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A review of the effects of very low nicotine content cigarettes on behavioral and cognitive performance

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Abstract

The present systematic review examines whether very low nicotine content (VLNC) cigarettes ameliorate withdrawal-induced impairments in behavioral/cognitive performance.

PubMed, PsycInfo, and Web of Science were searched for performance effects of VLNC cigarettes. For inclusion, reports had to be in English, published in a peer-reviewed journal through June 2017, examine VLNC cigarettes (<0.2 mg nicotine yield), include 2 hour smoking abstinence or reduced nicotine exposure, and examine performance. 19 of 1243 articles reviewed met inclusion criteria. Poorer performance after smoking VLNC versus normal nicotine content (NNC) cigarettes was observed across 7 of 10 domains, including reaction time (8/11), short-term memory (3/10), sustained attention (4/6), inhibitory control (1/4), long-term memory (3/3 studies), and response variability (2/2). In two studies, combining VLNC smoking with nicotine replacement therapy (NRT) resulted in performance that was comparable to performance after NNC smoking. VLNC versus NNC differences were not discerned in motor control/functioning (0/2), visuospatial processing (0/2), learning (0/1), or verbal fluency (0/1). Eleven of nineteen (58%) studies were rated of Good or Excellent quality. Overall, VLNC cigarettes may not fully ameliorate withdrawal-induced disruptions in performance, although this varies by domain, with the strongest evidence for reaction time. Importantly, combining VLNC cigarettes with NRT appears to ameliorate withdrawal that is not reduced by VLNC cigarettes alone. As only 19 studies were identified, many domains are under-investigated. A more thorough evaluation of the extent to which VLNC cigarettes affect withdrawal-impaired performance may be warranted.

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Competing interests

The authors have no conflicts of interest to report.

Transparency document

The Transparency document associated with this article can be found, in the online version.

Keywords

Nicotine; Performance; Reaction time; Sustained attention; Memory; Inhibitory control; Reduced nicotine content; Very low nicotine content cigarettes; Nicotine withdrawal; Smoking abstinence

1. Introduction

The Family Smoking Prevention and Tobacco Control Act gives the U.S. Food and Drug Administration (FDA) regulatory authority over nicotine levels in tobacco products (Family Smoking Prevention and Tobacco Control Act, 2009). That legislation includes authority to reduce, although not eliminate, the nicotine content of cigarettes if doing so is deemed important to protecting public health. Hence, a national policy available for consideration by the FDA is one that would reduce the nicotine content of cigarettes below a threshold necessary to produce nicotine dependence. Such a policy was recommended more than 20 years ago (Benowitz and Henningfield, 1994) and was well received by experts, but was not legally tenable until the passage of the Family Smoking Prevention and Tobacco Control Act.

Important to evaluating such a policy is examination of potential unintended consequences of reducing the nicotine content of cigarettes. As such, there has been interest in examining the behavioral, cognitive, and physiological effects of smoking very low nicotine content (VLNC) cigarettes. These cigarettes contain ~0.4 mg/g nicotine content (<0.2 mg nicotine yield) and share the taste, aroma, and respiratory effects of commercial-level nicotine content cigarettes (Johnson et al., 2004; Rose et al., 2000). VLNC cigarettes have been used as “placebo” cigarettes in research settings as they provide sensorimotor replacement for usual brand smoking with less nicotine exposure than normal nicotine content (NNC) cigarettes (Pickworth et al., 1999), although they do result in nicotine delivery to the brain (Brody et al., 2009).

There has been debate over whether it would be more beneficial to reduce the nicotine content of commercially-available cigarettes abruptly to a very low level or gradually over time (Donny et al., 2014). Although both methods are likely to improve population health in the long-term by decreasing smoking prevalence, it is nevertheless important to examine potential short-term unintended consequences of an abrupt versus gradual reduction (Hatsukami et al., 2015). In particular, an abrupt reduction in the nicotine content of commercially-available cigarettes may induce nicotine withdrawal in daily smokers.

Nicotine withdrawal is a valid, reliable, and clinically significant syndrome characterized by the Diagnostic and Statistical Manual, 5th Edition (American Psychological Association, 2013). Withdrawal begins approximately 2 h after the last cigarette, peaks within the first week, and lasts 2–4 weeks (Hatsukami et al., 1985; Hughes, 2007). Signs and symptoms include craving, disruption in behavioral and cognitive performance (referred to hereafter as “performance”), constipation/diarrhea, irritability, anxiety, restlessness, difficulty concentrating, sleep disruption, and decreases in appetite (Hughes, 2007; Colrain et al., 2004). More specifically, nicotine withdrawal disrupts reaction time, sustained attention, short-term memory, and inhibitory control (Hatsukami et al., 1985; Hughes, 2007;

Hatsukami et al., 1989; Ashare et al., 2014) and these performance disruptions predict relapse (Culhane et al., 2008; Krishnan-Sarin et al., 2007; Patterson et al., 2010; Powell et al., 2004; Rukstalis et al., 2005).

A compelling body of literature indicates that VLNC cigarettes reverse self-reported withdrawal scores and symptoms such as negative affect and craving (Butschky et al., 1995; Rose et al., 2004; Higgins et al., 2016; Benowitz et al., 2007; Donny et al., 2015; Hatsukami et al., 2013; Hatsukami et al., 2010). Less research has examined whether VLNC cigarettes reverse withdrawal-induced performance disruptions, which are based on observer ratings rather than self-report. If a national policy that abruptly reduces the nicotine content in cigarettes were enacted, unrestored performance disruptions could have short-term, but potentially important implications for workplace safety and productivity, especially in professions where smoking prevalence is high. For example, between the years 2004–2010 the prevalence of cigarette smoking was highest (~30%) among those working in the mining, construction, and hospitality industries (Syamlal and Mazurek, 2011). Recent reports also indicate high rates of smoking (~27%) among nurses (Syamlal et al., 2015) and (~24%) active duty military personnel (Barlas et al., 2013). This may be important, as converging evidence suggests that performance disruptions associated with nicotine withdrawal affect productivity and safety (Heimstra et al., 1967; Jansari et al., 2013; Mumenthaler et al., 2010; Sherwood, 1995; Sindelar et al., 2005; Waters et al., 1998). While these effects may be relatively minor and easily managed at the individual level, it is possible that the consequences of performance disruptions are amplified at the population level. Indeed, evidence of such amplified consequences has been noted, with a greater number of workplace accidents occurring annually on the United Kingdom's National No-Smoking Day (1987–1996), when up to 2 million regular smokers attempt to abstain (Waters et al., 1998).

Considered together, this data underscores the importance of examining whether VLNC cigarettes ameliorate withdrawal-induced impairments in performance. As an initial step towards addressing this aim, we systematically reviewed the literature on the effects of VLNC cigarettes on performance following smoking abstinence or reduced nicotine exposure.

2. Methods

Literature searches were conducted using PubMed, PsycInfo, and Web of Science (Supplementary Report 1 describes search strategy and terms in detail). We also reviewed references from published reviews on nicotine-related performance effects. Studies published through June 2017 were considered. Studies were included (Fig. 1) if they were (a) written in English, (b) published in a peer-reviewed journal, (c) examined VLNC/denicotinized cigarettes (i.e., < 0.4 mg/g nicotine content and/or <0.2 mg estimated nicotine yield), (d) required 2 h smoking abstinence or reduced nicotine exposure prior to experimental sessions, (e) examined at least one measure of performance, (f) utilized a design permitting experimental isolation of the effects of VLNC cigarettes on performance, and (g) was an original, prospective experimental study reporting previously unpublished data.

This search strategy generated 1243 articles. Articles were reviewed for inclusion by sets of two authors (DK + IZ or AK + DD). Each set of authors reviewed 617 articles applying the inclusion criteria. Discrepancies were resolved through discussion. Information extracted from each study included: (1) sample size; (2) nicotine dose (Supplementary Table 1 provides details on cigarette source/manufacturing); (3) duration of abstinence/reduced nicotine exposure; (4) task/outcome measure; (5) a summary of results; (6) if the results indicated differences in performance after smoking VLNC relative to comparison conditions; and (7) procedural notes/additional results of interest.

Study quality was determined using the NIH Study Quality Assessment tool (<https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools>). Authors DK, IZ, AK, and DD independently reviewed 4–5 studies each and provided an initial determination of poor, fair, good, or excellent quality according to guidelines. Quality ratings were then discussed as a group and consensus was reached for all studies with no disagreements.

3. Results

3.1. Studies meeting inclusion criteria

Nineteen studies met inclusion criteria. Eleven of nineteen (58%) studies were rated Good or Excellent quality (Supplementary Table 2 provides details on study quality). Seventeen studies included smokers who were abstinent for 2 h and two studies (AhnAllen et al., 2015; McClernon et al., 2016) included smokers who were abruptly switched from NNC to VLNC cigarettes for 2 h. Ten performance domains were identified across studies: reaction time, short-term memory, sustained attention, inhibitory control, long-term memory, response variability, motor control/functioning, visuospatial processing, learning, and verbal fluency. Most studies measured multiple domains. For studies wherein a single task yielded measures encompassing multiple domains, we discuss each outcome separately within each domain.

The most commonly examined domains were reaction time (58% or 11/19 studies), short-term memory (53% or 10/19 studies), sustained attention (32% or 6/19 studies), and inhibitory control (21% or 4/19 studies). Long-term memory, response variability, motor control/functioning, visuospatial processing learning, and verbal fluency were examined in three or fewer studies.

Of the nineteen studies, 79% (15/19) reported that performance was significantly worse among those who smoked a VLNC versus NNC cigarette (Rose et al., 2004; AhnAllen et al., 2015; McClernon et al., 2016; Bates et al., 1995; Colrain et al., 1992; Gilbert et al., 1997; Hale et al., 1999; Harrell and Juliano, 2012; Juliano et al., 2011; Kelemen, 2008; Lee et al., 2011; Marzilli et al., 2006; Peters and McGee, 1982; Warburton et al., 1992; Marzilli and Hutcherson, 2002). This effect was observed across 7 of 10 (70%) of the performance domains, including reaction time (73% or 8/11 studies), short-term memory (30% or 3/10), sustained attention (66% or 4/6 studies), inhibitory control (25% or 1/4 studies), long-term memory (100% or 3/3 studies), and response variability (100% or 2/2 studies). Four domains

with no evidence of differences were motor control/functioning (0/2), visuospatial processing (0/2), learning (0/1), and verbal fluency (0/1).

Additional details on the results within each of the domains are provided below. Domains are presented in the order of those examined in the largest to smallest proportion of the 19 studies.

3.2. Reaction time

Eleven studies examined reaction time (RT) (Rose et al., 2004; AhnAllen et al., 2015; McClernon et al., 2016; Bates et al., 1995; Hale et al., 1999; Harrell and Juliano, 2012; Juliano et al., 2011; Kelemen, 2008; Marzilli et al., 2006; Marzilli and Hutcherson, 2002; Smith et al., 2002), with four examining simple RT and eight examining complex RT. Among the four that examined simple RT, all noted worse performance among those who smoked VLNC compared to NNC cigarettes (AhnAllen et al., 2015; Bates et al., 1995; Marzilli et al., 2006; Marzilli and Hutcherson, 2002). This effect was discerned across variable study designs, including three studies that examined acute exposure to a VLNC cigarette after 2–12 h of smoking abstinence (Bates et al., 1995; Marzilli et al., 2006; Marzilli and Hutcherson, 2002), and a fourth that examined 5 h of VLNC exposure (AhnAllen et al., 2015). In addition to reporting similar results, the extended exposure study also demonstrated that performance was recovered by providing nicotine replacement therapy (NRT). Specifically, participants in AhnAllen et al. (2015) smoked either VLNC or NNC cigarettes during a 5-hour controlled smoking session, after which they completed two simple RT tasks. Simple RT was significantly slower after smoking VLNC versus NNC cigarettes in one of the two tasks, although performance was recovered when VLNC smoking was paired with an active nicotine patch.

Among the eight studies that examined complex RT, a majority (5/8 or 62.4%) reported that performance was worse among those who smoked a VLNC versus NNC cigarette (Rose et al., 2004; AhnAllen et al., 2015; Hale et al., 1999; Juliano et al., 2011; Kelemen, 2008), although two studies noted differences in one complex RT task, but not another (Rose et al., 2004; AhnAllen et al., 2015). Among the three studies that did not observe differences (McClernon et al., 2016; Harrell and Juliano, 2012; Smith et al., 2002), several variables may account for inconsistent results, including a lack of withdrawal-induced disruption, use of relatively lighter smokers, and contingencies on task performance.

Regarding a lack of disruption, smokers in McClernon et al. (2016) performed the N-back task following 24 h of wearing a nicotine or placebo patch while either smoking VLNC cigarettes or remaining abstinent. Performance in the placebo patch + smoking abstinence condition did not differ significantly from any of the other conditions (i.e., placebo patch + VLNC, nicotine patch + VLNC, nicotine patch + abstinence), suggesting that performance was not disrupted by abstinence.

Regarding participant characteristics and task contingencies, Harrell and Juliano (2012) failed to discern differences in complex RT during the Rapid Visual Information Processing (RVIP) task, while three other studies utilizing this task noted differences (AhnAllen et al., 2015; Juliano et al., 2011; Kelemen, 2008). Duration of smoking abstinence/reduced

nicotine exposure cannot account for this difference, as Harrell and Juliano (2012) required 12 h of abstinence, while the studies noting differences required 3–5 h of abstinence/reduced nicotine exposure (AhnAllen et al., 2015; Juliano et al., 2011; Kelemen, 2008). However, relative to the studies with significant effects, Harrell and Juliano (2012) included participants with a lower baseline smoking rate (>6 vs. >10 cigarettes per day, respectively), and placed contingencies on task performance (e.g., incentives for hits, penalties for misses) to increase participants' motivation to respond accurately, which may have bolstered performance against withdrawal-induced disruptions.

The third study is more difficult to reconcile. Smith et al. (2002) reported that VLNC and NNC cigarettes improved RT comparably among schizophrenic participants who abstained for 12 h. It is unlikely that these results are specific to this population, as a second study examining schizophrenic smokers noted differences between VLNC and NNC cigarettes (AhnAllen et al., 2015). AhnAllen et al. (2015) reported that RT was significantly slower after schizophrenic participants smoked VLNC cigarettes during a 5-hour controlled smoking session compared to when they smoked their usual brand cigarettes during a matched session. Other variables seem similar across the two studies (i.e., nicotine dose, extended exposure), making it difficult to account for the between-study differences.

Overall, differences in simple and complex RT after smoking VLNC versus NNC cigarettes were observed across studies with substantial differences in duration of abstinence (e.g., 2–24 h), VLNC smoking (e.g., single cigarette up to 5 h of smoking), task (e.g., CPT-II, RVIP), and research cigarette (e.g., Quest brand, Tobacco Research Institute cigarettes), suggesting that these performance differences have broad generality. The results also indicated that performance disruptions can be ameliorated by combining VLNC smoking with NRT (AhnAllen et al., 2015).

3.3. Short-term memory

Ten studies assessed short-term memory (Rose et al., 2004; AhnAllen et al., 2015; McClernon et al., 2016; Kelemen, 2008; Lee et al., 2011; Peters and McGee, 1982; Warburton et al., 1992; Smith et al., 2002; Krebs et al., 1994; Kelemen and Kaighobadi, 2007), with 30% (3/10) reporting worse performance (Table 2) among those who smoked a VLNC versus NNC cigarette (McClernon et al., 2016; Lee et al., 2011; Warburton et al., 1992). Given that only a minority of studies detected differences, it is important to discern the conditions under which performance differences are observed. These conditions do not include the type of task examined, as a wide variety of tasks were used across studies that did and did not note differences. Sample population also cannot account for inconsistencies, as smokers from the general population were examined in all three studies noting differences and five of the seven studies reporting negative results (Rose et al., 2004; Kelemen, 2008; Peters and McGee, 1982; Krebs et al., 1994). Two additional studies reporting negative results examined schizophrenic smokers (AhnAllen et al., 2015; Smith et al., 2002).

One variable that differentiates studies with positive and negative results was the duration of abstinence/reduced nicotine exposure. All three studies reporting differences required participants to abstain from smoking or smoke only VLNC cigarettes for 10–24 h (McClernon et al., 2016; Lee et al., 2011; Warburton et al., 1992), whereas all seven studies

that failed to discern differences required 2–10 h (Rose et al., 2004; AhnAllen et al., 2015; Kelemen, 2008; Peters and McGee, 1982; Smith et al., 2002; Krebs et al., 1994; Kelemen and Kaighobadi, 2007). This suggests that disruptions in short-term memory may only be discernible after longer periods of nicotine deprivation and/or reduced nicotine exposure.

One of the studies investigating short-term memory provided further evidence that performance improves by combining VLNC smoking with NRT. Smokers in McClernon et al. (2016) performed the N-back task following 24 h of wearing a nicotine or placebo patch while either smoking VLNC cigarettes or remaining abstinent. Performance was equally impaired when smokers wore a placebo patch during 24 h of smoking abstinence or wore a placebo patch and smoked VLNC cigarettes for 24 h. However, performance in both conditions was restored to similar levels when participants wore an active nicotine patch.

Overall, these data suggest that short-term memory is disrupted only after extended periods of nicotine deprivation/reduced nicotine exposure (>10 h), and while NNC cigarettes or NRT can reverse these disruptions, VLNC cigarettes alone do not appear to do so (Warburton et al., 1992).

3.4. Sustained attention

Six studies (Table 3) examined sustained attention (AhnAllen et al., 2015; Gilbert et al., 1997; Harrell and Juliano, 2012; Juliano et al., 2011; Kelemen, 2008; Lee et al., 2011). All utilized the RVIP task, in which participants view a series of digits on a computer screen and press a button whenever three consecutive odd or even digits appear. One study also included a second task, the Connors Continuous Performance Task (CPT-II) (AhnAllen et al., 2015). Overall, 66% (4/6) reported that performance was significantly worse after smoking a VLNC versus NNC cigarette (AhnAllen et al., 2015; Gilbert et al., 1997; Harrell and Juliano, 2012; Juliano et al., 2011), although one of these studies reported significant differences only when data were collapsed across two tasks (AhnAllen et al., 2015).

As all studies utilized the RVIP task, and five out of six utilized Quest brand research cigarettes, neither task nor cigarette can explain the between-study inconsistencies. Similarly, length of abstinence does not account for the variability in results, with the four studies noting differences requiring 3–12 h of smoking abstinence or reduced nicotine exposure (AhnAllen et al., 2015; Gilbert et al., 1997; Harrell and Juliano, 2012; Juliano et al., 2011) while the studies reporting no differences required 5–24 h (Kelemen, 2008; Lee et al., 2011). The more likely contributors to mixed results are a lack of withdrawal-induced disruption and/or an insufficiently demanding task (Kelemen, 2008; Lee et al., 2011). For example, in Lee et al. (2011) there was no evidence of performance disruption after 24 h of abstinence. Further, in contrast to the other studies that used a 12-minute task, these authors utilized a less demanding 5-minute version, which may have been too short to sufficiently challenge sustained attention.

The second study noting no differences examined performance exclusively among undergraduates, who were on average relatively light smokers (Kelemen, 2008). Although the study design could not directly determine whether smoking abstinence induced

disruptions in performance, by definition less dependent smokers would be expected to show relatively minimal signs of nicotine withdrawal.

Overall, the majority of studies suggest that smoking VLNC relative to NNC cigarettes do not fully reverse withdrawal-induced impairments in sustained attention, although more evidence is needed before any conclusions should be reached.

3.5. Inhibitory control

Four studies examined inhibitory control (AhnAllen et al., 2015; Gilbert et al., 1997; Juliano et al., 2011; Lee et al., 2011), with 25% (1/4) reporting that performance was significantly worse (Table 3) among those who smoked a VLNC versus NNC cigarette (AhnAllen et al., 2015). Length of abstinence/reduced nicotine exposure does not account for the variability in results, as the one study noting differences required 5 h of NNC abstinence (AhnAllen et al., 2015), whereas studies noting no differences required 3–24 h (Gilbert et al., 1997; Juliano et al., 2011; Lee et al., 2011). However, two variables that may contribute to between-study differences are task parameters and smoking history.

In terms of task parameters, the single study noting differences (AhnAllen et al., 2015) measured false alarms during a simple RT task and the CPT-II task, both of which require inhibition of continuous key pressing whenever a stimulus appears. In contrast, the three studies noting no differences measured false alarms during the RVIP task, in which participants made a key press only when three consecutive odd or even numbers were presented (Gilbert et al., 1997; Juliano et al., 2011; Lee et al., 2011). Therefore, in contrast to the RVIP, it is possible that key pressing during the CPT-II and simple RT tasks becomes rote or pre-potent, which may be more challenging to inhibit and thus more sensitive to withdrawal-induced disruption.

Regarding smoking history, participants in the three studies reporting no differences were also lighter smokers and/or less nicotine dependent than in the study noting differences. Average cigarettes per day among participants in Gilbert et al. (1997), Juliano et al. (2011), and Lee et al. (2011) were 15, 13.56, and 15.50, respectively, and none of these studies had inclusion criteria based on nicotine dependence scores. In contrast, AhnAllen et al. (2015) included smokers with schizophrenia and healthy smokers who were matched on smoking rate, with both groups smoking between 20 and 50 cigarettes per day (average CPD = 25.8). Further, all participants were required to score ≥ 6 (i.e., highly dependent) on the FTND (mean = 6.9 ± 1.5).

Overall, data suggest that smoking VLNC relative to NNC cigarettes may fail to reverse withdrawal-induced impairments in inhibitory control under some circumstances (e.g., on specific types of tasks, among heavier/more dependent smokers). However, given the relatively small number of studies and the negative results noted in the majority, more research in this domain is warranted.

3.6. Long-term memory

Three studies examined long-term memory (Colrain et al., 1992; Peters and McGee, 1982; Warburton et al., 1992), with all (100%) reporting that performance was worse among those

who smoked VLNC versus NNC cigarettes (Table 2). All three required 10 or more hours of smoking abstinence although they used a variety of memory tasks (e.g., free-, cued-, and recognition-recall), arrangements between smoking and learning (e.g., participants smoked before, during, or after learning), and temporal delays between learning and recall (e.g., 10 min, 24 h, 1 week).

Considering there are only three studies, additional studies are needed that investigate a wider range of nicotine deprivation. Nevertheless, the evidence available suggests that smoking VLNC versus NNC cigarettes may fail to fully reverse abstinence-induced impairments in long-term memory across a range of different recall arrangements and durations.

3.7. Response variability

Two studies examined response variability (AhnAllen et al., 2015; McClernon et al., 2016), with both (100%) reporting worse performance among those who smoked VLNC versus NNC cigarettes (Table 2). The studies were similar in several ways: Both defined response variability as the standard deviation of reaction time, examined extended exposure (5 h of VLNC smoking), and reported that performance was restored when an active nicotine patch was paired with VLNC smoking. The studies also differed in several ways, most notably in task (CPT-II and N-back), duration of VLNC smoking (5 and 24 h), and the comparison group (NNC cigarettes and smoking abstinence), suggesting that this effect may have broad generality.

Again, although the number of studies is small, results suggest that smoking abstinence/reduced nicotine exposure increases variability in reaction time and these disruptions are not fully ameliorated by smoking VLNC cigarettes, although they can be restored by NRT. Of note, similar results were reported in 8 of 11 studies on reaction time, suggesting that multiple aspects of reaction time are sensitive to withdrawal-induced disruption.

3.8. Motor control/functioning

Two studies examined motor control (Rose et al., 2004; AhnAllen et al., 2015), with neither (0/2) reporting differences in performance (Table 1) among those who smoked VLNC versus NNC cigarettes. The studies used distinct designs (acute versus extended exposure) and tasks (fine versus gross motor), suggesting that negative results were not specific to these variables. Neither study included a design that could document that withdrawal-induced performance disruptions occurred, leaving the possibility that there was no opportunity to discern differences between the two cigarette types. Additional studies are needed before any conclusions can be reached.

3.9. Visuospatial processing

Two studies examined visuospatial processing (Lee et al., 2011; Buchhalter et al., 2005), with neither (0/2) reporting differences in performance (Table 4) after smoking VLNC versus NNC cigarettes. Although the two studies differed in design (acute versus 5 days of VLNC smoking), both required smoking abstinence/reduced nicotine exposure for 24 h and used the Digit Symbol Substitution Task (DSST). The designs in both studies permitted

assessment of whether performance was disrupted by nicotine deprivation. There was no evidence of performance disruptions in either study, precluding an opportunity to discern differences in the ability of the two cigarette types to restore performance. These limited data suggest that visuospatial processing may be less sensitive to withdrawal-induced disruption and thus not differentially impacted by smoking VLNC or NNC cigarettes.

3.10. Learning

One study examined learning (Lee et al., 2011) using the Repeated Acquisition (RA) task. The authors were able to document that performance was disrupted after 24 h of smoking abstinence. However, smoking neither a VLNC nor NNC cigarette restored performance. While this limited data suggests that learning is sensitive to withdrawal-induced disruption, further assessment of the relative efficacy of VLNC and NNC cigarettes to restore disruptions is warranted.

3.11. Verbal fluency

One study examined verbal fluency (Smith et al., 2002) and found no differences in performance (Table 4) when abstinent schizophrenic smokers smoked VLNC versus NNC cigarettes. Performance did not improve relative to the abstinent baseline when participants smoked either VLNC or NNC cigarettes, ruling out the possibility that these cigarettes were equally effective at restoring performance disruptions. However, the study design could not address whether performance was disrupted due to smoking abstinence. Although little can be concluded with a single study, this data further underscores the importance of using research designs that allow documentation of withdrawal-induced performance disruption.

4. Discussion

The results from this review suggest that smoking VLNC cigarettes may fail to reverse withdrawal-induced disruptions in performance following complete smoking abstinence or reduced nicotine exposure. Of the 19 studies reviewed herein, 15 reported significant differences in performance when smokers smoked VLNC versus NNC cigarettes. All results were in the direction of performance being worse when participants smoked VLNC relative to NNC cigarettes.

The strength of evidence suggesting that VLNC cigarettes fail to restore withdrawal-induced performance disruptions varied across domains. Seventy percent or more of studies examining reaction time, long-term memory, and response variability reported worse performance among those who smoked VLNC versus NNC cigarettes, indicating that these domains may be particularly sensitive to withdrawal-induced disruption. The evidence is strongest in reaction time, where 8 of 11 studies documented the effect. Conclusions regarding response variability and long-term memory, which also showed ongoing disruption, must be tempered, as only two and three studies, respectively, examined these domains.

The minimal evidence of differences in a number of domains may suggest that VLNC cigarettes maintain or restore performance among nicotine-deprived smokers under certain conditions. In particular, the majority of studies examining short-term memory (70% or

7/10) and inhibitory control (75% or 3/4) noted equivalent performance after smoking VLNC and NNC cigarettes, although there was some evidence of differences among heavier smokers and after longer durations of smoking abstinence/reduced nicotine exposure. For motor control/functioning (0/2 studies), visuospatial processing (0/2 studies), learning (0/1 studies), and verbal fluency (0/1 studies), zero studies documented differences in performance after smoking VLNC versus NNC cigarettes. However, given that each of these domains were examined by two or fewer studies, it is again difficult to come to any conclusions.

Importantly, negative findings may indicate that performance was not disrupted following smoking abstinence/reduced nicotine exposure, or alternatively, that VLNC and NNC cigarettes were equally effective at restoring disrupted performance. In many instances it was impossible to distinguish between those two possibilities. In those studies that were designed in such a way as to indirectly address this question, there was evidence supporting both hypotheses but more pointing to a lack of disruption. Future studies may wish to employ more complex designs (i.e., baseline measures during nicotine satiation and deprivation) to allow determination of whether there was a withdrawal-induced disruption in performance.

The relative paucity of parametric research examining how duration of nicotine deprivation impacts VLNC versus NNC performance effects precludes firm conclusions. However, as might be expected, disruptions in performance after smoking VLNC versus NNC cigarettes were reported more often when participants were nicotine deprived for longer durations. This was particularly apparent in the domain of short-term memory, where differences were observed when participants were deprived for >10 h. This is consistent with a large body of literature indicating that nicotine withdrawal peaks at 1–3 days of abstinence, suggesting that performance deficits would be expected to also peak during this time (Hatsukami et al., 1985; Hughes, 2007). Indeed, Hatsukami et al. (1989) compared performance (RT, response variability, and inhibitory control) after varying lengths of nicotine deprivation to an ad libitum smoking baseline. Disruptions in performance were observed after 24 h of nicotine deprivation, but not 2, 4, or 8 h (Hatsukami et al., 1989). The vast majority of studies reviewed here (84% or 16/19) investigated performance after <24 h of deprivation (Rose et al., 2004; AhnAllen et al., 2015; Bates et al., 1995; Colrain et al., 1992; Gilbert et al., 1997; Hale et al., 1999; Harrell and Juliano, 2012; Juliano et al., 2011; Kelemen, 2008; Marzilli et al., 2006; Peters and McGee, 1982; Warburton et al., 1992; Marzilli and Hutcherson, 2002; Smith et al., 2002; Krebs et al., 1994; Kelemen and Kaighobadi, 2007), which underscores a knowledge gap in this area. Future studies investigating the effects of VLNC smoking on performance after longer periods of nicotine deprivation are needed.

It is important to underscore the evidence suggesting that combined NRT and VLNC cigarettes restore disrupted performance when smoking VLNC cigarettes alone does not. While only two studies examined this issue (AhnAllen et al., 2015; McClernon et al., 2016), improvements in performance with combined NRT and VLNC smoking were observed across multiple domains including reaction time (AhnAllen et al., 2015), short-term memory (McClernon et al., 2016), inhibitory control (AhnAllen et al., 2015), and response variability (AhnAllen et al., 2015; McClernon et al., 2016). Thus, if a reduced nicotine content policy

was adopted, supplemental use of NRT and likely other non-combustible forms of nicotine (e.g., e-cigarettes) would be a viable option for protecting against the type of performance disruptions revealed in this review, although a larger number of studies directly examining this matter would be helpful.

Several limitations in this literature review merit underscoring. One limitation is that most studies examined acute exposure to VLNC cigarettes. Investigating effects of more extended use of VLNC cigarettes will be important in delineating the time-course of differences between VLNC and NNC cigarettes in performance. Further, studies investigating performance disruptions during transitions from NNC to VLNC cigarettes will also be important. Two studies in the current review (AhnAllen et al., 2015; McClernon et al., 2016) used designs where smokers were transitioned from usual brand to VLNC cigarettes, mimicking conditions under a policy involving abrupt transition to reduced nicotine content. Performance impairments when smoking VLNC cigarettes alone were noted in both studies. Both studies also noted that combining NRT with VLNC cigarettes restored performance decrements. Another gap is the absence of studies using ecologically valid measures (e.g., driving simulator, virtual reality (Jansari et al., 2013)) to test the effects of VLNC cigarettes on performance. Use of such measures will help to determine the clinical relevance of any differences during a transition from NNC to VLNC cigarettes. Finally, as only 19 studies were identified, many domains remain under-investigated. A more thorough evaluation of the extent to which VLNC cigarettes affect withdrawal-impaired performance may be warranted.

Overall, the current review makes several potential contributions. First, the review raises the possibility that VLNC cigarettes may not sufficiently ameliorate withdrawal-induced disruptions in performance. As discussed above, unrestored performance disruptions could have adverse impacts on workplace safety and productivity. Importantly, this review also identified evidence that directing smokers switching to VLNC cigarettes to supplement with NRT protects against performance disruption. Second, the review identifies important knowledge gaps, including performance domains that have been understudied (e.g., visuospatial processing, learning), examining performance during/after extended exposure to VLNC cigarettes and across a more complete time-course of nicotine withdrawal, and inclusion of pre- and post-abstinence/reduced nicotine exposure performance measures to help discern whether performance is being restored relative to a withdrawal-induced disrupted baseline or enhanced relative to an undisrupted baseline. Of course, the potential of VLNC cigarettes to reduce nicotine dependence and potentially facilitate quitting among current smokers outweighs any time-limited risks of withdrawal-related performance decrements. However, the risks of such potential decrements are not trivial. As such, careful consideration of these potential unintended consequences and the potential to remedy them through the use of alternative sources of nicotine is worthwhile in the process of considering a national policy lowering the nicotine content of cigarettes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
Flowchart of studies included in review.

Table 1

Reaction time, response variability, and motor control.

Investigators	Participants	Period of abstinence and/or reduced nicotine exposure	Type of study design	Conditions/nicotine dose (mg)	Task and summary of results	Evidence for differences in performance between VLNC and larger nicotine dose?	Notes
McClemon et al. (2016)	33 smokers who smoked 10 cigarettes/day for at least 2 years	24 h; Participants either abstained from smoking or smoked VLNC only for 24 h; verified by expired CO (ABST CO = 3.6 ppm; VLNC CO = 15.3 ppm; no diff in CO by patch condition	Mixed conditions; No smoking condition	1	No smoking + placebo patch	1) N-back working memory task	Training session in mock scanner where participants required to achieve at least 40% accuracy on 2-back condition within 4 practice attempts
				2	No smoking + 21 mg patch	Complex RT: No diff between smoking abstinence and all other conditions	
				3	0.05 mg nic delivery/cig smoking for 24 h + placebo patch		
				4	0.05 mg nic delivery/cig for 24 h + 21 mg patch	RT variability: No difference in RT variability between smoking abstinence and VLNC, significantly improved when active patch present	
Marzilli et al. (2006)	11 smokers who smoked 20 cigarettes/day for at least 2 years; FTND 7	12 h; Verified by expired CO; mean CO = 10.46 ppm	Mixed conditions; Pre vs. post smoking comparison	1	0.05 mg nic delivery/cig	1) Simple reaction time task	Subjects trained with response manipulatives (mouse, keyboard, RT device). Practice with RT device to reduce learning effect. 10 min to adapt to session room
				2	0.6 mg nic delivery/cig	Simple RT: No difference in RT pre vs. post VLNC smoking, performance significantly improved with 0.6 mg	
Marzilli and Hutcherson (2002)	7 male smokers who either a) had CO > 20 or b) smoked 20 cigarettes/day for at least 2 years	12 h; Verified by expired CO < 7	Mixed conditions; Pre vs. post smoking comparison	1	0.0 mg nic/cig	1) Simple reaction time task	Simple RT: yes
				2	7.7 mg nic/cig	Simple RT:	

Investigators	Participants	Period of abstinence and/or reduced nicotine exposure	Type of study design	Conditions/nicotine dose (mg)	Task and summary of results	Evidence for differences in performance between VLNC and larger nicotine dose?	Notes
Smith et al. (2002)	31 smokers in inpatient hospital with schizophrenia or schizoaffective disorder; all currently taking one or more neuroleptic medications; cigarettes/day not reported. Mean FTND = 4.5 ± 2.1	10–12 h; Verified by inpatient ward staff and logbook; verified by expired CO 10 ppm	Mixed conditions; Pre vs. post smoking comparison	1	0.1 mg nic delivery/cig	No difference in RT pre vs. post VLNC smoking; performance significantly improved with 7.7 mg	Procedure note: smoked 2 cigs, completed interview/surveys for 45 min, smoked 2 more cigs. Cog tests administered 10 min after final cig. 45 min later, smoke a cig and repeat cog tests Additional interest of results of VLNC reversed negative (but not positive) schizophrenic symptoms
				2	1.9 mg nic delivery/cig	Complex RT: no significant difference between VLNC and 1.9 mg, but both improved performance relative to abstinence	
				3	10 mg nic nasal spray	Complex RT: no significant difference between VLNC and 1.9 mg, but both improved performance relative to abstinence	
				4	Placebo nasal spray	Complex RT: no significant difference between VLNC and 1.9 mg, but both improved performance relative to abstinence	
Hale et al. (1999)	10 smokers who smoked 20 cigarettes/day for at least 1 year	4–7 h; Not verified; instructed not to smoke for 4 h prior to session, but tested between 0 and 3 h after arriving	Mixed conditions; Pre vs. post smoking comparison	1	0.05 mg nic delivery/cig	1) Lexical decision making RT task Complex RT: No difference in RT between no smoking and VLNC	Procedure note: task performance compared pre-smoking vs. post-smoking; participants completed one practice test
				2	0.7 mg nic delivery/cig	Complex RT: yes	

Investigators	Participants	Period of abstinence and/or reduced nicotine exposure	Type of study design	Conditions/nicotine dose (mg)	Task and summary of results	Evidence for differences in performance between VLNC and larger nicotine dose?	Notes
Harrell and Juliano (2012)	80 smokers who smoked between 6 and 40 cigarettes/day; mean = 14.2 $\pm$ 2.3 cigs/day; mean FTND = 4.1 $\pm$ 2.3	12 h; Verified by expired CO; mean CO = 9.18 $\pm$ 0.96 ppm	Between conditions	<p>1 0.05 mg nic delivery/cig</p> <p>2 0.6 mg nic delivery/cig</p>	<p>conditions, performance significantly improved with 0.7 mg</p> <p>1) RVIP Participants completed one practice session</p> <p>Complex RT: No difference in RT across conditions</p> <p>Complex RT: no</p>		
Rose et al. (2004)	48 smokers who smoked 20 cigarettes/day; baseline CO = 15 ppm	5.5 h; CO measured before and after start of session; data not reported.	Between conditions	<p>1 0.06 or 0.1 mg nic delivery/cig</p> <p>2 Usual brand cig</p>	<p>1) Two choice RT</p> <p>Complex RT: No difference in RT across conditions</p> <p>2) Spatial rotation task</p> <p>Complex RT: RT slower for VLNC compared to 0.7 mg</p> <p>3) Finger tapping task</p> <p>Motor control: No difference in performance across conditions</p> <p>Motor control: no</p>	<p>1) Complex RT: no</p> <p>2) Complex RT: yes</p>	<p>Procedure note. One cig smoked through controlled smoke delivery apparatus matched to individual ad lib smoking behavior assessed at baseline; then 2 h ad lib session. Cog tasks administered before and after controlled smoking; pre vs. post smoking comparisons not reported.</p>
Ahn/Allen et al. (2015)	26 control smokers without psychiatric illness; 30 smokers with schizophrenia or schizoaffective	5 h; Participants not required abstaining before session. During 5 h controlled	Between conditions	<p>1 0.05 mg nic delivery/cig + placebo patch</p> <p>2 0.05 mg nic delivery/cig + 42 mg nic patch</p>	<p>1) Conners Continuous Performance task (CPT II)</p> <p>Simple RT: RT slower for VLNC +</p>	<p>Controls 1)</p> <p>Simple RT: yes</p> <p>Schizophrenics 1)</p> <p>Simple RT: yes</p>	<p>Data from conditions with smoking abstinence not reported. All results identical between</p>

Investigators	Participants	Period of abstinence and/or reduced nicotine exposure	Type of study design	Conditions/nicotine dose (mg)	Task and summary of results	Evidence for differences in performance between VLNC and larger nicotine dose?	Notes
disorder; Participants smoked 20–50 cigarettes/day for 1 year; FTND 6; smoking rate matched across schizophrenia and controls		smoking session; participants either remained abstinent (±active patch), smoked VLNC cigs (±active patch) or smoked usual brand cigs		3 Smoking abstinence + 42 mg nic patch	placebo patch compared to usual brand		schizophrenics and controls. Procedure note: 5 h controlled smoking session matched to ad lib smoking during baseline assessment; cog tests administered afterward
				4 Smoking abstinence + placebo patch	and VLNC + active patch conditions RT variability: yes RT variability: worse for VLNC +	RT variability: yes	
				5 Usual brand cig	placebo patch compared to usual brand and VLNC + active patch conditions		
				2) RVIP	2) RVIP	2)	
				Complex RT: RT slower for VLNC + placebo patch compared to usual brand and VLNC + active patch conditions	Complex RT: RT slower for VLNC + placebo patch compared to usual brand and VLNC + active patch conditions	Complex RT: yes	
				3) Simple RT task	3) Simple RT task	3)	
				Simple RT: No difference in RT across conditions	Simple RT: No difference in RT across conditions	Simple RT: no	
				4) Delayed match to sample task (visual recognition memory)	4) Delayed match to sample task (visual recognition memory)	4)	
				Complex RT: No difference in RT across conditions	Complex RT: No difference in RT across conditions	Complex RT: no	
				5) Motor screening task	5) Motor screening task	5)	

Investigators	Participants	Period of abstinence and/or reduced nicotine exposure	Type of study design	Conditions/nicotine dose (mg)	Task and summary of results	Evidence for differences in performance between VLNC and larger nicotine dose?	Notes
Kelemen (2008)	103 smokers who smoked cigarettes/day; mean FTND = 3.3 ± 1.9	5 h; Verified by expired CO; mean CO = 6.1 ± 4.0 ppm; excluded if CO 15 ppm	Between conditions	1	0.05 mg nic delivery/cig	Motor control: no No differences across conditions	Procedure note: pre vs. post smoking analyses not reported. Difference scores (post-cig minus pre-cig) were computed for each type of cig and then compared across cigs.
				2	0.6 mg nic delivery/cig	1) RVIP Complex RT: RT slower for VLNC compared to 0.6 mg	
Juliano et al. (2011)	148 smokers who smoked cigarettes/day for 1 year; mean cigs/day = 13.56 ± 5.60; mean years smoking = 10.59 ± 10.30 yrs; mean FTND = 3.76 ± 2.11	3 h; CO measured before and after start of session; data not reported	Between conditions	1	0.05 mg nic delivery/cig	1) RVIP	Procedure note: pre vs. post smoking data/analysis not reported. Participants completed one 12 min practice trial of RVIP
				2	0.6 mg nic delivery/cig	Complex RT: RT slower for VLNC compared to 0.6 mg	
Bates et al. (1995)	19 smokers who smoked 5–25 cigarettes/day	2 h; Verbal confirmation of smoking abstinence	Between conditions	1	Denicotinized cig (Philip Morris, Inc.; denicotinized by gas process)	1) Modified reaction time task	Participants completed 32 practice trials
				2	0.8 mg nic delivery/cig	Simple RT: RT slower for VLNC compared to 0.8 mg	

Notes. RT = reaction time; Nic = nicotine; VLNC = very low nicotine content cigarette; Cig = cigarette; CO = expired carbon monoxide in parts per million; FTND = Fagerstrom Test for Nicotine Dependence; RVIP = Rapid Visual Information Processing task.

Table 2

Short-term memory, long-term memory, and learning.

Investigators	Participants	Period of abstinence and/or reduced nicotine exposure	Type of study design	Conditions/nicotine dose (mg)	Tasks and summary of results	Evidence for differences in performance between VLNC and larger nicotine dose?	Notes
McClemon et al. (2016)	33 smokers who smoked 10 cigarettes/day for at least 2 years	24 h; Participants either abstained from smoking or smoked VLNC only for 24 h; verified by expired CO (ABST CO = 3.6 ppm; VLNC CO = 15.3 ppm; no diff in CO by patch condition)	Mixed conditions; No smoking condition	<p>1 No smoking + placebo patch</p> <p>2 No smoking + 21 mg patch</p> <p>3 0.05 mg nic delivery/cig smoking for 24 h + placebo patch</p> <p>4 0.05 mg nic delivery/cig for 24 h + 21 mg patch</p>	<p>1) N-back working memory task</p> <p>Accuracy (short-term memory): No difference in accuracy between smoking abstinence and VLNC, performance significantly improved with active patch</p>	Short-term memory: yes	Training session in mock scanner where participants required to achieve at least 40% accuracy on 2-back condition within 4 practice attempts
Lee et al. (2011)	20 smokers; mean cigs/day = 15.5 ± 6.9 ; baseline CO 12 ppm	24 h; Verified by expired CO 10 ppm; mean CO = 5.1 ± 1.9 ppm	Mixed conditions; No smoking condition	<p>1 No smoking</p> <p>2 0.05 mg nic delivery/cig</p> <p>3 0.6 mg nic delivery/cig</p> <p>4 0.9 mg nic delivery/cig</p>	<p>1) Repeated acquisition task</p> <p>Acquisition phase Correct (learning): Not impaired; no differences across condition</p> <p>Incorrect (learning): Impaired; no differences across conditions</p> <p>Errors index of curvature (learning): Not impaired; no difference across conditions</p>	Learning: no	During training session, participants practiced tasks until performance was consistent and accurate across consecutive trials

Investigators	Participants	Period of abstinence and/or reduced nicotine exposure	Type of study design	Conditions/nicotine dose (mg)	Tasks and summary of results	Evidence for differences in performance between VLNC and larger nicotine dose?	Notes			
Smith et al. (2002)	31 smokers in inpatient hospital with schizophrenia or schizoaffective disorder; all currently taking one or more neuroleptic medications; cigarettes/day not reported. Mean FTND = 4.5 ± 2.1	10–12 h; Verified by inpatient ward staff and logbook; verified by expired CO 10 ppm	Mixed conditions; Pre vs. post smoking comparison	1	0.1 mg nic delivery/cig	Performance phase Correct (short-term memory): Impaired; fewer correct with VLNC relative to both active nicotine conditions Short-term memory: yes	Procedure note: Smoked 2 cigs, completed interview/ surveys for 45 min, smoked 2 more cigs. Cog tests administered 10 min after final cig. 45 min later, smoke a cig and repeat cog tests Additional results of interest: VLNC reversed negative (but not positive) schizophrenic symptoms			
				2	1.9 mg nic delivery/cig					
				3	10 mg nic nasal spray	Incorrect (short-term memory): Not impaired; more incorrect with VLNC relative to both active nicotine conditions Short-term memory: yes				
				4	Placebo nasal spray					
								1)	ANAM neurocognitive battery, moderate repeat	Short-term memory: no
									Verbal memory (short-term memory): No difference between smoking abstinence and all conditions Visual match to sample (short-term memory): No significant difference between VLNC and 1.9 mg cig, but both improved performance relative to abstinence	Short-term memory: no

Investigators	Participants	Period of abstinence and/or reduced nicotine exposure	Type of study design	Conditions/nicotine dose (mg)	Tasks and summary of results	Evidence for differences in performance between VLNC and larger nicotine dose?	Notes
Colrain et al. (1992)	39 smokers who smoked 5 cigarettes/day; mean baseline CO = 14.27 ± 8.21 ppm	2 h; Not verified	Mixed conditions; No smoking condition	1	No smoking	2) Randt memory test (short-term memory)	<p>Procedure note: Participants completed acquisition phase of task, then smoked, then were tested to criterion. Also re-tested 1 week later.</p>
				2	0.07 mg nic delivery/cig	No difference between smoking abstinence and all conditions	
				3	0.6 mg nic delivery/cig	Short-term memory: no	
				4	1.12 mg nic delivery/cig	<p>1) Paired-associate learning task (PAL)</p> <p>Errors before achieving criterion (learning): No difference between smoking abstinence and VLNC, significantly improved with 0.6 mg cig, intermediate value for 1.12 mg cig</p> <p>Learning: yes</p>	
Peters and McGee (1982) Exp. 2	56 smokers who smoked 12	10 h; Not verified	Between conditions	1	0.2 mg nic delivery/cig	<p>Errors 1 week later (long-term memory): No difference in errors between smoking abstinence, VLNC, and 1.12 mg cig. performance significantly improved with 0.6 mg cig</p> <p>1) Immediate free recall (short-term memory):</p>	<p>Procedure note: On day 2, participants received either</p>
						Long-term memory: yes	

Investigators	Participants	Period of abstinence and/or reduced nicotine exposure	Type of study design	Conditions/nicotine dose (mg)	Tasks and summary of results	Evidence for differences in performance between VLNC and larger nicotine dose?	Notes
Warburton et al. (1992)	20 smokers who smoked 15 cigarettes/day	10 h; Verified by expired CO; data not reported	Between conditions	2	1.4 mg nic delivery/cig	2) Day 2 recognition memory: Proportion correct (long-term memory): H-L group performed worse than H-H, L-L, and L-H groups; no difference between H-H and L-L	2) Long-term memory: yes
				1	0.1 mg nic delivery/cig	1) Immediate free recall (short-term memory): Fewer correct after VLNC compared to 0.6 mg	1) Short-term memory: yes
				2	1.4 mg nic delivery/cig	Early position (memory): No difference across conditions	Early position (memory): no
						Late position (attention): Worse recall after VLNC compared to 0.6 mg cig	Late position (attention): yes
				2)	Delayed free recall		
							Procedure note: Authors wanted to see if nic affected memory storage/consolidation (early position) vs. attention (late position) in memory task that uses very long word lists.
							Long-term memory: yes
							Short-term memory: yes

Investigators	Participants	Period of abstinence and/or reduced nicotine exposure	Type of study design	Conditions/nicotine dose (mg)	Tasks and summary of results	Evidence for differences in performance between VLNC and larger nicotine dose?	Notes
Kelemen and Kaighobadi (2007)	103 smokers who smoked 10 cigarettes/day for at least 1 year; mean FTND = 9.3 ± 0.4	8 h; Verified by expired CO; mean CO = 6.2 ± 0.5 ppm; excluded if CO 15 ppm	Between conditions	1 0.05 mg nic delivery/cig 2 0.6 mg nic delivery/cig	(long-term memory): Fewer correct after VLNC compared to 0.6 mg	Long-term memory: yes	
					Early position (memory): Worse recall after VLNC compared to 0.6 mg	Early position (memory): no	
					Late position (attention): No diff across conditions	Late position (attention): yes	
					1) Free recall (short-term memory): 2) Prospective memory test (short-term memory): No difference across conditions	1) 2) Short-term memory: no	
Rose et al. (2004)	48 smokers who smoked 20 cigarettes/day; baseline CO 15 ppm	5.5 h; CO measured before and after start of session; data not reported.	Between conditions	1 0.06 or 0.1 mg nic delivery/cig 2 Usual brand cig	1) ANAM neurocognitive battery, moderate repeat Visual match to sample (short-term memory): No difference across conditions	Short-term memory: no	Procedure note: One cig smoked through controlled smoke delivery apparatus matched to individual ad lib smoking at baseline; then 2 h ad lib session. Cog tasks administered before and after controlled smoking; pre vs. post smoking

Investigators	Participants	Period of abstinence and/or reduced nicotine exposure	Type of study design	Conditions/nicotine dose (mg)	Tasks and summary of results	Evidence for differences in performance between VLNC and larger nicotine dose?	Notes
AlmAllen et al. (2014)	26 control smokers without psychiatric illness; 30 smokers with schizophrenia or schizoaffective disorder; Participants smoked 20–50 cigarettes/day for 1 year; FTND = 6; smoking rate matched across schizophrenia and controls	5 h; Participants not required abstaining before session. During 5 h controlled smoking session, participants either remained abstinent (±active patch), smoked VLNC cigs (±active patch) or smoked usual brand cigs	Between conditions	1	0.05 mg nic delivery/cig + placebo patch	1) ANAM neurocognitive battery, moderate repeat	comparisons not reported. Data from conditions with smoking abstinence not reported. All results identical between schizophrenia and controls. Procedure note: 5 h controlled smoking session matched to ad lib smoking during baseline assessment; cog tests administered afterward
				2	0.05 mg nic delivery/cig + 42 mg nic patch	Visual match to sample (short-term memory; accuracy); No difference in performance across conditions	1) Schizophrenics
				3	Smoking abstinence + 42 mg nic patch		Short-term memory: no
				4	Smoking abstinence + placebo patch		
				5	Usual brand cig		
Kelemen (2008)	103 smokers who smoked 10 cigarettes/day; mean FTND = 3.3 ± 1.9	5 h; Verified by expired CO; mean CO = 6.1 ± 4.0 ppm; excluded if CO 15 ppm	Between conditions	1	0.05 mg nic delivery/cig	1) Cued recall (short-term memory);	Procedure note: pre vs. post smoking analyses not reported. Difference scores (post-cig minus pre-cig) were computed for each type of cig and then compared across cigs.
				2	0.6 mg nic delivery/cig	No differences in performance across conditions	Short-term memory: no
Krebs et al. (1994)	45 daily smokers who smoked for 3 months	2 h; Not verified; subjects instructed to smoke 1 cig 2 h prior to session and then abstain	Between conditions	1	0.1 mg nic delivery/cig	1) Free recall (short-term memory);	
				2	0.7 mg nic delivery/cig	Trend (p = 0.068) for increasing recall with increasing nicotine dose	Short-term memory: no
				3	1.5 mg nic delivery/cig		

Notes. Nic = nicotine; VLNC = very low nicotine content cigarette; Cig = cigarette; CO = expired carbon monoxide in parts per million; FTND = Fagerstrom Test for Nicotine Dependence; ANAM = Automated Neuropsychological Assessment Metrics.

Table 3

Sustained attention and inhibitory control.

Investigators	Participants	Period of abstinence and/or reduced nicotine exposure	Type of study design	Conditions/nicotine dose (mg)	Task and summary of results	Evidence for differences in performance between VLNC and larger nicotine dose?	Notes
Lee et al. (2011)	20 smokers; mean cigs/day = 15.5 ± 6.9 ; baseline CO = 12 ppm	24 h; Verified by expired CO = 10 ppm; mean CO = 5.1 ± 1.9 ppm	Mixed conditions; No smoking condition	1 No smoking	1) RVIP	Sustained attention: no	During training session, participants practiced tasks until performance was consistent and accurate across consecutive trials
				2 0.05 mg nic delivery/cig	Rate (sustained attention; increases with correct); Not impaired; no difference in rate across conditions		
				3 0.6 mg nic delivery/cig			
				4 0.9 mg nic delivery/cig			
Harrell and Juliano (2012)	80 smokers who smoked between 6 and 40 cigarettes/day; mean = 14.2 ± 2.3 cigs/day; mean FTND = 4.1 ± 2.3	12 h; Verified by expired CO; mean CO = 9.18 ± 0.96 ppm	Between conditions	1 0.05 mg nic delivery/cig	Commission errors (inhibitory control; false alarms) Not impaired; no difference in errors across conditions	Inhibitory control: no	Participants completed one practice session
				2 0.6 mg nic delivery/cig	Hits (sustained attention; # correct); Fewer hits for VLNC		

Investigators	Participants	Period of abstinence and/or reduced nicotine exposure	Type of study design	Conditions/nicotine dose (mg)	Task and summary of results	Evidence for differences in performance between VLNC and larger nicotine dose?	Notes
Gilbert et al. (1997)	12 smokers who smoked 15 cigarettes/day	8 h; Not verified	Between conditions	1 0.05 mg nic delivery/cig 2 1.0 mg nic delivery/cig 3 Usual brand cig	compared to 0.6 mg	Sustained attention: yes	Sensitivity (sustained attention; hits/false alarms) Worse sensitivity for VLNC compared to 0.6 mg
					1) RVIP		
					Hits (sustained attention; # correct); Fewer hits for VLNC compared to 1.0 mg and usual brand		
					Sustained attention: yes		
Kelemen (2008)	103 smokers who smoked 10 cigarettes/day; mean FTND = 3.3 ± 1.9	5 h; Verified by expired CO; mean CO = 6.1 ± 4.0 ppm; excluded if CO 15 ppm	Between conditions	1 0.05 mg nic delivery/cig 2 0.6 mg nic delivery/cig	Commission errors (inhibitory control; false alarms) No difference in errors across conditions	Inhibitory control: no	Procedure note: Pre vs. post smoking analyses not reported. Difference scores (post-cig minus pre-cig) were computed for each type of cig and then compared across cigs.
					1) RVIP		
					Sensitivity (sustained attention; D'); No differences in sensitivity across conditions		
					Sustained attention: no		

Investigators	Participants	Period of abstinence and/or reduced nicotine exposure	Type of study design	Conditions/nicotine dose (mg)	Task and summary of results	Evidence for differences in performance between VLNC and larger nicotine dose?	Notes
AbnAllen et al. (2014)	26 control smokers without psychiatric illness; 30 smokers with schizophrenia or schizoaffective disorder; Participants smoked 20–50 cigarettes/day for 1 year; FTND 6; matched rate across schizophrenia and controls	5 h; Participants not required abstaining before session. During 5 h controlled smoking session, participants either remained abstinent ($\pm$ active patch), smoked VLNC cigs ($\pm$ active patch) or smoked usual brand cigs	Between conditions	1	0.05 mg nic delivery/cig + placebo patch	Controls 1) Connors Continuous Performance task (CPT II)	Data from conditions with smoking abstinence not reported. All results identical between schizophrenia and controls. Procedure note: 5 h controlled smoking session matched to ad lib smoking during baseline assessment; cog tests administered afterward
				2	0.05 mg nic delivery/cig + 42 mg nic patch	Sustained attention: no	
				3	Smoking abstinence +42 mg nic patch	Sustained attention: no	
				4	Smoking abstinence + placebo patch	Inhibitory control: yes	
				5	Usual brand cig	Inhibitory control: yes	
				2) RVIP		2)	Sustained attention: no
				Sensitivity (sustained attention; A'); No difference in sensitivity across conditions		3)	
				3) Simple RT task		3)	
				Commission errors (inhibitory control; false alarms)		Inhibitory control: yes	Inhibitory control: yes

Investigators	Participants	Period of abstinence and/or reduced nicotine exposure	Type of study design	Conditions/nicotine dose (mg)	Task and summary of results	Evidence for differences in performance between VLNC and larger nicotine dose?	Notes
Juliano et al. (2011)	148 smokers who smoked 10 cigarettes/day for 1 year; mean cigs/day = 13.56 ± 5.60 ; mean years smoking = 10.59 ± 10.30 yrs; mean FTND = 3.76 ± 2.11	3 h; CO measured before and after start of session; data not reported	Between conditions	<p>1 0.05 mg nic delivery/cig</p> <p>2 0.6 mg nic delivery/cig</p>	<p>More errors for VLNC + placebo patch relative to usual brand cig and VLNC + active patch conditions</p> <p>1) RVIP Hits (sustained attention; # correct): Fewer hits for VLNC compared to 0.6 mg</p> <p>Sensitivity (sustained attention; hits/false alarms) Worse sensitivity for VLNC compared to 0.6 mg</p> <p>Commission errors (inhibitory control; false alarms) No diff in errors across conditions</p>	<p>Sustained attention: yes</p> <p>Sustained attention: yes</p>	<p>Procedure note: Pre vs. post smoking data/analysis not reported. Participants completed one 12 min practice trial of RVIP</p>

Visuospatial processing and verbal fluency.

Table 4

Investigators	Participants	Period of abstinence and/or reduced nicotine exposure	Type of study design	Conditions/nicotine dose (mg)	Task and summary of results	Evidence for differences in performance between VLNC and larger nicotine dose?	Notes
Buchhalter et al. (2005)	32 smokers who smoked 15 cigarettes/day for 2 years; baseline CO = 15 ppm; mean FTND = 5.4 ± 1.7	5 days; Verified by expired CO relative to baseline CO; compliance was reinforced monetarily	Mixed conditions; No smoking condition	1	No smoking	1) DSST (visuospatial processing)	During training session, participants practiced tasks until performance was consistent and accurate across consecutive trials
				2	0.05 mg nic delivery/cig	Correct: No impaired; no difference in performance across conditions	
				3	0.6 mg nic delivery/cig	Visuospatial processing: no	
Lee et al. (2011)	20 smokers; mean cigs/day = 15.5 ± 6.9; baseline CO = 12 ppm	24 h; Verified by expired CO = 10 ppm; mean CO = 5.1 ± 1.9 ppm	Mixed conditions; No smoking condition	1	No smoking	1) DSST (visuospatial processing)	During training session, participants practiced tasks until performance was consistent and accurate across consecutive trials
				2	0.05 mg nic delivery/cig	Correct: No impaired; no difference in performance across conditions	
				3	0.6 mg nic delivery/cig	Visuospatial processing: no	
				4	0.9 mg nic delivery/cig	Visuospatial processing: no	
Smith et al. (2002)	31 smokers in inpatient hospital with schizophrenia or schizoaffective disorder; all currently taking one or more neuroleptic medications; cigarettes/day not reported. Mean FTND = 4.5 ± 2.1	10–12 h; Verified by inpatient ward staff and logbook; verified by expired CO = 10 ppm	Mixed conditions; Pre vs. post smoking comparison	1	0.1 mg nic delivery/cig	1) Verbal fluency task	Procedure note: smoked 2 cigs, completed interview/surveys for 45 min, smoked 2 more cigs. Cog tests administered 10 min after final cig. 45 min later, smoke a cig and repeat cog tests Additional results of interest: VLNC reversed negative (but not positive) schizophrenic symptoms
				2	1.9 mg nic delivery/cig	Verbal fluency: no	
				3	10 mg nic nasal spray	Not impaired; no difference in performance across conditions	
				4	Placebo nasal spray		

Notes. Nic = nicotine; VLNC = very low nicotine content cigarette; Cig = cigarette; CO = expired carbon monoxide in parts per million; FTND = Fagerstrom Test for Nicotine Dependence; DSST: Digit Symbol Substitution Task.