# The two-way relationship between nicotine and cortical activity: a systematic review of neurobiological and treatment aspects

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**Abstract**
Nicotine intake and cortical activity are closely related, as they can influence each other. Nicotine is implicated in the induction and modification of cortical plasticity and excitability, whereas a change on cortical plasticity and excitability can also lead to a modification of the smoking behaviour of an individual. The aim of this systematic review was, on the one hand, to evaluate the effects of nicotinergic modulation on cortical excitability and plasticity, and, on the other hand, to assess if modifying the brain's excitability and plasticity could influence one's smoking behaviour. Two systematic literature searches in the PubMed/MEDLINE and PsycINFO databases were conducted. Studies focusing either on the impact of nicotinergic modulation on cortical activity or the treatment effect of non-invasive brain stimulation techniques (NIBS) on smoking behaviour were included. A total of 22 studies for the first systematic search and 35 studies for the second one were included after full-text screening. Nicotine's effect on cortical activity appeared to depend on smoking status of the individual. While deprived smokers seem to generally profit from nicotine consumption in terms of cortical excitability and plasticity, the contrary was true for non-smokers. Regarding the questions of how changes in cortical excitability can influence smoking behaviour, a trend points towards NIBS being a potential intervention technique for smoking cessation.

**Keywords** Nicotine · Smoking · Plasticity · Cortical excitability · NIBS

## Introduction

Nicotine is widely known for its addictive properties; however, it has also shown to have an impact on brain plasticity, attention and higher cognitive processes. A meta-analysis published in 2010 including fourty-one studies demonstrated that either smoking or nicotine administration led to better performance in motor abilities, attention and memory in healthy adults ($N = 41$, $n$ ranging from 9 to 130) [1]. However, other studies found differential effects of nicotine administration on cognition depending on the smoking status of the individual, being a cognitive enhancer in smokers but leading to poorer performance in non-smokers [2, 3]. These results point towards a potential treatment approach for cognitive deficits in mental disorders. These deficits can be triggered by an altered brain plasticity occurring across several neurodevelopmental and neurodegenerative disorders [4]. Nicotine is thought to be able to work as an intervention in these patients cohorts, as it is implicated in the induction and modification of neuronal plasticity and excitability [5, 6], which form the basis of learning and memory [7]. This effect supposedly occurs through a modification of the neuronal physiology via the interaction between nicotine and nicotine acetylcholine receptors (nAChR) [5]. Past studies have indeed found positive effects of nicotine on cognition in samples consisting of, among others, depressive patients [8], schizophrenia patients [9] or Parkinson patients [10]. Thus,

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nicotine administration could become a treatment strategy used in such populations in need for better strategies to fight cognitive impairment.

Nevertheless, not only smoking status and nicotine consumption may modify an individual's neuronal excitability and plasticity, but the opposite may also be true, namely that smoking behaviour can be influenced through modifying the brain's excitability. If so, neurostimulation techniques could be used as intervention techniques for smoking cessation. In 2015, 15.2% of the worldwide population were identified as smokers, translating into 110.7 deaths per 100,000 attributable to smoking behaviour [11]. Indeed, smoking is one of the leading causes for disability and early death worldwide, being the cause of 15.5% of the global deaths in 2015 [12]. Consequently, developing further smoking cessation strategies is of utmost importance. Furthermore, reducing tobacco consumption would not only reduce disability and death rates, but has also proven to diminish depression, anxiety and stress and to improve quality of life and positive mood [13].

Brain reward systems could be tackled by neurostimulation techniques, with the potential to influence areas that are closely related to craving, relapse and continued nicotine consumption. Treatment techniques able to influence brain activity include transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). TMS, on the one hand, has been proven to be able to influence cortical excitability and the metabolic activity of neurons when applied repetitively [14]. TDCS, on the other hand, has also shown its potential to influence brain excitability, where in principle anodal tDCS increases brain excitability and cathodal tDCS decreases brain excitability [15, 16]. When either TMS or tDCS techniques are applied for a sufficient long time period or with sufficient repetition, long-lasting neuroplastic after-effects are visible [14, 17]. In sum, applying either repetitive transcranial magnetic stimulation (rTMS) or tDCS in smoker populations, e.g. combined with psychotherapeutical interventions, can be an attractive option for the reduction of smoking dependency symptoms.

This systematic review aims at, on the one hand, evaluating the effects of nicotinergic modulation in cortical excitability and plasticity, by means of electroencephalography (EEG), TMS, tDCS and Paired Associative Stimulation (PAS) protocols. While there are other techniques available to measure cortical activity (e.g. functional Magnetic Resonance Imaging or Positron Emission Tomography), these only allow for indirect measures of such activity [18], while neurophysiological measures (EEG, TMS) allow for a rather direct measurement of cortical activity [18, 19]. On the other hand, this review also aims at examining the reciprocal effect, namely assessing if also through modifying the brain's excitability and plasticity through either rTMS or tDCS, the smoking behaviour of an individual can be influenced. The recommendations from the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) [20] were taken into account and followed through the review process, excepting the risk of bias assessment within studies.

## Methods

### Information sources and search

Two systematic searches were carried out for this systematic review via the internet databases PubMed/MEDLINE and PsycINFO. One search aimed at systematically identifying studies evaluating the impact of nicotinergic modulation on neurophysiological assessments, such as TMS, tDCS, PAS or EEG. The second search focused on studies using non-invasive brain stimulation techniques (NIBS) not for evaluating brain functions as in search one, but the efficacy of rTMS and tDCS to treat tobacco dependency. The recommendations for the standardized reporting of systematic reviews (PRISMA) were taken into consideration during this search. The first search was executed on the 9th of December of 2019 and constrained studies published from January 1, 1929 to that day. The 1st of January of 1929 was chosen as starting search point, as the first publication using EEG was published in 1929. The second search was carried out on the 24th of January of 2020 and included studies published from January 1, 1985 until that day, as TMS was first implemented in the field in 1985. The complete search terms are displayed in the supplement.

### Eligibility criteria

Results from all search terms were combined for each systematic search and duplicates were removed using the ENDNOTE X9 deduplication feature. Then, the citations were screened by title and, when relevant, by abstract, and each potentially relevant citation was then retrieved and reviewed in a full-text basis. Exclusion criteria were case reports and abstracts of congress presentations, publications in non-English or -German language (no publication of potential interest was excluded due to this criterion), and studies not fulfilling the following inclusion criteria. Inclusion criteria were all research studies published either between 1 January 1929 and 9 December 2019 for the first systematic search or between 1 January 1985 (first publication with TMS) and 24 January 2020 for the second systematic search. For the first systematic search, additional inclusion criteria were the presentation of cortical excitability and plasticity measures (e.g. in terms of changes in corticospinal excitability of brain synchronicity) and the measurement of nicotinergic modulation. At full-text

level of this first search, four studies were excluded since the outcome was not cortical plasticity or excitability and three studies were excluded as no nicotinergic modulation took place. For the second systematic search, the additional inclusion criteria were the presentation of smoking behaviour measures (e.g. in terms of reducing or quitting smoking) as primary or secondary outcome and the use of neurostimulation techniques as treatment technique. Reviews, systematic reviews and meta-analyses were analysed regarding a possible overlap to our work and to detect further publications of potential interest.

### Data extraction

Data was extracted manually by one reviewer (CM) and independently controlled by another reviewer (BP). For search one we extracted 22 research articles and for search two we extracted 35 research articles. For both systematic searches first author, year, and sample characteristics were extracted from the articles. Additionally, for the first systematic search the way of nicotine administration, dosage and method, cortical excitability and plasticity measurement parameters, as well as the main cortical excitability and plasticity outcomes were extracted. For the second systematic search, the NIBS technique, the target area, the parameters used, the outcome measure in terms of tobacco dependency and the main results in this regard were extracted. Further information regarding the sociodemographic characteristics of the subjects are displayed in supplementary Tables 1 and 2.

## Results

For the first systematic search, a total of 873 studies were identified. After removal of duplicates, 234 records remained. A total of 205 records were excluded through title or abstract screening (see Fig. 1 and supplementary material). The remaining 29 were retrieved as full text and then further evaluated for eligibility. Finally, 22 records were included for this systematic review (see Table 1). Therefore, seven records were excluded as they met at least one of the exclusion criteria at full-text level (see Fig. 1).

For the second systematic search, we identified 691 records in total and 161 remained after removal of duplicates. 126 of them were excluded on title/abstract level (see Fig. 2). The remaining 35 studies were then retrieved as full texts and further assessed for eligibility. As all records met the inclusion criteria at full-text level, none was excluded in this step (see Table 2).

### Study characteristics for the first systematic search

Twenty-two studies were identified that tested the effect of nicotinergic modulation on cortical excitability and plasticity [21–42] (see supplementary results for sociodemographics, Table 1). Nicotinergic brain functions were manipulated in different ways across studies (see Table 1). From the 22 studies, seven used resting state EEG for measuring cortical excitability [21–27], 15 used TMS measurements either alone to measure cortical excitability [28, 29, 34], or in combination with intermittent theta-burst stimulation (iTBS) [30], tDCS [31–33, 35, 36, 38–40] and PAS [31–33, 35, 37, 38, 41, 42], therefore additionally allowing measurements of cortical plasticity (see Table 1).

1. EEG

   Seven studies analysed the effect of nicotinergic stimulation on cortical excitability by means of resting state EEG [21–27]. In terms of relative power, nicotine administration led across several studies to lower theta power [21, 22, 24, 25]. Similar findings applied to delta power, where nicotine administration was found to be related to a decrease of delta band power across several studies [22–26]. For alpha and beta power values the results were more mixed. When taking the whole alpha band as a measure nicotine administration led to an increase in alpha power in one study [22], while another study found a decrease in alpha power [21]. However, when dividing alpha into alpha1 and alpha2, alpha1 was found to be either decreased [26] or not affected by nicotine administration, while alpha2 seemed to be increased [24–26]. For beta power, although two studies found an increase after nicotine administration of beta power [21, 26] and another an increase in beta2 power [24], the remaining studies did not find such effects [22, 23, 25, 27]. Additionally, an increase of dominant alpha frequency was found in four studies [21–23, 25]. Moreover, smoking deprivation led to an increase in theta, delta and alpha power, as well as to a reduction of alpha mean frequency [27].
2. TMS to access motor-cortical excitability

   Twelve studies used TMS to measure the effect of nicotinergic modulation on cortical excitability [28–30, 32, 34–36, 38–42]. All studies evaluated the effects of either nicotine administration or smoker status in corticospinal excitability. While some studies failed to find an overall effect of either nicotine administration or smoking status on corticospinal excitability [30, 32, 35, 36, 38, 40–42], when focusing on intracortical inhibition and facilitation, an effect of nicotinergic modulation was visible [28, 29, 34]. In one study non-smoker healthy controls were compared to non-smoker patients with Tourette syndrome, and while before nicotine adminis-

**Table 1** Effects of nicotine on cortical excitability and plasticity

| References | Study design | Nicotine administration method and dose; waiting period between nicotine administration and measure | Cortical excitability/plasticity measure parameters; Measurement site | Summary of results (Cortical excitability/plasticity) |
|---|---|---|---|---|
| Golding, 1988 [21] | The effect of smoking a cigarette versus sham smoking on cortical activity was compared via EEG measurements in smokers ($N=30$) | Smoking 1.3 mg nicotine cigarette as compared to sham smoking; measurements took place after 1 h smoking abstinence | EEG was recorded from bipolar positions, midway between Cz and Oz, with reference to linked mastoids during 32 s of eyes open and 32 s of eyes-closed resting period; power spectra estimates were calculated for delta, theta, alpha, beta1 and beta2 bands | Real as compared to sham smoking increased the relative power in the beta bands and reduced alpha and theta activity. However, it had no effect on delta activity. A significant increase in dominant EEG was found in real as opposed to sham smoking |
| Knott, 1988 [22] | The effect of smoking a cigarette versus sham smoking on cortical activity was compared via EEG measurements in smokers ($N=20$) | Comparison between sham and real smoking of a single cigarette; measurements took place before, during and after smoking | EEG was recorded with electrodes placed at the right occipital and referred to linked earlobes for a 3 min eyes-closed resting period; power spectra estimates were calculated for delta, theta, alpha and beta bands | Real as compared to sham smoking led to a reduction of delta and theta power, while it increased alpha power, as well as peak alpha frequency |
| Michel et al., 1988 [23] | The electrocortical effects of nicotine administration as compared to placebo were studied via EEG measurements ($N=20$) | 4-mg nicotine chewing gum | EEG signal recorded during a 5-min resting period; power spectra estimates were calculated for theta, alpha and delta bands | Theta and alpha frequency were increased by a single dose of nicotine chewing gum, while delta power was decreased |
| Knott et al., 1999 [24] | The effect of transdermally administered nicotine on cortical activity in smokers was measured via EEG and compared to placebo ($N=16$) | Nicotine transdermal patch releasing 21 mg nicotine over 24 h; 4 h waiting period; smokers attended the sessions following overnight abstinence | EEG signal from 6 scalp sites (F3, C3, P3, F4, C4, P4) for 5 min eyes-closed rest period; absolute and relative power estimates were calculated for delta, theta, alpha1, alpha2, beta1 and beta2 bands | Nicotine resulted on power reductions through in slow-wave frequencies, while a power augmentation in fast-wave frequencies was found |
| Lindgren et al., 1999 [25] | The dose–response relationship of nicotine administered intravenously on cortical activity, measured via EEG, was studied in smokers ($N=14$) | Single intravenous infusions of 0.9% NaCl, or 3.5, 7.0, 14.0 and 28.0 µg/kg body weight nicotine; 25 min waiting period and measurements took place after 12 h of smoking abstinence | Resting EEG was recorded during the infusion period and until 2 min after the infusion with eyes-closed; absolute power estimates were calculated for delta, theta, alpha1, alpha2 and beta bands | A dose-dependent linear relationship was found between nicotine and delta and theta power. Nicotine administration also led to a rise in alpha2 power and alpha peak frequency |
| Domino, 2003 [26] | The effect of smokers smoking a cigarette versus non-smokers sham smoking on cortical activity was compared via EEG measurements ($N=85$) | Comparison between smokers and non-smokers, smokers smoked an average nicotine yield cigarette and non-smokers sham smoked an unlit placebo cigarette; smokers measurements took place either after overnight abstinence or after normal smoking | EEG signal from 16 scalp electrodes monitoring for 2 min resting state with eyes-closed before and after smoking; total summated activity for all 16 channels was computed for delta, theta, alpha1, alpha2 and beta frequency bands | In smokers, increasing plasma nicotine concentrations to 10–14.9 ng/ml led to a decrease of alpha1 and an increase of alpha2 activity. Nicotine concentrations of 15–19.99 ng/ml decreased delta and alpha1 and increased beta waves |

**Table 1** (continued)

| References | Study design | Nicotine administration method and dose; waiting period between nicotine administration and measure | Cortical excitability/plasticity measure parameters; Measurement site | Summary of results (Cortical excitability/plasticity) |
|---|---|---|---|---|
| Teneggi et al., 2004 [27] | The effect of either free smoking or 36 h of enforced smoking abstinence on cortical activity in healthy smokers was compared by means of EEG measurements ($N=12$) | Comparison between free smoking vs. smoking abstinence; for smoking abstinence measures were taken 24, 28 and 34 h of smoking abstinence | EEG signal from 19 scalp electrodes with linked-ears reference, with one additional channel for electrooculographic monitoring during rest and eyes-closed for a total of 5 min; absolute and relative power spectra and mean frequency of delta, theta, alpha and beta1 activities were calculated | Smoking abstinence led to a rise in theta, alpha and delta absolute power. In terms of frequencies, smoking abstinence was related to a reduced alpha mean frequency, whereas delta, theta and beta1 mean frequency increased. During a period of free smoking, no significant EEG changes were found |
| Orth et al., 2005 [28] | The effect of a single dose nicotine gum in non-smoking healthy controls and non-smoking patients with Tourette syndrome on cortical excitability was studied by means of TMS measurements ($N=18$) | Nicotine gum with a 2 mg dose | TMS measurements used included RMT, SAI, SICI/ICF and CSP; MEPs were evoked over the primary motor cortex and measured at the corresponding muscle, the right FDI | Although both SICI and SAI were reduced in patients when compared to the healthy control group, this difference was abolished when administering a single dose of nicotine. There was no effect of nicotine, and no difference between patients and controls in measures of motor or SICI threshold |
| Lang et al., 2008 [29] | Chronic smokers were compared to non-smokers in terms of cortical excitability via TMS measurements ($N=44$) | Comparison between smokers and non-smokers; for smokers, measures were taken after at least one hour of smoking abstinence | TMS measurements used included RMT, AMT, S1mV, I/O curves, SICI/ICF, LICI, aMEP and CSP; MEPs were evoked over the primary motor cortex and measured at the corresponding muscle, the right FDI | Smokers displayed reduced ICF compared to non-smokers. For CSP, smokers demonstrated a significant prolongation than non-smokers when S1mV was used as an intensity. For aMEP, smokers showed a reduction as compared to non-smokers |
| Swayne et al., 2009 [30] | The effect of nicotine as compared to placebo was studied on cortical plasticity and excitability by combining TMS measurements with iTBS stimulation in non-smokers ($N=10$) | Two mint-flavoured 2 mg nicotine lozenges; 45 min waiting time | MEP amplitude changes from pre- to post-iTBS-stimulation with intensity set for baseline MEPS of 1 mV peak-to-peak measured by 0.2 Hz single pulse TMS; The coil was held over the area representing the left FDI | An increase in MEPs was produced by iTBS which lasted for 5 min when receiving placebo. After nicotine intake, the MEP increase was more pronounced and lasted for 40 min |
| Grundey et al., 2013 [34] | The impact of nicotine on cortical excitability was studied in both smokers and non-smokers by means of TMS measurements ($N=24$) | Nicotine transdermal patch with a 16 mg dosage of nicotine; 6 h waiting time; smokers under smoking abstinence | TMS measurements used included RMT, AMT, input/output curves (100, 110, 130, and 150% RMT), SICI, ICF and SAI; MEPs were evoked over the motor cortex and measured at the corresponding muscle, the right ADM | Increased cortical excitability with regard to the I/O curve was displayed in smokers during smoking abstinence as compared to non-smokers, as well as enhanced inhibition (SAI) and diminished facilitation (ICF). Nicotine administration led to a rise in cortical facilitation (ICF) in smokers, whereas it led to an enhanced inhibition (SICI, SAI) in non-smokers |

**Table 1** (continued)

| References | Study design | Nicotine administration method and dose; waiting period between nicotine administration and measure | Cortical excitability/plasticity measure parameters; Measurement site | Summary of results (Cortical excitability/plasticity) |
|---|---|---|---|---|
| Strube et al., 2015 [36] | Healthy smokers and non-smokers were compared with smoking and non-smoking schizophrenia patients in terms of cortical excitability and plasticity by means of TMS before and after cathodal tDCS ($N=75$) | Smoking status used as nicotine measurement; in smokers, data was acquired after at least half an hour of smoking abstinence | MEP amplitude changes from pre- to post-cathodal tDCS stimulation with intensity set for baseline MEPs of 1 mV peak-to-peak measured by 0.25 Hz single pulse TMS; MEPs were evoked using single pulse TMS over the motor cortex representation of the right FDI | In non-smoking schizophrenia patients, cathodal tDCS-induced plasticity was found to be abolished, which was not the case for smoking patients. In healthy controls, significant cortical excitability (MEP) reductions following cathodal tDCS were observed in non-smoking individuals, but only trend-level reductions in smokers |
| Lugon et al., 2017 [39] | The effect of a combination of nicotine administration (vs. placebo) and different doses of dextromethorphan (DMO) on cortical plasticity was studied using a combination of tDCS stimulation with TMS measurements in non-smokers ($N=13$) | Nicotine transdermal patch releasing 15 mg of nicotine over 16 h either combined with DMO (NMDA-receptor antagonist) in different doses (50, 100 and 150 mg) or with placebo; 6 h waiting time | MEP amplitude changes from pre- to post-anodal tDCS stimulation with intensity set for baseline MEPs of 1 mV peak-to-peak measured by 0.25 Hz single pulse TMS; MEPs were evoked using single pulse TMS over the motor cortex representation of the right ADM | Nicotine administration abolished anodal tDCS-induced plasticity, which was restored under medium dosage of DMO. A low dosage of DMO did not have an impact on nicotine's action, whereas high-dosage DMO abolished plasticity. When DMO was administered alone, a low dosage had no effect, however, medium and high dosages abolished anodal tDCS-induced plasticity |
| Grundey et al., 2018a [40] | The effect of nicotine administration in combination with a calcium channel blocker (flunarizine) at three different doses or with placebo on cortical plasticity in non-smokers was tested via tDCS stimulation and TMS measurements. ($N=12$) | Nicotine transdermal patch releasing 15 mg of nicotine over 16 h and flunarizine at three different doses (2.5, 5, and 10 mg); 6 h waiting time | MEP amplitude changes from pre- to post-anodal tDCS stimulation with intensity set for baseline MEPs of 1 mV peak-to-peak measured by 0.25 Hz single pulse TMS; MEPs were evoked using single pulse TMS over the motor cortex representation of the right ADM | Nicotine administration abolished anodal tDCS-induced cortical plasticity. Plasticity was re-established when nicotine was combined with a calcium channel blocker (flunarizine) in a dose-dependent form |
| Thirugnanasambandam et al., 2011 [31] | The influence of nicotine on cortical plasticity as compared to placebo was studied in non-smokers using tDCS and PAS in combination with TMS measurements before and after the stimulations ($N=48$) | Nicotine transdermal patch releasing 15 mg of nicotine over 16 h; 6 h waiting time | MEP amplitude changes from pre- to post-stimulation with intensity set for baseline MEPs of 1 mV peak-to-peak measured by 0.25 Hz single pulse TMS; MEPs were evoked using single pulse TMS over the motor cortex representation of the ADM | PAS10- and cathodal tDCS-induced inhibitory plasticity was abolished or reduced by nicotine administration. This was also the case for anodal tDCS-induced facilitatory plasticity. However, PAS25-induced facilitatory plasticity was slightly prolonged by nicotine administration |

**Table 1** (continued)

| References | Study design | Nicotine administration method and dose; waiting period between nicotine administration and measure | Cortical excitability/plasticity measure parameters; Measurement site | Summary of results (Cortical excitability/plasticity) |
|---|---|---|---|---|
| Grundey et al., 2012a [32] | The impact of nicotine on cortical plasticity as compared to placebo was studied in non-smokers using tDCS and PAS in combination with TMS measurements before and after stimulations. ($N=48$) | Nicotine nasal spray, cumulative dose of 1 mg nicotine; 10 min waiting time | MEP amplitude changes from pre- to post-stimulation with intensity set for baseline MEPS of 1 mV peak-to-peak measured by 0.25 Hz single pulse TMS; MEPs were evoked using single pulse TMS over the motor cortex representation of the right ADM | PAS25- and anodal tDCS-induced facilitatory plasticity was abolished by the nicotine administration, whereas induced excitability diminution was abolished for PAS 10 but for cathodal tDCS it was delayed and weakened |
| Grundey et al., 2012b [33] | The effect of nicotine on cortical plasticity as compared to placebo was studied in smokers using tDCS and PAS in combination with TMS measurements before and after the stimulations ($N=48$) | Nicotine transdermal patch releasing 15 mg of nicotine over 16 h; 6 h waiting time; under smoking abstinence | MEP amplitude changes from pre- to post-stimulation with intensity set for baseline MEPS of 1 mV peak-to-peak measured by 0.25 Hz single pulse TMS; MEPs were evoked using single pulse TMS over the motor cortex representation of the right ADM | PAS25- and anodal tDCS-induced facilitatory plasticity was abolished during smoking abstinence but restored by nicotine administration. However, inhibitory plasticity was not affected by smoking abstinence. Here, after nicotine administration, cathodal tDCS-generated non-focal excitability reduction was abolished, whereas the inhibitory after-effects of PAS25 were delayed and prolonged |
| Batsikadze et al., 2015 [35] | The effect of nicotine administration on cortical plasticity as compared to placebo administration was studied in healthy non-smokers by means of tDCS and PAS stimulations and TMS measurements before and after the stimulations ($N=25$) | Placebo or verum with low (0.1 mg), medium (0.3 mg) or high (1.0 mg) dosages of varenicline (nicotine); 3 h waiting time | MEP amplitude changes from pre- to post-stimulation with intensity set for baseline MEPs of 1 mV peak-to-peak measured by 0.25 Hz single pulse TMS; MEPs were evoked using single pulse TMS over the motor cortex representation of the right ADM | Low dose varenicline had no impact on stimulation-induced plasticity. Medium-dose varenicline, however, had a positive effect on PAS25-induced excitatory plasticity and while it abolished anodal tDCS-induced facilitatory after-effects. Lastly, high-dose varenicline preserved both PAS25-induced facilitatory plasticity and cathodal tDCS effects |
| Batsikadze et al., 2017 [38] | The impact of either placebo or low or high dose of nicotine was studied on cortical plasticity by combining PAS and tDCS stimulations with TMS measurements in smokers ($N=20$) | Either placebo or verum with low (0.3 mg) or high (1.0 mg) dosages of varenicline (nicotine); 3 h waiting time; under smoking abstinence | MEP amplitude changes from pre- to post-stimulation with intensity set for baseline MEPs of 1 mV peak-to-peak measured by 0.25 Hz single pulse TMS; MEPs were evoked using single pulse TMS over the motor cortex representation of the right ADM | Under smoking abstineece, stimulation-induced plasticity was absent, however, a high-dose of varenicline restored plasticity, irrespective of focality. PAS10- and cathodal tDCS-induced inhibitory plasticity was also prolonged by a high dose. Low dose varenicline only re-established tDCS-induced plasticity having therefore no significant impact on PAS-induced plasticity |

**Table 1** (continued)

| References | Study design | Nicotine administration method and dose; waiting period between nicotine administration and measure | Cortical excitability/plasticity measure parameters; Measurement site | Summary of results (Cortical excitability/plasticity) |
|---|---|---|---|---|
| Bridgman et al., 2016 [37] | The effect of 5 doses of nicotine over a 3-day period on cortical plasticity as compared to placebo was studied by means of combining PAS stimulation with TMS measurements in non-smoking schizophrenia patients and non-smoking healthy controls ($N = 19$) | Varenicline (nicotine) 0.5 mg administered two times a day and one dose before commencement of testing for a total of 5 doses, or placebo, over a 3-day period | MEP amplitude changes from pre- to post-PAS stimulation with intensity set for baseline MEPs of 1 mV peak-to-peak measured by single pulse TMS; MEPs were evoked using single pulse TMS over the motor cortex representation of the relaxed APB muscle | A significant interaction between diagnosis and medication was found. Varenicline administration led to a significant rise in PAS25-induced facilitatory plasticity in schizophrenia patients |
| Grundey et al., 2018b [41] | The effect of nicotine administration on cortical plasticity measured via PAS stimulation and TMS measurements as compared to placebo administration in deprived smokers was studied ($N = 12$) | Nicotine nasal spray, cumulative dose of 1 mg nicotine; 10 min waiting time; under smoking abstinence | MEP amplitude changes from pre- to post-PAS stimulation with intensity set for baseline MEPs of 1 mV peak-to-peak measured by 0.25 Hz single pulse TMS; MEPs were evoked using single pulse TMS over the motor cortex representation of the right ADM | Smokers under smoking abstinence displayed reduced excitatory plasticity induced by PAS25. However, the nicotine administration re-established this PAS25 excitatory plasticity induction |
| Lavender et al., 2019 [42] | Healthy chronic smokers and non-smokers were compared in terms of cortical plasticity by means of PAS stimulation and TMS measurements ($N = 21$) | Smoking status used as nicotine measurement; in smokers, data was acquired between 90 and 120 min of smoking abstinence | MEP amplitude changes from pre- to post-PAS stimulation with intensity set for baseline MEPs of 1 mV peak-to-peak measured by 0.25 Hz single pulse TMS; MEPs were evoked using single pulse TMS over the motor cortex representation of the right FDI | In non-smokers, MEP response increased and remained above baseline level for at least 30 min after the intervention, indicating an effect of PAS25 plasticity induction. This was not the case for smokers |

aMEP, active motor-evoked potential; AMT, active motor threshold; ADM, adductor digiti minimi; APB, abductor pollicis brevis; CSP, cortical silent period; DMO, dextromethorphan; EEG, electroencephalography; FDI, first dorsal intraosseous; ICF, intracortical facilitation; I/O, input/output; iTBS, intermittent theta-burst stimulation; LICI, long-interval cortical inhibition; MEP, motor-evoked potential; NaCl, sodium chloride; NMDA, N-methyl-D-aspartate; PAS, paired associative stimulation; RMT, resting motor threshold; SAI, short-latency afferent inhibition; SICI, short interval intracortical inhibition; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation

**Table 2** Summary of NIBS intervention studies for smoking behaviour

| References | Study design | NIBS technique, target, parameters | Outcome measure | Summary of results |
|---|---|---|---|---|
| Eichhammer et al., 2003 [43] | Number of cigarettes smoked and craving levels in healthy smokers were compared between single days of active versus sham rTMS stimulation ($N=14$) | 20 trains of rTMS at a rate of 20 Hz for 2.5 s over 14 min over the left DLPFC. Stimulation intensity set at 90% of RMT | Craving was assessed with a 100-point VAS at baseline and 30 min after rTMS for the subjective state "desire to smoke". Number of cigarettes smoked was noted during a 6-h period after rTMS | Under active stimulation the number of cigarettes smoked was significantly smaller as compared to sham stimulation. However, no effect was found on craving levels |
| Johann et al., 2003 [44] | The effect of active rTMS as compared to sham stimulation was assessed on craving levels in a population of healthy smokers ($N=11$) | 20 trains of rTMS for 2.5 s at a rate of 20 Hz over the left DLPFC. 90% RMT was used as stimulation intensity | Craving was assessed through a VAS before and 3 min after rTMS administration | Lower levels of craving were found in the active rTMS stimulation condition as compared to the sham condition |
| Fregni et al., 2008 [45] | Craving levels were compared in healthy smokers between single days of active versus sham tDCS stimulation ($N=24$) | Three different types of brain stimulation with tDCS were performed: sham tDCS, anodal tDCS over the left DLPFC (F3) and anodal tDCS over the right DLPFC (F4). A constant current of 2 mA intensity was applied for 20 min | Before and after the tDCS stimulation participants were confronted with a 5-min video of people smoking. Craving was assessed with 5 items on a 100-point VAS before and after each video (i.e. four times) | Smoking craving increase significantly after the exposure to smoking-craving cues. However, active tDCS administered in both left and right DLPFC reduced craving significantly |
| Amiaz et al., 2009 [46] | Consumption of cigarettes was compared between sham and active rTMS treatment in healthy smokers ($N=48$) | Ten daily rTMS sessions were administered over the left DLPFC. The participants received 20 trains each day at 100% RMT stimulation intensity. Each train consisted of 50 pulses at 10 Hz and the inter-train interval was of 15 s | Cigarette consumption was assessed through cotinine levels in urine samples and participants' self-report. Craving level and dependence were evaluated through self-reported questionnaires | Cigarette consumption and nicotine dependence was found to be reduced by ten daily active rTMS sessions. Additionally, rTMS treatment blocked the craving induced when participants were presented with smoking-related pictures |
| Boggio et al., 2009 [47] | The effects of anodal tDCS over the left DLPFC, as compared to sham tDCS, were compared in terms of craving behaviour in healthy smokers ($N=27$) | Active anodal tDCS over the left DLPFC for five consecutive days with a constant current of 2 mA intensity applied for 20 min | Craving levels were measured through a VAS scale consisting of 5 items. This assessment was performed on the 5 days, at baseline and after watching a cue-provoking video. Additionally, number of cigarettes smoked was recorded | Active tDCS had a significant cumulative effect on modifying smoking cue-provoked craving. Craving even decreased after watching the cue-provoking video. Moreover, there was a significant decrease of number of cigarettes smoked by the participants in the active tDCS condition, as compared to the sham condition |

**Table 2** (continued)

| References | Study design | NIBS technique, target, parameters | Outcome measure | Summary of results |
|---|---|---|---|---|
| Rose et al., 2011 [48] | The effects of high and low-frequency rTMS were compared on subjective responses to smoking versus neutral cues in healthy smokers ($N=15$) | Stimulation was carried out for three rTMS conditions: 10 Hz over the SFG, 1 Hz over the SFG and 1 Hz over the motor cortex. The stimulation was performed for 3 trains of 2 min and 30 s duration, at an intensity of 90% RMT | Craving was assessed before and after watching neutral cues, smoking cues and after smoking a cigarette through a self-report questionnaire | Each condition provoked a different effect on craving after smoking versus neutral cues. There was a greater increase in craving after presentation of smoking cues in the 10 Hz SFG condition than in the others. Whereas a decrease in craving was found in this condition after the presentation of neutral cues relative to the other conditions. In the 10 Hz-condition before and after controlled smoking a decrease in the reduction of immediate craving was found |
| Wing et al., 2012 [49] | The effect of 20 sessions of active rTMS at a rate of 5 treatments per week was compared with sham rTMS as an add-on to group therapy and transdermal nicotine in smokers with schizophrenia for smoking cessation ($N=15$) | Bilateral 20 Hz rTMS stimulation was administered over the DLPFC. The intensity was set at 90% RMT. In each stimulation session, 25 trains of 30 pulses per train were administered at a frequency of 20 Hz | Smoking was assessed weekly via self-report and breath carbon monoxide levels. Additionally, cravings and withdrawal were assessed also via self-report once during each treatment week pre- and post-rTMS | Pre- and post-rTMS data collected in the first week displayed that active rTMS significantly reduced cravings, as compared to sham rTMS. However, it did not alter craving in weeks 2–4. Moreover, active rTMS also did not increase abstinence rates |
| Hayashi et al., 2013 [50] | The effect of a single active rTMS sessoin on subjective craving levels as compared to sham rTMS in combination of availability of smoking was tested in healthy smokers ($N=10$) | Low-frequency rTMS administered over the left DLPFC. 1800 pulses were delivered at a frequency of 1 Hz. Intensity was set at 59% of the stimulator maximum which should correspond to 110% average RMT in a different population of young subjects | Subjective craving level was measured using a VAS scale after watching a smoking cue-provoking or a neutral video | When sham rTMS was administered, if smoking was immediately available for the participant, the subjective craving was stronger than if the availability was delayed. This was not the case when active rTMS was administered, namely then craving levels decreased for the immediately available condition and the craving levels were similar to the ones for the delayed availability condition |
| Li et al., 2013 [51] | A single session of active rTMS and sham rTMS were compared in terms of their effect on craving levels in healthy smokers ($N=16$) | rTMS treatment was administered over the left DLPFC at 100% RMT, at 10 pulses per second for 5 s, with an inter-train interval of 10 s. In each treatment session 3000 pulses were administered for 15 min | Before and after watching either scenic images, neutral images or smoking cue images, participants had to rate through VAS their cravings by means of 10 different questions | Active rTMS over the left DLPFC reduced craving levels from baseline. This was not the case for sham rTMS. Moreover, when comparing the effect of neutral versus smoking cues on craving, active rTMS produced a significantly greater difference reduction than sham rTMS |

**Table 2** (continued)

| References | Study design | NIBS technique, target, parameters | Outcome measure | Summary of results |
|---|---|---|---|---|
| Sheffer et al., 2013 [52] | The effects of one session of either 20 Hz rTMS, 10 Hz rTMS or sham rTMS were compared in terms of cigarette consumption in healthy smokers ($N=47$) | 900 pulses of rTMS were administered in three conditions, 20 Hz rTMS, 10 Hz rTMS or sham rTMS over the left DLPFC. The stimulation was delivered at 110% intensity of RMT | Post-session number of cigarettes smoked was determined every hour via a tracking form and a timeline follow-back procedure administered by telephone 6 h and 24 h after stimulation | Self-reported number of cigarettes consumed after 6 h and 24 h post-stimulation did not differ across conditions |
| Xu et al., 2013 [53] | The effect of a single session of active tDCS, as compared to sham tDCS, on cigarette craving was assessed in overnight abstinent healthy smokers ($N=24$) | tDCS was delivered by placing the anode over the left DLPFC and the cathode over the contralateral supra-orbital area. The active tDCS stimulation was given at 2 mA constant current intensity for 20 min | Craving was assessed through 10 7-point items before and after watching cigarette smoking-related pictures and video clips for 5 min | No effect of active tDCS was found on the reduction on cigarette craving |
| Cailhol et al., 2014 [54] | The effects of 10 sessions of rTMS treatment on smoking cessation were recorded, as compared to sham rTMS in smokers with borderline personality disorder ($N=9$) | 2 series of 5 daily rTMS sessions at 10 Hz were administered over the right DLPFC. The intensity was set at 80% of the RMT | Self-report of the participants regarding smoking cessation was measured | 2 smoking cessations were observed in the group receiving active rTMS. The participants reported that this was due to loss of the desire to smoke |
| Dieler et al., 2014 [55] | The effect of 4 sessions iTBS was investigated as add-on treatment to CBT on reducing nicotine craving and improving long-term abstinence as compared to sham iTBS in healthy smokers ($N=74$) | 4 sessions of iTBS were administered over the right DLPFC. 3 trains of stimulation were repeatedly administered every 200 milliseconds for 2 s, at 50 Hz. These iTBS trains were repeated every 10 s, leading to a total of 600 pulses. The stimulation was performed at 80% intensity of the RMT | Urge to smoke and the expectation to successfully quit smoking were measured through self-reported questionnaires before and after treatment. Additionally, participants were contacted by phone after 3, 6 and 12 months to inquire about abstinence rates | No effect of active iTBS was found on craving. However, higher abstinence rates were found at 3 months in the active iTBS, as compared to sham iTBS. This was not the case for abstinence rates at 6 and 12 months after the treatment |
| Dinur-Klein et al., 2014 [56] | The effect of 13 daily sessions of high-frequency, low-frequency or sham rTMS was compared in terms of cigarette consumption, nicotine dependence and craving in healthy smokers ($N=115$) | rTMS was administered over the DLPFC at 120% intensity of the RMT. High-frequency sessions consisted of 33 trains of 10 Hz each lasting 3 s. Low-frequency sessions consisted of 600 continuous pulses at 1 Hz | Cigarette consumption was evaluated through self-report and cotinine levels in urine samples. Nicotine dependence and craving were assessed through self-reported questionnaires. Half of the participants were additionally exposed to smoking cues at each stimulation session. A follow-up interview was also performed after 6 months to assess cigarette consumption | Cigarette consumption and nicotine dependence was significantly decreased by high (but not low) frequency rTMS treatment. Moreover, this decrease was stronger when treatment was combined to exposure to smoking cues, which led to an abstinence rate of 44% at the end of the treatment and an abstinence rate of 33% after 6 months after the treatment |

**Table 2** (continued)

| References | Study design | NIBS technique, target, parameters | Outcome measure | Summary of results |
|---|---|---|---|---|
| Fecteau et al., 2014 [57] | The effect of 5 sessions of active tDCS on nicotine craving levels and cigarette consumption was evaluated in comparison with sham tDCS in healthy smokers ($N=12$) | tDCS was delivered by placing the anode over the right DLPFC and the cathode over the left DLPFC. Participants received a constant current of 2 mA intensity for 30 min | Smoking intake was assessed through a daily calendar were participants listed the number of cigarettes smoked each day. Additionally, CO was measured before and after treatment. Nicotine craving was measured through a self-report questionnaire, administered the first and last day of stimulation, before and after watching smoking cue-provoking videos | The number of cigarettes smoked decreased significantly in the active tDCS condition, as compared to sham tDCS. This effect was still present four days after the end of the stimulation. In terms of nicotine craving, active tDCS did have a significant impact on desire to smoke, but not on anticipation of positive outcome, intention to smoke and relief from negative affect |
| Meng et al., 2014 [58] | The effect of inhibiting the fronto-parietal-temporal association area through cathodal tDCS on visual attention to smoking-related cues and smoking behaviour was tested as compared to sham tDCS in healthy smokers ($N=27$) | Three stimulation conditions were used: bilateral cathodal over both sides of the FPT, cathodal over right FPT and sham tDCS. During the stimulation the current was set at an individual level from 0.1 mA to 5 mA intensity and applied for 20 min | Visual attention to smoking-related cues was measured through an eye tracking paradigm displaying smoking or cigarette related cues together with neutral stimuli. The participants also reported the number of cigarettes smoked since the stimulation for 24 h | The cigarette consumption was reduced significantly by bilateral cathodal stimulation. Although a trend was found on the effect of bilateral cathodal stimulation on attention to smoking-related cues, it did not reach significance. No effects were found under single cathodal tDCS or sham tDCS |
| Prikryl et al., 2014 [59] | The effect of 21 sessions of active rTMS during three consecutive weeks on cigarette consumptions was compared with sham rTMS in male smoking schizophrenia patients ($N=35$) | rTMS was performed over the left DLPFC with an intensity of 110% RMT, a stimulation frequency of 10 Hz, 20 trains with a 10 s duration and an inter-train interval of 30 s. In each stimulation session 2000 TMS pulses were administered | To monitor cigarette consumption, patients filled out forms recording the number of cigarettes smoking during 7 days before the treatment started, throughout the treatment and for 7 days after the treatment | A significantly lower consumption of cigarettes was observed in the active rTMS condition, as compared to sham rTMS. This was already the case in the first week of stimulation. The cigarette consumption decreased by almost 13% in the active rTMS group, while in the sham rTMS group, the consumption remained stable |
| Pripfl et al., 2014 [60] | The effect of 3 sessions of high-frequency rTMS on cue-induced nicotine cravings was assessed in comparison to sham rTMS in healthy smokers ($N=14$) | High-frequency rTMS at 10 Hz was applied over the left DLPFC for 11.6 min at an intensity of 90% RMT. The stimulation entailed 24 trains lasting each 5 s, with 25 s inter-train-interval | Craving was assessed after either neutral images or smoking images | Craving ratings were found to be significantly lower in the active rTMS condition, than in the sham rTMS condition |
| Pripfl & Lamm, 2015 [61] | The effect of one session of anodal tDCS as compared to sham tDCS on nicotine craving-cue appraisal was studied in healthy smokers ($N=20$) | Anodal tDCS was administered over the right or left DLPFC, while the cathode was placed over the contralateral DLPFC with a current intensity of 0.45 mA. The stimulation lasted for 15 min | Craving, arousal and valence were assessed by means of the cue-induced craving and affective picture appraisal task, with a rating ranging from very low craving to very strong craving | Anodal tDCS over the right DLPFC reduced negative affect in emotion appraisal but failed to have an effect on craving appraisal, as it did not induce any significant modifications on craving ratings |

**Table 2** (continued)

| References | Study design | NIBS technique, target, parameters | Outcome measure | Summary of results |
|---|---|---|---|---|
| Smith et al., 2015 [62] | 5 sessions of active tDCS were compared to sham tDCS in terms of their effect on smoking and cigarette craving in smoking schizophrenia patients ($N=37$) | The stimulation was carried out placing the anode over the left DLPFC and the cathode over the contralateral supra-orbital ridge. Active tDCS was administered with a 2 mA current intensity for 20 min | Cigarette smoking was assessed on one hand via self-report and on the other hand via analysing CO levels. Cigarette dependence was assessed via self-report. Finally, craving levels were measured through subject's rating of craving after the participants watched either neutral or smoking cues | No significant effects of active tDCS were found in cigarette smoking, cigarette dependence and cigarette cravings |
| Trojak et al., 2015 [63] | The effect of 10 sessions of active rTMS on relapse after quitting smoking in combination with nicotine replacement therapy was studied as compared to sham rTMS ($N=37$) | 1 Hz rTMS was administered over the right DLPFC with and intensity of 120% RMT. One rTMS session consisted of six trains of 60 pulses, with an inter-train-interval of 30 s | Successful smoking cessation was operationalised as the proportion of participants with continuous abstinence in each group. Continuous abstinence was based on self-report and verified with a breath CO monitor. Craving was assessed via a VAS regarding the desire to smoke and two validated craving scales | A significantly higher number of participants were abstinent in the active rTMS group as compared to sham rTMS group at the end of the combined treatment. Additionally, active rTMS led to significantly lower craving ratings in the compulsive factor. However, these effects were not present after 6 weeks and 12 weeks post-treatment |
| Falcone et al., 2016 [64] | The effect of a single session of anodal tDCS as compared to sham tDCS on the ability to resist smoking was tested in healthy smokers ($N=25$) | Active tDCS was administered by placing the anode over the left DLPFC and the cathode over the right supra-orbital area. Current was set at 1 mA intensity and the stimulation lasted for 19 min | Ability to resist smoking was tested via a paradigm where participants were asked not to smoked, and for every 5 min they resisted smoking they received 1$. Time to first cigarette and total number of cigarettes smoked during a period of 50 min were recorded and used as outcome variables | The latency to smoke was significantly increased by active tDCS as compared to sham. Additionally, the total number of cigarettes smoked also significantly decreased in the active tDCS condition when comparing it to sham tDCS |
| Huang et al., 2016 [65] | The effect of 21 sessions of active rTMS during three consecutive weeks on cigarette consumptions was compared with sham rTMS in male smoking schizophrenia patients ($N=37$) | Active rTMS was administered over the left DLPFC with an intensity of 110% RMT at a 10 Hz frequency. 20 pulses per second were delivered, at a stimulation time of 10 s and a inter-train-interval of 30 s. A total of 2000 pulses were administer per cycle | Number of cigarettes smoked 7 days before treatment, the 21 days into the treatment and from the 14th to the 17th day after treatment were used as outcome measure | Cigarette consumption was significantly decreased by active rTMS already in the first week of treatment. This effect lasted for at least for 3 weeks after the end of the treatment |
| Kroczek et al., 2016 [66] | The effect of active tDCS on craving during smoking-related cue exposure was assessed in comparison to sham tDCS in healthy smokers ($N=29$) | Active tDCS was administered by placing the anode over the left DLPFC and the cathode over the orbitofrontal cortex. Current was set at 2 mA intensity and the stimulation lasted for 15 min | Craving levels were assessed by self-reported craving during in vivo cigarette cue-exposure | There was no significant effect of active tDCS on craving levels |

**Table 2** (continued)

| References | Study design | NIBS technique, target, parameters | Outcome measure | Summary of results |
|---|---|---|---|---|
| Yang et al., 2017 [67] | The effect of active tDCS on craving during smoking-related cue exposure was assessed in comparison to sham tDCS in healthy smokers ($N=32$) | A symmetrical bilateral tDCS protocol was performed with the anode over the left DLPFC and cathode over the right DLPFC. Current was set at a constant level of 1 mA intensity and delivered for 30 min | Craving levels were assessed by a self-reported VAS scale before and after exposure to smoking cue-inducing images | Craving ratings were significantly lower across the cue-reactivity task in the active tDCS condition as compared to the sham condition |
| Kamp et al., 2018 [68] | The effect of 15 sessions of active rTMS on smoking behaviour was tested in smoking schizophrenia patients, as compared to sham rTMS ($N=67$) | 10 Hz rTMS was administered 5 days per week for 3 weeks over the left DLPFC. The intensity was set at 110% of the RMT. 1000 stimuli were delivered per session, i.e. 20 trains with 50 stimuli per train with an inter-train-interval of 30 s | Cigarette consumption was evaluated through self-reported daily smoked cigarettes | No significant effect from 10 Hz rTMS on daily cigarette consumption were found in the study. There was however a trend towards higher nicotine reductions in patients who smoked higher amounts of cigarettes in the active rTMS group |
| Kozak et al., 2018 [69] | 6 sessions delivered in 3 days of active rTMS and sham rTMS were compared in terms of their effect on craving levels in smokers with schizophrenia compared to non-psychiatric smoking controls ($N=27$) | Bilateral 20 Hz rTMS stimulation was administered over the DLPFC. The stimulation consisted on 25 stimulation trains of 30 pulses per train with a inter-train-interval of 30 s | Tobacco craving and withdrawal were assessed through self-reported questionnaires. These measures were taken under conditions of smoking satiation in day 2, under acute 16 h of smoking abstinence in day 3 and upon smoking reinstatement in day 3 | Active rTMS did not show an effect on tobacco craving and withdrawal |
| Chang et al., 2018 [70] | The effect of 10 days active rTMS treatment on smoking cessation was studied in healthy smokers ($N=14$) | 20 Hz rTMS over the left DLPFC and the supramedial frontal cortex (SMFC) was administered. 20 trains of 50 pulses for 2.5 s were delivered. The intensity was set at 90% RMT | Nicotine craving and withdrawal were measured through self-reported questionnaires daily during treatment and during a follow-up period of 25 days | Nicotine craving and withdrawal were significantly reduced after active rTMS treatment. This effect lasted for at least 25 days after treatment end |
| Mondino et al., 2018 [71] | The effect of 10 sessions of active tDCS was studied on cigarette consumption, craving and brain reactivity to smoking cues in healthy smokers ($N=29$) | Active tDCS was applied by placing the anode over the right DLPFC and cathode over the left occipital region. A constant current of 2 mA intensity was administered for 20 min | Smoking intake was assessed through a daily calendar were participants listed the number of cigarettes smoked each day. Smoking craving was assessed before and after each tDCS session with a self-reported questionnaire. Brain reactivity was measured through fMRI sessions before and after the first tDCS session and the last tDCS session. During each scan, participant viewed smoking, neutral and target images | No effect of active tDCS on nicotine consumption was found. However, active tDCS did lead to a decrease in craving scores. Moreover, 10 sessions of active tDCS led to an increase in brain reactivity to smoking cues within the right PCC as compared to sham |

**Table 2** (continued)

| References | Study design | NIBS technique, target, parameters | Outcome measure | Summary of results |
|---|---|---|---|---|
| Sheffer et al., 2018 [72] | The potential efficacy of 8 sessions of active rTMS for smoking cessation was tested as compared to sham stimulation, both combined with an evidence-based self-help intervention in healthy smokers ($N=29$) | Active 20 Hz rTMS was applied over the left DLPFC with an intensity of 110% RMT. Participants received 45 20-pulse trains of 1 s duration with an inter-train-interval of 20 s | Motivation and self-efficacy for quitting smoking, nicotine dependence, craving and withdrawal and motivation for abstinence were measured through self-reported questionnaires. Measures were taken at baseline, 4, 8 and 12 weeks after the quit date. Additionally, daily cigarette use was assessed weekly by telephone | Active rTMS reduced the relative risk of relapse threefold, increased abstinence rates and increased uptake of the self-help intervention. Participants in the active rTMS condition were more likely to be still abstinent 12 weeks after quitting smoking |
| Vitor de Souza Brangioni et al., 2018 [73] | The effect of 5 sessions of active tDCS and motivation to quit on cigarette consumption as compared to sham stimulation in healthy smokers ($N=36$) | tDCS was delivered by placing the anode over the left DLPFC and the cathode over the right contralateral supra-orbital region. A constant current of 1 mA intensity was applied for 20 min | Cigarette consumption was measured through a self-monitoring questionnaire assessing the number of cigarettes smoked at baseline, at the end of the stimulation sessions, 2 days later and at a 4-weeks follow-up | Active tDCS had a significant effect on the reduction of cigarettes smoked per day. This effect was moderated by motivation to quit, meaning that higher levels of motivation were associated with a larger impact of active tDCS on cigarette consumption |
| Alghamdi et al., 2019 [74] | The effect of 3 sessions of active tDCS on cigarette smoking as compared to sham tDCS in healthy smokers ($N=22$) | Active tDCS was delivered by placing the cathode over the right DLPFC and the anodal electrode at the left DLPFC. The stimulation was performed with a current of 1.5 mA intensity and applied for 20 min | Cigarette consumption was recorded by means of a daily calendar where participants reported the number of cigarettes smoked. This measure was taken at baseline, during the 3 days of stimulation and 8 days after the last treatment session | No significant effect of active tDCS as compared to sham tDCS was found regarding the number of cigarettes smoked |
| Falcone et al., 2019 [75] | The effect of 3 tDCS sessions, either of 1 mA, 2 mA or sham, where compared in terms of successful smoking cessation in healthy smokers ($N=106$) | For the tDCS procedure, the anode was placed over the left DLPFC and the cathode over the right supra-orbital area. The procedure was performed either with a current intensity of 1 mA, of 2 mA or sham stimulation for 20 min | Ability to resist smoking was tested via a paradigm where participants were asked not to smoked, and for every 5 min they resisted without smoking they received 1$. Time to first cigarette and total number of cigarettes smoked during a period of 50 min were recorded and used as outcome variables. After the last treatment session, the participants were instructed to quit smoking, and smoking behaviour was monitor for the next 7 days through a timeline procedure, CO measurement and craving rating | No effect of active tDCS was found regarding the ability to remain abstinent during a 7-day quit period. Also, no effect was found regarding the time to first cigarette and the number of cigarettes smoked during the smoking paradigm used in the study |

**Table 2** (continued)

| References | Study design | NIBS technique, target, parameters | Outcome measure | Summary of results |
|---|---|---|---|---|
| Friedrich et al., 2019 [76] | The effect of 5 sessions of active rTMS in a single day on cigarette craving was assessed in comparison to sham rTMS in healthy smokers ($N = 5$) | Active rTMS was delivered over the left DLPFC at an intensity of 110% of the RMT. Each session consisted of 3000 pulses of 10 Hz | Craving levels were assessed by a self-reported questionnaire | From the 2 participants receiving active rTMS one showed a decrease in craving, while the other remained stable. In the sham group,2 2 of the participants showed a decrease in craving, whereas the other one showed an increase |
| Ghorbani Behnam et al., 2019 [77] | Active tDCS (either 20 sessions in 4 weeks or 12 weeks), sham tDCS and 300 mg bupropion for 8 weeks were compared in terms of their efficacy in reducing smoking consumption in healthy smokers ($N = 170$) | Active tDCS was delivered by placing the anode over the left DLPFC and the cathode at the right DLPFC. The stimulation was performed with a current of 2 mA intensity and applied for 20 min | Smoking abstinence was assessed via salivary cotinine. Additionally, nicotine dependence and cigarette consumption were recorded via self-report. All outcomes were measured at baseline, post-intervention, and at a 6 months follow-up | The higher duration (12 weeks) stimulation treatment led to a significantly higher abstinence rate at 6 months that the shorter stimulation protocol and the sham protocols. However, it was not significantly different than treatment with bupropion |

CO, carbon monoxide; DLPFC, dorsolateral prefrontal cortex; FPT, frontal-parietal-temporal association area; iTBS, intermittent theta-burst stimulation; RMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation; SFG, superior frontal gyrus; tDCS, transcranial direct current stimulation; VAS, visual analogue scale

tration short-latency intracortical inhibition (SICI) and short-latency afferent inhibition (SAI) were reduced in patients, these differences were abolished by nicotine consumption [28]. However, when both groups were analysed separately, nicotine consumption did not have an effect on cortical excitability. The other two studies both found deprived smokers to display a larger SAI and a reduced intracortical facilitation (ICF) as compared to non-smokers [29, 34]. Nevertheless, nicotine administration via a 16 mg transdermal patch led to an increase in SAI in smokers while it led to an enhanced SICI and SAI in non-smokers [34]. Furthermore, one study used a form of rTMS, iTBS, to test the effect of nicotinergic modulation via 4 mg nicotine lozenges on cortical plasticity in non-smokers [30]. Although in the placebo condition a facilitation through iTBS took place, this only lasted for 5 min, whereas in the nicotine arm, the facilitation was more pronounced and still present after 40 min.

3. tDCS

   Eight studies tested the effect of nicotine on cortical plasticity by means of a tDCS protocol [31–33, 35, 36, 38–40]. In non-smokers nicotine applied as transdermal patch, nasal spray or varenicline capsules abolished anodal tDCS [31, 32, 35, 39, 40] and either abolished also cathodal tDCS [31, 35] or the effect of cathodal tDCS was weakened and delayed [32]. In smokers, nicotine withdrawal led to an abolition of anodal tDCS effect (i.e. facilitatory plasticity), which was restituted after nicotine administration [33, 38]. Nevertheless, for the effect of cathodal tDCS diverging results were found. In one study, cathodal tDCS's effect was abolished under nicotine withdrawal and re-established after nicotine consumption via varenicline capsules [38]. In another study, however, inhibitory neuroplasticity was not affected by nicotine withdrawal, and the inhibitory effect of cathodal tDCS was abolished after nicotine application via a 15 mg transdermal patch [33]. Lastly, one study compared healthy smokers and non-smokers and smokers and non-smokers suffering from schizophrenia in terms of inhibitory cortical plasticity [36]. In schizophrenia patients, smokers displayed a reduction of excitability expressed as motor-evoked potential (MEP) amplitudes after cathodal tDCS in terms of restituted LTD-like plasticity, while this was not the case in non-smoking schizophrenia patients. The opposite was found to be true in healthy controls, where cathodal tDCS had only a significant effect in non-smokers, whereas in smokers only a trend was identified [36].

4. PAS

   The effect of nicotinergic modulation on corticospinal plasticity measured via a PAS protocol was researched in eight studies [31–33, 37, 38, 41, 42]. In studies car-

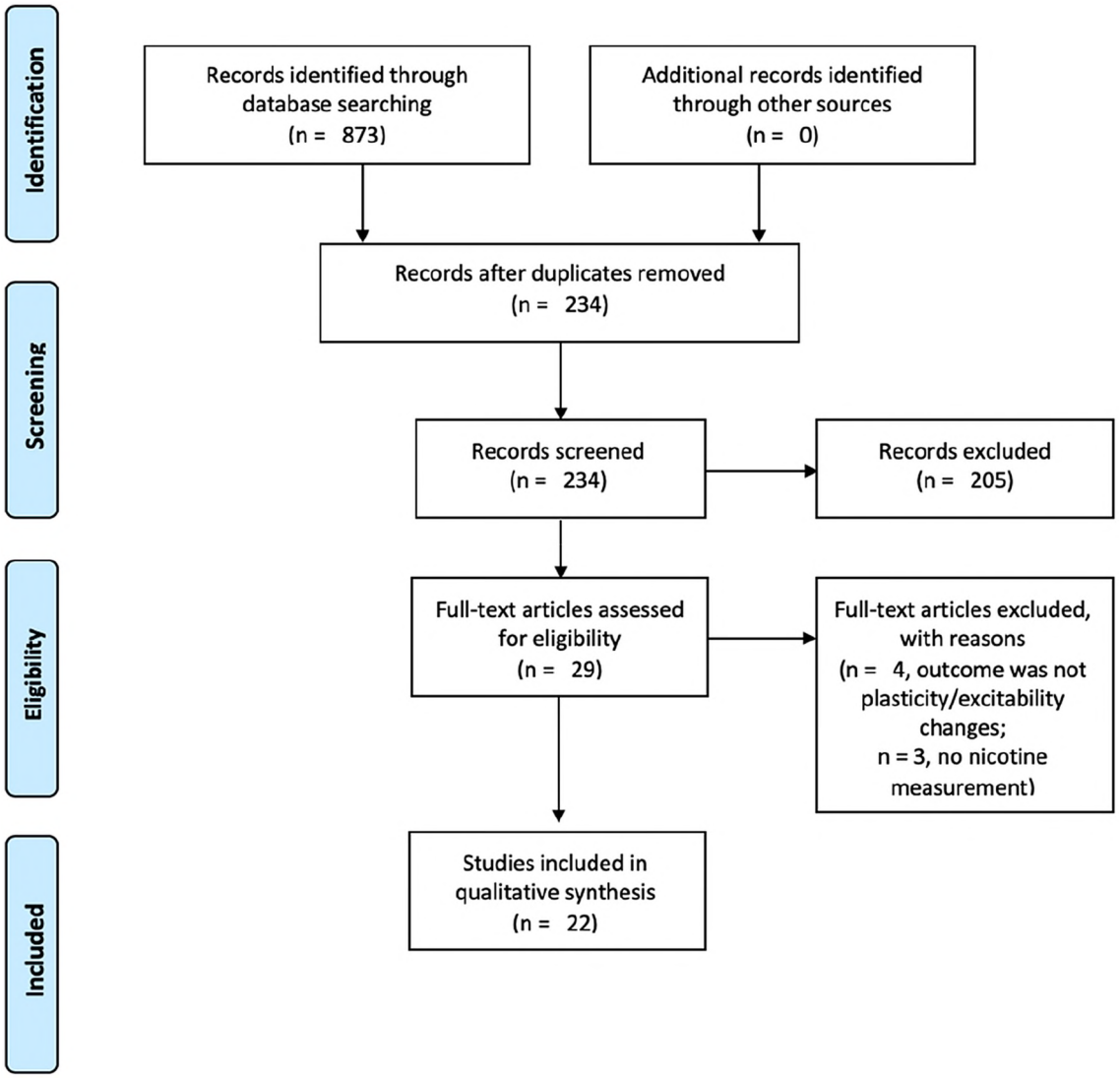


**Fig. 1** PRISMA diagram summarizing the flow of information through all phases of the first systematic search

ried out in non-smokers, three studies found nicotine administration via transdermal patch, nasal spray or varenicline capsules to abolish PAS 10 inhibitory effect as compared to placebo [31, 32, 35]. For the effect of PAS 25, diverging findings were detected. While two studies showed that the excitatory effect of PAS 25 was still present after nicotine administration via transdermal patch or varenicline capsules [31, 35], another study found this effect to be abolished through nicotine consumption [32]. In smokers the excitatory effect of PAS 25 was found to be abolished under nicotine withdrawal across studies, but restored after nicotine administration via transdermal patch, nasal spray or varenicline capsules [33, 38, 41]. For PAS 10 effects, one study also encountered an abolition of the inhibitory effects in deprived smokers before nicotine administration, however, inhibitory plasticity was re-established after nicotine consumption [38]. Nevertheless, in another study no abolition of PAS 10 inhibition was found in deprived smokers, although nicotine administration did lead to a delayed and prolonged response as compared to placebo [33]. Finally, one study compared the effect of PAS 25 on smokers and non-smokers [42]. While PAS 25 had an excitatory effect on non-smokers, such a response was not seen in smokers.

## Study characteristics for the second systematic search

Thirty-five records were identified which tested the effect of neurostimulation on smoking behaviour [43–77] (see Table 2, and sociodemographic information in

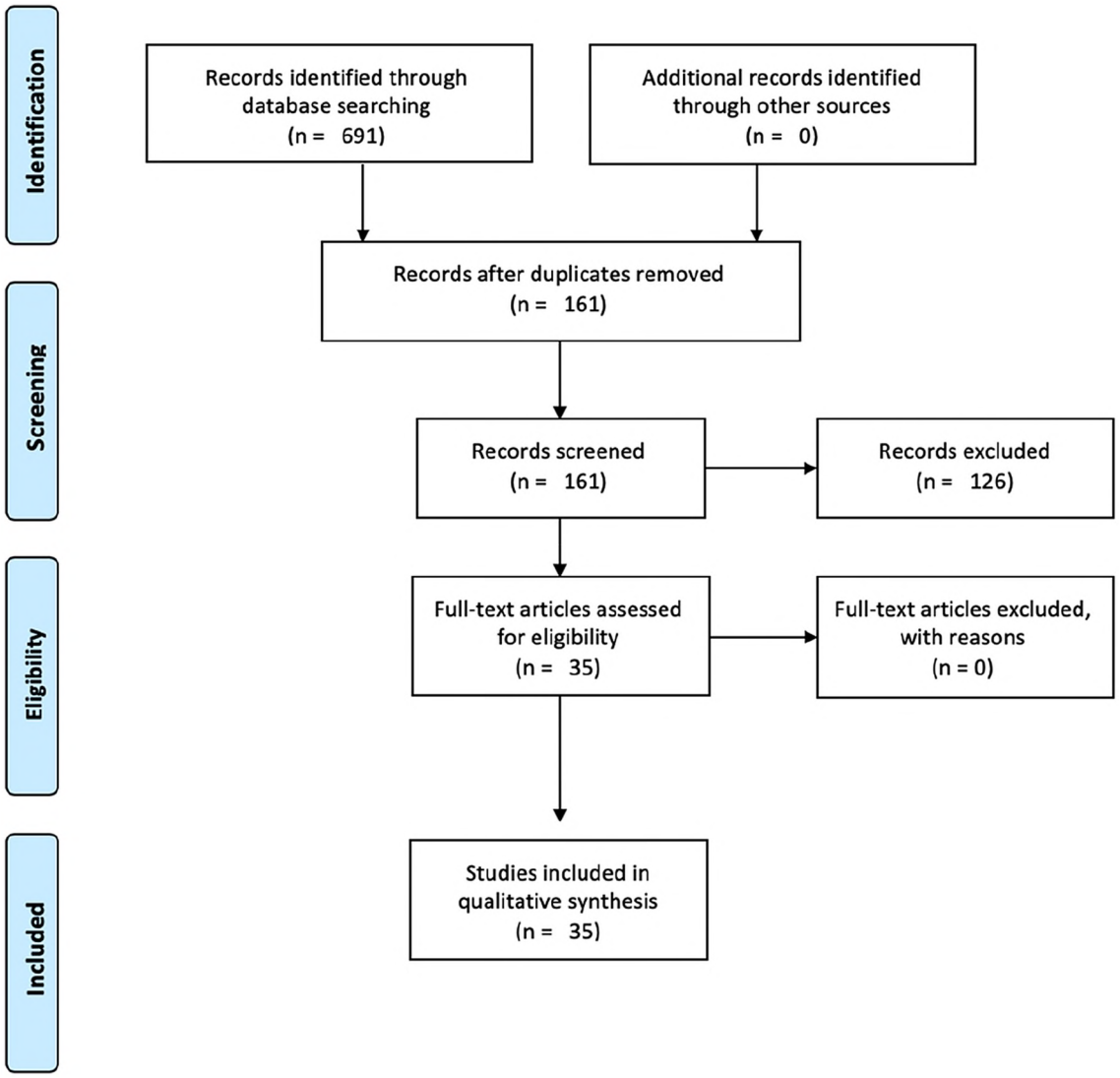


**Fig. 2** PRISMA diagram summarizing the flow of information through all phases of the second systematic search

supplementary Table 2). Across studies, smoking behaviour was operationalised in different ways. Eighteen studies measured cigarette consumption [43, 46, 47, 49, 52, 56–59, 62, 64, 65, 68, 71–73, 75, 77], 24 assessed cigarette craving [43–51, 53, 55–57, 60–63, 66, 67, 69–72, 76], five measured cigarette dependency [46, 56, 62, 72, 77], two assessed the ability to resist smoking [64, 75], four tested withdrawal symptoms reduction [49, 69, 70, 72], four focused on the maintenance of smoking abstinence [55, 63, 75, 77], one measured the amount of smoking cessations [54], one measured the visual attention to smoking stimuli [58], one measured brain reactivity to smoking cues [71] and two studies measure the motivation to quit smoking [72, 73].

1. rTMS

Twenty records used rTMS as treatment strategy for smoking behaviour [43, 44, 46, 48–52, 54–56, 59, 60, 63, 65, 68–70, 72, 76]. All in all, studies supported the reductive effect of rTMS administration applied to the dorsolateral prefrontal cortex (DLPFC) on cigarette consumption, craving and dependence [43, 44, 46, 49–51, 56, 59, 60, 63, 65, 70], although some studies failed to find such an effect [52, 55, 68, 69]. Moreover, several studies also found an increase in abstinence rates after rTMS administration [55, 56, 63, 72].

2. tDCS

From the selected articles, fifteen used tDCS as stimulation procedure for influencing smoking behaviour [45, 47, 53, 57, 58, 61, 62, 64, 66, 67, 71, 73–75, 77]. In the case of tDCS treatment, the results were rather mixed. While some studies did find an effect of stimulation on

cigarette craving or consumption [45, 47, 57, 58, 64, 67, 71, 73], others failed to do so [53, 61, 62, 66, 74, 75]. Additionally, a study focusing on abstinence rates found a positive effect of tDCS administration, namely that more participants remained abstinent after 6 months in the active tDCS condition as compared to sham [77].

## Discussion

This is the first systematic review to investigate the relationship between nicotininergic modulation and cortical excitability and plasticity in both directions. However, previous reviews have been published for the separate searches and aims of this systematic review. Regarding the first aim of this systematic review, only one review has examined the effect of tobacco smoking on neuronal activity and it only included studies using EEG measurements and is additionally forty years old [78]. Therefore, this is the first systematic review to date analysing the possible effect of nicotine on cortical activity in human subjects. A better understanding of this, could lead to potential treatment strategies through the modulation of nicotine levels. Nevertheless, in the case of the effect of neurostimulation on smoking behaviour more reviews have been published. However, past reviews either focused on one neurostimulation method only [79–82], included other addictions and were therefore not only focused on tobacco addiction [80, 83–85] or were at least four years old [86, 87]. Additionally, the largest study to date regarding the efficacy of tDCS to treat tobacco addiction was recently published [77], and is therefore not included in previous reviews. Moreover, no review to date did examine the relationship between nicotine and cortical activity in both directions. This examination of this two-way relationship allows for a better understanding of the complex influence exchange between nicotine and cortical activity.

Following two standardised literature searches and analyses, a total of 64 full-text articles were assessed for eligibility, 29 of them regarding the impact of nicotinergic modulation on cortical excitability and plasticity, and 35 of them related to NIBS as treatment for smoking behaviour. From these, 22 were finally included for the qualitative synthesis for the first systematic search and 35 for the second one. The quality of the included studies was variable, with some having rather small sample sizes or not including a placebo or control condition, limiting a meaningful interpretation of the results. Moreover, distinct stimulation protocols, as well as different nicotine administration techniques may have had an influence on the findings. Moreover, the quality of the included studies was not assessed formally, posing a greater limitation for the interpretation of the results.

Nevertheless, several patterns became visible when reviewing the studies that focused on how nicotinergic modulation may influence the individuals' cortical excitability and/or plasticity. EEG studies seem to agree in the effect of nicotinergic modulation on reducing both delta and theta power, while beta power seems to be increased by nicotine consumption [21–27]. When it comes to alpha power, results were rather mixed, although the trend was towards alpha1 being decreased by nicotine and alpha2 increased [26]. In sum, it seems like nicotine consumption tends to increase fast-wave frequencies and to decrease slow-wave frequencies. When looking at the nicotinergic modulation of cortical excitability measured through TMS [29, 34], under smoking withdrawal, a stronger intracortical inhibition was present, while intracortical facilitation was decreased [29, 34]. When nicotine was administrated an increase in facilitation in smokers was found, while in non-smokers an enhanced intracortical inhibition was displayed, therefore signalling an effect of nicotine administration on pronouncing facilitation in smokers, while in non-smokers, nicotine consumption leads to higher cortical inhibition [34].

With regard to the effect of nicotinergic modulation on cortical plasticity, studies using iTBS, tDCS and PAS were systematically reviewed. For smokers, similar effects on excitatory plasticity were found for both focal (PAS) and non-focal (tDCS) stimulation protocols. Nicotine withdrawal led to an abolition of facilitatory focal and non-focal plasticity, however, nicotine administration led to a re-establishment of this plasticity [33, 38, 41]. There is also a trend towards an abolition of inhibitory focal and non-focal plasticity and further restitution via nicotine administration in smokers [38, 41]. These findings point towards a potential focusing effect of nicotine administration through an improvement of the signal-to-noise ratio, as measured by the combination of tDCS and PAS experiments. As both facilitatory and inhibitory plasticity play a crucial role in cognitive processes, such as memory and learning [7], these results point towards a decrease in cognitive capabilities when smokers are under nicotine withdrawal, where these cognitive capabilities can be restored when nicotine is again consumed. Several studies did encounter this finding, namely that deprived smokers showed a decrease on cognitive performance, however, when nicotine was administered, the cognitive performance improved [2, 3, 41]. Concerning non-smokers, the opposite pattern seems to fit. Non-focal facilitatory plasticity, as well as focal and non-focal inhibitory plasticity were abolished through nicotine consumption in this population [31, 32, 35, 39, 40]. These outcomes suggest a possible negative impact of nicotine administration on cognitive processes, which is indeed also found in some studies, namely that nicotine administration led to a poorer cognitive performance in healthy non-smokers [2, 3].

Although similar patterns seem to arise across studies, these results should be interpreted with caution, as the majority of the studies did not measure the levels of nicotine

in blood and may therefore not be comparable to each other. Only two studies calculated the correlation between plasma/serum nicotine concentrations to cortical activity [26, 28]. While one of them did not find a significant correlation of serum nicotine and cortical excitability [28], the other did, showing that the effects of nicotine on EEG activity seem to be more pronounced for higher amounts of plasma nicotine (ca. 15–20 ng/ml) [26]. For the remaining studies, such correlations were not estimated. However, many based their doses and waiting period until the measurement on previous studies. For example, the studies using nasal spray as administering method had a waiting time of 10 min, as this is the estimated time for the plasma nicotine to peak, while studies using a nicotine patch had a waiting time of 6 h for the same reason. Still, although they had a waiting time adjusted for the nicotine peak, this peak signified a different level of plasma nicotine for each nicotine dose and administration technique. While 1 mg of nicotine administered via nasal spray peaks at 8–9 ng/ml plasma nicotine [88], a nicotine patch does it at 11–13 ng/ml [89] and 1 mg nicotine capsule at 4–5 ng/ml [90]. Yet, since the administration technique and dose were highly variable, and no study directly studied the relationship between nicotine blood levels and outcomes, no conclusion can be drawn in terms of which protocol will lead to a better effect. For this, further studies should attempt to find the optimal dose and administration method by controlling for nicotine blood levels.

The second systematic search focused on the effect of NIBS-treatment protocols on influencing smoking behaviour. Cigarette consumption, craving, dependence and abstinence rates were found to be improved via rTMS administration by the majority of reviewed studies [43, 44, 46, 49–51, 55, 56, 59, 60, 63, 65, 70, 72], supporting this technique as a potential treatment for smoking cessation. In the case of tDCS application for treatment purposes, although some studies failed to find an effect on smoking behaviour [53, 61, 62, 74, 75], there is a trend towards a positive impact of tDCS on craving levels, cigarette consumption or abstinence rates [45, 47, 57, 58, 64, 67, 71, 73, 77]. However, a large inter-study variability in outcomes must be acknowledged. The reasons for this variability are among others the response variability to NIBS in general including patient related factors like individual anatomy or genetic factors [91], differences in study designs (inclusion and exclusion criteria, endpoint definition, duration of treatment and follow-up) and differences in the applied stimulation techniques (see Table 2). In terms of craving symptoms, the results point towards an effect when the number of sessions is five or higher and this seems to be independent of the stimulation site (i.e. right or left DLPFC). The only study done under these conditions does not find an effect, however, this study was carried in a population of Schizophrenia patients, which might have an impact itself on the findings. For number of cigarettes smoked and abstinence rates, the results suggest that five or more sessions placing the anode over the left DLPFC are effective, again with the only exception of the study carried on the schizophrenic population. Additionally, the placing of the cathode is heterogeneous across studies and no clear pattern is recognizable from the findings. Thus, more research is needed to identify the optimal tDCS placement montage.

In conclusion, the effect of nicotinergic modulation on both intracortical excitability and cortical plasticity, and therefore its potential impact on cognitive processes, depends on smoking status of the individual. In terms of cortical excitability, while in smokers nicotine administration led to an increase of cortical facilitation, the contrary was visible in non-smokers, namely an increase in cortical inhibition. Regarding cortical plasticity, although nicotine administration has a favourable effect on plasticity when given to smokers, the opposite appears to be true with non-smokers. From this physiological perspective, one may discuss that nicotine has focusing function improving signal-to-noise ratios and paving the way for potential treatment options targeting cognitive deficits. Moreover, in the basis of these findings, nicotine receptors may be a potential target as treatment aids for cognitive impairments in neurodevelopmental or neurodegenerative disorders (for animal data review see: [92]). Nicotine receptors could be targeted either by nicotine substitution techniques (e.g. nicotine patch) or through influencing the calcium permeability of the receptors, as was done in two studies, either through fluoxetine [40] or dextromethorphan [39] or via novel compounds [93]. Nevertheless, studies confirming the efficacy of these techniques are still needed and the risk to develop a nicotine addiction, especially in psychiatric populations, must be considered. Regarding treatment strategies, not only has nicotinergic modulation a repercussion on cortical activity, but the inverse appears to be true as well, namely that a change of cortical activity can influence smoking behaviour. Brain stimulation protocols such as rTMS and tDCS constitute this way promising treatment strategies for smoking cessation. Nevertheless, it should be taken into account that the stated findings regarding neuroplastic modes of action of nicotine refer mainly to studies targeting the primary motor cortex, and therefore the effects of either nicotine on cortical activity or neurostimulation to target tobacco addiction might not translate to other brain areas.

Future research should focus on understanding how plasticity functions related to nicotinergic modulation impact the course of psychiatric disorders. Moreover, prospective studies should target understanding how this nicotinergic modulation effect can be used to develop NIBS-treatment protocols that combine both neurostimulation with nicotinergic stimulation. Additionally, since there is a high response variability to NIBS, as noticed by diverse study outcomes,

additional research should aim attention at understanding to which extent smoking contributes to this variability.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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