Advances in biofeedback and neurofeedback studies on smoking

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ABSTRACT

Smoking is a leading cause of morbidity and premature death constituting a global health challenge. Although, pharmacological and behavioral approaches comprise the mainstay of smoking cessation interventions, the efficacy and safety of pharmacotherapy is not demonstrated for some populations. Non-pharmacological approaches, such as biofeedback (BF) and neurofeedback (NF) could facilitate self-regulation of predisposing factors of relapse such as craving and stress. The current review aims to aggregate the existing evidence regarding the effects of BF and NF training on smokers. Relevant studies were identified through searching in Scopus, PubMed and Cochrane Library, and through hand-searching the references of screened articles. Peer-reviewed controlled and uncontrolled studies, where BF and/or NF training was administered, were included and evaluated according to PICOS framework. Narrative qualitative synthesis of ten eligible studies was performed, aggregated into three categories according to training provided. BF outcomes seem to be affected by smoking behavior prior to training; individualized EEG NF training holds promise for modulating craving-related response while minimizing the required number of sessions. Real-time fMRI NF studies concluded that nicotine-dependent individuals could modulate craving-related brain responses, while mixed results were revealed regarding smokers' ability to modulate brain responses related to resistance towards the urge to smoke. BF and NF training seem to facilitate modulation of autonomous and/or central nervous system activity while also transferring this learned self-regulation to behavioral outcomes. BF and NF training should a) address remaining issues on specificity and scientific validity, b) target diverse demographics, and c) produce robust reproducible methodologies and clinical guidelines for relevant health care providers, in order to be considered as viable complementary tools to standard smoking cessation care.

1. Introduction

1.1. Rationale

Smoking constitutes a leading cause of morbidity and premature death and remains a global health and societal challenge, imposing enormous economic burdens to healthcare and social security systems (Ekpu and Brown, 2015; World Health Organization, 2019). In this context, smoking cessation strategies are crucial, as successful attempts to quit without any assistance are limited to only about 4% (Cohen et al., 1989). Pharmacological and behavioral smoking cessation interventions are considered to demonstrate both high acceptance and increased effectiveness, while combining them could double the possibility of successful quitting (West et al., 2015). However, for some populations and patients pharmacotherapy should be tailored or even excluded from treatment options (Rigotti, 2015). Specifically, efficacy

and safety of pharmacotherapy is not demonstrated for patients that suffer from severe mental illness, acute coronary syndrome or seizures, as well as for pregnant smokers (Rigotti, 2015; Siu, 2015; ACOG Committee OPINION, 2017). Moreover, side effects of medication constitute a common reason for its premature discontinuation (Halperin et al., 2009; Williams et al., 2007). Although, initial concerns regarding neuropsychiatric effects of varenicline were recently suspended, US Food and Drug Administration (FDA) stated that the risk of negative impact of varenicline on mood, behavior or thinking remains present for individuals currently under treatment for anxiety disorders, schizophrenia, depression or former psychiatric patients (US Food and Drug Administration (FDA), 2016). Stress however, is considered an aggravating factor that promotes the vicious cycle of nicotine addiction (Pandria et al., 2018), while stress-related conditions and negative affective states are considered as predisposing factors for relapse (Brandon et al., 1990; Borland, 1990; Cummings et al., 1985; Shiffman,

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1982; Shiffman et al., 1996).

Biofeedback (BF) and neurofeedback (NF) training have been widely explored in the management of anxiety disorders, depression and stress-related conditions (Calderon et al., 2004; Hammond, 2005; Gruzelier et al., 2014; Scheinost et al., 2013; Choi et al., 2011; Tabachnick, 2015). Additionally, the application of BF and NF was early documented regarding addiction disorders (Peniston and Kulkosky, 1989; Saxby and Peniston, 1995; Lamontagne et al., 1977; DeGood and Valle, 1978). Although initial attempts to use BF or NF as an alternative smoking cessation approach were reported as early as 1983 (Griffith and Crossman, 1983; Szalai et al., 1986), scientific interest was quelled until recently revived with the emergence of advanced training modalities (Watanabe et al., 2017; Stoeckel et al., 2014; Koush et al., 2013; Sulzer et al., 2013). As BF and NF have shown encouraging findings in modulating craving response, it is crucial to aggregate existing evidence, in order to consolidate understanding on their indications and identify possible knowledge gaps.

1.2. Objectives

The current review aims to summarize existing evidence regarding the effect of BF and NF training on smokers, considering studies on current adult smokers that received a BF or NF intervention. We aim to present participants, interventions, comparators and outcomes regarding smoking cessation rates, behavioral measures, health status and training modalities (see Fig. 1).

2. Methods

2.1. Protocol and registration

The detailed protocol describing the review question being addressed, the study design, as well as the search and the data extraction strategy, has been submitted to the PROSPERO database (ID: 175379).

2.2. Eligibility criteria

Peer-reviewed studies, where BF and/or NF training was administered, were included and evaluated according to PICOS framework. (P): Participants older than 18 years, current smokers, smoking more than ten conventional tobacco cigarettes per day were included. (I): Studies which explore the effects of BF and/or NF training on smokers were considered to be eligible. No training protocol restrictions were

imposed. We did not set any threshold for number of smokers recruited in studies. (C): Control groups, if present, included those performing no training, a different training protocol or sham training, and were not limited to current smokers or healthy participants. (O): The main outcomes of the studies included were determined to be the effects of the intervention on (a) smoking cessation rates, (b) different behavioral measures such as anxiety and depressive symptomatology, self-esteem, motivation, withdrawal symptoms, readiness to quit, quality of life assessed by questionnaires and measures, (c) health status expressed by various clinical parameters such as exhaled carbon monoxide, spirometry indices, blood biomarkers, and (d) training modalities such as temperature, skin conductance, heart rate, brain activity. (S): Any controlled (randomized or non-randomized) and uncontrolled study designs were considered to be eligible.

2.3. Information sources and search strategy

Relevant studies were identified through searching in electronic databases (Scopus, PubMed and Cochrane Library) and through hand-searching the references of screened articles in March 2020. Missing abstracts of articles found through the search process were retrieved through independent searches on Web.

The review was conducted following the PRISMA-P 2015 statement standards (Moher et al., 2001; Liberati et al., 2009). We searched the aforementioned databases using the following keywords: "Neurofeedback", "EEG-biofeedback", "Neurotherapy", "Biofeedback" combined with the terms "Smoking", "Tobacco consumption", "Cigarette consumption", "Smoking dependence", "Nicotine dependence", "Nicotine addiction". Uncontrolled case reports, "grey literature" such as theses, internal reports, non-peer-reviewed articles, pharmaceutical industry files and theoretical articles such as reviews were excluded. To avoid over-representation bias, conference and journal papers were not included if those were presenting data that were also presented in subsequent journal articles. Language of search was limited to English while year of publication was not limited.

2.4. Study selection, data extraction and synthesis process

Two researchers (NP, AA) independently performed study selection, in order to minimize the possibility of rejecting relevant studies (Edwards et al., 2002). They carried out the searches according to the described strategy, removed duplicates, recorded entries in piloted forms and screened all relevant articles retrieved based on their title and abstract. If full-texts were unavailable, their authors were contacted by email. Subsequently, they manually searched the references of screened original articles and reviews in order to minimize the risk of missing relevant studies. Inter-rater agreement (Liberati et al., 2009) was calculated using Cohen's kappa (κ) (McHugh, 2012). Discrepancies on screened articles were ultimately decided by a third researcher (LK) who compiled a final list.

The full-texts of screened articles were further evaluated with respect to eligibility criteria. Finally, narrative qualitative synthesis of eligible studies was planned. We divided eligible studies into three categories according to the training provided, that were biofeedback (BF) studies, electroencephalography (EEG) based neurofeedback studies (NF EEG) and real-time functional magnetic resonance imaging (rtfMRI) based neurofeedback studies (NF rtfMRI).

3. Results and discussion

3.1. Study selection

In total 261 records were identified though searching in three electronic databases: Scopus (115), Cochrane Library (72) and PubMed (74). One additional record was identified through other sources. In the initial phase, 65 duplicates were removed. During the screening step,
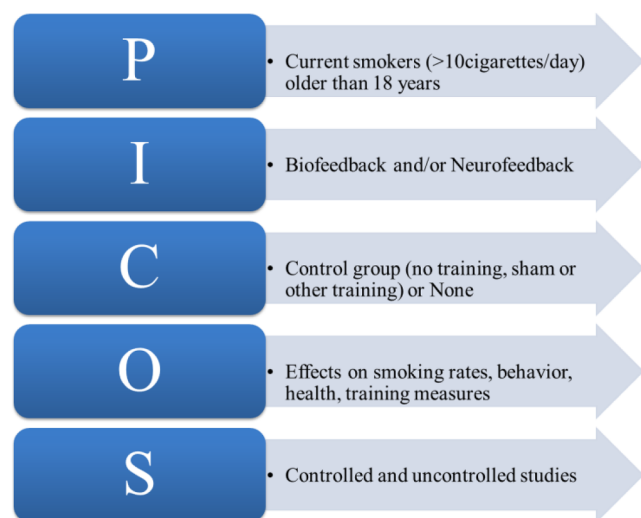

Fig. 1. Objectives of the systematic review and relevant eligibility criteria expressed according to PICOS framework.

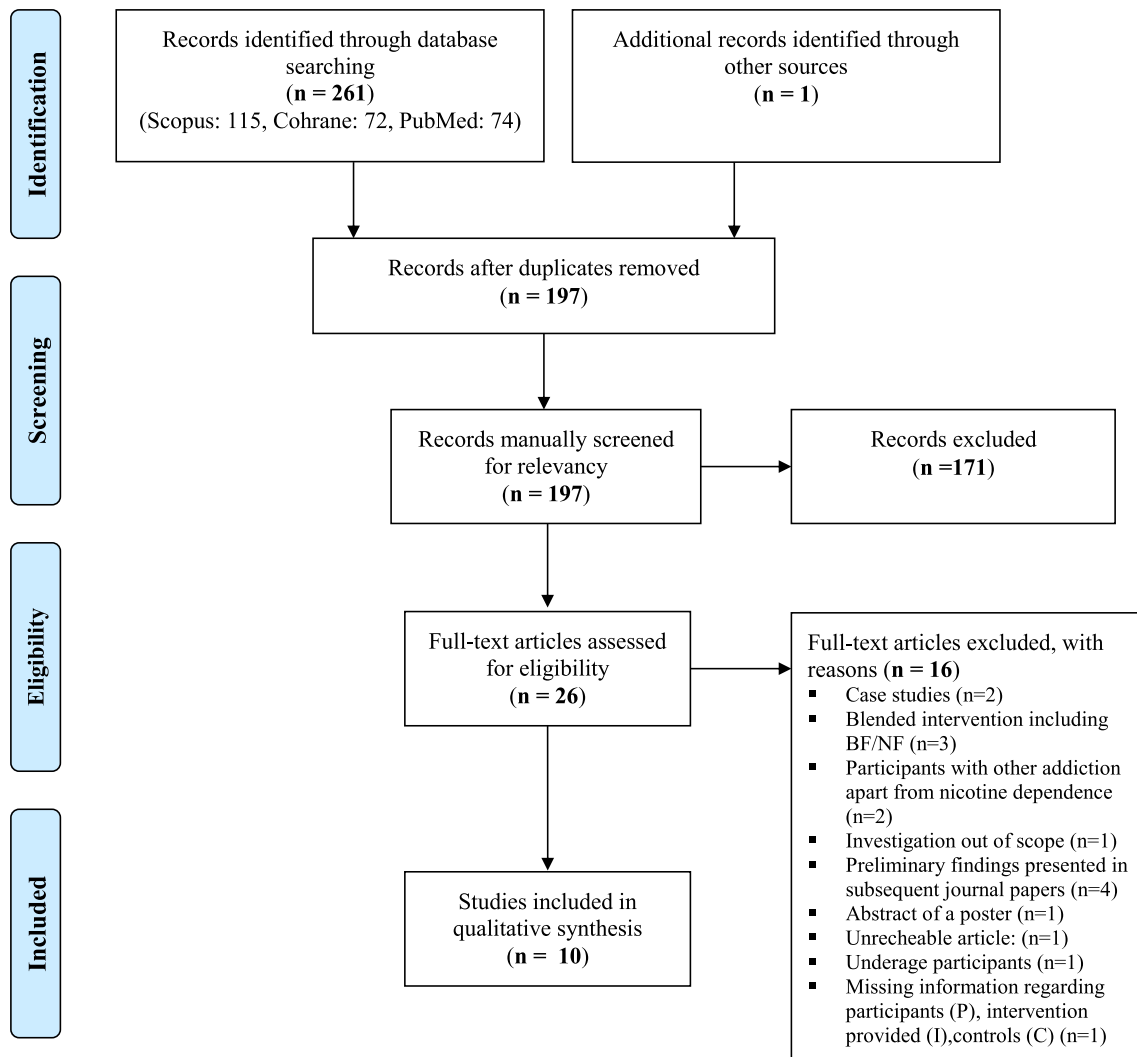| P | Current smokers (>10cigarettes/day) older than 18 years |
I	Biofeedback and/or Neurofeedback
C	Control group (no training, sham or other training) or None
O	Effects on smoking rates, behavior, health, training measures
S	Controlled and uncontrolled studies

Fig. 2. Flow diagram of the study selection procedure according to PRISMA-P 2015 guidelines (Moher, 2015).

197 records were manually screened for relevance to the review topic based on title and abstract of the entries (Moher et al., 2009; Liberati et al., 2009) (See Fig. 2 presenting the flow chart of the study selection process). A moderate agreement was found between the two independent reviewers with a Cohen's κ = 0.633 (95% CI, 0.18 to 1.09) (McHugh, 2012; Cohen, 1960) regarding general relevancy. As such, discrepancies were addressed by the third reviewer and 171 records were excluded as irrelevant to the scope of this review (e.g. other medical conditions, other interventions, technological articles etc.) and 26 records were retained for further assessment based on full texts and eligibility criteria. From the list of 26 full-text articles that was compiled for the eligibility assessment step, 16 articles were excluded from the qualitative synthesis for not matching any of the eligibility criteria (detailed reasons for exclusion are presented in the flowchart in Fig. 2). Finally, ten eligible studies were included in the qualitative synthesis (Table 1), from which two studies explored different types of BF training (Pandria et al., 2018; Grimsley, 1990), three explored EEG-based feedback (Griffith and Crossman, 1983; Szalai et al., 1986; Bu et al., 2019) and five used rtfMRI feedback (Hartwell et al., 2015; Kim et al., 2015; Hanlon et al., 2013; Canterberry et al., 2013; Li et al., 2013).

3.2. Synthesis of the results

3.2.1. BF studies

Two BF studies met the eligibility criteria to be included in the narrative synthesis, one from 1990 and one from 2018 (Pandria et al., 2018; Grimsley, 1990). Both involved skin temperature training as mode of biofeedback. Biofeedback has been demonstrated to influence sympathetic activity through modulating physiologic measures such as electrodermal activity, heart rate and extremity temperature, thus establishing a direct link to stress alleviation (Pandria et al., 2018). Grimsley (1990) attempted to compare hand warming BF between smokers not attempting to quit smoking and nonsmokers. Pandria et al. (2018) aimed to explore the clinical, behavioral and neuroplastic effects of the same method as an intervention for smoking cessation. The participants were motivated to quit smoking and were recruited voluntarily in the context of the SmokeFreeBrain project. The characteristics of both studies are comparatively presented below according to PICOS framework.

While the number of participants is comparable between the two studies (24 and 27), these participants differed between them in a number of aspects, including age, sex and smoking habits. In the 1990 study, 24 only female undergraduate subjects, ages 18 to 41, that included smokers and non-smokers were recruited; in the 2018 study, 27 smokers with an analogy 1:2 of males to females, ages 24 to 75 (mean

Table 1
Characteristics of the included eligible studies.

Article	Study objectives	Participants	Intervention	Comparator
		Biofeedback (BF) studies		
Grimsley (1990)	The effects of smoking on smokers' ability to modulate skin temperature through BF training	**N = 24** **n(nonsmokers) = 8** **Mean age:** 18–41 years old **Gender (male : female):** 0:24 **Mean cig./day:** 20 Group 1: smokers who smoked prior to BF **Mean age of smoking:** 22.8 years **Mean number of smoking years:** 5.6 years Group 2: smokers who did not smoke prior session for at least 1 h, **Mean age of smoking:** 21.4 **Mean number of smoking years:** 4.3 Group 3: non-smokers **Mean age of nonsmokers:** 24 years	**Skin temperature training (1.5 h)** Training goal→↑skin temperature by thinking of situations in which skin temperature is higher e.g. sunbathing, sitting close to an open fire. **Physiological data recording:** HR during training Group 1 → 2 cig. within 1 h prior to training Group 2 → 1 cig. within 1 h prior to training All participants completed a brief questionnaire	Yes Smokers who did not smoke prior biofeedback (group 2) and Nonsmokers (group 3)
Pandria et al. (2018)	Explore the possible effect of BF on DMN of active smokers through alleviating stress. Investigate the effects of BF on smoking status by means of clinical and behavioral data.	**N = 27** **Gender (male : female):** 9:18 **Mean age:** 50.52 ± 12.364 (24–75years) **Mean education years:** 15.04 ± 4.743 **Median cig./day = 20 (IQR: 20.0–40.0)** **Mean smoking dependence:** 358.50 ± 152.95	**Baseline Evaluation** **Session 1:** Clinical and behavioral evaluation • **Session 2:** EEG and neuropsychological evaluation **Intervention:** 5 skin temperature training **Post-training evaluation** • **Session 3 & 4:** following the procedures of Session 1 & 2 respectively	No
		Neurofeedback (NF) Electroencephalography (EEG) studies		
Griffith and Crossman (1983)	Investigate smoking cessation using neurofeedback (occipital alpha)	**N = 6** **Gender (male : female):** 6:0 **Age** = not reported (adults) **Cig./day:** 15–24 moderate smokers > 35 heavy smokers	No smoking 1 h prior experimentation **Multiple 30 min sessions** • Baseline A1 • Smoking B • Baseline A2 • NF : upregulate occipital 8–12 Hz, eyes open, music feedback Fadeout : use skill in everyday life to resist smoking craving **Physiological data recording:** Occipital EEG Frontalis EMG HR/Hand skin temperature	Yes
Szalai et al. (1986)	Investigate the effects of smoking status on EEG alpha amplitude	**N = 42** **Gender (male : female):** 22:20 **Mean age** = 27 years non deprived smokers (n = 10) deprived smokers (n = 10) ex-smokers (n = 10) non-smokers (n = 12)	Single session, eyes closed, occipital EEG • Audio stimuli/Backward recall test under EEG • Audio pitch/NF period (2 * 6mins) • Alpha ↑→↓ • Alpha ↓→↑ • Randomly each condition	Yes
Bu et al. (2019)	Investigate smoking cessation using individualized neurofeedback	**N = 60 (cohort)** n = 44 completed study **Gender (male : female):** 60:0 **Age:** 18–40 years **Cig./day:** > 10 for 2 years or more Real feedback (n = 30) Yoked feedback (n = 30)	No smoking 2hr prior to sessions **Baseline session:** Clinical and behavioral evaluation **NF training session 1/2** • adapted smoking cue reactivity task (smoking-related and neutral images) • pre-NF (train classifier) → visual feedback detect EEG patterns → select features → reward on suppression **Post-training behavioral session** **Follow-up session**	Yes

(continued on next page)

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Table 1 (*continued*)

Article	Study objectives	Participants	Intervention	Comparator
		Neurofeedback (NF) real-time functional Magnetic Resonance Imaging (rtfMRI) studies		
Li et al. (2013)	The feasibility of rtfMRI NF training to modulate the activation of frontal brain areas was investigated in nicotine-dependent individuals. Investigation on the ability of smokers to eliminate neural and subjective craving response to smoking-related stimuli through rtfMRI NF training	N = 12 right-handed treatment-seeking smokers n = 10 completed the study **Gender** (male; female): 4:8 **Mean age:** 28.7 ± 10.9 (21–60 years) **Mean cig./day:** 14.5 ± 4.69 **FTND mean score:** 4.7 ± 2.49 **Mean CO levels:** 15.3 ± 6.1 ppm (screening); 14.5 ± 8.3 ppm (scanning)	A single MRI scanning visit with 4 Runs • **Run1** (craving-ROI isolation) → free to crave while being exposed to smoking cues. **End of Run 1** → selection of ROI in the vicinity of ACC. • **Run 2** (NF) → rest period and five runs of a rest, smoke and neutral blocks followed by a subjective craving rating and visual thermometer-shaped feedback. Training goal → ↓ level of thermometer that was linked to the ROI's brain activity. • **Run 3** (resist-ROI isolation) → instructed to resist their urge to crave while viewing smoking-related stimuli. **End of Run 3** → selection in the vicinity of right mPFC • **Run 4** (NF) → similar procedures to Run 2. Training goal→↑level of thermometer linked to the ROI's brain activity.Subjective rating of craving during the experimental procedure. 1-week/1-month by telephone interview 4-month lab visit Offline analysis craving-related P300 ERP	No
Hanlon (2013)	Determination whether decreasing the activity in craving-related brain area is more effective than increasing the activity in a brain area linked to the resistance to urge to smoke or not.	N = 15 right-handed treatment-seeking smokers n = 60% of recruited participants completed the full study **Gender** (male : female): not reported **Mean age:** not reported (21–45 years) **cig./day:** ≥10	3 rtfMRI NF training visits (4 Runs/each visit) • **Run1** (craving-ROI isolation) → free to crave while being exposed to smoking cues. **End of Run 1** → selection of ROI in the vicinity of ventral ACC. • **Run 2** (resist-ROI isolation) → instructed to resist their urge to crave while viewing smoking-related stimuli. **End of Run 2** → selection in the vicinity of dorsal mPFC • **Run 3 &4** (NF) → 2 thermometer-shaped objects linked to the activity of ROIs providing simultaneous feedback. Training goal→ ↓level of "craving" thermometer and ↑the level of "resist" thermometer. Subjective rating of craving during the experimental procedure & before and after each fMRI Run.	No
Canterberry et al. (2013)	Investigation of the effectiveness of multiple sessions rtfMRI NF training of ACC. Exploration of the role of nicotine severity to the efficacy of ACC rtfMRI training.	N = 9 right-handed motivated to quit but not under treatment **Gender** (male : female): 8:1 **Mean age:** 32.7 ± 13.01(18–60 years) **Mean cig./day:** 13.44 ± 4.30 **FTND mean score:** 3.67 ± 1.73 **Mean CO levels:** 15.44 ± 7.14 ppm	3 rtfMRI NF training visits (4 Runs/each visit) • **Run1** (craving-ROI isolation) → free to crave while being exposed to smoking cues. **End of Run 1** → selection of ROI in the vicinity of ACC. • **Runs 2–4** (NF) → baseline craving block followed by a series of craving-decrease blocks (x5). In each block, a thermometer linked to the activity of the "crave" ROI as visual feedback. Training goal→ ↓level of "craving" thermometer during the exposure to smoking-related images. Subjective rating of craving during the experimental procedure & before and after each fMRI Run	No
Hartwell (2015)	Replication and extension of the piloting studies on rtfMRI NF training in craving-related brain area.	N = 44 non-treatment seeking nicotine-dependent randomized in 2 conditions depending on gender and FTND score (21 rtfMRI feedback group (F), 23 controls(C)) n = 33 completed the study (16F; 17C) **Gender** (male : female): 13:8 (F); 15:8 (C) **Mean age:** 34.1 ± 11.3 (F); 36.2 ± 10.6 (C)(18–60 years) **Mean cig./day:** 19.1 ± 4.5 (F); 18.5 ± 7.0 (C)	Random allocation in 2 groups, rtfMRI NF group & control group. Both groups: 3 rtfMRI NF training visits (4 Runs/each visit). Design similar to the one used in Canterberry et al. (2013). A rest period instead of a baseline craving period was used at the beginning of Runs 2–4. Subjective rating of craving during the experimental procedure as well as before and after each fMRI Run.	No feedback control group. Same experience as the feedback group without receiving any feedback.

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Table 1 (*continued*)

Article	Study objectives	Participants	Intervention	Comparator
Kim et al. (2015)	Comparison of a novel training protocol's (FC-added rtfMRI training) efficacy on modulating brain activity associated with cigarette craving and self-reported craving with traditional rtfMRI training.	**FTND mean score:** 5.3 ± 1.4 (F); 5.1 ± 1.7 (C) **Mean CO levels:** 17.8 ± 8.0 (F); 21.1 ± 10.9 (C) ppm N = 14 right-handed heavy smokers randomized in 2 groups (7 FC-added rtfMRI group (F); 7 traditional rtfMRI group (C)) **Gender (male : female):** 14:0 **Mean age:** 26.00 ± 1.29(F); 26.00 ± 2.16 (C) **Mean cig./day:** 15.71 ± 3.45(F); 17.29 ± 2.29(C) **FTND mean score:** 5.00 ± 1.00(F); 4.71 ± 0.95(C) **Mean CO levels:** 22.29 ± 3.99 (F);20.14 ± 4.30 (C) ppm	Random allocation in 2 groups, traditional rtfMRI neurofeedback group and FC-added rtfMRI-NF group Both groups: 2 visits (6 runs/each visit) as follows: 1. Calibration period for eye-tracker alignment 2. Fixation to a white cross on a black background screen 3. Presentation of a command "ready" 4. Presentation of a video with smoking-related stimuli for NF training 5. Subjective craving rating 6. Fixation to a white cross on a black background screen	Traditional rtfMRI training receiving feedback based on ROIs activity (ACC, OFC and mPFC bilaterally)

50.52 years) were recruited. Current smokers in the two studies were consuming at least 20 cigarettes per day and 10 cigarettes per day respectively, while grouping was also dissimilar. The 1990 study involved 8 non-smokers and 16 smokers, of whom half did not smoke prior to BF session. The 2018 study involved only current smokers, recruited from two demographic groups: long-term unemployed < 35 years of age and patients with asthma or chronic obstructive pulmonary disease over 35 years of age.

In both studies the experimental procedure involved hand finger temperature as the sole biofeedback training modality, aiming to allow the participants to exert control over the autonomic nervous system (ANS). Pandria et al. also involved EEG measurements (before and after the intervention), which were subsequently analyzed offline in order to document effects of neuroplasticity at the brain as a result of BF training and smoking cessation (Pandria et al., 2018). Number and duration of sessions were also different with one 20-minutes session of temperature control used in the 1990 study vs five 30-minutes sessions of temperature control, spanning four weeks, used in the newer one.

Grimsley employed an active comparator group, comprised of 8 non-smokers who participated in the BF session (Grimsley, 1990). Pandria et al. did not employ a comparator group in the 2018 study (Pandria et al., 2018). Moreover, three groups were defined in the 1990 study: smokers that smoke before session (SS), smokers that did not smoke before session (SNS) and non-smokers (NS) while all participants randomly took part in a morning or in an afternoon session. Comparisons between two groups, males and females were planned in the 2018 study to address gender disparity.

Grimsley (1990) demonstrated that smoking can affect the ability to control skin temperature as NS and SNS were able to increase their skin temperature by mean 2 and 1.9°F respectively, while not only SS did not manage to increase skin temperature but also presented a slight drop after the session by mean 0.4°F, a difference between groups that was significant. Moreover, SS had also started the session with already significantly lower skin temperature than SNS and NS. Grimsley (1990) reports that smoking, despite generally associated with tranquility by smokers, not only results in lower hand temperature due to vasoconstriction - denoting stress - but also hampers the ability to modulate skin temperature and may affect results of BF sessions and other psychological treatments that involve relaxation (Grimsley, 1990).

Regarding clinical effects of BF training, explored as an intervention for smoking cessation, Pandria et al. (2018) reported a non-significant reduction in total oxidative stress but also a non-significant increase in exhaled CO levels of the study participants. Nonetheless, in this study, 18.52% of participants reduced their exhaled CO levels below a value of 8 ppm, that may be useful to detect current smokers (Wald et al., 1981; Jarvis et al., 1987). No differences were observed between male and female participants. In the behavioral aspects, the severity of nicotine dependence and presence of psychiatric symptoms were significantly reduced after the BF intervention in the participants as a whole and the male group, and the number of participants with moderate and high nicotine dependence decreased (Pandria et al., 2018). A non-significant decrease with regards to withdrawal symptoms, depressive symptomatology and anxiety levels was also reported across participants with no differences between male and female groups. Regarding neuroplastic effects, the short-term BF intervention did not lead to reorganization of functional resting state networks of the participants. A degree of neuroprotective effect was hypothesized as the authors observed significant differences in: a) an increase in outflow of right vlPFC and TPC in the whole group, b) an increase of inflow in right temporal pole cortex (TPC) in females, c) an increase in outflow of left medial prefrontal cortex (mPFC) and left precuneus (PCU) in males, and d) in outflow of left mPFC between female and male groups (Pandria et al., 2018).

3.2.2. NF EEG studies

Three studies that administered real-time displays of brain activity measured by EEG met the eligibility criteria to be included in the

narrative synthesis, including two papers from 1983 and 1986 (Griffith and Crossman, 1983; Szalai et al., 1986) and a very recent one from 2019 (Bu et al., 2019). The studies by Griffith and Crossman (1983) and by Szalai et al. (1986) made use of occipital alpha (8–12 Hz) modulation protocols, while the newer study by Bu et al. (2019) used a novel individualized protocol to train EEG patterns associated with smoking cue reactivity. Also, the 1983 and 2019 studies comprised smoking cessation interventions (Griffith and Crossman, 1983; Bu et al., 2019), while the 1986 investigated the effects of smoking status on EEG alpha amplitude (Szalai et al., 1986). The characteristics of those studies are comparatively presented below according to PICOS framework.

The recruited participants were quite diverse among the eligible NF EEG studies in terms of numbers and smoking status. Six healthy male moderate or heavy smokers (15–24 or over 35 cigarettes daily), selected based on motivation to quit smoking and alpha rhythm stability, were recruited in the study by Griffith and Crossman (1983); age range was not reported. A total of 42 healthy participants with a mean age of 27 years, consisting of 20 current smokers (12 cigarettes daily) that had made an unsuccessful serious effort to quit smoking, ten ex-smokers (not smoking for one to ten years prior to the study) and 12 non-smokers were recruited by Szalai et al. (1986). Bu et al. recruited the largest cohort among all eligible studies in this systematic review regardless of modality of biofeedback, consisting of 60 initially enrolled participants, only males aged 18 to 40 years, 44 of whom completed all the follow-up assessments (Bu et al., 2019). They were all current smokers, consuming at least ten cigarettes daily for at least two years.

Occipital alpha rhythm regulation was used in the earlier studies. Griffith and Crossman used multiple 30-minutes sessions starting with baseline recordings, recording during smoking, baseline recording, NF sessions and fadeout sessions all in eyes-open (EO) condition (Griffith and Crossman, 1983). Szalai et al. performed a single session experiment in eyes-closed (EC) condition (Szalai et al., 1986).

An adapted smoking cue reactivity task containing smoking-related and neutral images was delivered in the 2019 study (Bu et al., 2019; Zhang et al., 2009). EEG patterns related to smoking cues were selected on time and time–frequency domains and were used to construct a linear support vector machine classifier to support real-time NF.

The studies that aimed at smoking cessation used a longitudinal design across multiple sessions (Griffith and Crossman, 1983; Bu et al., 2019), while the trial of Bu et al. employed a cohort of participants (Bu et al., 2019). Griffith and Crossman did not employ a comparator group (Griffith and Crossman, 1983). The study by Szalai et al. used four arms, splitting smokers in a group of ten deprived smokers (DS) and in another of ten not deprived smokers (NDS), including ex-smokers (ES) and non-smokers (NS) as active comparators (Szalai et al., 1986). The study by Bu et al. randomized smokers to an experimental arm performing real neurofeedback and to an active comparator arm performing sham neurofeedback (yoked to real participants) (Bu et al., 2019).

The study by Szalai et al. reported that DS and NS reduced alpha rhythm amplitude during backward recall task, while DS also significantly reduced alpha amplitude during the alpha suppression condition. Only NS were able to increase alpha amplitude, albeit non-significantly, during the alpha enhancement condition, while NDS instead showed a significant reduction during this task (Szalai et al., 1986). Griffith and Crossman reported that during smoking EEG theta activity (4–8 Hz) was increased in four participants, HR was increased in five participants and alpha rhythm was decreased in all participants, while afterwards skin temperature was decreased in four participants, findings consistent with physiological effects of smoking and nicotine (Griffith and Crossman, 1983). Training in the NF sessions resulted in four out of six participants (67%) being able to increase alpha activity compared to their baseline, while two of them (33%) were able to recruit the skill in fadeout sessions without NF and also succeeded in quitting smoking by the 6-months follow-up. Nonetheless, all six participants were either able to completely quit or decrease smoking by 12 to 61% in the follow-up compared to the baseline (Griffith and Crossman, 1983).

Bu et al. also reported decreased rates of smoking in the participants that were randomized to perform real feedback by 30.6% at 1-week interview, 38.2% at 1-month interview and 27.4% at 4-months follow-up session (Bu et al., 2019). In comparison, participants in the yoked feedback arm decreased rate of smoking by 14%, 13.7% and 5.9% accordingly. In accordance with this, cigarette craving was also significantly reduced in the real feedback arm ($p = 2.1 * 10^{-4}$) while it was not significantly reduced in the yoked feedback arm ($p = 0.07$). Successful deactivation of the EEG patters associated with smoking cues was observed in the real feedback arm ($p = 0.017$) and within this group of participants those who were more successful in this task also exhibited greater decrease in craving scores ($p = 0.03$). Craving-related P300 event-related potential (ERP) was chosen to demonstrate neural plasticity effects in this study and the P300 amplitude was significantly reduced in the real feedback arm ($p < 0.005$) while not so in the yoked feedback ($p > 0.1$). Additionally, greater decrease in mean P300 amplitude within the real feedback arm correlated with greater decrease in craving score ($p = 0.02$). The authors report that the degree of deactivation during the first cycle of neurofeedback successfully predicted the number of cigarettes smoked per day at the 4-month follow-up for participants in the real feedback arm ($p = 0.03$) but not for those in the yoked feedback arm ($p = 0.45$).

3.2.3. NF rtfMRI studies

Five studies which explored the use of rtfMRI training were included in our narrative synthesis. Four out of five studies were published by the same research group (Hartwell et al., 2015; Hanlon et al., 2013; Canterberry, 2013; Li, 2013). Moreover, three out of five studies were published in 2013 while the other two in 2015. In the eligible studies, a small sample of nicotine dependent individuals, between 18 and 60 years old, was explored (Table 1). Additionally, most of participants were motivated to quit but they were not undergoing any smoking cessation treatment. More precisely, in two (Hanlon et al., 2013; Li et al., 2013) out of five studies treatment-seeking nicotine-dependent individuals were enrolled; two (Kim et al., 2015; Canterberry et al., 2013) out of five studies recruited smokers who had motivation to quit smoking. Non-treatment-seeking smokers were enrolled only in the study of Hartwell et al. (2015). The reported outcomes were mainly focused on training-induced alterations in craving scores. However, changes in other variables such as smoking cessation rates and health status were not explored.

In all included studies, apart from Hanlon et al. (2013), Fagerstrom Test for Nicotine Dependence (FTND) was applied to assess the severity of nicotine dependence. Exhaled carbon monoxide (CO) levels were used in three out of five studies (Hartwell et al., 2015; Canterberry et al., 2013; Li et al., 2013) to confirm the recency of smoking. Kim et al. (2015) assessed the levels of exhaled CO to confirm the severity of nicotine dependence of participants. Participants enrolled in three out of five studies (Hartwell et al., 2015; Kim et al., 2015; Li et al., 2013) could be considered as moderate dependent smokers, while smokers recruited in Canterberry et al. were assessed as low to moderate dependent based on reported FTND scores. The Questionnaire of Smoking Urges-Brief (QSU-B) has been used in two out of five studies (Hartwell et al., 2015; Li et al., 2013). However, QSU-B scores were reported only in Hartwell et al. (2015).

In all studies, participants were instructed to abstain from smoking to experience some degree of craving. Subjective rating of craving was applied in all included studies during the experimental procedure as well as before and after each fMRI run in three out of five studies (Hartwell et al., 2015; Hanlon et al., 2013; Canterberry et al., 2013). A smoking cue paradigm conducted by the same research group in a previous study (Hartwell et al., 2011) was applied in four out of five studies (Hartwell et al., 2015; Hanlon et al., 2013; Canterberry et al., 2013; Li et al., 2013). Even though the structure and the procedures involved in the experimental design of those studies were different,

they incorporated multiple fMRI scanning runs. Three out of five studies (Hanlon et al., 2013; Canterberry et al., 2013; Li et al., 2013) did not use a comparator to the interventional group while Hartwell et al. (2015) and Kim et al. (2015) randomly allocated the participants involved into two groups. Hartwell et al. randomized their participants according to sex and severity of nicotine dependence to a feedback or non-feedback group (control group). In the study of Kim et al., participants were randomly assigned to either a rtfMRI training or a rtfMRI training enriched by functional connectivity index.

Four out of five studies (Hartwell et al., 2015; Hanlon et al., 2013; Canterberry et al., 2013; Li et al., 2013) followed a similar methodology to calculate the feedback signal. In the aforementioned studies, intermittent feedback was preferred, instead of continuous-based signal, even though intermittent feedback superiority remains controversial (Watanabe et al., 2017). A dynamic ROI estimation algorithm was enabled selecting top 33% voxels. The feedback signal was calculated as a statistical measure of difference between baseline state and feedback state. In the studies of Li et al. and Hartwell et al. the baseline was a resting state while in Canterberry et al. a craving state was used as baseline. The estimation of feedback signal in Hanlon et al. is not clearly described. On the other hand, in the study of Kim et al. the percentage of BOLD change (PSC) was calculated according to a cross—fixation period voxelwise by averaging the latest 3 trials. Median PSC in anterior ROIs (ROI 1) was used as feedback signal for the traditional rtfMRI group. Functional connectivity (FC) between anterior and posterior ROIs was estimated by Pearson correlation coefficient. The average of median PSC in ROI1 and FC between anterior and posterior ROIs was used as feedback signal in FC-added rtfMRI-NF group.

More precisely, in the study of Li et al. (2013) participants underwent Run 1 where they instructed to allow themselves crave while viewing smoking-related stimuli in order to identify a "craving" region of interest (ROI). At the end of session 1, a ROI in the vicinity of anterior cingulate cortex (ACC) was selected. Subsequently, a neurofeedback run (Run 2) was carried out to reduce craving. The Run 3 was a "resist" ROI identification scan where participants were instructed to resist their urge to crave while viewing smoking-related stimuli. At the end of this session a ROI in the vicinity of right mPFC was selected. Finally, a neurofeedback run (Run 4) was performed in order to increase the resistance to urge to crave.

In the study of Hanlon et al. (2013), Run1 and Run2 were implemented to identify a "craving" and "resist" ROI in the vicinity of ventral ACC (vACC) and dorsal medial prefrontal cortex (dmPFC) respectively. In the subsequent runs (Run 3 and 4) brain activity from the identified "craving" and "resist" ROI was translated to thermometers' level providing simultaneous feedback.

The following two studies from the same research group were focused on craving reduction. Canterberry et al. (2013) used an initial "crave"-ROI identification run followed by three neurofeedback runs (Run 2–4). A "crave" ROI was found approximate to the ACC. In the study of Hartwell et al. (2015) smokers recruited were randomly allocated depending on sex and severity of nicotine dependence assessed by FTND score (low/high) to a feedback or control group.

In the study of Kim et al. (2015), participants were randomly allocated to two groups which received traditional rtfMRI neurofeedback training and rtfMRI neurofeedback training enriched by a functional connectivity (FC) component (FC-added rtfMRI-NF) respectively. Both groups completed two visits consisting of six runs; feedback in the control group was linked to the neuronal activity of anterior regions (ROIs1) while in the other group the feedback was associated with the average of neuronal activity and FC between anterior and posterior regions (ROIs1 and ROIs2). Anterior ROIs included bilateral ACC, orbitofrontal cortex (OFC) and mPFC while posterior ROIs included precuneus brain areas and posterior cingulate cortex bilaterally. The information regarding the corresponding NF signal of each group was provided through the opacity change of the presented smoking scene.

All participants were instructed to resist their urge to crave following a mental strategy that seems to be more suitable for them. At the end of experimental procedure mental strategies used were discussed and subjective performance score along with stimulus strength score were reported.

Four out of five studies (Hartwell et al., 2015; Hanlon et al., 2013; Canterberry et al., 2013; Li et al., 2013) showed that smokers were able to modulate the craving-related activity in the vicinity of ACC by decreasing their blood oxygenation level dependent (BOLD) response during training compared to baseline scans. Self-reported craving scores were characterized by diversity in findings. In Li et al. (2013) self-reported craving was shown to be reduced during the craving reduction NF run while in other studies craving scores were found to be diminished after the NF training compared to the baseline (Hanlon et al., 2013; Canterberry et al., 2013). Additionally, the post-scan scores in QSU-B (factor 1) were lower in NF relative to controls (Hartwell et al., 2015). The subjective ratings were positively correlated with activation of craving-related brain regions in two out of five studies (Hanlon et al., 2013; Li et al., 2013), indicating that reduction of activity in these regions during a craving-eliciting paradigm could lead to a decrease in subjective craving scores. Canterberry et al. (2013) showed a similar trend but they failed to show a significant correlation between craving-related activity and self-reported scores.

On the other hand, modulation of brain regions associated to the resistance to the urge to smoke showed mixed results. Two studies showed that nicotine dependent individuals were not able to increase the activity of resistance-related brain regions located in mPFC (right mPFC and dmPFC respectively) (Hanlon et al., 2013; Li et al., 2013). In contrast, Kim et al. (2015) showed that both FC-added NF group and activity-based NF group showed increased neuronal activity from Visit 1 to Visit 2 with greater gains across visits in ROIs2 for FC-added NF group. In addition, FC-added NF group was characterized by enhanced neuronal activity and FC in both ROIs across the four non-rtfMRI runs. However, both groups showed increased activity in ROIs1 at post-rtfMRI scan of Visit 2 compared to the pre-rtfMRI scan of Visit 1.

Furthermore, a strong negative correlation was reported between the activity of ROIs1 in the FC-added NF group and self-reported craving scores at Visit 2 whereas a moderate correlation was found at Visit 1. For the activity-based NF group a moderate association was found at Visit 2. A significant correlation between the activity of ROIs2 and subjective craving scores was not revealed. Moreover, FC across the ROIs was higher in FC-added NF group compared to activity-based NF group during each visit. Greater deviations in FC between groups were observed in Visit 2 in which FC was negatively correlated to subjective craving scores in both groups. By averaging neuronal activity and FC, a negative correlation was observed with craving scores at Visit 2. Exploring the pre-post training rtfMRI data, a negative correlation was also reported between the craving scores in FC-added NF group and the following: the activity of two ROIs, FC, average neuronal activity and FC in both ROIs. In the activity-based group, a similar trend was mentioned between the activity levels of ROIs1 and self-reported craving scores. On the contrary, Li et al. (2013) and Hanlon et al. (2013) failed to show a correlation between self-reported craving scores and the activity of right mPFC and dmPFC respectively.

Mental strategies employed during training were explored in two out of five studies. The most common strategy used in the study of Li et al. (2013) during training was distraction compared to mental imagery of an adverse effect of smoking in the study of Kim et al. (2015). Other strategies included self-talk (Li et al., 2013), social support (Li et al., 2013), coursework recall (Kim et al., 2015), passive viewing (Kim et al., 2015) and memorizing English vocabulary (Kim et al., 2015). Methodological details of the included studies could be found in Supplementary Material S2.

Table 2
Main clinical and behavioral outcomes of the included studies.

Article	Biofeedback (BF) studies			
Grimsley (1990)	*Deprived smokers* Slight ↑ skin temperature after session (mean: 1.9o F, p > 0.05) High heart rate (mean: 80.9 bpm, SE = 2.8)	*Non deprived* Slight ↓ skin temperature after session (mean: 0.4o F, p > 0.05) Significant ↑ basal skin temp. before treatment (mean = 89.8, SE-1.3, F = 7.9, df = 2,21, **p < 0.01***) Highest heart rate (mean: 85.9 bpm, SE = 5.6)	*Ex-smokers* -	*Never smokers* Slight ↑ skin temperature after session (mean: 2o F, p > 0.05) Mean normal heart rate 73.1 ± 3.9 bpm
	Ratio of smokers who quit: *N/A* **reduced daily cigarettes:** *N/A* **change in Fagerström score:** *N/A*			
Pandria et al. (2018)	Slight ↓ Total oxidative stress after five sessions of BF training compared to the pretraining phase (p = 0.3) Unaffected CO levels after the intervention (p = 0.6) ↓ Fagerström Test (**p = 0.016***) & General Health Test (**p = 0.045***) post-BF **Ratio of smokers who quit:** *not reported* **reduced daily cigarettes:** *not reported*			

Article	Neurofeedback (NF) Electroencephalography (EEG) studies			
Griffith and Crossman (1983)	During smoking a cigarette: ↑ (n = 4) 4–8 Hz // ↑ (n = 5) HR (bpm) // ↓ (n = 6) 8–12 Hz After smoking a cigarette: ↓ (n = 4) skin temperature // - brain waves Neurofeedback: ↑ (n = 4) percentage of time spent producing 8–12 Hz compared to baseline Fadeout: (n = 2) continue producing high levels of 8–12 Hz without use of biofeedback equipment // same n = 2 quit smoking at 6-month follow-up (p-values not reported) **Ratio of smokers who quit:** *33%* **reduced daily cigarettes:** *12–61%* **change in Fagerström score:** *not reported*			
Szalai et al. (1986)	*Deprived smokers* ↓ alpha amplitude after backward recall (**p < 0.05***) ↓ alpha amplitude to the alpha suppression	*Non deprived* - alpha amplitude after backward recall ↓ alpha amplitudes to the alpha enhancement instruction (**p < 0.05***)	*Ex-smokers* - Performances in all conditions	*Never smokers* ↓ alpha amplitude after backward recall (**p < 0.05***)
	ratio of smokers who quit: *N/A* **reduced daily cigarettes:** *N/A* **change in Fagerström score:** *N/A*			
Bu et al. (2019)	Real-feedback: ↓cigarette craving (**p = 2.1 * 10–4*****) / Significant ↓ rates of cigarettes smoked per day at 1 week (30.6% **p = 0.01***), 1 month (38.2% **p < 0.005****) and 4 months follow-up (27.4% p = 0.03) Yoked-feedback: ↓ rates of cigarettes/day at 1 week, 1 month and 4 months follow-up (14.0%, 13.7% & 5.9%, p > 0.05) **Ratio of smokers who quit:** *not reported* **change in Fagerström score:** *not reported*			

Article	Neurofeedback (NF) real-time functional Magnetic Resonance Imaging (rtfMRI) studies			
Li et al. (2013)	Self-reported strategies: distraction (n = 6), self-talk (n = 2), social support (n = 1) and contemplating adverse effects of smoking (n = 1) Significant ↓ anterior cingulate cortex (ACC) activity (**p = 0.028***) // Significant ↓ craving scores (**p = 0.002****) // mean ACC activity significantly correlated to mean cue craving rating (**p = 0.011***) Cue induced craving significantly correlated with BOLD activation in bilateral occipital areas, ACC, nucleus accumbens, frontal cortex, parietal cortex and hippocampus (**p < 0.005****) **ratio of smokers who quit:** *not reported* **reduced daily cigarettes:** *not reported* **change in Fagerström score:** *not reported*			
Hanlon (2013)	High dropout rate (60% completed the study) Non-completers were able to lower their craving scores following only the instructions Crave ROIs localized at vACC // Resist ROIs at dorsomedial prefrontal cortex (dmPFC) Significant correlation between craving scores & vACC activity during feedback Significant ↓ craving scores in later runs compared to first run (**p = 0.04***) **ratio of smokers who quit:** *not reported* **reduced daily cigarettes:** *not reported* **change in Fagerström score:** *not reported*			
Canterberry et al. (2013)	Significant ↓ percent signal change (PSC) across sessions (**p = 0.004****) Significant ↓ reported craving (**p = 0.024***) Non-significant correlation of PSC & reported craving **ratio of smokers who quit:** *not reported* **reduced daily cigarettes:** *not reported* **change in Fagerström score:** *not reported* // Fagerström score significantly predicted PSC at visit 3 (**p = 0.028***)			
Hartwell (2015)	ROIs localized at ACC/mPFC Feedback group significantly ↑ craving-related attenuation of activation compared to controls (**p = 0.001****) Feedback group significantly ↓ Questionnaire of Smoking Urges-Brief Factor 1 compared to controls (**p = 0.041***) **ratio of smokers who quit:** *not reported* **reduced daily cigarettes:** *not reported* **change in Fagerström score:** *not reported*			

Table 2 (*continued*)

Article	Biofeedback (BF) studies
Kim et al. (2015)	Significant ↓ CO level before visits compared to interview ($p < 10^{-4}$***) - craving scores, performance, stimulus strength scores, mental strategies Mean neuronal activity and FC was significantly associated with craving score only in participants who performed the FC-added NF ($p < 0.05$*) Subjective craving score was significantly associated with neuronal activity in the anterior ROIs ($p = 0.028$*) Heavy smokers who received FC-added NF exhibited a significant association between: (1) neuronal activity and cigarette craving score ($p = 0.038$* for ROIs1 and corrected $p = 0.002$** for ROIs2) (2) mean neuronal activity and FC and cigarette craving score at the second visit ($p = 2.42 * 10^{-8}$ *** for ROIs1 and $p = 1.2 * 10^{-5}$ *** for ROIs2) **ratio of smokers who quit:** *not reported* **reduced daily cigarettes:** *not reported* **change in Fagerström score:** *not reported*

N/A = not available in this study

p → p value not significant, **p** *→p value below 0.05, **p** **→p value below 0.005, **p** ***→p value equal to or below 0.001

3.3. Clinical and behavioral outcomes

The main clinical and behavioral findings from the studies investigating the effect of BF and NF in smoking are summarized in Table 2 according to smoking status of the participants and grouped by modality of feedback.

Smoking is considered to be a cause for chronic inflammatory response mediated through different pathways (Csordas and Bernhard, 2013; Messner and Bernhard, 2014). Tobacco smoke constitutes a mixture of > 9000 chemicals including carcinogens and oxidizing chemicals among others. Oxidizing chemicals, such as free radicals, are considered top contributors to multiple tissues damage, mainly to endothelium leading to inflammation, lipid abnormalities and DNA (Karademirci et al., 2018; Benowitz and Gourlay, 1997; Halliwell, 1987). The effect of BF training on total oxidative stress was evaluated only by Pandria et al. (2018) extending BF's utility from a clinical point of view. Although nicotine addiction has detrimental effects on smokers' health, it also affects behavior during smoking maintenance (Heishman, 1999) but mainly during abstinence from smoking (Hughes, 2007). Erickson et al. (2004) reported that highly nicotine-dependent individuals experience greater worsening in their health-related quality of life (HRQoL) after one week into a smoking cessation attempt compared to less addicted smokers. Thus, smoking cessation strategies should address, among others, the behavioral aspects of addiction. To this direction, Pandria et al. (2018) indicated that BF resulted in attenuation of nicotine dependence severity and presence of psychiatric symptoms. A decreasing trend was found in anxiety, depressive and withdrawal symptom while self-esteem showed an increasing trend after BF compared to baseline.

Most included studies using rtfMRI specially targeted craving modulation as it is considered as a predisposing factor to relapse (Killen and Fortmann, 1997; Shiffman et al., 1997, 1996). The earlier studies of Grimsley (1990), Griffith and Crossman (1983) and Szalai et al. (1986) did not report craving modulation indices. From the NF EEG studies, only Bu et al. (2019) showed that their feedback group achieved significant short-term and long-term reduction in craving scores and number of cigarettes per day after an individualized NF EEG training. Griffith and Crossman reported that 2 out 6 individuals, those who retained the trained alpha modulation skill, quit smoking at the end of the follow up period (Griffith and Crossman, 1983). From BF studies, Pandria et al. (2018) indirectly targeted craving through targeting alleviation of stress, as a predisposing factor to relapse. The primary index was nicotine dependence (measured by Fagerstrom) that was shown to be significantly reduced after training. All rtfMRI studies showed reduction in self-reported scores (Hartwell et al., 2015; Kim et al., 2015; Hanlon et al., 2013; Canterberry et al., 2013; Li et al., 2013) and most of them (Hartwell et al., 2015; Kim et al., 2015; Hanlon et al., 2013; Li et al., 2013) revealed correlations between subjective craving scores and targeted brain activity. Two out of five rtfMRI studies (Kim et al., 2015; Canterberry et al., 2013) pointed out the possible interference of nicotine dependence severity on training outcomes.

Heavy smokers enrolled in Kim et al. (2015) successfully modulated their resistance-to-urge brain activity but also decreased their craving scores. On the other hand, in the study of Canterberry et al. (2013) where low to moderate dependent individuals were enrolled, FTND score was related to successful use of rtfMRI over time. The authors suggested that low nicotine-dependent individuals may have greater gains in craving-related brain modulation over time compared to high nicotine-dependent individuals. This is consistent with past research showing that nicotine dependence severity is a strong predictor for long-term smoking cessation whereas motivation was less effective to predict quit of smoking (Hyland et al., 2004). Although nicotine dependence severity could be a modulating factor of the NF effectiveness, further research is needed to shed light on its role on BF and NF training.

Even though the role of male gender as predictor to smoking cessation remains non conclusive (Hyland et al., 2004), most of the studies enrolled mainly male participants. At the same time, Kim (2014) research in Korean adults found that women smokers are more likely to quit smoking taking into account smoking trends and the increasing rates of women smokers. Among possible explanations of this gender disparity could be the interference of menstrual cycle on smoking behavior and thus, training outcomes. Sakai and Ohashi (2013) attempted to associate menstrual phase with smoking behavior, mood and other related symptoms and concluded that smoking levels are increased during the menstrual and luteal phases, as the craving is enhanced and depressive symptoms appear. Additionally, Franklin et al. (2015) noted that the menstrual cycle of women may impair the used methodology and alter the results. Hence, it is crucial that these gender disparities are addressed as the disparity obstructs generalization of scientific findings.

3.4. Effect of smoking on biofeedback/neurofeedback

Two of the included studies (Szalai et al., 1986; Grimsley, 1990) did not investigate any smoking-related outcomes but revolved their main message around the confounding effects of smoking behavior, prior to training, on the biofeedback/neurofeedback training. In these studies, the number of cigarettes smoked by the subjects before each study was discussed as a possible negative modulator factor of training outcomes (Elliott and Thysell, 1968) and the impact of smoking on physiological processes was explored, as in other earlier studies (Griffith and Crossman, 1983; Grimsley, 1990; Lecerof et al., 1990). This suggestion is further supported by the sympathetic system activation due to nicotine consumption (Benowitz and Gourlay, 1997) as well as the modulation of training outcomes in the study of Szalai et al. (1986), depending on recent nicotine consumption. Szalai et al. used four arms, splitting smokers in a group of ten deprived smokers (DS) and in another of ten not deprived smokers (NDS), including ex-smokers (ES) and non-smokers (NS) as active comparators (Szalai et al., 1986). They associated cigarette smoking with decreased alpha suppression during a vigilance task, but could not identify a consistent role of cigarette smoking in alpha self-regulation.

Grimsley (1990) reported different profiles of skin temperature alterations and training outcomes depending on smoking abstinence prior to training. Non-deprived smokers showed higher basal temperature compared to deprived smokers and non-smokers. Even though this finding is in line with nicotine paradox (Gilbert, 1979; Kassel et al., 2003; Parrott, 1998), so-called "Nesbitt's paradox", two physiological mechanisms were hypothesized to be involved. The increased skin temperature could be attributed either to vasodilation after smoking-induced relaxation or to a rebound vasodilation as a homeostatic response, following the vasoconstrictive effect of nicotine consumption. However, non-deprived smokers were not efficient in modulating their skin temperature as they showed a decrease in skin temperature compared to the other groups. The aforementioned outcome could be attributed to sympathetic stimulatory effects of nicotine that result in enhanced plasma epinephrine, cardiac work, increasing heart rate as much as 10–15 bpm, cardiac contraction and filling (Benowitz and Burbank, 2016). Cardiac filling is increased due to nicotine-induced vasoconstriction in the coronary and skin vessels and vasoconstriction of skin vessels leads to decreased skin blood flow and skin temperature at fingertips (Benowitz and Burbank, 2016). Although mean HR was non-significantly higher for smokers (SS higher than SNS) than NS in baseline and during session, a significant decline in mean HR across the session was also observed for all groups, attributed to the relaxation effect of BF that is not hampered by the vasoconstrictive properties of nicotine.

From the included studies focusing on smoking-related outcomes, Griffith and Crossman (1983) also reported attenuation of skin temperature after nicotine consumption and increase of heart rate during active smoking. However, a more recent study indicated that there was no alteration in heart rate variability (HRV) of smokers and passive smokers, concluding to an absence of alternation in autonomic regulation after exposure to smoke (Gondim et al., 2015). The differences between those studies are mostly located in the methodology used, the number of subjects, as well as the parameter of heart function which was measured. Specifically, more recent studies measure HRV, instead of heart rate, in order to extract more information about heart function under nicotine consumption (Gondim et al., 2015; Verplaetse et al., 2017). Among the excluded studies, DeGood and Valle (1978) investigated the effect of chronic nicotine and alcohol consumption on neurofeedback, introducing a brief (4 h) period of abstinence prior to training. They reported poor performance in self-regulation of occipital alpha activity compared to non-users of nicotine or alcohol and also discussed this in comparison to similar effects of anxiety status (DeGood and Valle, 1978).

3.5. Concept and documentation on neuroplastic effects

Most of the studies that investigated neuroplastic alterations (Bu et al., 2019; Hartwell et al., 2015; Kim et al., 2015; Hanlon et al., 2013; Canterberry et al., 2013; Li et al., 2013) induced by provided training are mainly focused on response modulation to craving, aiming at reduction or control over craving. Craving is considered as a key-predictor of relapse (Killen and Fortmann, 1997; Shiffman et al., 1997, 1996) and thus it is an expected but crucial aspect of focus of studies related to smoking research, cessation and relapse.

Pandria et al. (2018) focused on stress alleviation based on the idea that physiological response to stress and nicotine share similar characteristics. They hypothesized that stress management through BF could probably eliminate stress-induced craving (Kassel et al., 2003; Sinha, 2001) and thus the possibility to relapse, as a relationship between stress and relapse is well-established (Brandon et al., 1990; Borland, 1990; Shiffman, 1982). On the other hand, stress and nicotine dependence could have additive effect on different physiological responses (Calderon et al., 2004; Perkins et al., 1992; MacDougall et al., 1988; Pomerleau and Pomerleau, 1990). Therefore, effects of training could be transferred to brain activity modulation. A ROI-specific

hypothesis was not determined as BF training was provided. However, the default-mode network was investigated for possible neuroplastic training effects as both smoking (Tanabe et al., 2011; Wetherill et al., 2015; Weiland et al., 2015) and stress (Soares et al., 2013; Clemens et al., 2016) have been separately found to affect this network. Bu et al. (2019) used the ERP component P300 induced by exposure to smoking-related stimuli to explore the effect of NF training. A correlation between P300 component and cigarette craving is highly supported by the majority of studies (Knott et al., 2008; Field et al., 2009; Campanella et al., 2014). Moreover, a smoking-cue reactivity task, including smoking-related, neutral and animal-related images, was used to extract EEG activity patterns elicited by smoking-related stimuli and then compared them to patterns related to neutral stimuli. The deactivation of smoking-elicited EEG patterns was targeted rewarding participants whose response to smoking stimuli converged to that of neutral stimuli. Griffith and Crossman (1983) mentioned that occipital alpha upregulation was provided as substitute for smoking without explaining the underlying rationale for choosing this protocol.

In rtfMRI studies craving-related brain regions were reported, citing overlapping groups of studies, in order to form the concept of their designs. Studies conducted by the same research group (Hartwell et al., 2015; Hanlon et al., 2013; Canterberry et al., 2013; Li et al., 2013) formed their concept based on their previous work (Hartwell et al., 2011) and that of Brody et al. (2007). Hartwell et al. (2011) showed that a crave condition is associated with enhanced activation of brain areas related to attention, episodic memory and decision-making (left ACC, left mPFC, left middle cingulate gyrus, middle OFC, bilateral PCC and bilateral) precuneus. On the other hand, Brody et al. (2007) revealed enhanced activation in primary and secondary visual processing brain regions (left lateral occipital gyrus, bilateral supramarginal gyri, left cuneus, precuneus, angular and lingual gyri), comparing a crave to a neutral condition. A resist to crave condition in Hartwell et al. (2011) was associated with increased activation of ACC, superior frontal orbital gyrus and frontal superior medial gyrus in the left hemisphere and right frontal middle gyrus. Meanwhile, in Brody et al. (2007) increased activation in secondary visual processing areas (bilateral PCC spanning the retrosplenial area and precuneus, bilateral supramarginal gyrus, left angular gyrus), dorsal ACC (dACC) extending to midline and medial superior frontal gyrus was observed, along with a deactivation in the bilateral cuneus and sensorimotor regions (bilateral postcentral gyrus and right precentral gyrus). Additionally, a deactivation pattern was shown in inferior prefrontal cortex, occipital cortex as well as precentral and postcentral gyri bilaterally at both conditions (crave, resist) (Hartwell et al., 2011). Comparing brain activations between the conditions, an increased activation of left cuneus, right middle gyrus and bilateral precuneus was found (crave > resist) (Hartwell et al., 2011). Enhanced activation (resist > crave) was observed in inferior frontal cortex, temporal superior pole, precentral gyrus (all in left hemisphere) in Hartwell et al. (2011), while activation in medial superior frontal gyrus, dACC, PCC and precuneus on the left hemisphere was mentioned in Brody et al. (2007). Additionally, a reduction of activation was evident in bilateral cuneus, left middle temporal gyrus, bilateral occipital gyri and right postcentral gyrus in the same comparison (Brody et al., 2007). Both studies discussed that resistance towards urge to smoke may be a complex task involving brain areas associated with decision-making and enhanced attention.

Although ACC, PFC, OFC, PCC and cuneus have been highly involved in brain activation patterns during exposure to smoking-related stimuli (Parrott, 1998); (Csordas and Bernhard, 2013; Messner and Bernhard, 2014; Karademirci et al., 2018; Benowitz and Gourlay, 1997) there is a considerable overlap in activation patterns during a resist and a crave condition. That makes it challenging to characterize the ACC as craving-related region and mPFC as a region associated with resistance towards urge to smoke (Goldstein and Volkow, 2011). However, two studies (Hanlon et al., 2013; Li et al., 2013) have focused on exploring the ability of smokers to reduce brain activity in ACC while being

instructed to reduce craving and increase brain activity in mPFC while being instructed to increase resistance. Taken into consideration the results of their previous work, the following studies of the same group have focused on craving reduction attempting to train smokers to reduce activation in the vicinity of ACC (Hanlon et al., 2013; Canterberry et al., 2013; Li et al., 2013). Hartwell et al. (2015) reported that the selected ROI was localized in the PFC including vACC, dACC, mPFC. On the contrary, Kim et al. (2015) defined both anterior ROIs (including ACC, OFC and mPFC bilaterally) as craving-related brain areas and posterior ROIs (including PCC and precuneus). Nonetheless, they commented that the involvement of the latter in cigarette craving remains unclear. Participants were instructed to resist their urge attempting to increase the NF signal either coming from the neuronal activity of ROIs1 (control group) or from the average of both activity and FC between ROIs1 and ROIs2 (FC-added feedback group).

Possible neuroplasticity effects, induced by BF or NF training, were explored according to the concept of the aforementioned studies. Most of them concluded that nicotine-dependent individuals could successfully modulate craving-related brain activity (Bu et al., 2019; Hartwell et al., 2015; Hanlon et al., 2013; Canterberry et al., 2013; Li et al., 2013). This conclusion emerged as smokers decreased their BOLD response in the vicinity of ACC or ACC/mPFC during training compared to baseline scans (Hartwell et al., 2015; Hanlon et al., 2013; Canterberry et al., 2013; Li et al., 2013) or successfully deactivated smoking cue reactivity patterns and decrease P300 amplitude in fronto-parietal brain regions (Bu et al., 2019). On the other hand, smokers' ability to modulate brain activity related to resistance towards urge to smoke was supported only by Kim et al. (2015). Two (Hanlon et al., 2013; Li et al., 2013) out of five rtfMRI studies failed to reveal a self-regulation mastery on a resist ROI's activity located in mPFC, while in Canterberry et al. (2013) the interest was focused on ACC training. Hartwell et al. (2015) showed effective self-regulation of craving-related brain activity defining a ROI localized to ACC/mPFC.

Many theories have been developed attempting to define the phenomenon of craving (Anton, 1999). Craving constitutes a multifaceted phenomenon which implicates complex cognitive processes, including memory, attention and emotional processes, among others (Bu et al., 2019; Robinson and Berridge, 1993). In line with this suggestion, P300 attenuation was found in fronto-parietal areas where attention regions are located (Bu et al., 2019). Advances in the field of neuroscience fostered the development of models that link the psychological aspect of craving to brain structures. To this direction, a model including nucleus accumbens, amygdala, basal ganglia and frontal cortex (mainly dPFC and OFC) that combined clinical and laboratory data, was proposed for alcohol addiction in Anton (1999).

In drug addiction the disruption of PFC was proposed to lead in iRISA syndrome (Goldstein and Volkow, 2011, 2002). This expanded traditional concepts that mainly focused on brain circuits involved in conditioning, reward and habit formation (Wise, 1996; Di Chiara and Imperato, 1988). The iRISA syndrome is characterized by excessive salience to drug-related stimuli jointly with attenuated sensitivity to non-drug reinforcers and inability to inhibit risky or maladaptive behaviors. In the context of this syndrome craving is described as the combination of attention bias and drug expectation (Goldstein and Volkow, 2011). Although craving was considered as the result of a learned behavior connecting the drug and drug-related cues with its reward effects and past pleasurable experience highlighting the involvement of hypothamus and amygdala (Goldstein and Volkow, 2002), different brain regions and processes subserved by PFC were also showed to participate to a different extent (Goldstein and Volkow, 2011). PFC, including OFC, ACC, mPFC, dPFC, inferior frontal gyrus (IFG) and ventrolateral PFC (vlPFC), is a functionally heterogeneous brain region that encompasses cognition, emotion and behavior (Goldstein and Volkow, 2011). Localizing functions to specific subdivisions of PFC (e.g whether dACC and dorsolateral PFC are associated with craving response, the resistance to crave or both processes) is

elusive (Goldstein and Volkow, 2011). This is due to the extreme functional flexibility of prefrontal systems that prevails over that of primary sensorimotor systems, along with multiple interconnections with other brain regions and different strategies employed to carry out a task (Goldstein and Volkow, 2011). Even though, the need of a unified concept when applying methods that provide feedback based on regional neural activity is probably reasonable, rtfMRI studies have showed that modulation is achieved not only at the training ROI but also in connectivity patterns of various brain areas (Ruiz et al., 2014; Haller et al., 2013; Lee et al., 2012). In line with this finding, Kim et al. (2015) proposed a novel FC-added rtfMRI NF protocol taking into account both regional neuronal activity of ROIs and functional connectivity between ROIs.

A guiding model proposed by Goldstein and Volkow (2011) suggests that enhancement in PFC activity (e.g. dlPFC in the formation of drug-related memories, ACC in attention bias, medial OFC and vlPFC in craving, OFC in drug expectation), is anticipated in drug-related processes and cues, while non-drug related cues result in attenuation in the activity of PFC. The outcomes of four out of five rtfMRI studies (Hartwell et al., 2015; Hanlon et al., 2013; Canterberry et al., 2013; Li et l., 2013) are assumed to be in agreement with this model. On the contrary, Kim et al. (2015) showed that FC-added rtfMRI group showed greater gains in neuronal activity and enhanced FC between targeted ROIs, compared to control group, interpreting their findings as increased volitional control over craving resistance brain areas.

A neuroprotective effect of BF was hypothesized in Pandria et al. (2018) as an increase was observed in the outflow of right vlPFC and TPC after training performing network analysis for alpha bands networks. Between-gender differences showed enhanced outflow of left mPFC and precuneus in male smokers confirmed by within-analysis, while increased inflow of right TPC was found in females. The vlPFC is involved in declined cognition related to addiction (Sweitzer et al., 2016) and emotional and working memory processes through its interconnections with limbic system and temporal areas (Chen et al., 2015; Takahashi et al., 2007). TPC is associated with autobiographical memory (Sutherland et al., 2012) and higher cognitive processes including emotional processing (Buckner et al., 1995). Attenuated functional connectivity of TPC was linked to emotional dysregulation (Fan et al., 2014), while greater coupling between TPC and modulated areas is accomplished through emotional music (Pehrs et al., 2015). BF training incorporated pleasant music possibly affecting the connectivity of TPC in the same way. Increased inflow in this area observed in females could be due to their enhanced responsiveness to emotional cues (Lithari et al., 2010). On the other hand, enhanced outflow of left mPFC and precuneus, shown in male participants, was interpreted as possible counteracting award and emotion-related mechanisms between BF and dysfunction in stress and smoking (Weiland et al., 2015; Soares et al., 2013; Swan and Lessov-Schlaggar, 2007; Lin et al., 2015; Janes et al., 2012; Tsourtos et al., 2008). Therefore, they concluded that observed alterations could indicate favorable qualitative network reorganization attenuating negative affective states and deficits in cognitive abilities related with nicotine as well as boosting autobiographical and emotional processing. Neuroplastic effects on alpha band was mentioned in the early study of Griffith and Crossman (1983) as alpha NF up-training resulted in self-regulation of alpha activity in 67% of participants and the 33% of them retained their skill mastery in fadeout sessions.

3.6. Is biofeedback plausible in the context of smoking?

Regarding the scientific interest on the biofeedback-based interventions for smoking, the timeline of the eligible studies included in this review easily reveals an interesting observation. This interest is temporally concentrated during either before 1990 (Griffith and Crossman, 1983; Szalai et al., 1986; Grimsley, 1990) or from 2013 onwards (Bu et al., 2019; Hartwell et al., 2015; Kim et al., 2015; Hanlon et al., 2013; Canterberry et al., 2013; Li et al., 2013; Pandria et al.,
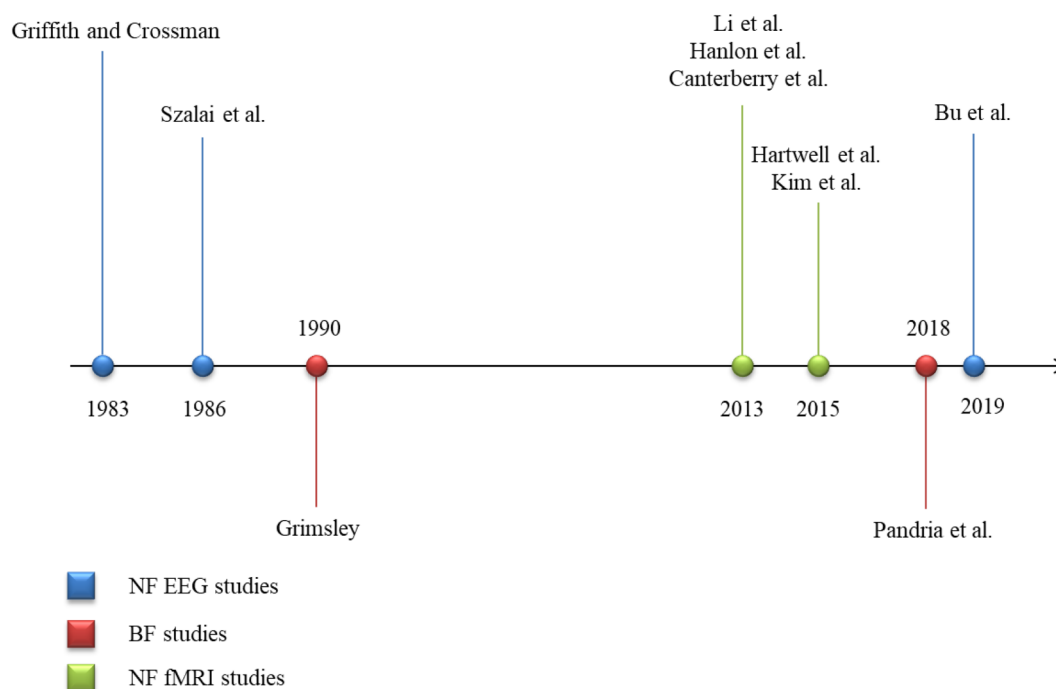
Fig. 3. Timeline of included studies on biofeedback (BF) and neurofeedback (NF) using electroencephalography (EEG) or real-time functional Magnetic Resonance Imaging (rtfMRI) training on smoking addiction.

2016), when the advent of rtfMRI largely renewed the scientific interest in this field as also in neurofeedback in general (Arns et al., 2017; Bruhl, 2015) (See Fig. 3). This observation was also similar with regards to non-eligible studies; only one out of 16 was published between 1986 and 2012 (see Supplementary material S1 for more details).

Although initial works reported some interesting results with regards to both investigative power of BF (Szalai et al., 1986; Grimsley, 1990) and to clinical and behavioral outcomes in smoking addiction (Griffith and Crossman, 1983), the application of BF techniques for smoking seems to have followed the general trend of decline of the field in the same era (Gruzelier, 2014). Some of the reasons for this decline, per Gruzelier's critical discussion (Gruzelier, 2014), can be recognized in the methodology of these studies namely using oversimplistic theoretical approaches to EEG biofeedback, and low power of evidence or of scientific validation (Griffith and Crossman, 1983; Szalai et al., 1986), although the three included eligible studies arguably did not suffer from overstatement of clinical outcomes. Nonetheless, Grimsley's work explored peripheral BF (Grimsley, 1990), a more widely accepted application of clinical psychophysiology at that time, and yet only a handful of related works were retrieved, even among non-eligible studies. Newer studies either relying on EEG (Pandria et al., 2018; Bu et al., 2019) or rtfMRI have attempted to address these shortcomings through a number of strategies to increase specificity and scientific validity (Gruzelier, 2014). Localizing neural substrates of addiction related behavior to better aim neurofeedback interventions was the main theme behind rtfMRI studies, taking advantage of the excellent spatial resolution of the technique. As we previously thoroughly discussed, though, accurate definition of anatomical underpinnings for neurobehavioral functions may still remain a challenge for these studies. EEG, although not as spatially accurate as fMRI, allows for a similar approach through individualized training, abled by detection of abnormal patterns and selection of features to target with neurofeedback (Bu et al., 2019). Advanced techniques of EEG analysis, in addition to allowing personalized use as a training modality, can also provide documentation of training effects at the level of the brain and prove the validity of BF/NF interventions (Pandria et al., 2018). Moreover for both BF and NF studies the importance of demonstrating a learning effect across

sessions, as well as within sessions, cannot be underestimated, constituting a direct indicator that behavioral and clinical outcomes can be attributed to the intervention rather than to non-specific factors that may include motivation and experience (Gruzelier, 2014).

As smoking remains a significant global health issue that proves to be resilient to pharmacological treatment and smoking cessation interventions (World Health Organization, 2019), promising results from newer BF and NF studies regarding clinical and behavioral outcomes reveal a complementary role for these techniques in smoking cessation (Pandria et al., 2018; Bu et al., 2019; Kim et al., 2015; Canterberry et al., 2013). Such studies have yet to be incorporated in the mainstay of clinical treatment despite evidence of usefulness in a variety of disorders such as attentional-deficit/hyperactivity disorder, stress disorders and addiction (Arns et al., 2017). In order to solidify their renewed role and allow their consideration in designing national strategies and policies for dealing with smoking pandemic (Bamidis et al., 2017), BF and NF should address remaining issues on specificity and scientific validity, target diverse demographics and produce robust, reproducible methodologies and clinical guidelines for relevant health care providers.

4. Limitations

Limitations at study and outcome level could be identified in the included studies, as we previously discussed, of which the most prominent probably lie with sex disparity and age demographics. From a total of 238 participants in nine studies with available information on participant sex, 151 (63,45%) were male participants; this ratio reached 100% in three studies representing a total of 80 participants (Griffith and Crossman, 1983; Bu et al., 2019; Kim et al., 2015). Regarding age, only one study (Pandria et al., 2018) included participants from the age group of above 65 years and other two reported an age range of 18–60 (including participants above 41yo) (Hartwell et al., 2015; Canterberry et al., 2013). These limitations of the demographics of the participants hamper the generalization of reported outcomes, as female current smokers are estimated from 12% to 19% of the female population in US and Europe (compared to 16% to 38% of males) (World Health

Organization, 2020; Creamer et al., 2019), while in certain countries the disparity is < 5% (World Health Organization, 2020). Also current smokers constitute approximately 16% of the age group 45–64 and 8% of the above 65 age group (World Health Organization, 2020; Creamer et al., 2019). Furthermore, only one included study attempted to address the question of how severity of nicotine dependence interacts with the effectiveness and outcomes of biofeedback training (Canterberry et al., 2013). Limitations regarding the methodology of the included studies were discussed in the previous sections on neuroplastic effects and plausibility of biofeedback in smoking addiction. Although there is no gold standard, experts have argued for the importance of adequate number of sessions to detect or induce training effects (Gruzelier, 2014). From the included studies, only two deployed five or more sessions in an intervention design (Pandria et al., 2018; Griffith and Crossman, 1983), with all the remaining ranging from one to three sessions. Nonetheless, there is an ongoing discussion on individualized protocols being able, through increased specificity, to reduce the effective number of needed sessions (Bu et al., 2019). Finally, we should add that some of the included studies may be considered underpowered for the research target they set. The reasons for this are mainly two: a) they either recruited small participant groups: N = 6 in the study by Griffith and Crossman (1983), n = 10 that completed the study by Li et al. (2013), n = 9 that completed the study by Hanlon et al. (2013), N = 9 in the study by Canterberry et al. (2013) or b) a lack of a comparator group (Pandria et al., 2018; Griffith and Crossman, 1983; Hanlon et al., 2013; Canterberry et al., 2013; Li et al., 2013). As such, the findings of these studies should be interpreted with caution, as the impact of confounding factors cannot be underestimated and learning effects are more difficult to be established.

A few limitations at review level should also be discussed. Searches and screening for relevancy revealed a small pool of relevant studies to begin with (26 entries). Eligibility for inclusion in this systematic review further limited that pool as it entailed rejecting studies that either administered blended interventions, were case reports, included underage participants or participants with multiple addictions (see Supplementary Material S1 for our decisions regarding these studies) in order to increase reporting vigor. Nonetheless, this decision limited the absolute number of included studies (ten studies finally included) and some relevant clinical and behavioral outcomes may have been omitted, although their interpretation could not have been directly comparable to those included. From the included studies, two publications did not directly investigate the effect of biofeedback and neurofeedback on smokers, but were single-session investigations and rather reported the influence of smoking on peripheral and EEG biofeedback, introducing some heterogeneity to the narrative. Reporting bias was avoided by mentioning and discussing negative results, maximizing retrieval of full-texts (only one unavailable) and by rejecting entries that gave incomplete information on participants and methodology. Overall, the authors tried to minimize effects of limitations at review level to this work by strictly adhering to the PRISMA-P 2015 statement standards for conducting the review, to the review methodology submitted for registration to PROSPERO and to the PICO framework for reporting our results.

5. Conclusions

This systematic review attempted to aggregate existing knowledge and identify possible knowledge gaps, and consolidate understanding of findings from BF and NF studies on smokers. BF and/or NF training seems to facilitate modulation of autonomous and/or central nervous system activity transferring this learned self-regulation to behavior. Most of the studies that investigated neuroplastic alterations due to provided training are mainly focused on response modulation to craving aiming at reduction or control. Thus, behavior-related outcomes included craving reduction, decrease of nicotine dependence severity and psychiatric symptoms. Limited evidence exists regarding

the effects of BF or NF training on clinical status of smokers. A common limitation among the retrieved studies was the sex disparity and age demographics. Moreover, the effect of severity of nicotine dependence on training and the optimal dosage of training should be further explored. Furthermore, it seems crucial to take into consideration the confounding effect of smoking behavior prior to training on training outcomes. BF and NF should address remaining issues on specificity and scientific validity, target diverse demographics and produce robust, reproducible methodologies and clinical guidelines for relevant health care providers, in order to play a complementary role and allow their consideration in designing national strategies and policies for dealing with smoking pandemic,

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2020.102397.

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