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**Neuropsychological assessment fails to predict relapse among cigarette smokers :
A prospective study of neurocognitive abilities**

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Abstract

Objectives. Understanding the factors that lead to relapse is a major challenge for the clinical support of smoking cessation. Neurocognitive abilities such as attention, executive functioning and working memory, are possible predictors of relapse and can be easily assessed in everyday clinical practice. In this prospective longitudinal study, we investigated the relationship between pre-smoking cessation neurocognitive performance and relapse at six months in a sample of patients being treated for their tobacco dependence.

Methods. 130 tobacco consumers were included in the study. They completed a comprehensive neuropsychological and clinical assessment before smoking cessation. The targeted abilities were intelligence, inhibition, shifting, working memory updating, verbal fluency and decision-making.

Results. The rate of tobacco relapse at 6 months was 58%. Logistic regressions were used to assess which variables best explained relapse. None of the neuropsychological tests was a significant predictor of relapse at either 1, 3 or 6 months, either alone, or controlling for other covariates acting as significant predictors of relapse.

Conclusions. Common neuropsychological tests, even those specifically targeting executive functioning such as inhibition, are not useful predictors of the success of a smoking cessation program in a clinical setting. Other variables, such as motivation to quit smoking or the presence of comorbid depression or anxiety disorders, appear to be more useful predictors of relapse.

Keywords: tobacco relapse, neuropsychological assessment, executive functioning, inhibition, working memory

1. Introduction

Despite the prevalence of tobacco consumption having decreased of about 25% in 14 years, it remains relatively high, with 17% of the world's population using tobacco [1], smoking cessation constitutes a major stake for public health policies. Unfortunately, smoking cessation represents a major challenge: as many as 70% of patients relapse on the 6 first months following detoxification [2]. A better understanding of the factors influencing relapse is thus urgently needed to improve treatment outcomes.

Many factors have been shown to affect relapse risk. Based on the classic biopsychosocial model [3,4], three main categories of relapse predictors have been identified: (1) Biological and physiological factors, (nicotine has been noted as more addictive than alcohol, marijuana and cocaine [5]); (2) Socio-demographic factors (relapse is more likely in e.g. smokers with an earlier initiation age [6], smokers with a lower socio-economical status [7], or smokers who live with other smokers [8]); and (3) Psychiatric factors (especially the presence of comorbidities such as depression [9] or another drug abuse problem [6]).

Psychological processes are also thought to play a critical role in tobacco relapse, and these processes have been comparatively less studied, which makes them a critical avenue of current research. The influential dual-process model of addiction [10] postulates that two neuropsychological systems are involved in addictive states: (1) the "affective/ automatic system", an appetitive system underpinned by limbic structures and involved in the impulsive processing of a stimulus, triggering automatic responses based on associative learning; and (2) the "reflective system", a control and inhibitory system underpinned by frontal regions, involved in the cognitive processing of stimuli, relying on memory and executive functions and initiating controlled-deliberate response. Tobacco-use disorders would develop when there is an imbalance between these two systems, such that the impulsive system becomes sensitized – for example, by repeated exposure to cigarette and accompanying reward – while the reflective

1 regulatory system is compromised (possibly due to frontal dysfunction related to the neurotoxic
2 effect of the substance), leading to dysregulated approach and consumption in the presence of
3 tobacco-related cues.

4 This model has been widely used in alcohol use disorders, but remains to be thoroughly
5 explored in nicotine dependence. Early works mostly focused on the automatic system by
6 exploring the role of craving, usually defined as the "urge to smoke" [11], in relapse [12]. This
7 intense focus on the affective/automatic system (see for example [13]) was accompanied by
8 very limited investigation of the reflective system, potentially due to the fact that, contrary to
9 other addicted populations (e.g., alcohol-dependent individuals), tobacco smokers do not
10 usually present massive cognitive disorders.

11 However, recent works have also started exploring neurocognitive functions related to
12 the reflective system [14,15]. Memory, learning, and especially executive control (the ability to
13 control one's behavior in a situation that cannot be solved automatically, with a focus on
14 inhibition: the ability to inhibit unwanted thoughts or behaviors) [16–18] have been identified
15 as predictors of smoking or relapse. For instance, a recent study exploring impairment of
16 neurocognitive functions (memory, attention, language and impulsivity) in a large sample of
17 smokers ($N = 1002$) [19] showed reduced visual attention and increased cognitive impulsivity
18 among smokers compared to non-smokers. These and other results [20–22] underline the role
19 played by attention and inhibition in the emergence and/or maintenance of nicotine dependence.
20 A more recent study also showed cognitive difficulties in tobacco users, especially for selective
21 attention, alternating attention, short-term and working memory, long-term memory, processing
22 accuracy, and executive functioning [23].

23 Despite these interesting preliminary results, prior studies were mostly based on cross-
24 sectional explorations of specific cognitive functions (or performance on cognitive tasks

1 considered in isolation) in the context of smoking. Studies with this design are critical to
2 identify potentially relevant psychological processes, but they present major limitations in
3 terms of clinical implications, including our own work [22]. Indeed, finding a correlation
4 between smoking and performance on a given task in a cross-sectional design does not mean
5 that assessing the corresponding psychological process will be useful in clinical practice when
6 attempting to prevent tobacco relapse. For instance, the effect size for the relation may be too
7 weak for the task to be a useful predictor of relapse; the relation between smoking and
8 performance may be more usefully captured by other predictors such as socio-demographical
9 covariates; or neurocognitive performance may be related to smoking at a given point in time
10 but fail to predict future relapse in a longitudinal design. To our knowledge, there is currently
11 no answer to these questions in the literature.

12 The objective of the current study was to bridge this gap, and capitalize on prior research
13 stressing the potential role of psychological processes as predictors of smoking and smoking
14 cessation, in order to identify relevant neurocognitive predictors of tobacco relapse. To
15 determine the clinical usefulness of these predictors, patients registering for a smoking
16 cessation program were included prospectively, and followed-up over six months with a
17 longitudinal design. All patients completed a battery of cognitive tests with a focus on the
18 reflective system. The battery included two reasoning and decision-making tasks, and five tasks
19 measuring the main functions of executive control [24] : two tasks for inhibition, and one task
20 each for working memory updating, shifting, and verbal fluency. The relation between these
21 tasks and tobacco relapse was tested, controlling for relevant socio-demographic and
22 psychiatric variables involved in the biopsychosocial model of addiction disease. We expected
23 executive control tasks – especially inhibition, the most relevant function in this context [23] –
24 to be related to tobacco relapse above and beyond other variables, indicating that executive
25 control tasks could serve as clinically useful predictors.

2. Method

2.1. Study design and participants

Patients were recruited in the context of a tobacco smoking cessation program, conducted by psychiatric units at the local university hospital in one of two academic centers (Montpellier and Clermont-Ferrand, France), over a period of 2.5 years. A total of 159 eligible patients were invited to participate in the study, out of which 130 agreed and provided usable data (mean age = 47.47 years, SD = 10.64; 58 men, 72 women). Socio-demographic data are detailed in Table 1.

All participants were current and non-deprived smokers at the time of the first assessment, completed immediately before the beginning of a smoking cessation program. Inclusion criteria were: 1) being a tobacco consumer with nicotine dependence (Fagerström \geq 3), 2) age between 18 and 60 years old, and 3) being a native or fluent French speaker. The non-inclusion criteria were pregnancy, presence of a physical disease that could interact with cognitive performance, inability to complete cognitive tests and inability to be followed for 6 months. The local institutional review board approved the study (*Comité de protection des personnes Sud-Méditerranée IV*, CHU de Montpellier, France) and all participants provided written informed consent.

Because the tobacco cessation program was conducted by psychiatric units, the sample had a higher-than-average representation of patients with psychiatric disorders. 53% of patients had a psychiatric disorder in the broad sense, mostly anxiety (16%), depression (14%) or dysthymia (11%), or excessive alcohol consumption (11%). 54% of patients were under medication, mostly benzodiazepine (22%), antidepressants (20%), or anxiolytics (19%). Presenting a comorbid psychiatric disorder or being under treatment were not exclusion criteria, and were instead controlled as covariates in statistical analyses.

1 2.2. Inclusion and follow-up

2 All patients were followed by a senior medical doctor specialized in tobacco
3 dependence. Tobacco-cessation support was chosen independently of the present study by both
4 the medical doctor and the patient after a preliminary interview, in line with recommendations.
5 The proposed supports were mostly nicotine substitute (60% of patients), pharmacological
6 treatments (mainly Bupropion or Varenicline, for 20% of patients), and/or cognitive and
7 behavioral therapy. After this preliminary interview, patients were always seen to initiate
8 treatment after the first week of smoking cessation, then at a frequency determined by the
9 therapist. The smoking cessation program was unrelated to the current study, and the doctor in
10 charge of the smoking cessation program was blind to the results of the study.

11 Participation in the study was proposed to all eligible patients immediately after the
12 initial interview. Patients who agreed to participate completed the clinical and
13 neuropsychological assessment with a trained psychologist before the initiation of smoking
14 cessation. They were then seen 3 times to assess the occurrence of a relapse: one month (+/- 7
15 days), three months (+/-7 days) and six months (+/- 15 days) after smoking cessation.

16 2.3. Data collection and assessments

17 The standardized pre-treatment preliminary interview included questions on
18 demographic characteristics, education level, employment status, marital status; medical
19 information regarding current psychiatric conditions, current medication, and the existence of
20 other current addictions; as well as information including number of smokers at home, age of
21 the first cigarette, number of attempts to stop smoking, number of cigarettes per day, and time
22 since last cigarette (see Table 1 for a summary).

23 Tobacco craving was assessed by the French Tobacco Craving Questionnaire (TCQ-12)
24 [25] (12 items assessing emotionality, expectancy, compulsivity, and purposefulness with a 7-

1 point rating scale). Level of nicotine dependence was assessed by the French version of the
2 Fagerström test [26] (six questions, total ranging from 0 to 10). Motivation to quit smoking was
3 assessed using the Richmond scale [27]. The extent of depressive symptoms was assessed using
4 the French version of the Montgomery-Asberg Depression Rating Scale (MADRS) [27] (10
5 questions each rated from 0 to 6). We also used the CAGE test (four questions scored as yes-
6 no) to assess problematic alcohol use [28].

7 Relapsers were identified based on a level of carbon monoxide above 10 ppm during
8 the control visit, and/or as self-reported consumption of at least one cigarette per day during at
9 least five consecutive days. Relapsers were dropped out of the study and did not complete the
10 next assessments. Patients who discontinued the smoking cessation program, who never
11 stopped to smoke, or who were lost to follow-up were considered as relapsers [9].

12 Neuropsychological tests were used to assess the following cognitive abilities:

13 (1) Premorbid intelligence, using the French language adaptation of the National Adult
14 Reading Test (fNART), a 33-item test of word reading using words with ambiguous
15 pronunciation. The test was scored in terms of number of errors, converted into an intellectual
16 quotient estimate (with mean 100 and standard deviation 15). [30]

17 (2) The executive function of inhibition, using the word-color Stroop, which requires
18 reading color names (W), then saying the color of "XXXX" strings printed in colored ink (C),
19 then saying the color of color names printed in colored ink (WC). The test was scored in terms
20 of response times (total response time on the color-word section, and interference score
21 computed as $WC - [(W \times C)/(W + C)]$), and number of errors on the color-word section. [31]

22 (3) The executive function of inhibition, using the Hayling test, which uses one section
23 with sentences that have to be completed using the expected word (A) and one section with
24 sentences that have to be completed using a completely unrelated word (B). The test was scored

1 in terms of response times (total response time on section B, and inhibition score computed as
2 B-A) and number of errors on section B (computed either as number of items with a fully correct
3 answer, or as a composite error score giving higher penalties for responses closer to the
4 expected word). [32]

5 (4) The executive function of working memory updating, using a spatial n -back test,
6 which presents squares located in a matrix presented on-screen, and requires the patient to
7 decide if the spatial location currently displayed is the same as the location displayed n trials
8 before. Patients performed 3 blocks of 15 trials in a 1-back condition serving as training, then
9 a 2-back (deciding whether the location displayed is the same as the location displayed two
10 trials before: 3 blocks of 15 trials), and a 3-back condition (3 blocks of 15 trials). The test was
11 scored as the total number of correct answers across all blocks, for each difficulty level
12 separately and overall. [33]

13 (5) The executive function of shifting, using the trail-making test (TMT), which includes
14 one section where the patient has to draw a path between digits 1 to 25 in ascending order (A)
15 and one section where the patient has to draw a path alternating between digits 1 to 13 and
16 letters A to L in ascending order (B). The test was scored in terms of response times (total
17 response time on section B, and shifting score computed as B-A). [34]

18 (6) Verbal fluency, using a verbal fluency test, including a semantic fluency task which
19 requires the participant to name as many words as possible belonging to the categories of
20 animals and pieces of furniture (1 minute each), and a lexical fluency task which requires the
21 participant to name as many words as possible starting with the letters P and V (1 minute each).
22 The test was scored in terms of number of correct words produced (excluding out-of-category
23 items and repetitions). [35]

1 (7) Decision-making ability and risk-taking, using the Iowa Gambling Task (IGT),
2 which requires patients to draw cards allocating positive and negative numbers of points from
3 one of four decks: two disadvantageous (A, B) and two advantageous (C, D). The test was
4 scored in terms of number of correct decisions, computed as $(D+C)-(B+A)$. [36]

5 The time since last cigarette was recorded prior to neuropsychological assessment (see
6 Table 2). Patients were generally not in withdrawal at the time of assessment (median time =
7 60 minutes, median absolute deviation = 30 minutes).

8 2.4. Statistical analyses

9 There was a small amount of missing data (1.68% of all data, with at most 5% of missing
10 data for a given participant), which were imputed using package *mice* for *R*. Variables were
11 checked for normality prior to analysis. A few variables had very high skewness (above 2.0 in
12 absolute value for age at first cigarette, age at first regular smoking, number of cigarettes per
13 day, time since last cigarette, number of errors on the Stroop test) due to a few extreme outliers;
14 these were rank-transformed prior to analysis. Using non-transformed variables did not
15 substantially change the results.

16 A first set of analyses tested which neuropsychological tests were significant predictors
17 of relapse at 1, 3 and 6 months (scored as 1=having relapsed or dropped out of the study). This
18 was done using univariate logistic regressions, separately for each possible predictor.

19 The second set of analyses tested which tests retained a significant effect on relapse after
20 controlling for meaningful covariates unrelated to neuropsychological performance. Given the
21 limited size of the sample and the wide range of possible covariates that could contribute to
22 dropping out or relapsing (including all socio-demographic variables; current psychiatric
23 disorders and medication, including scores on the MADRS and CAGE; center where the patient
24 was treated; scores on the Fagerström, Richmond and TCQ scales; all variables regarding

1 tobacco consumption, such as age at first consumption; and time since last cigarette), not all
2 covariates could be included in the same analysis. Instead, we used a preliminary analysis to
3 test which of these possible covariates had a significant effect on relapse; all variables with a
4 significant effect at any of the three timepoints were included as covariates in the analysis
5 testing the effect of neuropsychological tests. Retained covariates included scores on the
6 Fagerström and Richmond scales, number of previous attempts to quit smoking, center where
7 the patient took part in the study (Montpellier vs. Clermont-Ferrand), marital and employment
8 status, score on the MADRS, and having a current psychiatric disorder (yes vs. no).

9 To quantify evidence in favor of the null, we complemented the analyses for each
10 variable with a Bayesian analysis comparing a model with the predictor to a model without the
11 predictor. We report Bayes Factors (noted BF_{01}), quantifying the ratio of the probability of the
12 null versus the alternative hypothesis (e.g. a Bayes Factor $BF_{01} = 3$ means that the null is three
13 times more likely than the alternative hypothesis).

14 2.5. Deviations from the clinical registration:

15 This cohort study was designed to evaluate neurocognitive factors and in particular
16 attentional abilities, involved in smoking relapse (clinicaltrials.gov NCT01554436). Since the
17 initial clinical registration, recent data including our own publication [22] showed that other
18 cognitive functions may be involved in tobacco dependence beyond just attentional abilities,
19 prominently including executive functioning and the executive function of inhibition. For this
20 reason, we used all neuropsychological tests collected in the context of the study as predictors
21 of relapse, instead of just the initially planned attentional abilities measures. Moreover, the
22 RVIP/CPT task mentioned in the preregistration did not yield usable data due to data collection
23 errors and was not analyzed.

24

3. Results

Descriptive statistics for all neuropsychological measures are displayed in Table 2, for the whole sample and separately for relapsers and non-relapsers at 6 months. As can be seen in Table 2, relapsers had generally lower scores descriptively, but the differences were very small.

The results of univariate logistic regressions predicting relapse at 1 month, 3 months and 6 months from all neuropsychological tests separately are displayed in Table 3. Out of the 51 statistical tests performed, none were significant at the $p < .05$ level. Bayesian analyses confirmed that evidence was firmly in favor of the null for all predictors (all $BF_{01} > 3$). In other words, there was no relation between neuropsychological tests and relapse, contrary to our predictions.

The results of multivariate logistic regressions confirmed this conclusion: after controlling for covariates with a significant effect on the success of smoking cessation (listed in Table 4), none of the neuropsychological tests had a significant effect on relapse, as detailed in Table 5. The number of errors on the word-color Stroop was a marginal predictor of relapse, but the effect was in the direction opposite to hypotheses, with marginally more errors for non-relapsers; this marginal result is certainly a false positive given the large number of statistical tests performed here without correction for multiple comparisons. Apart from the number of errors on the word-color Stroop, Bayesian analyses were again in favor of the null for all neuropsychological variables (all $BF_{01} > 3$).

An alternative way to analyze the results would be to exclude all patients who were lost to follow-up, and only analyze data for the patients who completed the smoking cessation program without a relapse ($n = 54$), and those who were excluded after relapsing at any point during the program ($n = 37$). Replicating the univariate and multivariate logistic regressions with this approach did not substantially change the results, and showed no significant effect of any of the neuropsychological tests (all $ps > .05$). Another reasonable alternative analysis would

1 have been to test for significant differences, on average, between the group of relapsers and
2 non-relapsers (although this would have been more sensitive to unbalanced group sizes and it
3 would have been less straightforward to control for covariates). This alternative analysis led to
4 the same conclusions: whether considering relapsers at 1, 3 or 6 months, there were no
5 significant differences between groups at the $p < .05$ level for any of the neuropsychological
6 tests.

7 **4. Discussion**

8 We had set out to identify which neuropsychological tests were the best predictors of
9 tobacco relapse, with high expectations for tests of executive control including inhibition (the
10 "reflective system") based on the literature, including our prior work [23]. Contrary to our
11 hypotheses, we did not find an association between performance on standard
12 neuropsychological tests and relapse for patients wishing to reduce their tobacco consumption.
13 To our knowledge, this was the first study exploring neurocognitive predictors of tobacco
14 relapse, with a robust design (prospective inclusion of patients, longitudinal follow-up, and
15 control for factors of the biopsychosocial model other than cognitive performance). We believe
16 this confers some weight to our findings.

17 4.1. Implications for clinical practice

18 In light of our results, it appears that the use of "classic" standardized cognitive tests is
19 of little interest in assessing relapse. All of the tests used in the current study are standard
20 cognitive assessment tools used in psychiatry, yet none of them appears to have any relation to
21 relapse, even those tests measuring inhibition that should theoretically be related to the ability
22 to inhibit craving.

23 Part of the problem may be that these tools, while effective and with adequate validity
24 in assessing neurocognitive *deficits*, are ill-suited to measuring individual differences in the

1 absence of deficits. For example, the ability to connect a series of letters and digits in the trail-
2 making-test may decrease in the face of lesions of the prefrontal cortex, but this does not mean
3 that the test will pick-up on more subtle difficulties in non-lesioned patients. In this case, more
4 fine-grained psychological tests might possibly be helpful. In anorexia, for example, it has been
5 shown that computerized tests of mental flexibility are more sensitive than standard tools [37].
6 Similarly, the computerized Attentional Network Task (ANT) used to assess attentional
7 abilities has produced interesting results in student smokers [38]. This type of test includes
8 several hundreds of trials, and leverages the use of a computer to precisely register trial-level
9 response times, potentially leading to more precise measurement. No test of this type is
10 commonly used in clinical practice, which opens up a new avenue for future research.

11 Another possibility is that tobacco smokers simply do not have major difficulties with
12 executive or attentional control, generally speaking, which means no broad test of executive-
13 attentional abilities can be helpful in this population. It could be the case that these patients
14 have no difficulties at all (and that smoking is not related to a problem with executive control),
15 or it could be the case that they have more local difficulties with certain types of stimuli related
16 to their addiction. These difficulties could potentially be detected by tests specifically targeting
17 these stimuli. An example would be a picture-word Stroop task with pictures of cigarettes,
18 similar to emotional Stroop tasks [39,40]. Barring the development and use of such tests in
19 clinical practice, however, it seems more worthwhile to turn to other predictors when attempting
20 to predict and prevent relapse.

21 4.2. Others predictors of relapse in our population

22 There were three broad categories of good predictors of relapse in our sample. The most
23 important predictor of relapse was the presence of a psychiatric comorbidity (usually depression
24 or anxiety disorders in this sample), which came with the highest odds of relapse throughout

1 the follow-up program; this also includes the extent of depressive symptoms, as measured with
2 the MADRS. These results are consistent with what Piper et al. [41] observed in their study,
3 where anxiety and depressive symptoms were associated with higher relapse rates.

4 The second category of significant predictors included socio-demographic information:
5 marital status (not being single) and employment status (currently having a job) were both
6 associated with lower odds of relapse. However, the effect of these predictors was more
7 predominant at short term, and both became marginally significant after six months of follow-
8 up.

9 Lastly, variables directly related to smoking cessation were predictive of relapse: a high
10 motivation to quit smoking was associated with lower odds of relapse throughout the program.
11 Relapse also decreased with the number of prior attempts to quit smoking, which is broadly
12 compatible with Proschaska's theory of behavior change [42,43], which emphasizes that
13 cessation attempts are generally more and more effective as time goes on. However, this
14 predictor had more effect at short term and became non-significant after six months of follow-
15 up. This suggests that patients who have tried to quit smoking before are less likely to drop-out
16 in the short term, although not necessarily over the whole duration of the program. Note that
17 motivation to quit smoking and prior attempts to quit smoking were uncorrelated, suggesting
18 that both were useful as predictors ($r = -.02, p = .794$).

19 All three types of predictors – presence of high anxiety, depression or other psychiatric
20 comorbidities; socio-demographic variables; and motivation to quit smoking and number of
21 prior attempts – are quick and easy to assess and should be part of any psychiatric interview in
22 the context of tobacco cessation anyway. This makes them much more cost-effective to assess
23 in a clinical context than the neuropsychological tests used in the current study.

1 4.3. Limitations and perspectives

2 The sample size for this study ($N = 130$) was reasonable for a dataset collected in a
3 clinical context and with a longitudinal design, but still limited considering the number of
4 variables. Replicating these results with a larger sample size would provide more statistical
5 power to detect a possible relation between relapse and neuropsychological tests. However, it
6 is unlikely that this would change the conclusions and clinical implications of the current study.
7 First, Bayesian analyses confirmed that the evidence was firmly in favor of the null hypothesis,
8 indicating that null results were not due to a lack of statistical power. Second, given the sample
9 size, a post-hoc power analysis using G*Power (Faul et al., 2009) suggested that our study
10 achieved 0.80 power for an effect of $z = 1.96$ (approximate OR = 1.69) in the analyses using
11 univariate logistic regressions, which qualifies as a small effect size (Chen et al., 2010). In other
12 words, the design would have been sufficient to detect even small-to-medium effects. The effect
13 size for neuropsychological tests (or in other words, the difference of performance between
14 relapsers and non-relapsers) was so small that even if the effects had been significant, their
15 clinical usefulness as predictors of relapse would have been close to zero.

16 It would be comparatively more helpful to diversify the sample: our study focused on
17 patients consulting a psychiatric unit at a university hospital. Although psychiatric status was
18 controlled as a covariate and although most psychiatric conditions were mild (usually anxiety
19 and depression), these patients could still have a different pattern of tobacco dependence and
20 different predictors of relapse, compared to a broader sample. On the other hand,
21 neuropsychological tests (and particularly tests of executive functions) can lead to ceiling
22 performance, or fail to be sensitive to executive functioning abilities, in more restricted samples
23 such as non-clinical young adults. This implies that these classic tests are unlikely to function
24 better as predictors of relapse in a broader sample.

1 A related point is that the current sample was not characterized by especially impaired
2 neurocognitive processes. Many of the tests used here lacked reliable norms, but the available
3 data did not suggest that patients had severe difficulties (e.g. setting the threshold for
4 pathological scores as the bottom 2.5% of the norming sample, no patient had a pathological
5 score on the Hayling test of inhibition, and only three had an aggregate verbal fluency score in
6 the pathological range). This was not a problem for the current study: for example, there are
7 meaningful individual differences in executive control[24] which could have predicted relapse,
8 and given the relapse rate in smokers, we did not expect a large share of relapsers to have
9 pathological executive control scores. However, it does mean that relapse might be more
10 usefully related to executive performance in a more pathological sample (e.g. a sample with
11 dysexecutive syndrome). This could be a point worth exploring in a future study, but even if
12 common neuropsychological tests could predict relapse under extreme conditions of pathology,
13 this would not enhance their usefulness in a broad sample such as the one collected here.

14 4.4. Conclusion

15 Classic neuropsychological tests used in psychiatric practice appear to have little
16 relevance in the context of a tobacco cessation program: contrary to our expectations, even tests
17 of executive control and inhibition selected to be the most theoretically related to addiction do
18 not appear to predict relapse. Using different assessment tools, such as more precise
19 computerized tests or tests specifically designed to target stimuli related to addiction, might
20 provide more predictive power. It could also be the case that there is no connexion between
21 addiction and neurocognitive difficulties strong enough to be useful in a clinical context.
22 Relapse was comparatively well predicted by depression and other comorbid psychiatric
23 disorders, by motivation to quit smoking, and by socio-demographic variables. Therefore it
24 seems essential to prioritize investing resources into supporting motivation to quit smoking,
25 and treating comorbid disorders in parallel, rather than assessing neurocognitive performance.

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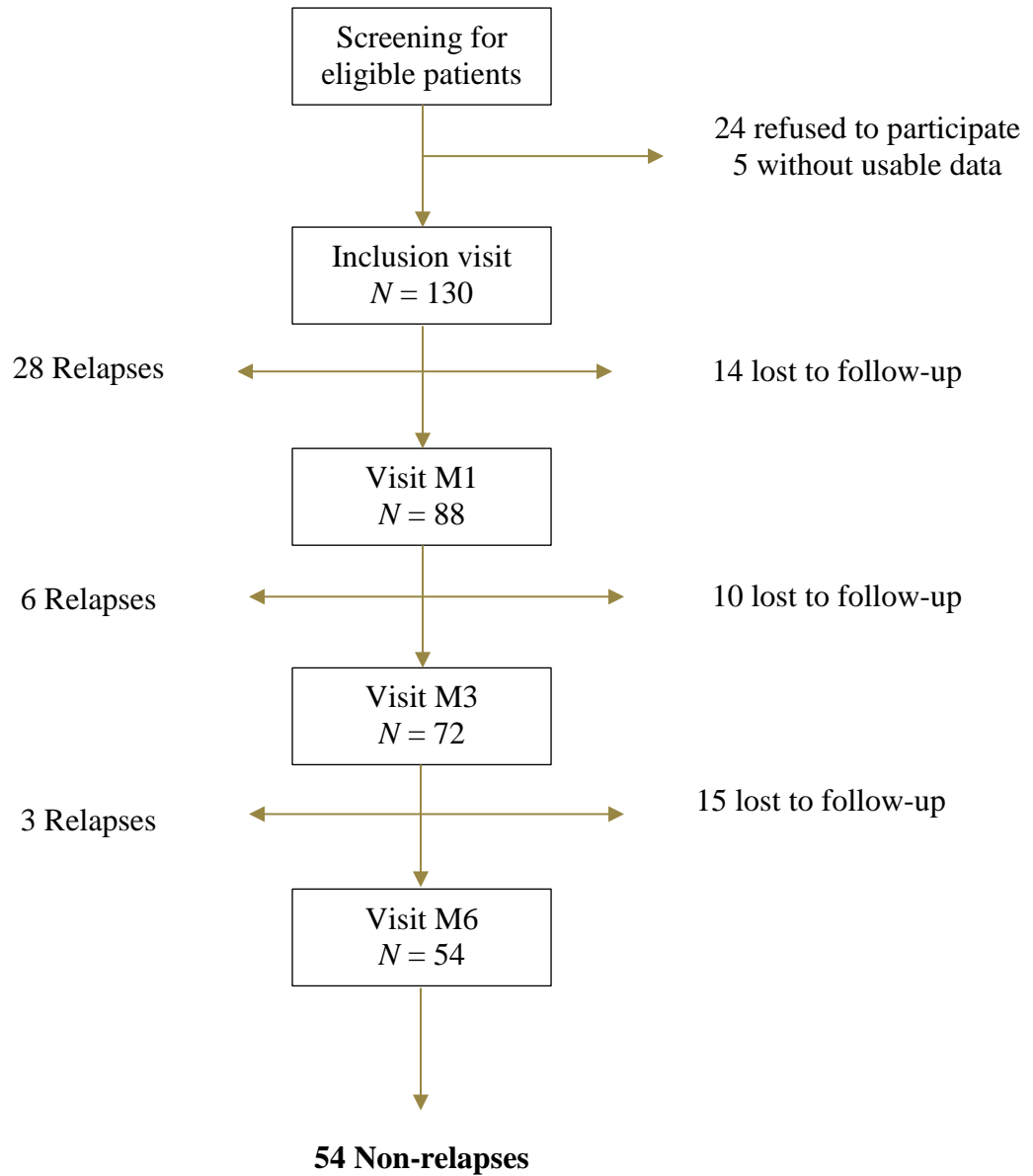


Figure 1. Flow-chart of the study

Table 1. *Descriptive statistics and coding for socio-demographic variables and other covariates*

Variable	6 months
Center of inclusion	0 = Clermont-Ferrand (<i>n</i> = 80), 1 = Montpellier (<i>n</i> = 50)
Sex	0 = Female (<i>n</i> = 72), 1 = Male (<i>n</i> = 58)
Age	<i>M</i> = 47.47 years, <i>SD</i> = 10.68, range = 21.57-69.02
Study level	0 = No degree (<i>n</i> = 13), 1 = Below high school (<i>n</i> = 32), 3 = High school (<i>n</i> = 21), 4 = Below bachelor (<i>n</i> = 32), 5 = Bachelor or above (<i>n</i> = 32)
Marital status	0 = Single (<i>n</i> = 51), 1 = Non-single (<i>n</i> = 79)
Employment status	0 = Unemployed (<i>n</i> = 53), 1 = Employed (<i>n</i> = 77)
Program: nicotin substitute	0 = No (<i>n</i> = 50), 1 = Yes (<i>n</i> = 80)
Program: other treatment	0 = No (<i>n</i> = 95), 1 = Yes (<i>n</i> = 35)
Montgomery-Asberg depression rating scale	<i>M</i> = 7.28, <i>SD</i> = 6.74, range = 0-40
CAGE	<i>M</i> = 0.91, <i>SD</i> = 1.24, range = 0-4
Any psychiatric disorder	0 = No (<i>n</i> = 61), 1 = Yes (<i>n</i> = 69)
Any psychoactive medication	0 = No (<i>n</i> = 60), 1 = Yes (<i>n</i> = 70)
Any other addiction	0 = No (<i>n</i> = 125), 1 = Yes (<i>n</i> = 5)
Fagerström	<i>M</i> = 6.05, <i>SD</i> = 2.02, range = 3-10
Richmond	<i>M</i> = 6.92, <i>SD</i> = 1.72, range = 3-10
French tobacco-craving questionnaire	<i>M</i> = 43.42, <i>SD</i> = 13.73, range = 16-79
Prior attempts to quit smoking	<i>M</i> = 2.58, <i>SD</i> = 3.14, range = 0-20
Age at first cigarette	<i>M</i> = 16.46, <i>SD</i> = 4.76, range = 6-53
Age at first regular smoking	<i>M</i> = 19.00, <i>SD</i> = 5.09, range = 8-53
Number of cigarettes per day	<i>M</i> = 20.01, <i>SD</i> = 11.76, range = 3-90
Time since last cigarette	<i>M</i> = 103.91 minutes, <i>SD</i> = 184.37, range = 3-1440
Other smokers at home	0 = No (<i>n</i> = 89), 1 = Yes (<i>n</i> = 41)

Note. *M* = Mean, *SD* = Standard deviation.

Table 2. *Descriptive statistics for all neuropsychological tests*

Task	Variable	Whole sample		Non-relapsers at 6 months		Relapsers at 6 months	
		<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
French National Adult Reading Test	Intellectual quotient (IQ) estimate	107.56	8.26	107.73	8.13	107.44	8.40
Stroop	Word-color RT	41.06	11.13	41.35	10.47	40.86	11.64
	Word-color errors	2.79	2.63	3.31	3.05	2.42	2.24
	Interference score	-0.41	8.73	0.26	8.02	-0.88	9.22
Hayling	Section B RT	2.25	1.24	2.17	1.14	2.31	1.30
	Inhibition score	1.78	1.09	1.66	1.03	1.86	1.14
	Section B correct	13.93	1.62	13.96	1.59	13.91	1.66
	Section B errors	1.19	1.91	1.13	1.85	1.24	1.95
n-back	2-back	40.02	5.36	40.19	5.41	39.89	5.36
	3-back	32.81	6.72	33.39	5.75	32.39	7.34
	Total	72.83	9.76	73.57	9.94	72.29	9.66
Trail-Making Test	Section B RT	84.40	38.66	86.68	39.49	82.78	38.24
	Shifting score	50.41	35.27	52.92	35.73	48.63	35.07
Verbal fluency	Lexical fluency	40.02	11.32	41.11	12.13	39.25	10.72
	Semantic fluency	44.01	10.55	45.43	10.55	43.00	10.51
	Total fluency	84.03	19.17	86.54	19.50	82.25	18.85
Iowa Gambling Task	Total score	5.58	26.71	7.37	30.44	4.30	23.84

Note. *M* = mean, *SD* = standard deviation, RT = response time.

Table 3. Results of univariate logistic regressions predicting relapse, for each test separately

Task	Variable	Relapse at 1 month		Relapse at 3 months		Relapse at 6 months	
		OR	<i>p</i>	OR	<i>p</i>	OR	<i>p</i>
French National Adult Reading Test	IQ estimate	0.98	.409	0.99	.639	1.00	.844
Stroop	Word-color RT Interference score	0.98	.349	0.98	.306	1.00	.801
	Word-color errors	0.97	.142	0.97	.203	0.98	.461
Hayling	Word-color errors	0.38	.121	0.49	.216	0.42	.128
	Section B RT	0.94	.673	1.09	.546	1.09	.535
	Inhibition score	1.01	.951	1.19	.283	1.18	.315
	Section B correct	0.88	.248	0.98	.829	0.98	.848
n-back	Section B errors	1.42	.474	1.02	.966	0.66	.823
	2-back	0.98	.537	0.98	.623	0.99	.760
	3-back	0.96	.183	0.98	.403	0.98	.405
Trail-Making Test	Total	0.98	.210	0.98	.398	0.99	.459
	Section B RT	1.01	.140	1.00	.527	1.00	.571
	Shifting score	1.01	.283	1.00	.572	1.00	.474
Verbal fluency	Lexical fluency	0.98	.215	0.98	.331	0.99	.355
	Semantic fluency	0.98	.232	0.98	.274	0.98	.197
	Total fluency	0.99	.165	0.99	.240	0.99	.209
Iowa Gambling Task	Total score	1.00	.939	1.00	.641	1.00	.518

Note. OR = odds-ratio, *p* = uncorrected *p*-value, RT = response time. For each line of this table, a univariate logistic regression was performed with relapse as the outcome and the neuropsychological score as the predictor. No predictors were significant.

Table 4. Results of univariate logistic regressions predicting relapse, based on possible covariates

Variable	Relapse at 1 month		Relapse at 3 months		Relapse at 6 months	
	OR	p	OR	p	OR	p
Center of inclusion	0.67	.050	0.86	.403	0.81	.238
Sex	0.90	.781	0.61	.170	0.61	.163
Age	0.99	.607	0.98	.349	0.97	.129
Study level	0.82	.194	0.86	.311	0.89	.426
Marital status	0.21	<.001	0.29	.001	0.49	.061
Employment status	0.27	<.001	0.44	.024	0.51	.071
Program: nicotin substitute	0.74	.479	0.78	.528	0.77	.495
Program: other treatment	0.45	.179	1.07	.881	1.54	.376
Montgomery-Asberg depression rating scale	1.05	.077	1.07	.022	1.09	.009
CAGE	1.04	.776	1.14	.366	1.04	.772
Any psychiatric disorder	6.44	<.001	4.37	<.001	3.09	.002
Any psychoactive medication	1.22	.603	1.42	.328	0.78	.493
Any other addiction	9.16	.051	5.26	.143	2.94	.340
Fagerström	1.19	.064	1.13	.181	0.98	.824
Richmond	0.68	<.001	0.80	.037	0.80	.039
French tobacco-craving questionnaire	1.01	.498	1.00	.917	1.00	.789
Prior attempts to quit smoking	0.25	.028	0.40	.114	0.58	.345
Age at first cigarette	1.18	.796	1.25	.711	1.32	.647
Age at first regular smoking	1.05	.937	1.19	.770	1.21	.752
Number of cigarettes per day	1.01	.441	1.35	.623	0.65	.478
Time since last cigarette	1.94	.307	1.19	.772	1.95	.286
Other smokers at home	1.55	.268	1.48	.305	2.16	.056

Note. OR = odds-ratio, p = uncorrected p-value. For each line of this table, a univariate logistic regression was performed with relapse as the outcome and the possible covariate as the predictor. Predictors with a significant effect at any of the three timepoints are in boldface. Predictors were coded as detailed in Table 1.

Table 5. Results of multivariate logistic regressions predicting relapse, for each test separately, while controlling select covariates

Task	Variable	Relapse at 1 month		Relapse at 3 months		Relapse at 6 months	
		OR	<i>p</i>	OR	<i>p</i>	OR	<i>p</i>
French National Adult Reading Test	Intellectual quotient (IQ) estimate	1.00	.987	1.00	.852	1.00	.912
Stroop	Word-color RT	1.02	.481	1.00	.923	1.01	.537
	Interference score	0.99	.753	0.99	.772	1.00	.968
	Word-color errors	0.20	.055	0.31	.097	0.34	.097
Hayling	Section B RT	0.97	.859	1.11	.518	1.14	.435
	Inhibition score	1.04	.848	1.22	.292	1.24	.261
	Section B correct	1.07	.703	1.12	.459	1.17	.276
	Section B errors	0.77	.740	0.77	.693	0.66	.504
n-back	2-back	1.06	.331	1.03	.515	1.02	.674
	3-back	0.98	.611	1.00	.966	0.99	.738
	Total	1.00	.886	1.01	.751	1.00	.996
Trail-Making Test	Section B RT	1.00	.732	1.00	.840	0.99	.264
	Shifting score	1.00	.722	1.00	.940	0.99	.316
Verbal fluency	Lexical fluency	1.00	.929	0.99	.634	0.99	.449
	Semantic fluency	1.00	.988	0.99	.721	0.99	.434
	Total fluency	1.00	.951	0.99	.629	0.99	.376
Iowa Gambling Task	Total score	1.00	.913	0.99	.478	0.99	.494

Note. OR = odds-ratio, *p* = uncorrected *p*-value, RT = response time. For each line of this table, a multivariate logistic regression was performed with relapse as the outcome and the neuropsychological score as the main predictor, controlling for select covariates: Richmond score, MADRS score, current employment and marital status, center of inclusion, having a current psychiatric disorder, and number of previous attempts to quit smoking (rank-transformed). No predictors were significant.