered closed-loop auditory stimulation paradigm to actively drive slow oscillations (Ngo et al., 2013, 2015).

Depending on the stimulation site (Mutanen et al., 2013) a major challenge are the various NTBS-related artefacts in MEG and EEG. The removal of these artefacts usually requires thorough and manually guided offline analysis involving spatial filter and template subtraction techniques (Helfrich et al., 2014; Hernandez-Pavon et al., 2012; Ilmoniemi and Kicic, 2010; Marshall et al., 2015a; Neuling et al., 2015; Siebner et al., 2009a; Soekadar et al., 2013) to avoid corruption of the readout, especially when targeting transient spectral power changes (Walter et al., 2012). For TCS, amplitude-modulated TACS at higher carrier frequencies enables the immediate online assessment of lower oscillatory frequencies of interest without any additional processing steps (Witkowski et al., 2015), thus being highly suitable for closed-loop approaches. For TMS, proper sham control is needed to control for the neural effects of auditory and somatosensory input associated with NTBS, even at subliminal stimulation intensities (Herring et al., 2015).

The computational effort to remove artefacts to quickly recover the readout of interest depends on the very brain state of interest. For example, to adjust the phase, frequency or intensity of ongoing TACS it is necessary to obtain reliable online recordings of phase, frequency or power of a spontaneous oscillation, in analogy to the tremor-informed closed-loop paradigm discussed above (Brittain et al., 2013). Hence the TACS artefacts need to be removed online with high precision to uncover the underlying true neuronal activity, which was not possible so far (cf. section "Concurrent application to read out immediate effects of online NTBS"), or amplitude modulation needs to be employed (Witkowski et al., 2015). For TMS, a closed-loop example would be to trigger single pulses based on the phase of a certain TEP component evoked by the previous pulse to constantly drive (or entrain) a certain TMS-locked oscillation, which is currently done with fixed, though often individually adjusted, frequencies (Thut et al., 2011b). Alternatively, intensity of an ongoing rTMS protocol could be constantly adapted based on the amplitude of the individual TEPs to adjust for changes in excitability due to the ongoing build-up of after-effects during stimulation. Also an individual termination criterion for rTMS protocols is conceivable based on such a functional readout provided that spatial filtering techniques can offer sufficient SNR for single trial analyses. The technical equipment and computational power required for real-time analyses of M/EEG and online adjustment of NTBS are already available. It is therefore up to the NTBS community to face the methodological challenges associated with closed-loop NTBS in the strict sense and develop those paradigms as a tool for systems and cognitive neuroscience. Technical feasibility is necessary but not sufficient for closed-loop NTBS protocols to be effective. It is crucial to select the appropriate brain state of interest as well as the appropriate imaging and electrophysiological indices supposed to measure it. Another challenge is to design NTBS protocols that are capable of modulating the brain state of interest in the desired direction. Presumably, a closed-loop interference with specific brain states will be easier to accomplish than their facilitation. The latter may first be achieved by targeting well-described brain states (e.g. specific oscillatory patterns) for which the neurophysiological underpinnings are sufficiently understood, allowing for a hypothesis-driven approach (Horschig et al., 2014).

Conclusion

NTBS strongly benefits from the information accessible via brain mapping techniques. Firstly, neuroimaging and electrophysiology can optimize NTBS with regard to where, when and how to stimulate. While information with high inter- but low intra-subject variability can be derived before NTBS, those fluctuating over time within a subject, such as the current of brain state, need to be monitored continuously to enable informed open-loop NTBS. Secondly, neuroimaging and electrophysiology can provide appropriate readouts for either immediate (online) or subsequent (offline) effects of NTBS on neuronal activity, depending on whether applied concurrently or consecutively. For closed-loop NTBS in the strict sense, NTBS can be informed about the momentary brain state by concurrent readouts of neuronal activity and be adjusted accordingly to interfere with or modulate neuronal activity to reach or maintain the desired brain state. Future lines of research should further develop these combined paradigms to increase the precision and effectiveness of NTBS for systems neuroscientific research and to boost the therapeutic potential of NTBS.

Acknowledgments

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