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Reviews and perspectives

Altered amygdala function in nicotine addiction: Insights from human neuroimaging studies

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ABSTRACT

More than 5 million deaths a year are attributable to tobacco smoking, making it the largest single cause of preventable death worldwide. The primary addictive component in tobacco is nicotine. Its addictive power is exemplified by the fact that by far most attempts to quit smoking fail. It is therefore mandatory to understand the biological mechanisms by which nicotine leads to continued smoking despite its harmful consequences. While current research perspectives on nicotine addiction emphasize the contribution of reward-related mesocorticolimbic dopamine (DA) systems, the role of the amygdala remains less well characterized, although it is crucially engaged in the emotional and motivational modulation of cognition and behavior. Consequently, we here review brain imaging studies reporting altered neural responses of the amygdala in nicotine addiction. A major focus is placed upon resting-state and cue-induction studies documenting that nicotine addiction is associated with aberrant amygdala activity. Importantly, unprovoked abstinence-induced nicotine cravings have been shown to interfere with the amygdala's ability to detect and adequately respond to harm signals. In light of this empirical evidence, we propose that impaired amygdala-guided harm avoidance and executive functions may be instrumental in maintaining nicotine addiction despite serious health consequences.

Contents

1. Introduction

Tobacco smoking is the major preventable cause of death and disability in industrialized countries. In the United States cigarette smoking is responsible for one in every five deaths, the chronic diseases caused by smoking lead the causes of death and disability, and the economic burden of cigarette use amounts more than $193 billion annually in health care costs and loss of productivity (U.S. Department of Health and Human Services, 2010). Clearly, there is an urgent need to reduce and prevent tobacco use. However, although 70% of smokers in the United States report they want to quit, and approximately 44% report that they try to quit each year (Fiore et al., 2008), of those who try, only 3–5% remain abstinent without the use of nicotine replacement therapies, and no more than 30% are successful with them (Dome, Lazary, Kalapos, & Rihmer, 2010; Stead, Perera, Bullen, Mant, & Lancaster, 2008). The efficacy of public health awareness programs based on warning messages and pictorial stimuli has been questioned (Reardon, 2011; Wilson, 2011). Moreover, even the direct confrontation with its deleterious health

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consequences has little impact on smoking behavior, as documented by reports on sustained heavy smoking in cancer patients with tracheostoma or in patients with Buerger's Disease (thromboangiitis obliterans; Malecki, Zdrojowy, & Adamiec, 2009). To improve the efficacy of smoking cessation programs, it is therefore mandatory to understand the brain mechanisms underlying this failure in self-protective threat avoidance (Kenny & Markou, 2001). In this regard, and in view of its critical engagement in threat perception (Adolphs et al., 2005), social transmission of fear (Olsson, Nearing, & Phelps, 2007; see also Goossens et al., 2009), conditioned avoidance of aversive stimuli (LeDoux, 2007), and related executive functions (Davis & Whalen, 2001; Phelps, 2006; Schaefer & Gray, 2007; Seymour & Dolan, 2008) the amygdala deserves special attention. In the present review we discuss evidence from human neuroimaging studies for the involvement of the amygdala in the neural circuitry mediating smoking addiction.

There is abundant evidence that nicotine promotes addiction by activating nicotinic acetylcholine receptors (nAChR) densely distributed in reward-related mesocorticolimbic dopamine systems (De Biasi & Dani, 2011). Nucleus accumbens is thought to interact critically with the amygdala and the orbitofrontal cortex to mediate reinforcement for addiction (Everitt & Robbins, 2005; Whitelaw, Markou, Robbins, & Everitt, 1996; Alderson, Robbins, & Everitt, 2000) and drug relapse (Kalivas & McFarland, 2003; Shaham, Shalev, Lu, de Wit, & Stewart, 2003). Repeated exposure to nicotine may further promote addiction through incentive salience sensitization (Benowitz, 2010; Robinson & Berridge, 2001), such that smoking-associated cues elicit the urge to smoke, a phenomenon also referred to as cue-induced craving (Caggiula et al., 2001; Conklin, 2006). Whereas the hippocampus is involved in the association of specific context with drugs of addiction, the amygdala is involved in the association of discrete stimuli with drugs of addiction (Everitt & Robbins, 2005). Two meta-analyses summarizing the literature on drug cue-reactivity have shown that activation of the amygdala and the striatum are among the most robust neural responses to drug-related cues (Chase, Eickhoff, Laird, & Hogarth, 2011; Kühn & Gallinat, 2011, although see Engelmann et al., 2011). Consequently, much research has been carried out on the involvement of the amygdala in cue-induced craving. The experimental paradigms used to induce and characterize the neural correlates of cue-induced craving typically expose participants to smoking-related stimuli during functional magnetic resonance imaging (fMRI).

Nicotine can exert a rewarding effect by enhancing cognitive functions or by alleviating pre-existing cognitive deficits. It has consistently been shown that smoking specifically facilitates vigilance-related executive performance (Heishman, Kleykamp, & Singleton, 2010; Heishman, Taylor, & Henningfield, 1994; Swan & Lessov-Schlaggar, 2007). Intriguingly, smoking as a self-medication to enhance vigilance and attention has been implicated as contributing to the high smoking prevalence in patients with schizophrenia (Kumari & Postma, 2005; Newhouse, Singh, & Potter, 2004) and major depression (Aubin, Rollema, Svensson, & Winterer, 2011; Dome et al., 2010). Since the amygdala is critically involved in both attention (Gallagher & Holland, 1994; Holland & Gallagher, 1999) and vigilance (Davis & Whalen, 2001; Schaefer & Gray, 2007) it is conceivable that it mediates, at least in part, the facilitative effects of nicotine on executive functions. Along with its positive reinforcing action, nicotine can exert negative reinforcing effects: in chronic smokers, nicotine abstinence is often characterized by a dysphoric affective state and executive deficits which can be alleviated by reinstating smoking (Durazzo, Meyerhoff, & Nixon, 2010; Heishman et al., 1994). Core symptoms of the nicotine withdrawal syndrome listed by both DSM-IV-TR and ICD-10-TR are: anxiety, difficulty concentrating, dysphoric or depressed mood, increased appetite or weight gain, insomnia, and irritability, frustration or anger (American Psychiatric Association, 2000; World Health Organization, 1993). The most widely used tests to assess smoking withdrawal as a covariate were the Minnesota Nicotine Withdrawal Scale (MNWS, Hughes & Hatsukami, 1986), Mood and Physical Symptoms Scale (MPSS, West & Hajek, 2004), Wisconsin Smoking Withdrawal Scale (WSWS, Welsch et al., 1999), Questionnaire on Smoking Urges (QSU, Tiffany & Drobes, 1991), Smoker Withdrawal Questionnaire (Shiffman & Jarvik, 1976), Smoker Complaint Scale (Schneider & Jarvik, 1984), and the Cigarette Withdrawal Scale (CWS, Etter & Hughes, 2006). Nicotine dependence has been most widely assessed with the Fagerström Test of Nicotine Dependence (Fagerström, 1978, Heatherton, Kozlowski, Frecker, & Fagerström, 1991). The withdrawal syndrome typically begins within the first two days after smoking cessation, peaks in the first week, and lasts 2–4 weeks, although the individual symptoms differ in their time course, and there are marked interindividual differences (Hughes, 2007). The abstinence-induced urge to smoke in order to reverse these symptoms can be referred to as abstinence-induced craving (Wang et al., 2007). Based on its significant predicting value for relapse (Killen & Fortmann, 1997; Schiffmann, Paty, Gwaltney, & Dang, 2004), abstinence-induced craving can be regarded as one of the major factors sustaining nicotine addiction (Evans & Drobes, 2008; Heishman et al., 1994). Given its pivotal role in emotion and affective processing (Adolphs, Tranel, Damasio, & Damasio, 1994; LeDoux, 2007; Phelps, 2006) and at least some of the executive functions impaired by smoking withdrawal (Schaefer & Gray, 2007; Seymour & Dolan, 2008; Swan & Lessov-Schlaggar, 2007), the amygdala is likely to be involved in the cognitive and affective symptoms of smoking withdrawal.

However, the role of the amygdala in smoking has been widely neglected—in fact, there is not a single review dedicated to the role of the amygdala in smoking addiction. Here, we address this issue by summarizing evidence from brain imaging studies employing different techniques to measure amygdala activity in smokers. Whereas positron emission tomography (PET) and arterial spin-labeled perfusion MRI (ASL) have been mainly employed to investigate the effects of smoking abstinence or the acute application of nicotine on resting state activity, blood oxygen level-dependent (BOLD) fMRI, due to its better temporal resolution, has been used to specifically investigate the reactivity of the amygdala to smoking-related or otherwise emotionally evocative, as compared to neutral, stimuli. Although widely neglected, amygdala responses to emotionally evocative stimuli in smoking is a particularly important topic since the amygdala likely mediates the putative effects of tobacco packaging warning messages aiming to stimulate the public's awareness of the harmful effects of smoking (Reardon, 2011; Wilson, 2011). Indeed, the literature rather supports the notion of decreased amygdala reactivity to aversive emotional stimuli in smoking (Kobiella et al., 2010; Onur et al., 2012), questioning the efficacy of awareness campaigns, based on the motivational impact of aversive pictorial stimuli.

2. Human neuroimaging studies of amygdala function in tobacco smoking

2.1. Amygdala reactivity to neutral, smoking-related, and emotionally evocative stimuli

Studies investigating amygdala reactivity to smoking-related or otherwise emotionally evocative, as compared to neutral, stimuli, are summarized in Table 1. The vast majority of studies employed BOLD fMRI. Within-group comparisons for the contrast 'smoking-related cues > neutral cues' were calculated in all studies as a direct comparison, or as a part of a factorial model

Table 1
Amygdala reactivity to smoking-related, otherwise emotionally evocative, and neutral cues.

Authors	Samples(s)	Treatment	Sample characteristics	Abstinence	Task/stimuli	Modality/ analysis	Amygdala reactivity
Artiges et al. (2009)	13 smokers (5 female) 13 nonsmokers (5 female)	No	Smokers age=26 20.5 c/d FTND=5.4 nonsmokers age=24	Smokers: 2 h abstinence	Emotion recognition task preceded by neutral or smoking-related images	ROI analysis	Accuracy was lower for smokers than for nonsmokers for smoking-related cues specifically. In smokers smoking-related cues decreased right amygdala activity
Brody et al. (2007)	42 smokers (12 female)	Yes	Age=38 23.3 c/d 24.1 pack years FTND=5.7	Satiety	45 s videos with smoking-related or neutral content; instructions: resist vs. allow craving	Whole brain analysis	No effect
David et al. (2005)	9 smokers 11 nonsmokers	No	Smokers age=34.4 (5 female) FTND=4.7 18.3 c/d Nonsmokers age=28.3 (8 female)	Smokers: Overnight abstinence	Smoking-related or neutral pictures, task: indicate the gender of the person on the picture	Whole brain analysis	No effect
Due et al. (2002)	11 smokers (4 female) 6 nonsmokers (2 female)	No	Smokers age=22.7 23.5 c/d nonsmokers age=25	Smokers: 10 h abstinence	Smoking-related, neutral, and target images (animals)	ROI analysis	Smoking cues elicited increased amygdala activity in abstinent smokers but not in nonsmokers
Franklin et al. (2007) ASL	21 smokers (11 female)	Yes	Age=34.4 FTND=4.8 19.6 c/d	Satiety	In vivo exposure to smoking-related vs. neutral stimuli followed by audio-video clips with neutral or smoking-related content	ROI analysis	Amygdala perfusion increased for smoking cues
Hartwell et al. (2011)	32 smokers (19 female)	Yes	Age=33.5 17.7 c/d FTND=5.6	2 h abstinence	Block design, smoking-related and neutral images; instruction: resist craving vs. allow craving; craving ratings after each block during scanning	Whole brain analysis	No effect
Janes et al. (2009)	13 smokers (13 female)	Yes	Age=43 FTND=6.2	Satiety vs. after about 7 weeks participation in a smoking cessation trial	Smoking-related, neutral, and target images (animals)	Whole brain analysis	No effect
Janes et al. (2010)	21 smokers: (21 female) 9 slip 12 abstinence	Yes	Age slip=47.7 abstinence=44.4 FTND Slip=6.9 abstinence=5.0 Pack Years Slip=33 Abs=25.8	Satiety	Smoking-related, neutral, and targets images (animals)	ROI analysis	The contrast 'smoking cues > neutral cues' was greater in the amygdala of the slip group than in the group which remained abstinent
Jasinska et al. (2012)	82 smokers (28 female) 45 quitters (18 female) 37 non-quitters (20 female)	Yes	Quitters Age=36.4 15.6 c/d Pack years=15.1 Non-quitters Age=38.4 18.1 c/d Pack-years=19.4	Satiety	Passive block-wise audio-visual presentation of smoking-cessation or neutral messages	ROI analysis	The contrast 'smoking-cessation messages > neutral messages' yielded greater bilateral amygdala responses in quitters than in non-quitters
Kober et al. (2010)	21 smokers (9 female)	No	Age=26.8 15.7 c/d 9.3 yrsm	2 h abstinence	Presentation of cigarette and food pictures under the instructions NOW (consider the immediate consequences of consuming the pictured stimulus) vs. LATER (consider the long-term consequences)	ROI analysis	Cognitive down-regulation of craving was associated with decreased activity in regions associated with craving, including the amygdala
Kobiella et al. (2010)	14 smokers (0 female) 14 nonsmokers (0 female)	No	Smokers age=30.4 FTND=5.6 13.1 yrsm 20.5 c/d nonsmokers age=30.9	Satiety	Passive viewing task comprising pleasant, neutral, and unpleasant stimuli	ROI analysis	Amygdala reactivity to unpleasant stimuli was decreased in smokers
Lee et al. (2005)	8 smokers (0 female)	Yes	Age=17 15.3 c/d FTQ=4.4	7 h abstinence	Virtual reality containing smoking-related and neutral items	Whole brain analysis	No effect
Luijten et al. (2010)	18 smokers (5 female) 19 nonsmokers (7 female)	No	Smokers age=23.6 16.7 c/d 7.1 yrsm FTND=3.7 nonsmokers Age=22.8	3 h abstinence	Attentional bias task with smoking-related vs. neutral images	Whole brain analysis	No effect

Table 1 (*continued*)

Authors	Samples(s)	Treatment	Sample characteristics	Abstinence	Task/stimuli	Modality/ analysis	Amygdala reactivity
McBride et al. (2006)	19 smokers (9 female)	No	Age=27 22 c/d	12 h abstinence vs. satiety; Instructions: cigarette availability post scan vs. prolonged abstinence	Six 2 min videos, alternating between smoking and neutral content; craving assessment after each video	ROI analysis	No effect
McClernon et al. (2005)	13 smokers (8 female)	No	Age=29.9 25.4 c/d 13.4 yrsm	Overnight abstinence vs. satiety	Smoking-related, neutral, and target images (animals)	ROI analysis	No effect
McClernon et al. (2007)	16 smokers (14 female)	Yes	Age=39.1 22.6 c/d 20.4 yrsm FTND=6.5	2 h abstinence	Smoking-related, neutral, and target images (animals)	ROI analysis	Amygdala activity to smoking-related cues decreased during therapy
McClernon et al. (2008)	18 smokers (11 female)	No	Age=28.6 17.8 c/d 11.6 yrsm FTND=4.4	24 h abstinence vs. satiety	Passive viewing task, block design, smoking-related vs. neutral images	Whole brain analysis	No effect
Nestor et al. (2011)	10 smokers (5 female) 10 ex-smokers (7 female) 13 nonsmokers (8 female)	No	Smokers age=23 6.7 yrsm FTND=3.2 ex-smokers age=25.4 7.7 yrsm controls age=23.6	Satiety	Attentional bias task with smoking-related or neutral images	ROI analysis	The contrast 'smoking-related images > neutral images' was greater in the left amygdala in smokers vs. controls
Okuyemi et al. (2006)	17 smokers 9 CC (5 f) 8 AA (6 f) 17 nonsmokers 9 CC (6 f) 8 AA (6 f) CC=Caucasian AA=African American	No	CC smokers age=36.7 18.9 yrsm FTND=6.1 AA smokers Age=38.6 18.5 yrsm FTND=6.0 CC nonsmokers Age=35 AA nonsmokers age=36.6	12 h abstinence	Smoking-related or neutral images were presented in a blocked design	ROI analysis	The contrast 'Smoking cues > Baseline' was greater in the left dorsal amygdala of AA than in CC
Onur et al. (2012)	28 smokers (14 female) 28 nonsmokers (14 female)	No	Smokers age=26.3 9.1 yrsm 17.1 c/d FTND=4.1 nonsmokers age=26.9	Satiety vs. overnight abstinence	Passive viewing of happy, neutral, and fearful faces	ROI analysis	In smokers abstinence reduced the activation in the right amygdala in response to fearful, but not neutral and happy, faces; the effect was more pronounced in heavy smokers
Rubinstein et al. (2011)	12 smokers (5 female) 12 nonsmokers (5 female)	No	Smokers age=16.3 3.6 c/d mFTQ=2.8 nonsmokers age=15.7	Satiety	Passive viewing task: smoking-related vs. neutral images; craving ratings between blocks	ROI analysis	In smokers smoking-related cues elicited higher left amygdala activation than neutral images
Stippekohl et al. (2010)	39 smokers: 20 deprived (10 female) 19 satiated (11 female) 17 controls (9 female)	No	Deprived smokers age=25.8 19.4 c/d FTND=4 satiated smokers Age=27.2 20.79 c/d FTND=4.6 nonsmokers age=24.6	12 h abstinence	Video stimuli in an event-related design: SAM ratings and craving ratings	ROI analysis	"Last puff"-video evoked amygdala activation bilaterally in nondeprived smokers and in the right amygdala of deprived smokers
Wilson et al. (2005)	20 smokers (0 female)	No	Condition: available $N=10$ Age=24.1 21.3 c/d 7.8 yrsm condition: nonavailable $N=10$ age=25.3 22 c/d 8.1 yrsm	8 h abstinence; Instructions: smoking available during experimental session vs. not	In vivo exposition to smoking-related or neutral cues, followed by a resting state scan.	Whole brain analysis	No effect

FTND, Fagerström Test for nicotine dependence (Heatherton et al., 1991); **S**, seconds; **h**, hours; ***yrsm***, years smoking; ***c/d***, cigarettes per day; Except Franklin et al. (2007), all reported investigations employed BOLD fMRI.

(McClernon, Hiott, Huettel, & Rose, 2005; Nestor, McCabe, Jones, Clancy, & Garavan, 2011; Okuyemi et al., 2006), and the amygdala was investigated as a ROI or within a whole brain analysis.

Mostly, pictures were used as visual stimuli (Artiges et al., 2009; David et al., 2005; Due, Huettel, Hall, & Rubin, 2002; Hartwell et al., 2011; Janes et al., 2009; Janes et al., 2010; Luijten et al., 2011; McClernon et al., 2005; McClernon et al., 2007; McClernon, Kozink, & Rose, 2008; Nestor et al., 2011; Okuyemi et al., 2006; Rubinstein et al., 2011). Two of these studies employed a passive viewing task (Okuyemi et al., 2006; Rubinstein et al., 2011) and demonstrated higher amygdala reactivity to smoking-related, as compared to neutral cues. Modified versions of the passive viewing task, including smoking cues, neutral images, and target images requiring a button press, have been used in several investigations (Due et al., 2002; Janes et al., 2009, 2010; McClernon et al., 2005, 2007, 2008). Among them, two reported significant amygdala activation for smoking-related cues (Due et al., 2002; Janes et al., 2010). Employing an active attentional-bias task, Nestor et al. (2011) reported significant amygdala reactivity to smoking-related images, whereas David et al. (2005) and Luijten et al. (2011) found no significant effect on amygdala reactivity. Using a different paradigm in which emotion recognition trials were preceded by a smoking-related or neutral images, Artiges et al. (2009) found deactivation of the amygdala after presentation of smoking cues. Alternative ways of stimulus presentation include film clips (Stippekohl et al., 2010; McBride, Barrett, Kelly, Aw, & Dagher, 2006; Brody et al., 2007), virtual reality or augmented reality scenarios (Lee, Lim, Wiederhold, & Graham, 2005), and in vivo presentation (Franklin et al., 2007; Wilson, Sayette, Delgado, & Fiez, 2005) of smoking-related stimuli. Wilson et al. (2005) reported no effect of an in vivo exposition to smoking-related, as compared to neutral, objects on amygdala activity, while Franklin et al. (2007) combined audio-video stimuli with an in vivo smoking-cue exposition to demonstrate increased amygdala reactivity to smoking-related cues. Lee et al. (2005) found no effect of smoking-related cues from a virtual reality setting on amygdala reactivity. Several studies used videos in their experimental paradigms (Stippekohl et al., 2010; McBride et al., 2006; Brody et al., 2007). Whereas Stippekohl et al. (2010) found increased amygdala responses to videos depicting the end of a smoking ritual ('last puff'), McBride et al. (2006), and Brody et al. (2007), found no such effect. Overall, passive viewing tasks, imposing no cognitive demands and without presenting target stimuli, appear at least as effective as more elaborate experimental paradigms in eliciting amygdala responses to smoking-related cues.

Among the studies employing pictorial stimuli to investigate neural reactivity to smoking-related cues, three studies (Janes et al., 2009; McClernon et al., 2005, 2008) investigated the effects of cues on abstinent *and* satiated smokers whereas the other studies investigated either abstinent (Artiges et al., 2009; David et al., 2005; Due et al., 2002; Hartwell et al., 2011; Luijten et al., 2011; McClernon et al., 2007; Okuyemi et al., 2006) or satiated (Janes et al., 2010; Kobiella et al., 2010; Nestor et al., 2011; Rubinstein et al., 2011) smokers. Five out of eight studies in satiated smokers reported increased amygdala activity to smoking-related, as compared to neutral, cues (Franklin et al., 2007; Janes et al., 2010; Nestor et al., 2011; Rubinstein et al., 2011; Stippekohl et al., 2010), whereas three did not (Brody et al., 2007; Janes et al., 2009; McClernon et al., 2005). In contrast, only one (Stippekohl et al., 2010) out of six studies employing an abstinence of 12 h or more reported significant amygdala reactivity to smoking-related cues (David et al., 2005; Janes et al., 2009; McBride et al., 2006; McClernon et al., 2005, 2008). Four studies in smokers abstinent for 2–7 h found no effect (Hartwell et al., 2011; Lee et al., 2005; Luijten et al., 2011; Wilson et al., 2005), one reported a decrease after 2 h of smoking abstinence (Artiges et al., 2009), and one demonstrated an increase in amygdala reactivity for smoking-related, as compared to neutral, cues after 10 h abstinence (Due et al., 2002). Taken together, these results suggest that amygdala reactivity to smoking-related cues is at least as high in satiety as during nicotine abstinence.

Four studies investigated the effects of actively regulating craving on amygdala reactivity to smoking-related stimuli (Brody et al., 2007; Hartwell et al., 2011; Kober et al., 2010; Jasinska et al., 2012). Brody et al. (2007) administered smoking-related or neutral videos to smokers, and instructed participants to either allow or resist craving. Amygdala activity did not differ between cigarette and neutral cues and showed no modulation by voluntary control of craving. These results were supported by Hartwell et al. (2011) in a study employing a passive viewing task with the instruction to allow or resist craving (Hartwell et al., 2011) to smoking-related cues. Kober et al. (2010) administered images of cigarettes and food (no neutral stimuli) to smokers and instructed them to regulate craving by thinking either of immediate (now) or of long-term consequences (later) of consuming the presented stimulus. Cognitive down-regulation (later) decreased amygdala activity. Jasinska et al. (2012) chose another approach and simultaneously presented auditory and visual smoking-cessation messages vs. neutral messages to smokers before an attempt to quit. They found that amygdala activity to smoking-cessation messages, as compared to neutral ones, was positively correlated with the success of smoking cessation. Taken together, the literature presents limited evidence suggesting that amygdala reactivity to smoking-related simuli can be suppressed by cognitive strategies to resist craving and that amygdala activity to smoking-cessation messages is a prerequisite of successful smoking cessation.

Surprisingly, across studies neither the FTND score nor the number of cigarettes smoked per day, age, or craving scores reliably influenced the amygdala reactivity to smoking-related cues. However, statistical power (ROI-based vs. whole brain analysis) did have an impact. Thus, altered amygdala reactivity for smoking cues was reported in ten out of twelve studies employing ROI analysis: Due et al. (2002), Franklin et al. (2007), Janes et al. (2010), Nestor et al. (2011), Okuyemi et al. (2006), Rubinstein et al. (2011), and Stippekohl et al. (2010) reported increased amygdala activity, Kober et al. (2010) showed that cognitively resisting craving decreases amygdala activation, McClernon et al. (2007) demonstrated decreased amygdala activity after a smoking cessation trial, and Artiges et al. (2009) reported a decrease in amygdala activity after presentation of smoking-induced stimuli, while McBride et al. (2006) and McClernon et al. (2005) found no effect. In contrast, none of eight studies using whole brain analyses found a significant alteration of amygdala activity (Brody et al., 2007; David et al., 2005; Hartwell et al., 2011; Janes et al., 2009; Lee et al., 2005; Luijten et al., 2011; McClernon et al., 2008; Wilson et al., 2005). In keeping with this, Engelman et al. (2011) showed that excluding ROI-based reports from a meta-analysis yields no significant amygdala or nucleus accumbens activation to smoking-related cues.

While amygdala activation to 'appetitive', smoking-related, stimuli was challenged by numerous studies, so far, only two BOLD fMRI investigations specifically examined amygdala reactivity to smoking-irrelevant although emotionally evocative stimuli. This is surprising, since the amygdala's response to emotionally salient stimuli, and facial expressions of emotion in particular, are very robust and present an excellent tool for the study of smoking-related change in amygdala functioning (Rosen & Donley, 2006). Using a passive viewing task, Onur et al. (2012) found that overnight abstinence decreased the amygdala response to fearful, but not to happy or neutral facial expressions in smokers. Importantly, nicotine dependence, as measured by the FTND, was correlated with a decrease in the amygdala's reactivity to fearful faces, an effect that was most pronounced in heavy smokers. Consistent with this, Kobiella et al. (2010) employed neutral and emotionally evocative images to demonstrate

permanently reduced amygdala reactivity to unpleasant stimuli in smokers.

2.2. Resting state amygdala activity during satiety, nicotine abstinence, and the effects of acute nicotine administration

Smoking-related alterations in amygdala resting state activity have been investigated by arterial spin-labeled perfusion MRI (ASL) and positron emission tomography studies (PET) studies, summarized in Table 2. ASL techniques allow the measurement of absolute regional cerebral blood flow without exposing participants to radiation as is the case in PET studies (Reardon, 2011; Wilson, 2011). When assessing resting state ASL in chronic smokers after overnight smoking deprivation in comparison to smoking as usual, Wang et al. (2007) found no global effect of abstinence-induced craving on amygdala regional cerebral blood flow (rCBF). However, there was a positive correlation between abstinence-induced craving and absolute rCBF changes in the bilateral amygdala. Thus, as craving increased during smoking abstinence, so did rCBF in the bilateral amygdala. This finding is of a particular importance as it suggests that interindividual variance in the experience of craving moderates the effects of abstinence on resting state-amygdala activity.

PET measures the effects of a radioactive isotope attached to a biologically relevant compound. Among the numerous PET radiotracer protocols available, nicotine and tobacco studies summarized here have employed those for measuring global and regional cerebral blood flow ($[^{15}O]H_2O$), and glucose metabolism ($[^{18}F]$FDG). With one exception (Rose et al., 2007) all PET studies described in the following have generally followed a similar design: chronic cigarette smokers were asked to remain abstinent overnight; abstinence was verified by a measurement of exhaled carbon monoxide (CO); deprived smokers were treated with placebo or nicotine; and resting state brain activity was measured subsequently. Thus, participants were not engaged in a particular behavioral task. Furthermore, it is noteworthy that the majority of PET studies evaluating the effects of nicotine and smoking on the rCBF have reported normalized rCBF values, which are expressed as a regional change in blood flow relative to a global value for the entire brain or a baseline value for a specific control region (Brody, 2006; McClernon & Gilbert, 2004).

A study employing the $[^{15}O]H_2O$ PET protocol to measure rCBF (Domino et al., 2000a) contrasted the effects of a nicotine spray with placebo spray after an overnight abstinence in chronic smokers. No significant modulation of amygdala activity was found. A study employing $[^{18}F]$FDG PET to measure rCBF in smokers following overnight abstinence (Domino et al., 2000b) found no significant modulation of amygdala activity by a nicotine-containing spray relative to placebo. Both studies (Domino et al., 2000a; 2000b) used whole brain analyses to test for significant effects of nicotine abstinence on amygdala activity. Another study, employing a $[^{15}O]H_2O$ PET protocol and a ROI-based analysis to compare the effects of a nicotine spray with a placebo spray in chronic smokers after overnight abstinence showed a decrease in right amygdala rCBF after nicotine administration (Zubieta et al., 2001).

Using the $[^{15}O]H_2O$ PET protocol to compare denicotinized with nicotine-containing cigarettes, Rose et al. (2003) found a dose-dependent rCBF decrease in the left amygdala after smoking a nicotine-containing cigarette. Using a similar experimental protocol (denicotinized cigarettes, nicotine-containing cigarettes, and intravenous nicotine injections), Domino et al. (2004) detected no significant change in amygdala rCBF. Zubieta et al. (2005) showed that after overnight deprivation, smoking a nicotine-containing cigarette decreased rCBF in the bilateral amygdala, as compared to smoking a denicotinized cigarette.

Using a combined $[^{15}O]H_2O$ and $[^{18}F]$FDG PET scan, Rose et al. (2007) investigated chronic smokers under three experimental conditions: at baseline (1); after one week of smoking denicotinized cigarettes while using nicotine patches (2); and after returning to usual brand cigarettes (3). To quantify brain activity changes, the mean rCBF from conditions (1) and (3) was compared to rCBF from condition (2). $[^{15}O]H_2O$ was measured during resting state, while $[^{18}F]$FDG measurements were performed during a cognitive task similar to the '1-back' working memory task. Finally, changes in rCBF were correlated with changes in behavioral indices, such as enjoying the taste and smell of smoke, or smoking to calm down. This study showed that after one week of smoking denicotinized cigarettes a decrease in smoking pleasure (as a result of reduced taste and smell) and the absence of tranquilization and mood stabilization were both associated with an increase in amygdala activity, an effect that was particularly strong in men.

Taken together, four PET studies reported that resting state amygdala activity increases during nicotine abstinence (Rose et al., 2003; 2007; Zubieta et al., 2001; 2005), and three studies found no effect of abstinence on amygdala rCBF (Domino et al., 2000a; 2000b; Domino et al., 2004), while none reported a significant decrease in amygdala rCBF during abstinence. Interestingly, three out of the four studies demonstrating significantly enhanced amygdala rCBF during abstinence employed ROI-based analyses (Zubieta et al., 2001; Rose et al., 2003; 2007), while all three studies reporting no effect of abstinence on amygdala rCBF relied on whole brain analyses. This raises the possibility that abstinence induces a moderate increase in amygdala rCBF, which requires adequate statistical power (as in ROI-based analysis) in order to be reliably detected. Employing ASL, Wang et al. (2007) demonstrated that in the absence of a global abstinence-induced alteration, amygdala activity correlates positively with abstinence-induced craving. Interindividual differences in nicotine dependence and related nicotine consumption (amount of cigarettes smoked per day) might, indeed, account for a part of the variance in results reported in the literature. Accordingly, studies reporting no global effect of abstinence on amygdala rCBF investigated samples with lower numbers of cigarettes smoked per day (16.1 in Domino et al., 2004; 16.9 in Wang et al., 2007; 22.5 in Domino et al., 2000a, b), as compared to those demonstrating an abstinence-induced increase in amygdala activity (15.8 in Zubieta et al., 2005; 21 in Zubieta et al., 2001; 23 in Rose et al., 2007; 28 in Rose et al., 2003). Furthermore, differences in study results may reflect, at least in part, various methodological differences, including the PET protocol ($[^{15}O]H_2O$ vs. $[^{18}F]$FDG), or the type of nicotine application (spray vs. cigarettes). Thus, cigarette smoke per se can inhibit monoamine oxidase (MAO), thereby exerting antidepressant-like mood-lifting activity and reducing some of the affective symptoms of smoking withdrawal (Fowler et al., 1996a; Fowler et al., 1996b). Moreover, personality-related variables, as have been discussed for many other psychotropic agents (Caspi et al., 2005; Dalley et al., 2007; Hamidovic, Dlugos, Skol, Palmer, & de Witt, 2009; Ludwig, Mihov, & Schwarting, 2008; Retey et al., 2007; Reuter et al., 2002; Schumacher et al., 2009) might have contributed to the variable study results.

2.3. The amygdala and smoking-related effects on executive functions

The effects of smoking and smoking abstinence on human performance have been extensively studied. A comprehensive review of the nicotine and human cognitive performance literature, examining papers published between 1970 and 1993 (Heishman et al., 1994), concluded that in nonsmokers nicotine produces absolute enhancement of finger tapping rate and motor responses in brief tests of attention, while abstinent smokers

Table 2
Synopsis of human neuroimaging studies of amygdala function during smoking withdrawal.

Authors	Technique	Sample	Sample characteristics	Abstinence	Analysis	Task	Results
Domino et al. (2000)	PET: FDG	11 smokers (0 female)	Age=34 22.5 c/d	Overnight abstinence: nicotine spray vs. placebo spray	Whole brain analysis	Resting state	No effect reported
Domino et al. (2000)	PET: H_2O	18 smokers (9 female)	Age range: 18–52 15–40 c/d	Overnight abstinence: nicotine spray vs. placebo spray	Whole brain analysis	Resting state	No effect
Domino et al. (2004)	PET: H_2O	19 smokers	Age=26 16.1 c/d	Overnight abstinence: research tobacco cigarettes with an average (1.0 mg) or reduced (0.08 mg) nicotine	Whole brain analysis	Resting state	No effect
Rose et al. (2003)	PET: H_2O	18 smokers (4 female)	Age=39 28 c/d	Overnight abstinence: nicotine-containing cigarettes vs. denicotinized cigarettes vs. intravenous injection of nicotine	ROI analysis	Resting state	Interaction of hemisphere and dose: nicotine dose-dependently decreased rCBF in the left amygdala and increased (a trend towards significance) rCBF in the right amygdala.
Rose et al. (2007)	PET: H_2O PET: FDG	15 smokers (9 female)	Age=36.7 23 c/d Sessions 1 and 3: FTND=6.8 SJ=5.9 Session 2: FTND=6.4 SJ=5.2	Three conditions: (1) Baseline; (2) After 1 week of smoking denicotinized cigarettes with nicotine patches; (3) one week after return to usual brand cigarettes	ROI analysis	Task similar to the '1-back'	An increase in the rCBF of condition (2), as compared to the mean of conditions (1) and (3), was associated with a decrease in the calming effect of smoking (in the left amygdala) and a decrease in enjoying the taste and smell of the smoke (in the right and left amygdala), respectively.
Wang et al. (2007)	ASL MRI	15 smokers (8 female)	Age=38.9 16.9 c/d FTND=4.9 four-point Likert scale for craving: Abstinence=3.6 satiety=0.7	Satiety vs. overnight abstinence	Whole brain analysis	Resting state	Abstinence had no effect on amygdala activity (whole brain analysis). Individual subjective abstinence-induced craving ratings were positively correlated with abstinence-induced increase in amygdala CBF.
Zubieta et al. (2001)	PET: H_2O	18 smokers (8 female)	Age=32 21 c/d FTND=5.2	Overnight abstinence: nicotine spray vs. placebo spray	ROI analysis	Resting state	Nicotine application decreased rCBF in the right amygdala
Zubieta et al. (2005)	PET: H_2O	19 smokers (11 female)	Age=27 15.8 c/d Craving visual analogu scale (0–10): Significant reduction after the first cigarette, no significant differences in craving thereafter	Overnight abstinence Scan 1, baseline; scan 2, after inhalation of the first cigarette; scan 3, baseline; scan 4, after inhalation of the second cigarette; scan 5, baseline; scan 6, after inhalation of the third cigarette Smoking nicotine-containing cigarettes (1 mg) vs. denicotinized (0.08 mg) cigarettes. The first cigarette was always a nicotine-containing cigarette, the second and third were a nicotine-containing and a denicotinized one, in a randomized order	Whole brain analysis liberal threshold	Resting state	Smoking a nicotine-containing cigarette decreased rCBF in the bilateral amygdala, as compared to smoking a denicotinized cigarette.

FTND, Fagerström test for nicotine dependence (Heatherton et al., 1991); ***c/d***, cigarettes per day; ***SJ***, Shiffman-Jarvik score (Shiffman & Jarvik, 1976). All studies were carried out in non treatment-seeking subjects, with two exceptions: Rose et al. (2003) offered their subjects free participation in a smoking cessation trial as a part of the compensation for study participation; Rose et al. (2007) informed their subjects about ongoing smoking cessation trials in their research group.

show greater frequency of nicotine enhancement in sensory abilities, finger tapping, selective, and sustained attention. A more recent review on the cognitive effects of tobacco smoke and nicotine emphasized that improved performance and reaction times on tasks that require vigilant attention is the most commonly replicated cognitive effect of nicotine administration in nicotine dependent smokers (Swan & Lessov-Schlaggar, 2007). This view was further substantiated by a meta-analysis (Heishman et al., 2010) which showed that nicotine enhances performance in six executive domains, four of which are related to attention and motor response (alerting attention-accuracy and response time, orienting attention response time, short-term episodic memory-accuracy, and working memory response times). Importantly, individuals with attention-related cognitive deficits are more likely to benefit from the procognitive effects of nicotine (Kumari & Postma, 2005; Newhouse, Potter, & Singh, 2004; Newhouse et al., 2004). Indeed, smoking prevalence in schizophrenia, which is associated with severe deficits in the abovementioned executive domains, is reported to be as high as 60–90% (Aubin et al., 2011; Dome et al., 2010). Importantly, there is mounting evidence that the amygdala is involved in the vigilance-related cognitive functions which are enhanced by nicotine or/and impaired by smoking withdrawal, including most of the executive domains affected by smoking abstinence (Holland & Gallagher, 1999; Schaefer et al., 2006; Schaefer & Gray, 2007; Whalen, 1998). The amygdala functions, at least in part, in the acquisition of an increased state of non-specific attention or arousal to enhance sensory processing (Holland & Gallagher, 1999; Kapp, Whalen, Supple, & Pascoe, 1992). In support of this, across species electrical stimulation of the amygdala has been shown to facilitate attention or cognitive processes associated with increased attention. Importantly, this function is mediated, at least in part, via acetylcholine receptor signaling, which is enhanced by smoking (Everitt & Robbins, 1997). Individual differences in amygdala activity, for instance, have been shown to alter reaction times but not accuracy in a working memory task, which parallels the specific impairment in reaction times, but not accuracy, in abstinent smokers (Schaefer et al., 2006).

While the evidence on the involvement of the amygdala in vigilance-related executive functions is still growing, it is now widely accepted that the amygdala registers events of biological significance, especially threat (Adolphs et al., 1994; LeDoux, 2007). Laboratory animal studies have shown impaired fear expression and avoidance behavior after amygdala lesions in monkeys (Kluver & Bucy, 1939; Weiskrantz, 1956; Aggleton & Passingham, 1981; Kalin, Shelton, Davidson, & Kelley, 2001) and rodents (Blair, Sotres-Bayon, Moita, & Ledoux, 2005; Blanchard & Blanchard, 1972; Gale et al., 2004; LeDoux, 2000). Imaging studies in humans have consistently demonstrated the involvement of the amygdala in fear conditioning (Büchel & Dolan, 2000; Büchel, Morris, Dolan, & Friston, 1998; Cheng, Knight, Smith, Stein, & Helmstetter, 2003; Dolan, 2002; Knight, Smith, Cheng, Stein, & Helmstetter, 2004; LaBar, LeDoux, Spencer, & Phelps, 1995; LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998; Phelps & Anderson, 1997). Consistently, humans with amygdala damage display profound impairments in fear conditioning (Bechara et al., 1995; LaBar et al., 1995) and the experience of fear (Feinstein, Adolphs, Damasio, & Tranel, 2011). Furthermore, in humans amygdala damage is associated with impaired recognition of social-emotional communication of fear and threat (Adolphs et al., 1994; Anderson & Phelps, 2000; Becker et al., 2012; Hurlemann et al., 2007) and impaired facilitation of explicit memory for unpleasant emotional stimuli (Cahill, Babinsky, Markowitsch, & McGaugh, 1995; Hamann, 2001; Strange, Hurlemann, & Dolan, 2003). Amygdala damage eliminates monetary loss aversion (De Martino, Camerer, & Adolphs, 2010) and the associated autonomic reaction (Bechara, Damsio, Damasio, & Lee, 1999). The amygdala is critically involved in generating autonomic activation as a 'somatic marker' to aid decision making (Bechara & Damasio, 2005; Gospic et al., 2011; Paton, Belova, Morrison, & Salzman, 2006; Scheele et al., 2012; Seymour & Dolan, 2008). This notion is consistent with numerous reports on impaired decision-making during smoking abstinence (Field, Santarcangelo, Sumnall, Goudie, & Cole, 2006; Mitchell, 2004; Ohmura, Takahashi, & Kitamura, 2005). In this regard, reduced amygdala reactivity to emotionally evocative aversive stimuli (Onur et al., 2012; Kobiella et al., 2010) can be viewed as a functional impairment, resulting in the inability to detect environmental dangers and/or to integrate them in appropriate goal-directed behavioral responses. More generally, transiently diminished amygdala reactivity during smoking abstinence may compromise threat perception and reduce the effectiveness of public health awareness campaigns based on fear appeals, such as warning labels on cigarette packaging depicting the fatal consequences of cigarette smoking, such as described by Reardon (2011) and Wilson (2011), from having their intended effect to promote abstinence (Onur et al., 2012). This concept is further supported by the observation that amygdala reactivity to smoking-cessation messages correlates positively with the success of a smoking cessation attempt (Jasinska et al., 2012).

3. Conclusions

To our knowledge, this is the first review dedicated to altered amygdala function in smokers. The literature on abstinence-induced changes in resting state activity suggests an increased rCBF in the amygdala after overnight abstinence. Given the predictive value of abstinence-induced cravings, it would be intriguing to investigate whether abstinence-induced resting state amygdala activation can serve as a neural marker for the risk of relapse. Furthermore, in smokers, amygdala reactivity is greater for smoking-related, as compared to neutral, cues. This finding appears to be at least as robust in satiated smokers administered a simple passive viewing task, as in more elaborate experimental paradigms. Intriguingly, we found no convincing evidence that the number of cigarettes smoked daily or nicotine dependence as measured by the FTND moderates amygdala reactivity to smoking-related cues (although amygdala responses to smoking cues has been shown to decrease during a smoking cessation trial). Importantly, ROI analysis-based studies found enhanced amygdala reactivity to smoking cues more often than studies employing whole brain analyses, suggesting that amygdala reactivity to smoking-associated cues requires sufficient power to be detected. Smoking cue-elicited amygdala activation has been implicated as a neural marker of the risk for relapse after smoking cessation attempt by one study—an important finding which needs to be replicated. Some limited evidence suggests that amygdala reactivity to smoking-associated cues can be reduced by the application of cognitive strategies to resist craving. Two investigations have independently demonstrated reduced amygdala reactivity to harm signals in smokers. Based on the latter findings, we propose that aberrant amygdala reactivity critically contributes to the nicotine withdrawal syndrome. Specifically, impaired processing of threat signals and reduced expression of harm avoidance behavior during withdrawal may contribute to the high smoking relapse-rates during abstinence. Furthermore, it is conceivable that blunted amygdala reactivity contributes to the impairment in both self-protective avoidance behavior and vigilance-related executive deficits in smokers. This notion is consistent with the recent observation that amygdala activity to smoking-cessation messages is positively correlated with the success of a smoking cessation attempt.

Clearly, further research is needed to investigate the validity of these findings. Pinpointing the neurochemical substrates of altered amygdala function in chronic smoking presents another challenge for future research. Currently, a major methodological problem is that we cannot determine whether alterations in amygdala activity during smoking withdrawal reflect a pre-existing vulnerability, the consequences of chronic nicotine exposure, or an interaction of both aspects. This issue could be addressed by prospective longitudinal investigations. Finally, the evidence we present questions the effectiveness of tobacco packaging warning messages in smokers (Reardon, 2011; Wilson, 2011). Understanding the etiology and functional impact of amygdala dysfunction in smoking may help to improve the efficacy of smoking cessation programs and reduce its enormous burden on the health-care and economic systems worldwide.

Conflicts of interest

The authors report no competing biomedical financial interests or personal affiliations in connection with the content of this manuscript.

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