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The Influence of Nicotine Metabolic Rate on Working Memory over 6 Hours of Abstinence from Nicotine

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Abstract

Background.—A faster rate of nicotine metabolism has been associated with smoking more cigarettes, greater nicotine withdrawal symptoms, and lower smoking quit rates. However, the association between nicotine metabolic rate (NMR) and cognitive functioning during withdrawal has not been determined.

Methods.—We compared cognitive function in 121 fast or slow nicotine metabolizers after smoking, and at 3 and 6 Hours of nicotine abstinence. Cognitive functioning was assessed using N-back working memory tests with outcomes of accuracy and processing speed. Participants smoked two cigarettes and then abstained from smoking for 6 Hours. N-back tests were administered after smoking (0 Hours) and at 3 and 6 Hours of nicotine abstinence.

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Conflicts of interest: NLB is a consultant to Pfizer and Achieve Life Sciences, companies that market or are developing medications to aid smoking cessation and has served as a paid expert witness in litigation against tobacco companies. The other authors have no conflicts to declare.

Results.—An effect of processing speed was found over time on the 2-back, in that participants had significantly longer average reaction times when the stimuli presented did not match the target letter. NMR was not significantly associated with the processing speed change over time. Within-race differences in working memory were evident in that Caucasian fast metabolizers had significantly poorer accuracy and processing speed.

Conclusions.—Minimal change in working memory over 6 Hours of nicotine abstinence was observed. Overall, NMR was not significantly associated with the change in processing speed, however Caucasian fast metabolizers displayed poorer accuracy and processing speed at discrete time points.

Keywords

nicotine; nicotine metabolite ratio; NMR; cognition; smoking; working memory

1. Introduction

The rate of nicotine metabolism is an important determinant of smoking behavior and nicotine dependence. Nicotine is metabolized primarily in the liver by enzyme CYP2A6, with 70–80% of nicotine converted to cotinine and cotinine further metabolized to trans-3' hydroxycotinine (3HC) (Benowitz et al., 2009). The ratio of 3HC/cotinine, termed the nicotine metabolite ratio (NMR), is a biomarker for the rate of nicotine metabolism and can be measured in plasma, urine and saliva (Dempsey et al., 2004). The higher the NMR, the greater the CYP2A6 activity, and the faster the metabolism of nicotine. The level of CYP2A6 activity and nicotine metabolism varies by race (Ho et al., 2009). On average African Americans have significantly lower clearance of nicotine and cotinine compared to Caucasians (Perez Stable et al., 1998).

A faster rate of nicotine metabolism is associated with smoking more cigarettes per day (Tanner et al., 2015), experiencing more intense nicotine withdrawal symptoms as measured by the Minnesota Nicotine Withdrawal Scale (Lerman et al., 2006; Liakoni et al., 2018; Sofuoglu et al., 2012), less efficacy with transdermal nicotine therapy for smoking cessation (Lerman et al., 2015), and overall lower quit rates (Ho et al., 2009). One possible explanation why faster metabolizers have a more difficult time quitting is that faster metabolizers experience more intense nicotine withdrawal symptoms (Liakoni et al., 2018). Previous research supports that smokers with fast NMRs experience more symptoms of anxiety (Kaufmann et al., 2015), insomnia, anger, difficulty concentrating, and impatience (Rubinstein et al., 2008) when abstinent from nicotine. Another explanation is that as nicotine is eliminated more rapidly from the body, tolerance to psychoactive effects dissipates more rapidly, and therefore the subsequent nicotine exposures are more rewarding. In support of this idea, faster metabolizers when given smoking cues exhibit greater neural responses in dopamine-dependent reward circuitry (Tang et al., 2012) and have greater neural responses to smoking cues during periods of abstinence (Lerman et al., 2006).

An important but less explored subset of the effects of nicotine withdrawal is impairment of cognitive function. If such impairment is more pronounced in faster metabolizers, this could contribute to faster metabolizers having greater difficulty quitting. Cognitive function

decline has been a longstanding topic of interest to researchers as a factor contributing to relapse when smokers attempt to quit (Heishman et al., 1994; Warburton et al., 1992). During abstinence from nicotine, as smokers' blood levels of nicotine decrease, difficulty concentrating and decreased alertness are self-reported (Hughes, 2007). In cognitive tests, smokers undergoing nicotine withdrawal show compromised working memory (as measured on the N-back tests) and attentional processes (as measured by the Stroop task) (Mendrek et al., 2006). In Mendrek et al. (2006), significant differences in smokers were found such that when undergoing 13 hours of abstinence, reaction times were slower on the 2-back, as compared to when undergoing only 1 hour of abstinence. Snyder et al. (1989) found that after only 4 hours of abstinence from nicotine, smokers demonstrated significantly decreased accuracy and longer response times on a recall test, as compared to their scores pre-abstinence. This association between nicotine abstinence and cognitive decline has been established (Hughes, 2007; Mendrek et al., 2006; Snyder et al., 1989).

Here we use the NMR, a biomarker of the rate of nicotine clearance (metabolism), to prospectively study the influence of nicotine metabolism on cognitive functioning during nicotine abstinence. The cognitive function outcome of interest in our study is working memory (as measured on the N-back) as it is a broad measure of short-term memory (Baddeley, 2003). The N-back is a visuospatial task involving encoding, maintaining and matching (Chen, Miltra & Schlaghecken, 2008) via recollection, and is moderately correlated with other measures of working memory such as memory span tasks (Shelton et al., 2009). One encodes a stimulus (a target letter), maintains the stimulus in memory, and matches via recollection a current stimulus against the original stimulus that occurred *N* items prior in the sequence. The maintenance load increases as the number of items between the stimuli increase. For example, in the 0-back, the maintenance load is low; the target letter is directly before each stimuli to match. In the 2-back, the maintenance is higher as the target letter is sequenced two items back from the stimuli to match. The outcome variables calculated from the N-back tasks broadly fall into categories of accuracy (i.e. how many times does someone correctly respond) or processing speed (i.e. the average time it takes to respond) (Jonides et al., 1997).

The first aim of our study was to measure the change in working memory over 6 hours of abstinence from nicotine, hypothesizing that accuracy and processing speed will decrease as time in abstinence increases. The second aim was to evaluate the association of NMR with working memory changes over time, hypothesizing that smokers with fast NMR will experience significantly greater decreases in accuracy and processing speed than slow. We also hypothesized that nicotine levels will be a significant mediator in NMR's association with decreases in accuracy and processing speed.

2. Material and methods

Participants were healthy smokers (e.g. no unstable medical or psychiatric conditions), ages 18 to 70, of African American and Caucasian descent (both parents & grandparents of same race), who were recruited through Craigslist, flyers, and newspaper ads. Participants were required to have smoked at least 5 cigarettes per day regularly for the last year. Smoking status was confirmed with a saliva cotinine ≥ 50 ng/mL. Participants were recruited to be

fast or slow metabolizers of nicotine based the top or bottom quartile of the saliva nicotine metabolite ratios (NMR). Since on average Caucasians metabolize nicotine faster than African Americans, the distribution of NMR will vary by race. The pre-determined quartile cut-points were different by race as follows: ≤ 0.20 or ≥ 0.37 for African Americans and ≤ 0.26 or ≥ 0.45 for Caucasians (within 0.01). These cut-points were based on data from of plasma and saliva NMR levels in African American and Caucasian participants, who participated in prior studies in our laboratory (Benowitz et al., 2011).

Participants were recruited as part of a larger study looking at the effects of NMR on nicotine withdrawal symptoms and nicotine reinforcement. Recruitment and screening procedures have been previously described (Liakoni et al., 2018). The severity of smoking dependence was assessed by the Fagerstrom Test for Cigarette Dependence (FTCD), with scores ranging from 0–10, 10 indicating very high dependence (Heatherton et al., 1991). Working memory was assessed using the 0-back and 2-back of the N-back tasks (Kirchner, 1958).

After a clinic screening visit and eligibility determination, participants returned to the clinic for a 0-back and 2-back practice session. This allowed them to become familiar with the tasks and to ask any questions. They were later admitted to the research ward at Zuckerberg San Francisco General Hospital for a one day study. Participants were admitted the evening before study procedures to ensure overnight abstinence from nicotine.

In the morning of the study day, participants smoked two cigarettes with a standardized puffing protocol. Participants then abstained from smoking for 6 hours and remained in the sequestered, hospital environment. The 0-back and 2-back were administered immediately after smoking both cigarettes at 0 Hours (0 H), and then at 3 Hours (3 H), and 6 Hours (6 H) nicotine abstinence. Nicotine blood concentrations were sampled before smoking (Baseline), after smoking (0 Hours), and before each cognitive test administration at 3 H and 6 H nicotine abstinence. As part of the parent study, participants completed additional questionnaires at 3 H and 6 H. One hundred twenty-five participants completed the study and cognitive tests.

Participants completed two N-back tasks; the 0-back and the 2-back. In the 0-back task, a series of 60 letters (stimuli) appeared on the screen with a 3,000 millisecond interval. Stimuli appeared in a pseudo-random order, meaning that it appeared random to the participants but was actually in a fixed order for each participant. In the 0-back, participants were assigned a target letter and were asked to press the ‘C’ key for ‘correct’ when their target letter appeared on the screen or the ‘N’ key for ‘not correct’ when a different letter appeared on the screen. In the 2-back task, participants were also presented with a series of 60 letters with a 3,000 millisecond interval. Participants were instructed to remember two letters back by pressing ‘C’ for ‘correct’ when the letter is the same as two letters back or ‘N’ for ‘not correct’ if a different letter appeared. Out of the 60 letters in both the 0 and 2-backs, there were 20 trials where the same letter later appeared (a match) and 40 where a different letter appeared (a non-match). The tasks were not counterbalanced; however, the target letters and sequence of letters changed for each administration in order to minimize practice effects, as previous literature has described (Grundey et al., 2015).

2.1 Analytical chemistry

Saliva concentrations of the components of NMR, *trans*-3'-hydroxycotinine (3HC) and cotinine (COT) were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (Jacob et al., 2011). NMR was calculated as the 3HC to cotinine ratio. Nicotine concentrations in plasma were determined by GC-MS/MS modified for tandem mass spectrometry for improved sensitivity (Jacob et al., 1991).

2.2 Data cleaning and analysis

Data were cleaned by removing any individual average response times (ART) below 100 milliseconds or greater than 2,000 milliseconds (Mendrek et al., 2006). One participant met criteria for responding in <100ms and the data was removed. Additionally, responses were reviewed for overall accuracy. If a participant did not have at least 90% accuracy on the 0-back test, they were considered to not have understood the test and their data were excluded. Two participants met this criteria. Another participant was removed, because it was discovered that they did not smoke the standardized cigarettes. This gave a final N=121 participants.

The variables calculated from the N-back were either accuracy (i.e. correct responses) or processing speed (i.e. average reaction times) outcomes. Accuracy outcomes included the following: total correct responses, false alarms and null responses. Processing speed outcomes included total average reaction times and average reaction times when identifying a match or a non-match. For descriptions of each outcome variable see Table 1.

Demographic differences were examined using *t*-tests for continuous dependent variables and chi-squares when categorical. Differences in accuracy and processing speed over time were assessed with one-way repeated-measures ANOVA and ANCOVA. We evaluated several potential covariates, including those that had significant (or near significant) differences at Baseline and others with known associations (i.e. sex, age, race, cigarettes per day, time to first cigarette, dependence, urine total nicotine equivalents (a measure of daily intake of nicotine), years of education, etc. The final model included sex and race as covariates as race demonstrated a consistent relationship with our outcomes and sex was significantly unbalanced at Baseline by fast and slow NMR. Additionally, previous work has shown that the effect of NMR on smoking behavior differed by race, so this was an important variable to control for (Ross et al., 2016). For any variables that were skewed, variables were log transformed before entered as dependent variables in the analysis. Within-time comparisons between fast and slow NMRs were examined using a *t*-test.

3. Results

One hundred and twenty-one participants (62% male; 74% Caucasian; 56% fast NMR; average age = 36.1 years) were included in our analysis. Demographic characteristics by fast and slow NMR are shown in Table 2. A significant sex difference was found such that males were significantly more likely to have slow NMR than females (p=0.03). As expected, fast NMRs had significantly higher NMR values than slow NMRs (p<0.001). The pre-specified NMR cut-points by race (i.e. ≤ 0.20 or ≥ 0.37 in African Americans and ≤ 0.26 or ≥ 0.45 in

Caucasians (within 0.01)) corresponded reasonably well to the top and bottom quartiles observed of the entire screening sample (N=303; ≤ 0.17 or ≥ 0.35 in African Americans and ≤ 0.23 or ≥ 0.50 in Caucasians). On average participants smoked 13.6 cigarettes per day and had FTCD scores of 4.1, which indicates low to moderate levels of nicotine dependence (Heatherton et al., 1991).

We examined differences between fast and slow metabolizers on plasma nicotine at each time point. In a within-time t-test analysis, plasma nicotine concentrations were significantly higher in slow vs. fast NMR at all time points; Baseline $t(116)=4.99$, $p<0.001$; 0 H $t(115)=3.0$, $p=0.003$; 3 H $t(117)=6.3$, $p<0.001$ and 6 H $t(117)=5.1$, $p<0.001$ (Figure 1).

3.1 Accuracy and processing speed over time

We first conducted a one-way unadjusted repeated measures ANOVA, and found several significant main effects of time. On the 2-back, the total number correct increased over time. On the 2-back ART-NM significantly increased over time, and total Nulls, Null-M and Null-NM significantly decreased over time. In our adjusted model, when adding race and sex as covariates, on the 0-back, there were no statistically significant main effects of time. On the 2-back, one statistically significant main effect remained in that ART-NM significantly changed over time, $F(1,117)=5.01$, $p=0.02$, such that ART-NM was significantly higher at 3 H vs. 0 H, $p<0.001$ and at 6 H vs. 0 H, $p<0.001$. There was no significant difference in ART-NM between 6 H and 3 H, $p=0.62$. Interactions between changes over time and our covariates, sex and race, were not found. Descriptive data and p-values for the adjusted and unadjusted models are shown in Table 3.

3.2 Influence of NMR on the change in processing speed

We evaluated NMR as a between-subjects factor on 2-Back ART-NM and found that NMR did not significantly interact with changes in scores over time, $F(1, 0.8)=1.1$, $p=0.30$. As NMR did not significantly interact with changes in ART-NM over time, we could not test plasma nicotine as a mediator of this relationship.

3.3 Exploratory analysis

When evaluating which variables to control for in our analysis of change model, race consistently predicted various outcomes. As an exploratory analysis, we examined within race comparisons on all working memory outcomes. Within African American participants, no statistically significant differences were found between fast and slow NMRs on the 0-back or 2-back accuracy or processing speed outcomes. In Caucasian participants on the 0-back, fast NMRs vs. slow had significantly more nulls at 6 H ($p<0.05$). On the 2-Back, fast NMRs vs. slow had significantly less total correct at 0 H ($p<0.05$), more total nulls at 0 H ($p<0.05$), more Nulls-M at 0 H ($p<0.05$) and Nulls-NM at 0 H ($p<0.05$), higher ART at 0 H ($p<0.01$), 3 H ($p<0.05$) and 6 H ($p<0.05$) and higher ART-M at 0 H ($p<0.01$), 3 H ($p<0.05$) and 6 H (p<0.05). See Supplementary Table 1 for descriptive data for Caucasians and Supplementary Table 2 for descriptive data for African Americans.

4. Discussion

Differences in working memory, between fast and slow nicotine metabolizers, were explored by examining several outcomes of the 0-back and 2-back tests after smoking and after 3 hours and 6 hours of nicotine abstinence. The first aim was to evaluate changes in accuracy and processing speed over 6 hours of nicotine abstinence. When adjusting for covariates, we found no significant differences in 0-back scores and only one significant difference in 2-back scores; increased average reaction times for non-matches. This effect was seen when comparing reaction times at 0 hours to 3 hours and 0 hours to 6 hours. This processing speed change demonstrates that over time, individuals were responding slower on what was one of the hardest tasks; discriminating a non-match from a target letter shown two letters previously. We see this effect despite a trend in increasing accuracy (total correct scores), so participants were performing better over time, but in the cases of non-matches, taking longer to do so. This could be due to a speed-accuracy trade off (Liu and Wantanabe, 2011), so as the task becomes more difficult the cost associated with increased attention for accuracy is lack of speed. Participants may focus more on performing the task accurately rather than responding quickly. Why this affect was seen for non-matches and not for matches is unclear, as responding to non-matches and matches both involve the process of matching via recollection. There is some evidence that participants are quicker to respond to matches than non-matches (Harbison, Atkins & Dougherty, 2012), which our results reflected. Why we would see a processing speed change over time for non-matches and not for matches needs further replication.

Our second aim was to evaluate NMR's association with this processing speed change. We found that overall NMR did not significantly interact with increased average reaction times for non-matches, meaning that fast NMRs increased reaction times at a similar rate to slow NMRs. Plasma nicotine levels were significantly higher at each time point in slow compare to fast metabolizers. We had planned to examine nicotine levels as a mediator in NMR's association with cognitive changes over time, but were unable to perform this analysis due to lack of significant effect of NMR.

There may be several reasons for our lack of significant findings; first, the relatively short duration of abstinence (6 hours), may have been insufficient to see maximal withdrawal-induced impairments on tasks. Previous literature has observed cognitive impairment on other cognitive non-N-back tasks at a minimum of 4 hours abstinence (Snyder et al., 1989) though it enrolled much heavier smokers (all 20 or more cigarettes per day) than our study (average cigarettes per day=13.6), so nicotine withdrawal may have been more severe and experienced faster than in our study. Others utilizing the N-back found an increase in overall errors and slower reaction times on the 2-back after an abstinence period of 13 hours (Mendrek et al., 2006), which was much longer than our period of nicotine deprivation. Second, in general participants were not displaying working memory impairments. Out of 60 trials, the vast majority were completed correctly, and though not significant in our adjusted model, some outcomes showed improvement over time (e.g. 2-back total correct and 2-back total nulls).

Of considerable interest, despite negative finding for the full study group, our exploratory analysis did suggest different effects within race. Caucasian fast metabolizers exhibited lower accuracy and slower processing speed compared to Caucasian slow metabolizers. These preliminary results were in the direction we hypothesized for the entire sample, however this effect was not seen in African Americans, nor did we see a trend in this direction. We have previously reported that NMR is a stronger influence on the amount of nicotine consumed (Ross et al., 2016) in Caucasians than African Americans. Our results would suggest that NMR is an important influence on working memory during nicotine withdrawal in Caucasians, though the mechanism underlying the racial difference is unclear and warrants further investigation.

4.1 Strengths and limitations

Strengths of the current study include prospective selection of fast and slow metabolizers and validation of nicotine deprivation via a study design that sequestered individuals in an environment where they did not have access to nicotine. Additionally, the cognitive tasks were well understood by all but one participant, who was excluded. Limitations include potential practice effects, in which changes in scores may be attributed to increasing familiarity with exposure to the test. This may have confounded our ability to detect cognitive decline over time. Also, lack of a Baseline measure of cognitive performance before individuals began their standardized smoking protocol limits our ability to adjust for Baseline competency on the tests. We studied fewer African American than Caucasian smokers, which reduced statistical power in the analysis of racial differences in effects. Finally, the majority of our findings were negative and potentially due to an insufficient amount of time in nicotine withdrawal (6 hours). Further studies should test these questions using a longer duration of abstinence.

5. Conclusions

A processing speed effect over time was found in that participants were slower to discriminate a non-match to a target stimuli shown two letters previously. Overall, the rate of nicotine metabolism and the rate of nicotine decline did not impact this change in processing speed. In Caucasians, fast metabolizers displayed the more cognitive impairment over time than slow metabolizers. Such an effect was not seen in African Americans, but this observation needs to be replicated in a larger number of African American smokers. Future research should test working memory over a longer abstinence duration and utilize tasks of greater difficulty (e.g. 4-back or 5-back, etc.) and/or different types of cognitive function tests. Others have suggested tasks involving sustained attention versus working memory are more sensitive to nicotine effects (Faulkner et al., 2018). Within-race differences between fast and slow metabolizers should be further examined to elucidate the mechanisms influencing NMR’s effect in Caucasians.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Baddeley A, 2003 Working memory: looking back and looking forward. Nat Rev Neurosci. 4, 829. [PubMed: 14523382]

Benowitz NL, Dains KM, Dempsey D, Wilson M, Jacob P, 2011 Racial differences in the relationship between number of cigarettes smoked and nicotine and carcinogen exposure. Nicotine Tob Res. 13, 772–783. doi: 10.1093/ntr/ntr072. [PubMed: 21546441]

Benowitz NL, Hukkanen J, Jacob P, 2009 Nicotine chemistry, metabolism, kinetics and biomarkers. Handb Exp Pharmacol. 192, 29–60. doi: 10.1007/978-3-540-69248-5_2.

Benowitz NL, Lessov-Schlaggar CN, Swan GE, Jacob P, 2006 Female sex and oral contraceptive use accelerate nicotine metabolism. Clin Pharmacol Ther. 79: 480–488. doi: 10.1016/j.clpt.2006.01.008. [PubMed: 16678549]

Chen YN, Mitra S, Schlaghecken F. Sub-processes of working memory in the N-back task: an investigation using ERPs. Clinical Neurophysiology. 2008 7 1;119(7):1546–59. [PubMed: 18448388]

Dempsey D, Tutka P, Jacob P, Allen F, Schoedel K, Tyndale RF, Benowitz NL, 2004 Nicotine metabolite ratio as an index of cytochrome P450 2A6 metabolic activity. Clin Pharmacol Ther. 76, 64–72. doi: 10.1016/j.clpt.2004.02.011. [PubMed: 15229465]

Faulkner P, Ghahremani DG, Tyndale RF, Paterson NE, Cox C, Ginder N, Hellemann G, London ED, 2018 Neural basis of smoking- induced relief of craving and negative affect: Contribution of nicotine. Addict Biol, doi: 10.1111/adb.12679.

Grundey J, Amu R, Ambrus GG, Batsikadze G, Paulus W, Nitsche MA, 2015 Double dissociation of working memory and attentional processes in smokers and non-smokers with and without nicotine. Psychopharmacology. 232, 2491–2501. [PubMed: 25721074]

Harbison J, Atkins S, Dougherty MR. N-back Performance: Comparing Assessment and Training Performance. In Proceedings of the Annual Meeting of the Cognitive Science Society 2012 (Vol. 34, No. 34).

Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO, 1991 The Fagerström test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict. 86, 1119–1127. doi: 10.1111/j.1360-0443.1991.tb01879.x. [PubMed: 1932883]

Heishman SJ, Taylor RC, Henningfield JE, 1994 Nicotine and smoking: a review of effects on human performance. Exp Clin Psychopharmacol. 2, 345.

Ho MK, Mwenifumbo JC, Al Koudsi N, Okuyemi KS, Ahluwalia JS, Benowitz NL, Tyndale RF, 2009 Association of nicotine metabolite ratio and CYP2A6 genotype with smoking cessation treatment in African- American light smokers. Clin Pharmacol Ther. 85, 635–643. [PubMed: 19279561]

Hughes JR, 2007 Effects of abstinence from tobacco: valid symptoms and time course. Nicotine Tob Res. 9, 315–327. [PubMed: 17365764]

Jacob III P, Yu L, Duan M, Ramos L, Yturralde O, Benowitz NL, 2011 Determination of the nicotine metabolites cotinine and trans-3′-hydroxycotinine in biologic fluids of smokers and non-smokers using liquid chromatography–tandem mass spectrometry: biomarkers for tobacco smoke exposure and for phenotyping cytochrome P450 2A6 activity. Chromb. 879, 267–276. doi: 10.1016/j.jchromb.2010.12.012.

Jacob III P, Yu L, Wilson M, Benowitz NL, 1991 Selected ion monitoring method for determination of nicotine, cotinine and deuterium- labeled analogs: absence of an isotope effect in the clearance of (S)- nicotine- 3′, 3′- d2 in humans. Biol Mass Spectrom. 20, 247–252. doi: 10.1002/bms.1200200503. [PubMed: 1883864]

Jonides J, Schumacher EH, Smith EE, Lauber EJ, Awh E, Minoshima S 1997 Verbal working memory load affects regional brain activation as measured by PET. Journal of Cognitive Neuroscience, 9(4): 462–475. [PubMed: 23968211]

Kaufmann A, Hitsman B, Goelz PM, Veluz-Wilkins A, Blazekovic S, Powers L, Leone FT, Gariti P, Tyndale RF, Schnoll RA, 2015 Rate of nicotine metabolism and smoking cessation outcomes in a community-based sample of treatment-seeking smokers. Addict Behav. 51, 93–99. [PubMed: 26240944]

Kirchner WK, 1958 Age differences in short-term retention of rapidly changing information. J Exp Psychol Gen. 55, 352.

Lerman C, Tyndale R, Patterson F, Wileyto EP, Shields PG, Pinto A, Benowitz N, 2006 Nicotine metabolite ratio predicts efficacy of transdermal nicotine for smoking cessation. Clin Pharmacol Ther. 79, 600–608. doi: 10.1016/j.clpt.2006.02.006. [PubMed: 16765148]

Lerman C, Schnoll RA, Hawk LW Jr, Cinciripini P, George TP, Wileyto EP, Swan GE, l Benowitz N, Heitjan DF, Tyndale RF, PGRN-PNAT Research Group, 2015 Use of the nicotine metabolite ratio as a genetically informed biomarker of response to nicotine patch or varenicline for smoking cessation: a randomised, double-blind placebo-controlled trial. Lancet Respir Med. 3, 131–138. doi: 10.1016/S2213-2600(14)70294-2. [PubMed: 25588294]

Liakoni E, Edwards KC, St. Helen G, Nardone N, Dempsey DA, Tyndale RF, Benowitz NL, 2018 Effects of Nicotine Metabolic Rate on Withdrawal Symptoms and Response to Cigarette Smoking After Abstinence. Clin Pharmacol Ther. doi: 10.1002/cpt.1238.

Liu CC, Watanabe T, 2012 Accounting for speed–accuracy tradeoff in perceptual learning. Vision Res. 61, 107–114. doi: 10.1016/j.visres.2011.09.007. [PubMed: 21958757]

Mendrek A, Monterosso J, Simon SL, Jarvik M, Brody A, Olmstead R, Domier CP, Cohen MS, Ernst M, London ED, 2006 Working memory in cigarette smokers: comparison to non-smokers and effects of abstinence. Addict Behav. 31, 833–844. doi: 10.1016/j.addbeh.2005.06.009. [PubMed: 16009504]

Perez-Stable EJ, Herrera B, Jacob III P, Benowitz NL, 1998 Nicotine metabolism and intake in black and white smokers. JAMA. 280, 52–156.

Ross KC, Gubner NR, Tyndale RF, Hawk LW Jr, Lerman C, George TP, Cinciripini P, Schnoll RA, Benowitz NL, 2016 Racial differences in the relationship between rate of nicotine metabolism and nicotine intake from cigarette smoking. Pharmacol Biochem Behav. 148, 1–7. doi: 10.1016/j.pbb.2016.05.002 [PubMed: 27180107]

Rubinstein ML, Benowitz NL, Auerback GM, Moscicki AB, 2008 Rate of nicotine metabolism and withdrawal symptoms in adolescent light smokers. Pediatrics. 122, 643–647. doi: 10.1542/peds.2007-3679.

Shelton JT, Elliott EM, Hill BD, Calamia MR, Gouvier WD. A comparison of laboratory and clinical working memory tests and their prediction of fluid intelligence. Intelligence. 2009 5 1;37(3):283–93. [PubMed: 20161647]

Snyder FR, Davis FC, Henningfield JE, 1989 The tobacco withdrawal syndrome: performance decrements assessed on a computerized test battery. Drug Alcohol Depend. 23, 259–266. doi: 10.1016/0376-8716(89)90090-2. [PubMed: 2752917]

Sofuoglu M, Herman AI, Nadim H, Jatlow P, 2012 Rapid nicotine clearance is associated with greater reward and heart rate increases from intravenous nicotine. Neuropsychopharmacol. 37, 1509–1516. doi: 10.1038/npp.2011.336.

Tang DW, Hello B, Mroziewicz M, Fellows LK, Tyndale RF, Dagher A, 2012 Genetic variation in CYP2A6 predicts neural reactivity to smoking cues as measured using fMRI. Neuroimage. 60, 2136–2143. doi: 10.1016/j.neuroimage.2012.01.119. [PubMed: 22342802]

Tanner JA, Chenoweth MJ, Tyndale RF, 2015 Pharmacogenetics of nicotine and associated smoking behaviors, in Balfour DJK, Munafo MR (Eds.), The Neurobiology and Genetics of Nicotine and Tobacco. Springer, Cham., Switzerland, pp. 37–86.

Warburton DM, Rusted JM, Müller C, 1992 Patterns of facilitation of memory by nicotine. Behav Pharmacol. 3, 375–378. [PubMed: 11224139]

Highlights

- Select working memory functions decrease during abstinence from nicotine
- Slow and fast metabolizers decrease working memory functions at similar rates
- Within Caucasians, working memory scores decrease in fast nicotine metabolizers

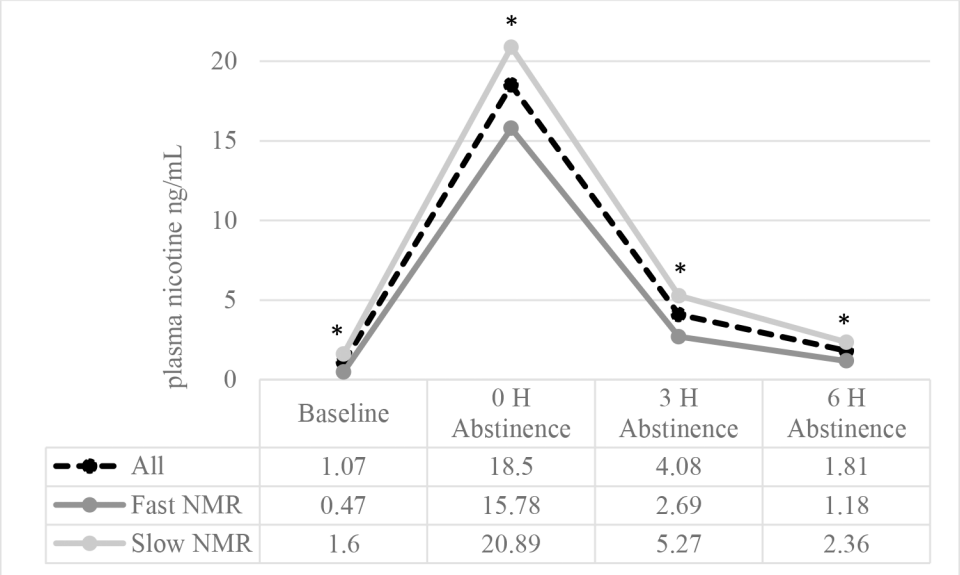

Figure 1. Mean Nicotine Levels by Fast and Slow NMR, Pre-Smoking (Baseline) and After Smoking (0, 3 and 6 Hours Abstinence)

*Fast vs. Slow NMR (Nicotine Metabolite Ratio)

Table 1.

Accuracy and Processing Speed Outcomes, Abbreviated Names and Descriptions

	Outcome Names (abbreviations)	**Outcome Descriptions**
Accuracy Outcomes	Total correct	The sum of the correct responses out of 60 trials.
	False alarms	The sum of identifying a non-match as a match, and/or identifying a match as a non-match.
	Null responses	The sum of when no response was given.
	Null when Match (Null-M)	The sum of when no response was given when the target was a match.
	Null when non-match (Null-NM)	The sum of when no response was given when the target was not a match.
Processing Speed Outcomes	Average reaction time (ART)	The average length of time in milliseconds for a response.
	Average reaction time when match (ART-M)	The average length of time in milliseconds for correctly identifying a match.
	Average reaction time when non-match (ART-NM)	The average length of time in milliseconds for correctly identifying a non-match.

Table 2.

Demographics by Fast and Slow Nicotine Metabolite Ratio (NMR), *N*=121

Baseline Characteristics	**Fast NMR (*N*=56)**	**Slow NMR (*N*=65)**	**Totals (*N*=121)**	***p*-value**
Age, mean years (st. dev)	38.1 (11.9)	33.8 (12.4)	35.8 (12.3)	0.06
Saliva NMR, average (st. dev)	0.59 (0.18)	0.17 (0.05)	0.36 (0.25)	<0.001
Sex *n* (%)				
Male	29 (52%)	46 (71%)	75 (62%)	0.03
Female	27 (48%)	19 (29%)	46 (38%)	
Race *n* (%)				
Caucasian	44 (79%)	45 (69%)	89 (74%)	0.25
African American	12 (21%)	20 (31%)	32 (26%)	
Education, average years (st. dev)	14.2 (2.0)	14.7 (2.3)	14.5 (2.2)	0.29
CPD, average (st. dev)	13.9 (5.8)	13.4 (6.6)	13.6 (6.2)	0.63
Menthol *n* (%)				
Yes	15 (27%)	18 (28%)	33 (27%)	0.91
No	41 (73%)	47 (72%)	88 (73%)	
FTCD, average (st. dev)	4.0 (2.0)	4.1 (2.0)	4.1 (2.0)	0.84
TFC, average minutes (st. dev)	50.4 (71.6)	31.6 (33.6)	40.3 (55.1)	0.06

st.dev=standard deviation; CPD=cigarettes per day; FTCD; Fagerstrom Test for Cigarette Dependence; TFC=time to first cigarette

Table 3.

0-Back & 2-Back Accuracy and Processing Speed Scores over Time

N=121	Mean Values (ranges)			p-values	
	0 Hours	3 Hours	6 Hours	unadjusted	adjusted
Accuracy					
0-back Total Correct	58.7 (47–60)	58.2 (24–60)	58.7 (51–60)	0.25	0.69
2-back Total Correct	50.4 (10–60)	50.7 (12–60)	52.1 (16–60)	0.003	0.08
0-back False Alarms	0.37 (0–4)	0.36 (0–4)	0.43 (0–4)	0.60	0.89
2-back False Alarms	2.30 (0–33)	2.07 (0–15)	1.94 (0–13)	0.40	0.17
0-back Total Nulls	0.24 (0–9)	0.43 (0–33)	0.18 (0–5)	0.45	0.21
2-back Total Nulls	3.05 (0–40)	2.21 (0–41)	1.77 (0–40)	0.03	0.43
0-back Null-M	0.06 (0–1)	0.09 (0–9)	0.08 (0–3)	0.78	0.06
2-back Null-M	0.89 (0–17)	0.55 (0–13)	0.51(0–14)	0.02	0.94
0-back Null-NM	0.18 (0–9)	0.34 (0–24)	0.10 (0–2)	0.36	0.34
2-back Null-NM	2.16 (0–29)	1.66 (0–28)	1.26 (0–27)	0.03	0.23
Processing Speed					
0-back ART	723.4 (506–1344)	726.7 (485–1388)	708.7 (505–1262)	0.08	0.28
2-back ART	989.2 (488–1725)	994.7 (526–1829)	995.5 (495–1752)	0.95	0.30
0-back ART-M	722.2 (484–1298)	724.7 (499–1390)	703.1 (503–1254)	0.04	0.10
2-back ART-M	968.3 (506–1656)	966.2 (488–1916)	962.1 (492–1707)	0.88	0.30
0-back ART-NM	724.5 (517–1389)	728.7 (470–1386)	714.4 (500–1270)	0.27	0.74
2-back ART-NM	1010.2 (470–1917)	1023.1 (526–1828)	1028.9 (491–1930)	0.001	0.02

The adjusted model includes the covariates of race and sex. The unadjusted model has no covariates included. ART: Average Reaction Time; ART-M: Average Reaction Time for Identifying a Match; ART-NM: Average Reaction Time for Identifying a Non-Match; Null-M: Null when Target Letter is a Match; N-NM: Null when Target Letter is a Non-Match.