Not all smokers appear to seek nicotine for the same reasons: implications for preclinical research in nicotine dependence

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ABSTRACT

Tobacco use leads to 6 million deaths every year due to severe long-lasting diseases. The main component of tobacco, nicotine, is recognized as one of the most addictive drugs, making smoking cessation difficult, even when 70 percent of smokers wish to do so.

Clinical and preclinical studies have demonstrated consistently that nicotine seeking is a complex behavior involving various psychopharmacological mechanisms. Evidence supports that the population of smokers is heterogeneous, particularly as regards the breadth of motives that determine the urge to smoke.

Here, we review converging psychological, genetic and neurobiological data from clinical and preclinical studies supporting that the mechanisms controlling nicotine seeking may vary from individual to individual. It appears timely that basic neuroscience integrates this heterogeneity to refine our understanding of the neurobiology of nicotine seeking, as tremendous progress has been made in modeling the various psychopharmacological mechanisms driving nicotine seeking in rodents.

For a better understanding of the mechanisms that drive nicotine seeking, we emphasize the need for individual-based research strategies in which nicotine seeking, and eventually treatment efficacy, are determined while taking into account individual variations in the mechanisms of nicotine seeking.

Keywords animal model, cue, individual differences, nicotine, seeking, self-administration.

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Tobacco is recognized as one of the most addictive products, with more than 70 percent of smokers wishing to quit (National Center for Health Statistics 2012) and less than 10 percent succeeding without medical support (Rigotti 2012). Although tobacco dependence is not associated with obvious behavioral disruptions, alleviating it is a major public health concern and a main societal challenge, as it produces severe long-lasting health-related problems (WHO 2015). Available therapies for smoking cessation have limited efficacy (Schuit et al. 2017), warranting the need for developing better therapeutic strategies, which depend on understanding the mechanisms that underlie tobacco dependence. Compromising this pursuit, tobacco dependence in humans has been difficult to define (Hiroi & Scott 2009; Piper 2015; Potvin et al. 2015) as attested by the various available diagnostic tools assessing different dimensions of smoking behavior (Shiffman, Waters, & Hickcox 2004; Etter 2005; Hiroi & Scott 2009; Baker et al. 2012). Despite that diagnostic tools in addiction should help clinicians in tailoring treatment for drug cessation (West & Miller 2011), accumulating evidence suggests that those developed for tobacco dependence are often incongruent between each other, and none of them accurately and consistently predicts cessation or treatment outcome against tobacco dependence (Heatherton et al. 1989; Breslau & Johnson 2000; Patten et al. 2001; Etter, Le Houezec, & Perneger 2003; Etter 2005; Baker et al. 2007; Donny & Dierker 2007; Hiroi & Scott 2009; Courvoisier & Etter 2010). This apparent inefficacy may be due to their inability to directly assess the heterogeneity of the population of smokers, which has been observed and reviewed repeatedly (Kassel et al. 1994; Hiroi & Scott 2009; Conway et al. 2010; Courvoisier & Etter 2010; Baker et al. 2012; Loukola...
et al. 2014; Hall et al. 2015; Potvin et al. 2015), particularly as regards the breadth of motives and mechanisms that determine the urge to smoke (Donny et al. 2008; Hiroy & Scott 2009; Conway et al. 2010).

It is acknowledged that a major motive for smoking is seeking for nicotine, which is recognized as the main psychoactive compound of tobacco responsible for dependence (Benowitz 1992). The paradoxical contrast between the strong addictive profile of tobacco and the relatively weak primary reinforcing effect of nicotine (Caggiula et al. 2001; Rose 2006) has been explained by both clinical and preclinical studies consistently demonstrating that complex interactions between environmental cues and nicotine also play a critical role in promoting and maintaining nicotine seeking (Shiffman et al. 2012; Bani, Andorn, & Heidbreder 2014; McClernon et al. 2015; Stoker & Markou 2015; Shiffman, Dunbar, & Ferguson 2015). As comprehensively described by Rupprecht et al. (2015), data support that smokers would seek nicotine (1) for its primary reinforcing effects; (2) for its ability to relieve withdrawal symptoms; (3) in response to external or internal cues, which have acquired the ability to promote nicotine seeking due to their Pavlovian association with the primary reinforcing effects of nicotine, or the alleviation of withdrawal; and (4) for its ability to enhance the reinforcing value of natural reinforcers or the incentive value of environmental stimuli that have acquired reinforcing properties through conditioning to primary reinforcers.

Most studies in tobacco addiction have explored these mechanisms of nicotine seeking from what is inferred from the mean observations in their study populations. Over the last 15 years, preclinical addiction research, in particular in regards to cocaine, has shown an interest for individual variability in factors governing initial drug intake, transition to habitual use and the progression to compulsive drug use (Piazza et al. 1998, 2000; Deroche-Gamonet, Belin, & Piazza 2004; Kasanetz et al. 2010, 2013; Bardo, Neise wander, & Kelly 2013; Lenoir et al. 2013; Piazza & Deroche-Gamonet 2013; Pelloux, Murray, & Everitt 2015). Despite their possible relevance, individual variations in the previously mentioned mechanisms contributing to nicotine seeking have been scarcely explored in human or animal research on nicotine dependence, while they may contribute to explain the heterogeneity of smoking behavior (Baker et al. 2012), the inconsistent relationship between craving and smoking cessation outcome (Wray, Gass, & Tiffany 2013), the limited therapeutic predictive validity of the existing preclinical models (Lerman et al. 2007; O’Dell & Khroyan 2009; Le Foll et al. 2014; Schuit et al. 2017), the limited reliability of diagnostic clinical tools (Hiroy & Scott 2009) and the inconsistent success of approved therapies for tobacco cessation (Schuit et al. 2017). Based on this premise, we recently emphasized the need for an individual-based preclinical research on the mechanisms of nicotine seeking (García-Rivas, Cannella, & Deroche-Gamonet 2016).

Here, we present a review of behavioral and neurobiological data, both clinical and preclinical, that support the role of individual variations in the mechanisms underlying nicotine seeking. Experimental disentangling of the psychopharmacological mechanisms of nicotine seeking is complex, as some of these mechanisms are intimately linked and are difficult to be distinguished one from the other. Nevertheless, considering the decisive steps that have been taken in preclinical modeling of nicotine seeking and in molecular characterization of nicotine targets over the last 30 years, we propose that conditions are met for starting to explore individual variations in the mechanisms of nicotine seeking and their consequence in research strategies on therapeutic targets. Table 1 summarizes the different nicotine-related domains, in which individual variations from the acknowledged mean observation have been evidenced in tobacco smokers, as well as related relevant preclinical observations.

**PSYCHOPHARMACOLOGICAL MECHANISMS OF NICOTINE SEEKING**

Through the activation of nicotinic cholinergic receptors (nAChRs) in the dopaminergic neurons in the ventral tegmental area (VTA), nicotine directly increases dopamine release in the nucleus accumbens (NAcc) (Kenny & Markou 2006), which is thought to be central for the rewarding actions of nicotine that underlie positive reinforcement of tobacco use (Corrigall, Coen, & Adamson 1994; Ikemoto, Qin, & Liu 2006; Peng et al. 2017). However, there is plenty of evidence that the rewarding effects of nicotine are relatively poor, in comparison with other psychostimulants (Risner & Goldberg 1983; Caggiula et al. 2001). Furthermore, nicotine can produce very unpleasant aversive effects such as nausea and vomiting at high doses in regular smokers, but also particularly during the first cigarette ever smoked (Sartor et al. 2010; Agrawal et al. 2014). Why would then individuals sustain volitional administration of nicotine chronically? Factors other than the balance of nicotine reward and aversion seem to play a role. Since nAChRs are largely distributed in the central nervous system (Changeux 2010; Brunzell, Stafford, & Dixon 2015), nicotine can enhance cognitive function (Levin 1992; Warburton 1992; Sutton et al. 2016), regulate mood and affect (Kassel et al. 2007) and regulate appetite and body weight (Bowen, Eury, & Grunberg 1986; Grunberg, Popp, & Winders 1988; Huang, Xu, & van den 2011), all of which have been self-reported as primary sources of reinforcement by nicotine and motivations for smoking (Pulvers et al. 2014;
Table 1  Evidence of individual differences affecting nicotine seeking. Most studies in tobacco addiction have explored the mechanisms of nicotine seeking from what is inferred from the mean observations in their study populations. Summarized in this table is selected evidence of individual differences in domains that impact nicotine seeking in humans, as well as preclinical observations that can shed light on the mechanisms of this inter-individual variability. Highlighted in bold are the rare preclinical studies that have directly explored individual differences in nicotine seeking.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Well-known mean observation</th>
<th>Clinical evidence for individual differences</th>
<th>Preclinical observations</th>
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<tr>
<td>NICOTINE REWARD</td>
<td>Primary reinforcing effects, although much less than other psychostimulants (Risner &amp; Goldberg 1983; Caggiula et al. 2001)</td>
<td>- Carriers of CHRNA4 rs6122429 allele: ↑experience of euphoria after cigarette (Hutchison et al. 2007)</td>
<td>- Hypersensitive alpha4-containing nAChRs ↑ the rewarding properties of acute nicotine (Tapper et al. 2004)</td>
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<td>- Carriers of CHRNA4 rs2236196 allele: ↑experience of euphoria after cigarette (Hutchison et al. 2007), ↑probability of being a smoker (Li et al. 2005; Breitling et al. 2009; Esterlis et al. 2016), ↑cession outcome when using nicotine nasal spray (Hutchison et al. 2007)</td>
<td>- KO of alpha4 subunit in the ventral midbrain ↓nicotine self-administration (Pons et al. 2008) and nicotine place preference (Peng et al. 2017)</td>
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<td>- Naturally-occurring CHRNA4 A529T SNP in mice: ↓sensitivity to nicotine reward (Butt et al. 2005; Wilking et al. 2010)</td>
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<td>- CHRNA5 rs16969968 allele introduced in mice ↓sensitivity to rewarding effects of low doses of nicotine, compared to WT (Frahm et al. 2011; Morel et al. 2014)</td>
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<td>- KO of alpha5 subunit ↓nicotine self-administration in mice, but rescued after reintroduction of alpha5 in medial habenula, key structure mediating aversion to nicotine (Fowler et al. 2011)</td>
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<td>- In rats previously selected according to their high incentive salience to food cues (‘sign trackers’), a nicotine-associated cue was a stronger conditioned reinforcer than in ‘goal trackers’ (Yager &amp; Robinson 2015).</td>
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<td>NICOTINE AVERSION</td>
<td>Aversive effects that can limit volitional administration at high doses (Norton &amp; Barske 1977)</td>
<td>- Increased aversive side effects after first cigarette linked to ↓risk for nicotine dependence (Sartor et al. 2010; Hoft et al. 2011; Svyryd et al. 2016)</td>
<td>- KO of alpha5 subunit ↓nicotine self-administration in mice, but rescued after reintroduction of alpha5 in medial habenula, key structure mediating aversion to nicotine (Fowler et al. 2011)</td>
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<td>- Carriers of CHRNA5 rs16969968 risk allele: ↓aversive symptoms after acute nicotine administration (Jensen et al. 2015)</td>
<td>- Overexpression of beta4 subunit in the medial habenula ↓nicotine self-administration in rodents, which is rescued with introduction of CHRNA5 rs16969968 allele (Frahm et al. 2011)</td>
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<td>NICOTINE-ASSOCIATED CUES</td>
<td>Nicotine establishes paired environmental cues as conditioned reinforcers (Caggiula et al. 2001; Cohen et al. 2005; Feltenstein et al. 2012)</td>
<td>- Carriers of CHRNA5 rs16969968 risk allele: ↓cue-reactivity to smoking cues (Janes et al. 2012)</td>
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NICOTINE-INDUCED ↑ IN ATTENTION TO ENVIRONMENTAL CUES
Nicotine ↑ the attention to environmental cues (Witte et al. 1997)
- Carriers of CHRNA4 rs1044396 allele: ↑ risk for nicotine dependence (Feng et al. 2004; Kamens et al. 2013), ↓ basal visuospatial attention performance, but which ↑ after nicotine exposure (Ahrens et al. 2015; Behler et al. 2015)
- Nicotine ↑ attentional performance to visual cues, but only in individuals that have poor attentional performance baseline (Hammersley et al. 2016)

NICOTINE-INDUCED ↑ OF INCENTIVE SALIENCE FOR REINFORCING ENVIRONMENTAL CUES
Nicotine ↑ the incentive value of environmental non-drug reinforcers (Caggiula et al. 2009; Grimm et al. 2012; Palmatier et al. 2013a,b; Perkins & Karelitz 2013a,b)
- Individuals with low hedonic capacity have ↑ risk for tobacco use and dependence, possibly due to nicotine incentive-enhancing effects (Perkins 2009; Audrain-McGovern et al. 2012; Leventhal 2016; Perkins et al. 2017)

NICOTINE METABOLISM
Nicotine is metabolized to cotinine and has a half-life of 2 hours (Hukkanen, Jacob, & Benowitz 2005).
- Speed of nicotine metabolism predicted nicotine reinforcement threshold and degree of compensation when unit dose of nicotine was reduced in rats (Grebenstein et al. 2015).

SLOW NICOTINE METABOLIZERS:
- ↓ cigarettes smoked (Styn et al. 2013; Wassenaar et al. 2011).
- ↑ cessation success with NRTs (Kaufmann et al. 2015; Mammou et al. 2015)
Fast nicotine metabolizers:
- ↑ cigarettes smoked, attempting to titrate falling nicotine plasma levels (Olfson et al. 2016)
- ↑ risk for nicotine dependence in adulthood (Wassenaar et al. 2011; Sofuoglu et al. 2012)
- ↑ cue-reactivity to smoking cues, compared to slow metabolizers (Tang et al. 2012; Falcone et al. 2016)

PSYCHOLOGICAL TRAITS MODULATING NICOTINE SEEKING
Novelty/sensation seeking, anxiety and impulsivity/poor decision making can be associated with increased risk for tobacco dependence (Falco & Bevins 2015)
Controversial data:
- High impulsivity is associated with high smoking relapse only in subjects with high cue-induced craving (Bourque et al. 2013; Erblich & Michalowski 2015)
- Carriers of CHRNA3 rs578776 allele: amount of nicotine consumed correlates with functional coupling in circuitry associated with risky decision making (Hong et al. 2010, Wei et al. 2016)

- High impulsive rats show ↑ cue-induced relapse and ↓ control of nicotine seeking during self-administration under increasing workload (Diergaarde et al. 2012) and during abstinence (Diergaarde et al. 2008).
Hall et al. 2015). In addition, avoidance and/or relief of pharmacological withdrawal from nicotine can be a major reinforcing effect of nicotine driving smoking behavior (Hughes 2007; Allen et al. 2008; Scott & Hiroi 2011).

Abundant evidence also suggests that the role of surrounding cues accompanying nicotine intake is pivotal to nicotine seeking, much more than in other drugs of abuse (Caggiula et al. 2001; Donny et al. 2003; Rupprecht et al. 2015). Clinical evidence shows that the sight, smell or touch of cigarettes, observing others smoking, visiting the habitual places for smoking or consuming alcoholic beverages might act as powerful motivators for nicotine seeking (Niaura et al. 1992; Conklin & Tiffany 2001; Van Gucht et al. 2010; Shiffman et al. 2015). Behavioral rituals in anticipation to smoking, such as rolling a cigarette, can by themselves trigger craving (Baker et al. 2006; Perkins et al. 2008), and expectation of withdrawal, as well as expectation of tobacco availability, can trigger nicotine craving (Wertz & Sayette 2001; Dar et al. 2010; Scott & Hiroi 2011). On this regard, in some smokers, the use of non-nicotine-containing electronic cigarettes can decrease craving (Van Heel et al. 2017), most probably through the sensorimotor cues accompanying smoking. The powerful role of nicotine-associated cues in modulating nicotine seeking has also been demonstrated in rodents self-administering nicotine: nicotine alone is poorly self-administered, but when its delivery is paired with a discrete cue light, self-administration is enhanced synergistically (Caggiula et al. 2001; Donny et al. 2003). Alone, the cue can maintain self-administration over an extended number of sessions; the behavior resisting to extinction much longer than for the other drugs of abuse (Cohen et al. 2005). Additionally, in rats trained to extinguish seeking for both nicotine and associated cue, only presentation of both nicotine and cue induces a strong reinstatement, with a weaker effect of nicotine and cue when presented alone (Feltenstein, Ghee, & See 2012).

The first mechanism evoked for this control of nicotine seeking by cues is the establishment of paired environmental cues as strong conditioned reinforcers driving nicotine seeking through Pavlovian conditioning. More recently, it was evidenced that nicotine can further increase the incentive value of these classically conditioned cues through a non-associative mechanism (Palmatier et al. 2007), which also applies to, and has been particularly characterized for, non-nicotine conditioned cues. Indeed, nicotine can increase the incentive value of sensory cues that have gained secondary reinforcing properties after association with a primary reinforcer, such as sucrose (Chaudhri et al. 2006; Liu et al. 2007; Palmatier et al. 2007, 2013; Caggiula et al. 2009; Grimm et al. 2012). Nicotine also directly enhances the reinforcing effect of non-drug or drug reinforcers (Grimm et al. 2012; Palmatier, O’Brien, & Hall 2012). Supporting a non-associative mechanism, it is also noteworthy that these effects of nicotine can occur in nicotine-naïve individuals, suggesting that it is part of the acute psychopharmacology of nicotine, does not involve a learning process and is not due to nicotine dependence (Rupprecht et al. 2015; Perkins, Karelitz, & Boldry 2017).

The term initially used to define these effects of nicotine was ‘reinforcer-enhancing’. Now, mechanisms have been refined (Palmatier et al. 2013,b) supporting that nicotine increases the incentive salience of cues and not just their reinforcing effects. Both these ‘incentive-enhancing’ (Palmatier et al. 2013) and ‘reinforcer-enhancing’ (Donny et al. 2003) effects of nicotine occur regardless of schedule of nicotine delivery, that is, whether it is contingent or not to reinforcer or conditioned cue presentation (Chaudhri et al. 2006; Liu et al. 2007; Palmatier et al. 2007, 2012). This contrasts with the classical Pavlovian conditioning mechanism, where an otherwise non-salient cue becomes salient, acquiring drug-like reinforcing properties, only when drug and cue are paired contingently. Altogether, this evidence suggests that the influence of nicotine depends on the intrinsic nature of the environmental cue and the timing and coincidence of cue and nicotine presentation.

Then, in addition to attributing nicotine-associated cues with specific and stronger incentive salience (Cohen et al. 2005; Yager & Robinson 2015), this non-associative mechanism confers other natural and non-natural reinforcers (Grimm et al. 2012; Palmatier et al. 2012) and their associated cues with increased reinforcing and incentive properties under nicotine effect (Palmatier et al. 2013), which could be an additional motive for nicotine seeking. Although the attention to this non-associative mechanism in clinical studies has been widely overlooked (Perkins et al. 2017), there is evidence supporting that nicotine increases the reinforcement of non-nicotine sensory stimuli that are primary reinforcers by themselves, such as auditory (Perkins & Karelitz 2013a,b) and visual rewards (Perkins & Karelitz 2014), but not of monetary rewards (Perkins et al. 2017). In addition, acute nicotine withdrawal may involve sensory anhedonia that can be reversed with nicotine (Dawkins et al. 2006; Dawkins, Acaster, & Powell 2007; Cook et al. 2015, 2017). Thus, it is possible that tobacco cessation attempts prove difficult also due to nicotine making daily activities, natural reinforcers and environments much more pleasurable (Leventhal et al. 2009; Perkins 2009; Perkins et al. 2017).

Taken together, the motivations and mechanisms for nicotine seeking are diverse and the interplay between them is complex. As they involve distinct neurobiological mechanisms (Antolin-Fontes et al. 2015; Stoker & Markou 2015), they offer multiple sources of individual

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Addiction Biology
INDIVIDUAL DIFFERENCES IN THE PSYCHOPHARMACOLOGICAL MECHANISMS OF NICOTINE SEEKING MAY CONTRIBUTE TO THE HETEROGENEITY OF SMOKER POPULATION

Evidence of differences in the mechanisms of nicotine seeking among smokers comes notably from the work of S. Shiffman and colleagues (for review Coggins et al. 2009). Using cue-reactivity and ecological momentary assessments, which involves the self-report of current behaviors and experiences in real time during habitual daily life, they have notably shown that factors driving seeking are different in daily and non-daily intermittent smokers, with environmental cues associated with smoking playing a stronger role in determining nicotine seeking among non-daily intermittent smokers (Shiffman, Stone, & Hufford 2008; Shiffman et al. 2014). Although they solicit global impressions of smokers’ behavior, studies using questionnaires have also proposed a predominant role of smoking-associated environmental cues in non-daily smokers (Pulvers et al. 2014; Scheuermann et al. 2015).

The acute psychopharmacological effects of nicotine in enhancing the incentive salience of environmental cues could be a possible explanation for the importance of nicotine-associated cues in this population (Perkins & Karelitz 2013a,b). Some of these non-daily smokers progress into daily smoking, and it is proposed that in these individuals nicotine seeking is determined more by withdrawal alleviation and/or avoidance rather than environmental cues, thus requiring smoking at regular intervals to mitigate nicotine intake (Shiffman et al. 2012, 2015; Bani et al. 2014; Piasecki et al. 2014; Roberts et al. 2015; Ferguson et al. 2016; Shiffman & Terhorst 2017). However, this shift is incomplete, as some degree of responsiveness to environmental cues is maintained even among heavy daily smokers (Baker et al. 2012; Shiffman et al. 2015). Only those who progress to very high daily tobacco consumption appear to be less sensitive to environmental stimuli (Ferguson et al. 2016). Altogether, this data suggests a wide range of smokers, where those non-daily irregular smokers who transit to become daily smokers become more susceptible to pharmacologically-induced nicotine craving and less reliant on environmental stimuli signaling smoking opportunities.

However, non-daily and daily smoker populations are more heterogeneous than this proposed view, as evidence accumulates that individual vulnerabilities appear to modulate, independently from each other, smoking behavior, smoking frequency, craving, withdrawal, relapse timing and cessation success (McCarthy et al. 2006; DiFranza et al. 2007; Tindle & Shiffman 2011; Rigotti 2012; Piper 2015; Potvin et al. 2015). For instance, it has been shown that about 72 percent of the non-daily smokers, traditionally neglected in the discussions about nicotine dependence, fail to maintain abstinence for more than 90 days after a quit attempt (Tindle & Shiffman 2011). Despite suggestions that all non-daily smokers are ‘social smokers’ (Philpot et al. 1999), recent evidence suggests that only a small subset of them smoke exclusively in social settings and in the presence of other smokers, while the other non-daily smokers appear less dependent on these factors (Shiffman et al. 2014, 2015). In addition, despite the prediction that nicotine withdrawal may play a major role in heavy daily smokers, not all of them respond positively to nicotine replacement therapies (NRTs) (Rigotti 2012). Other daily smokers report reductions in craving scores upon switching to denicotinized cigarettes, suggesting that in these individuals, factors other than nicotine pharmacology contribute to smoking (Gross, Lee, & Stitzer 1997; Pickworth et al. 1999; Dallery et al. 2003; Bickel & Kirshenbaum 2004; Donny & Jones 2009). Among those daily smokers who eventually reach abstinence, some have responded to approved pharmacological therapies (Tang, Law, & Wald 1994; Cepeda-Benito, Reynoso, & Erath 2004; King et al. 2012), others required joint pharmacological and psychological support (Willemsen et al. 1998), while others achieve abstinence without any therapy (Rigotti 2012). Although limited, there is evidence suggesting that individuals experiencing low hedonic effect of natural reinforcers are more likely to become tobacco smokers later in life (Audrain-McGovern et al. 2012; Stone, Audrain-McGovern, & Leventhal 2017). The exact mechanisms behind this association are still to be explored, but it remains a possibility that these individuals may seek nicotine for its ‘reinforcer-enhancing’ effect on environmental cues, contributing to differences in prevalence, dependence score, progression into heavier use and cessation success among smokers (Audrain-McGovern et al. 2012; Leventhal 2016; Perkins et al. 2017).

Heterogeneity among daily and non-daily smokers is further evidenced in the dynamic shifts observed between these subpopulations: some non-daily smokers continue occasional and infrequent smoking, while others progress to become daily smokers, and a proportion of the latter revert to non-daily smoking habits (Shiffman et al. 2015). The exact mechanisms of such dynamic shifts are poorly understood (Coggins et al. 2009), as the timing between the transitions is highly variable, but recent epidemiological evidence suggests that individual neurobiological vulnerabilities may be responsible. Some individuals can reduce their smoking behavior following newer
tobacco policies and increasing negative societal pressures (National Center for Health Statistics 2012), while others with specific psychobiological traits or psychiatric comorbidities are more likely to become and remain heavy daily smokers, despite such deterrents (Thorgeirsson & Stefansson 2008; Plasecki et al. 2014; Steinberg, Williams, & Li 2015; Parikh, Kutlu, & Gould 2016; Talati, Keyes, & Hasin 2016; Shiffman & Terhorst 2017). Taken together, this behavioral data supports the notion that smokers with the same smoking pattern of consumption may differ in the mechanisms that drive their smoking behavior, their vulnerability for dependence and their response to therapy. Although increased smoking, through neurobiological adaptations following chronic high nicotine use (Hiroi & Agatsuma 2005), may be a source of such variation, biologically predetermined factors may also account for differences in nicotine seeking, smoking and cessation outcome, which occur independently from, or even are causal for, smoking severity. Unfortunately, the vast majority of clinical and preclinical studies in nicotine addiction do not consider individual variability, thus limiting the exploration of the sources of individual differences in human tobacco smoking. Despite this, there is new neurobiological evidence, described below, that sheds light on the possible mechanisms of this individual variability in the mechanisms of nicotine seeking.

**NEUROPSYCHOBIOLOGICAL BASIS FOR THE INDIVIDUAL DIFFERENCES IN THE MECHANISMS OF NICOTINE SEEKING**

A wide range of specific gene mutations, biological factors and personality traits appear to contribute to, or protect against, smoking initiation, maintenance and cessation (Bierut 2007; Thorgeirsson & Stefansson 2008; Doran et al. 2009; Gold & Lerman 2012; Fowler & Kenny 2014; Loukola et al. 2014; Erblich & Michalowski 2015; Lee et al. 2015; Olsson et al. 2016). It has been shown that combinations of risk and protective factors cumulatively affect smoking behavior (Greenbaum & Lerer 2009; Haller et al. 2014; Yang et al. 2015). Although only a limited body of research has explored the mechanisms of these vulnerabilities, this research suggests that they contribute differently to the different mechanisms of nicotine seeking.

**Individual differences in nAChR subunit function can modulate the risk for dependence and the mechanisms of nicotine seeking**

**Alpha5-containing nAChRs**

The pentameric nAChRs are the primary sites of action of nicotine and are composed by a combination of alpha and beta subunit assemblies (Changeux 2012). Genome-wide associated studies have linked vulnerability to nicotine dependence to single nucleotide polymorphisms (SNPs) in the CHRNA5/CHRNA3/CHRNβ4 gene cluster, which encodes the alpha5, alpha3 and beta4 subunits. In particular, a SNP in the rs16969968 allele of the CHRNA5 gene has been associated with smoking that is heavy, out of control, and manifests in strong craving (Saccone et al. 2007; Thorgeirsson et al. 2008; Chen et al. 2012; Gabrielsen et al. 2013). Converging evidence suggests that rs16969968 allele reduces susceptibility to the rewarding and aversive aspects of nicotine, but also to cue-induced craving, paradoxically leading to a ‘heavy smoker’ phenotype, as explained below.

In terms of reducing the rewarding actions of nicotine, it has been demonstrated that introduction of the human rs16969968 allele in mice causes a rightward shift of the dose–response curve for nicotine self-administration (Frahm et al. 2011; Morel et al. 2014), suggesting a decreased sensitivity to the rewarding effects of low nicotine doses. This is also evidenced by higher nicotine levels needed to engage the dopaminergic neurons in the VTA to NAcc pathway, involved in nicotine reward, compared to wildtype mice (Morel et al. 2014). In exploring the molecular basis for this poor sensitivity, studies have identified that the rs16969968 risk allele decreases receptor function of alpha5-containing nAChRs (Bierut et al. 2008; George et al. 2012). In the particular case of (alpha4beta2)2-alpha5 nAChRs, which are also expressed in the VTA and are deemed central for nicotine reinforcement, the rs16969968 allele promotes loss of permeability for Ca2+ ions and a faster desensitization of this receptor (Kuryatov, Berrettini, & Lindstrom 2011; Sciaccaluga et al. 2015). Since nAChR desensitization can also contribute to modulating nicotine reward (Rice & Cragg 2004; Zhang & Sulzer 2004), carriers of the rs16969968 risk allele may increase nicotine intake to titrate for the desired activation of the mesolimbic dopaminergic pathway.

In terms of reducing the aversive effects of nicotine, the alpha5-containing nAChRs in the medial habenula (mHb) appear to play a pivotal role (Fowler et al. 2011; Tuesta, Fowler, & Kenny 2011; Fowler, Tuesta, & Kenny 2012; Fowler, Tuesta, & Kenny 2013; Tuesta et al. 2017). By reducing the function of alpha5-containing nAChRs in the mHb, the rs16969968 risk allele decreases sensitivity to nicotine aversion. Confirming this, and in a manner similar to the behavior observed in mice lacking the alpha5 subunit (Fowler et al. 2011), mice with forced expression of the rs16969968 risk allele in the mHb self-administer nicotine at quantities that are aversive to wildtype mice (Morel et al. 2014). This body of evidence suggest that this risk allele prevents the habenular nAChRs from inducing the inhibitory signal intended to limit intake of
nicotine (Bierut et al. 2008), thus promoting the intake of high nicotine doses. Supporting this notion, at least one clinical study with rs16969968 risk allele human carriers has reported lower aversive effects of intravenous nicotine following an overnight abstinence, compared to non-carriers (Jensen et al. 2015).

As regards the effect on nicotine-related cues, the rs16969968 allele has been associated with circuit deficiencies that could impair the formation of proper nicotine-cue associations that drive cue-induced nicotine craving. Firstly, the rs16969968 allele has been associated with lower resting state functional connectivity between the dorsal anterior cingulate cortex (dACC) and the ventral striatum (Hong et al. 2010), regions whose coupling has been recently linked to tobacco craving (Janes et al. 2014). Secondly, this risk allele has been associated to impairments in the n-back test, which assesses working memory (Winterer et al. 2010). Finally, and most importantly, carriers of this allele have reduced cue-responsiveness to smoking cues in the posterior cingulate cortex (PCC), caudate nucleus and hippocampus (Janes et al. 2012), brain regions implicated in learning, conditioning and habit formation (Heimer 2003). This evidence suggests that these individuals, despite their heavy smoking, may be less sensitive to smoking-associated cues.

Taken together, this evidence suggests that the heavy, daily smoking of the rs16969968 phenotype is surprisingly due to a lower sensitivity to the pharmacological effects of nicotine, whether reinforcing or aversive, as well as low sensitivity to environmental cues signaling smoking opportunities (Johnson et al. 2010). It seems that this risk allele may strengthen nicotine seeking as a means to alleviate or avoid nicotine withdrawal after heavy use (Gabrielsen et al. 2013), but other risk or protective factors may modulate the extent at which this phenotype is ultimately expressed. In fact, not all carriers of the rs16969968 allele respond to NRT (Leung et al. 2015; Tyndale et al. 2015), but some do in specific environmental situations (Chen & Bierut 2013; Chen et al. 2014), possibly due to the interplay between different genetic variants influencing nicotine seeking (Barrie et al. 2017).

**Alpha4-beta2 containing nAChRs**

**Variations of Alpha4-beta2 in the rewarding properties of nicotine.** The alpha4-beta2-containing nAChRs constitute the most abundant nAChR type in the brain (Whiting & Lindstrom 1986) and play a central role in the rewarding actions of nicotine (Tapper et al. 2004). It follows that genetic variability in the CHRNA4 gene, encoding for the alpha4 subunit, can modulate the subjective rewarding actions of nicotine, impacting the motivations to smoke and the potential therapeutic options for these individuals (Hutchison et al. 2007). Preclinical studies have shown that hypersensitive alpha4-containing nAChRs enhance the rewarding properties of acute nicotine administration (Tapper et al. 2004). Conversely, deletion of the alpha4 subunit in the ventral midbrain decreases nicotine self-administration (Pons et al. 2008) and nicotine place preference (Peng et al. 2017). In humans, the CHRNA4 risk allele rs2236196 has been associated with a higher probability for being a smoker (Li et al. 2005; Hutchison et al. 2007; Breitling et al. 2009; Esterlis et al. 2016), with greater self-reported euphoria after nicotine consumption and a better response to rapid release NRTs compared to non-carriers (Hutchison et al. 2007). New evidence suggests that the rs2236196 risk allele increases the relative upregulation of cerebellar and cortical beta2-containing nAChRs after nicotine exposure, compared to non-carriers (Esterlis et al. 2016). Thus, carriers of this risk allele appear more sensitive to the rewarding aspects of nicotine, and this could be due to a higher upregulation of beta2-containing nAChRs in key brain areas.

Variations of Alpha4-beta2 in the effects of nicotine on selective attention. The alpha4beta2-containing nAChRs also play a central role in cognition and in selective attention to environmental stimuli (Witte, Davidson, & Marrocco 1997; Phillips et al. 2000; Wallace & Bertrand 2013), thus providing a potential source of individual differences in the modulatory effects of nicotine on sensory cues. The high incidence of tobacco smoking among populations with trait attention deficits has led to the hypothesis that some individuals may smoke to counteract for these deficits (Poirier et al. 2002; Gardner, Dishion, & Posner 2006). Indeed, recent evidence suggests that individuals with particular SNPs may benefit more of the effect of nicotine on attentional performance. In fact, the rs1044396 SNP of the CHRNA4 gene, involved in nicotine dependence (Feng et al. 2004; Kamens et al. 2013), is also involved in visuospatial and auditory attention deficits (Parasuraman et al. 2005; Greenwood et al. 2009). In particular, individuals that are homozygotes for the rs1044396 SNP C risk allele have an attention deficit to surrounding cues, but which may be alleviated upon nicotine administration. When asked to fix their attention on a particular visual cue, these individuals are more likely to disengage their attentional focus to the targeted cue, and respond quicker to interfering cues appearing outside the target zone (Espeseth et al. 2010). Notably, nicotine enhances the selective attention to cues and improve distractor suppression (Thiel, Zilles, & Fink 2005; Hahn et al. 2009; Ahrens
et al. 2015; Behler, Breckel, & Thiel 2015), but only when
the baseline performance is low, as it is the case with
these individuals (Ahrens et al. 2015; Behler et al.
2015; Hammersley et al. 2016). Thus, it could be
argued that in the rs1044396 SNP C/C homozygotes,
the primary reinforcing properties of nicotine come
from its ability to compensate for their cue attention
deficits, compared to non-carriers (Eseseth et al. 2010).

The precise mechanisms behind the effects of the
rs1044396 SNP on both attentional performance and
vulnerability to nicotine dependence are poorly un-
derstood, but newer evidence shows that gene-gene inter-
actions may solve part of the puzzle. On one side, the
effect of the rs1044396 SNP C/C homozygote on the scaling of
attentional focus manifests itself only if the individuals
are also T/T homozygote for the CHRM2 rs8191992 al-
lee, an SNP of the muscarinic M2 receptor (Greenwood
et al. 2009). Furthermore, nicotine-enhancing effects on
attentional performance were strong in the rs1044396
SNP C carriers, but only if they were also carriers of the
dopaminergic DRD2 T allele, an SNP for the dopaminer-
gic D2 receptor (Ahrens et al. 2015; Breckel et al.
2015). This new evidence highlights the complex inter-
play between genetic factors in brain networks, which
could shape individual differences in the psychopharma-
cology of nicotine (Ahrens et al. 2015) and by extension,
in the vulnerability for nicotine dependence.

Variations in nAChR subunits can protect against nicotine
dependence

Genetic variability in nAChR subunits can also protect in-
dividuals against nicotine dependence. Genome-wide as-
associated studies have identified rare missense SNPs in
the alpha4 (Xie et al. 2011), beta2 (Hoef et al. 2011;
Svyray et al. 2016) and beta4 (Haller et al. 2012) sub-
units, which appear to decrease risk of nicotine depend-
ence in humans, and are thus underrepresented in
smoker populations (McClure-Begley et al. 2014). Protec-
tion against nicotine dependence through these rare
SNPs in the CHRB2 gene appears mediated by increased
sensitivity to the subjective aversive effects of nicotine, in-
cluding increased nausea, heart palpitations and sweat-
ing compared to non-carriers (Hoef et al. 2011; Svyray
et al. 2016), which can deter further experimentation
with nicotine. Since alpha2beta4-containing nAChRs
are central in nicotine aversion, the protection given by
beta4 variants may also be due to increased sensitivity to
the aversive effects of nicotine (Haller et al. 2014;
McClure-Begley et al. 2014). Supporting this view, there
is evidence that forced overexpression of the beta4 sub-
unit in the mHb limits nicotine self-administration in ro-
dents (Frahm et al. 2011). Finally, genetic variability at
the level of the CHRNA4 gene can also protect against
nicotine dependence through decreased sensitivity to nic-
otine reward (Butt et al. 2005; Wilking et al. 2010) or to
depressed benefit of the attention-enhancing effects of
nicotine (Feng et al. 2004; Greenwood, Parasuraman, &
Eseseth 2012).

Individual differences in CYP2A6 function can modulate
the mechanisms of nicotine seeking

Genetic variability in the systemic clearance of plasma
nicotine levels, determined by the metabolic activity of
the hepatic enzyme CYP2A6, has been linked to differ-
ences in nicotine seeking, vulnerability to nicotine depen-
dence and cessation outcome (Lerman et al. 2015;
Mamoun et al. 2015). Slow CYP2A6 metabolizers have
approximately 50 percent reduction in nicotine metabo-
ilism compared to fast metabolizers (Benowitz et al.
2006). Even though adolescent slow nicotine metabo-
izers progress faster into habitual cigarette consump-
tion (Audrain-McGovern et al. 2007; Olsson et al.
2016, O’Loughlin et al. 2004), once they reach adult-
hood they have reduced risk for nicotine dependence (Ru-
binstein et al. 2008; Wassenaar et al. 2011; Sofuoglu et
al. 2012; Olsson et al. 2016), are more likely to smoke less
 cigarettes per day than fast metabolizers (Wassenaar
et al. 2011; Styn et al. 2013), but also experience less
withdrawal symptoms (Mamoun et al. 2015), and report
higher cessation success with NRTs (Kaufmann et al.
2015; Mamoun et al. 2015).

The association between decreased nicotine depend-
ence risk and low smoking profile among slow
metabolizers can be explained by the peculiar nicotine
pharmacokinetics and the effects of prolonged nicotine
exposure on neural activity in these individuals: despite
the sustained presence of nicotine in their system, the
neurobiological changes produced by nicotine over time
are less easily overcome by NRTs, thus easing their ces-
sation success dramatically. Recent evidence suggest that
slow and fast metabolizers do not differ in their risk for
smoking initiation (Olsson et al. 2016), and, among
non-smokers, individuals with slow and fast CYP2A6 me-
abolism did not differ in the activity of striatal-cingulate
neural circuits computing for reward and impulsivity (Li
et al. 2017). However, once they become smokers, slow
metabolizers experience less functional connectivity be-
tween the VS and the dACC, which is translated into def-
icits in reward processing and inhibitory control during
abstinence, but which are alleviated after exposure to
nicotine through a patch (Li et al. 2017). Remarkably,
for smokers who are fast metabolizers, absence or pres-
ence of nicotine did not alter their neural response in
VS and dACC in the same experimental conditions. These
data suggest that the prolonged exposure to nicotine in
slow metabolizers changes the neuroplasticity of these
neural networks, over time reducing their sensitivity to reward processing and response inhibition in the absence of nicotine. However, their slow metabolism of nicotine ensures that only a small number of cigarettes are needed to achieve this nicotine-induced alleviation of these changes in network connectivity. In fact, there is evidence that slow metabolizers have reduced thalamic nAChRs during early abstinence (Dubroff et al. 2015), which are normally upregulated during chronic nicotine exposure in normal and fast metabolizers. Activation of low nAChR densities in the thalamus following slow transdermal delivery of nicotine may reduce background craving associated with abstinence (Allenby et al. 2016). Since NRTs appear to mimic the same pharmacokinetic profile of their smoking patterns, slow metabolizers are thus more likely to benefit from this cessation strategy than fast metabolizers.

The increased heaviness in the smoking behavior of fast nicotine metabolizers can be explained by an attempt to titrate nicotine intake given its rapid clearance (Olfson et al. 2016). Furthermore, increased sensitivity to both the rewarding and withdrawal-alleviating actions of nicotine appears to play a role in the nicotine seeking in these individuals (Benowitz, Hukkanen, & Jacob 2009; Sofuoglu et al. 2012). Fast metabolizers report higher subjective craving scores (Patterson et al. 2008), dose-dependent effect of nicotine in subjective withdrawal alleviation (Faulkner et al. 2017) and greater rewarding effects of intravenous nicotine following an overnight abstinence (Sofuoglu et al. 2012). Although preclinical evidence for these observations is still scarce, a study from Grebenstein et al. (2015) showed in rats that nicotine clearance predicts nicotine reinforcement threshold and degree of compensation when decreasing nicotine dose, i.e. the fastest the clearance, the lowest the reinforcement threshold and the highest the degree of compensation. This raises important implications for cessation strategies in fast metabolizers, as switching to low dose nicotine cigarettes in an attempt to curtail nicotine dependence could lead to the opposite: an increase desire to titrate nicotine dose, and thus, increase smoking heaviness (Grebenstein et al. 2015).

Furthermore, reaching faster for the next cigarette also increases the opportunity for stronger temporal relationship between nicotine intake and its effects on surrounding stimuli, including both Pavlovian conditioning and the reinforcer-enhancing effect of nicotine (Donny et al. 2008; Caggiula et al. 2009). This could explain the reported higher smoking cue-reactivity in several brain areas of fast metabolizers, including amygdala, hippocampus, caudate and cingulate cortex (Tang et al. 2012; Falcone et al. 2016) in comparison with slow metabolizers. Interestingly, a recent study done by Faulkner et al. (2017) suggests that nicotine dose, more than the ritualistic and sensory cues accompanying smoking, alleviates craving and withdrawal better in fast metabolizers, compared to slow metabolizers. However, this study was only conducted in young smokers; thus, it is possible that a more prolonged history of tobacco smoking is needed to observe higher cue reactivity among fast metabolizers. Altogether, this evidence suggests that individuals with fast nicotine metabolism relapse more frequently, probably due to a combination of increased sensitivity to nicotine, nicotine withdrawal and higher reactivity to environmental cues signaling nicotine availability.

Individual differences in psychological traits can modulate the mechanisms of nicotine seeking

Three main personality traits, anxiety, novelty/sensation-seeking and poor decision making/impulsivity have been associated with increased risk or severity of nicotine dependence (Falco & Bevins 2015). We take here the example of impulsive choice, because data are controversial, and controversy could result from individual variations. Higher delay discounting scores, a measure of impulsive choice, have been observed among highly dependent daily smokers compared to daily smokers with lower Fagerström Test for Nicotine Dependence scores (Switzer et al. 2008) or to non-daily smokers (Heyman & Gibb 2006). However, other studies have failed to see this differential relationship between delay discounting and smoking behavior (Johnson, Bickel, & Baker 2007; Carim-Todd, Mitchell, & Oken 2016; Rass, Ahn, & O'Donnell 2016).

Rather than a risk for dependence, evidence suggests that impulsive choice could be a risk factor for increased difficulty to control nicotine seeking, once craving is triggered. Supporting this, not all high impulsive smokers relapse more than low impulsive smokers, but only those with high cue-induced craving (Bourque et al. 2013; Erblich & Michalowski 2015). This impulsivity-driven enhancement of smoking relapse seems also to involve increasing cue-induced neural reactivity, suggesting that impulsive individuals react more to nicotine-associated cues and are less likely to resist the accompanying urges. Studies show that the PCC, involved in trait impulsivity and control of craving to psychoactive substances (Brody et al. 2007; Potvin et al. 2015), is negatively coupled with the insula, dACC and dorsolateral prefrontal cortex, involved in nicotine cue reactivity (Bourque et al. 2013). In fact, hypofunction of the PCC is correlated with higher impulsivity, and at the same time with increased function of the insula, dACC and dorsolateral prefrontal cortex after smoking cue presentation (Bourque et al. 2013). Supporting a decreased inhibitory control by impulsivity, rats that score higher in impulsive choice, measured via delay discounting, not only show increased cue-induced relapse, but also fail to inhibit nicotine seeking during...
abstinence (Diergaard et al. 2008) and show a less elastic demand for nicotine (Diergaard et al. 2012), i.e. they maintain nicotine intake while price (workload) increases. Highly impulsive individuals are thus more likely to react to cues signaling nicotine availability, and are less likely to control their urges, resulting in higher relapse rates.

Impulsivity might be pre-existing, but data suggest that it could also be induced or amplified by nicotine itself. Individuals carrying a the risk allele of the alpha3 nAChR subunit, rs578776, have higher resting functional coupling between the dACC-thalamus (Hong et al. 2010), a coupling recently implicated with risky decision making (Wei et al. 2016). Interestingly, the observed increased dACC-thalamus resting state functional connectivity was correlated to the amount of cigarettes smoked before the test session (Hong et al. 2010), suggesting that in these individuals, nicotine may act as positive feedback for riskier behavior, predisposing them for more deleterious consequences of craving episodes.

CONCLUSIONS

In this review, we have sought to provide converging epidemiological, clinical and preclinical evidence that individuals may differ in the neurobiological mechanisms behind nicotine seeking, and this may explain the variety of smoking behaviors, and the individual profiles for craving, withdrawal, relapse timing, responsiveness to therapy and cessation success. Combinations of risk and protective factors do not necessarily have the same impact in the different mechanisms of nicotine seeking, but they shape the overall vulnerability for nicotine seeking, and eventually, transitioning into nicotine dependence. To complicate the picture, it is interesting to note that expression (hence contribution to tobacco seeking) of individual differences, notably individual differences in reward-enhancing effects of nicotine, might be influenced by socioeconomic or health conditions associated with abundant or poor opportunities for reward (Perkins 2009; Leventhal 2016). However, most studies in tobacco addiction have neglected individual variations in the mechanisms of nicotine seeking, obscuring the existence of subpopulations with specific characteristics that could better define their treatment.

Preclinical animal models of nicotine seeking have been proved useful, as they have helped in understanding the mechanisms underlying nicotine seeking. These models, in line with clinical studies, have consistently demonstrated that pharmacological and non-pharmacological factors interact in a complex manner to exert control on nicotine seeking. They have poorly considered, however, that these interactions may vary among nicotine users, and thus individual differences in nicotine-seeking and nicotine-taking in these preclinical models are scarcely described in the literature. Over the last 15 years, tremendous progress has been made in modeling nicotine seeking in rodents using intravenous self-administration (Cohen & George 2013). Procedures are available (Palmatier et al. 2013; Robinson et al. 2014) that appear useful for exploring individual differences in the mechanisms by which nicotine attributes incentive salience to rewards, reward-related cues and contexts (Yager & Robinson 2015).

In a recent review on the individual differences in the behavioral effects of nicotine, Falco and Bevins (Falco & Bevins 2015) refer only to four self-administration studies, which investigated the relationships between nicotine self-administration and psychobehavioral traits associated with tobacco dependence (impulsivity, sensation-seeking and anxiety). Nevertheless, these studies (Suto, Austin, & Vezina 2001; Guillem et al. 2005; Diergaard et al. 2008, 2012) do not explore whether differences in nicotine self-administration between high and low scoring animals involve differential control of nicotine seeking by nicotine and/or nicotine-associated cues, for example, thus highlighting the need to further explore these questions in available animal models.

Advances in rodent models of genetic risk markers for nicotine dependence (Morel et al. 2014), as well as in in vivo tracing and manipulation of neuronal circuit activity (Cruz et al. 2013; Jennings & Stuber 2014) have been made recently. They could be incorporated to study the neurobiological mechanisms underlying individual differences in the mechanisms driving nicotine seeking. It is becoming evident that an individual-based strategy of the neurobiology of nicotine self-administration could increase the predictive validity of preclinical models of nicotine dependence and help develop individual-based therapeutic strategies for tobacco dependence, as we have recently suggested (Garcia-Rivas et al. 2016).

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