Does Tobacco Abstinence Decrease Reward Sensitivity?

A Human Laboratory Test

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1   **Abstract**

2   **Introduction**: Animal studies report abstinence from nicotine makes rewards less

3   rewarding; however, the results of human tests of the effects of cessation on reward

4   sensitivity are mixed. The current study tested reward sensitivity in abstinent smokers

5   using more rigorous methods than most prior studies.

6   **Methods:** A human laboratory study compared outcomes for 1 week prior to quitting to

7   those during 4 weeks post-quit. The study used smokers trying to quit, objective and

8   subjective measures, multiple measures during smoking and abstinence, and monetary

9   rewards to increase the prevalence of abstinence. Current daily smokers (n = 211) who

10 were trying to quit completed an operant measure of reward sensitivity and a survey of

11 pleasure from various rewards as well as self-reports of anhedonia, delay discounting,

12 positive affect and tobacco withdrawal twice each week. A comparison group of long-

13 term former smokers (n = 67) also completed the tasks weekly for 4 weeks. Primary

14 analyses were based on the 61 current smokers who abstained for all 4 weeks.

15 **Results**:   Stopping smoking decreased self-reported pleasure from rewards but did not

16 decrease reward sensitivity on the operant task. Abstinence also decreased self-

17 reported reward frequency and increased the two anhedonia measures. However, the

18 changes with abstinence were small for all outcomes (6-14%) and most lasted less than

19 a week.

20 **Conclusion:** Abstinence from tobacco decreased most self-report measures of reward

21 sensitivity; however, it did not change the objective measure. The self-report effects

22 were small.

23   **Implications**:

24   •   Animal research suggests that nicotine withdrawal decreases reward sensitivity.

25   Replication tests of this in humans have produced inconsistent results.

26   •   We report what we believe is a more rigorous test

27   •   We found smoking abstinence slightly decreases self-reports of reward sensitivity

28   but does not do so for behavioral measures of reward sensitivity

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32   **INTRODUCTION**

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34   When animals are administered nicotine chronically and this is stopped, then

35   during withdrawal, the animals are less willing to work for rewards [1-5] as indicated by

36   increased thresholds for intracranial self-stimulation during abstinence. These effects

37   could represent an "offset" or a "withdrawal effect"[6]. In terms of the former, acute doses

38   of nicotine increase the willingness of animals to work for drug and non-drug rewards[7-9]

39   and this appears to be true in humans [8 10, 11]; thus, when smokers quit and lose this

40   effect, they should experience decreased reward sensitivity, simply due to the loss of

41   the direct effects of nicotine; i.e., independent of any neural compensation.. This "offset

42   effect" should produce a gradual unilateral change over time. On the other hand,

43   several studies have labeled the decreased sensitivity as a "withdrawal effect. If this is

44   correct, then deprivation should produce a transient change resulting in an inverted U

45   shaped time course. Whether animal studies indicate an offset or withdrawal effect is

46   unclear, in part, because few have measured reward sensitivity on multiple occasions

47   over time

48

49   Several human studies have directly, or indirectly measured reward sensitivity

50   with nicotine abstinence. These studies usually either measure a) a behavioral

51   outcome in which participants either work less hard to obtain presumably rewarding

52   stimuli (e.g. money or preferred music) or, in choice situations, allocate less responding

53   to higher magnitude or more probable rewards or b) a self-report measure of the

54   enjoyment or frequency of rewards or an anhedonia scale. We located 19 such trials [5,

55   10-26] and two additional studies [13, 16] that included only self-report outcomes. Most of

56   the above studies used experimental within-participant designs (52%), dependent

57   smokers (67%), overnight abstinence (67%), and smokers not trying to quit (85%).

58   Overall, eight studies had positive results and 13 had null results or results that varied

59   across dependent variables. These mixed results could be due to one or more of the

60   following methodological decisions: a) use of smokers who are not trying to quit for

61   good [27], b) only overnight abstinence, c) small sample sizes, d) only one test during

62   abstinence, e) confounding of measures from behavioral tasks by learning/practice

63   effects, f) use of insensitive measures (e.g. only 1-3 questions), and g) outcomes

64   measured well-after the usual time course for withdrawal effects [28]. The current study

65   attempted to provide a more valid test of abstinence-induced reward sensitivity in

66   humans by minimizing these problems. In addition, our study was designed to

67   determine whether any effects of abstinence appeared to be due to the simple offset of

68   drug effects or due to drug withdrawal.   Our major hypotheses were that abstinence

69   would a) decrease reward sensitivity on a behavioral task, and b) decrease ratings of

70   enjoyment from rewards.

71

72   **METHODS**

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74   **Study Design:** We recruited 211 smokers who were trying to quit for good to a study in

75   which they attended two sessions/week for 5 weeks. In the first week, they smoked

76   their usual number of cigs/day. They then quit smoking and were to remain abstinent

77   for 4 weeks. To obtain an adequate number of continuously abstinent smokers to

78   decrease selection bias, we used a schedule of escalating monetary incentives to

79   encourage abstinence. The two primary outcomes were performance on a behavioral

80   task that measures reward sensitivity, and a scale that measures enjoyment from

81   various events/activities.   We also recruited a comparison group of 67 long-time former

82   smokers to a) determine whether measures in abstinent smokers have returned to a

83   level similar to long term abstinence and, b) whether repeated testing influences our

84   outcomes. The study occurred at the University of Vermont and Dartmouth College and

85   was approved by the ethics committees of both sites. The study was registered at

86   www.clinicaltrials.gov (NCT01824511).

87

88   **Participants:** Potential participants were recruited by flyers (22%), Craigslist

89   (www.craigslist.com) (19%), newspaper ads (18%), word-of-mouth (14%), radio ads

90   (11%), and other sources. Generic inclusion criteria for both current and former

91   smokers were a) ≥18 years old, b) able to read and understand English, c) no current

92   (last year) mood or non-nicotine alcohol/drug-related psychiatric disorder, nor any

93   neurological condition that could influence reward sensitivity; e.g. Parkinsonism [29, 30], d)

94   no current use of psychoactive medications; e.g. antidepressants or anxiolytics, e) used

95   marijuana $\leq$ 2 times in the last month, f) agree to no use of non-cigarette tobacco, non-

96   tobacco nicotine, marijuana, illegal drug, electronic cigarettes, or smoking cessation

97   products during the study, and g) not currently pregnant.

98

99   The inclusion criteria for the current smoker condition were a) currently smoke

100   $\geq$10 cigarettes daily for $\geq$ 1 year, b) want to quit smoking for good via abrupt cessation

101   without treatment, c) willing to quit 7-14 days from study entry and not reduce before

102   quitting, e) have carbon monoxide (CO) level ≥ 8 ppm at consent. We included only

103   those wanting to quit to increase generalizability and sensitivity[27] and because such

104   smokers have more withdrawal when they quit [31] The most common reasons for

105   exclusion were use of a psychoactive medication, use of cannabis and too few

106   cigarettes/day (Figure 1). Just over half of those eligible consented and entered the

107   study (n = 211). Current smokers were generally similar to US current smokers who

108   had recently tried to quit or were planning on quitting in gender, race, age,

109   cigarettes/day and Fagerstrom Test for Cigarette Dependence [32] but were more

110   educated (Table 1).

111

112   The inclusion criteria for the former smoker condition were a) smoked >10

113   cigs/day for >1 years in past, b) used ≤ 5 cigarettes in last year, and c) have not used

114   any non-cigarette tobacco or nicotine products in the last month. Our sample of former

115   smokers was similar to the US average former smoker except for a higher educational

116   level. Former smokers were similar to current smokers except they were older

117   (Wilcoxon rank sum test Z = 3.4, p < 0.001) and more educated (x^2 = 49.9, p < 0.001).

118

119   **Sample Size:** Our original aim was to recruit until we obtained 70 smokers who

120   abstained for 4 weeks. This sample size would provide > 90% power to detect a change

121   of 20% in scores on most of our dependent variables after abstinence, if we assumed a

122   within-participant correlation of 0.8, which is similar to that found in our prior withdrawal

123   studies [31].

124

125   **Procedures:** We used an escalating payment schedule to increase abstinence

126   rates. Participants attended two laboratory visits/week to provide breath samples for

127   CO and urine samples for cotinine to verify self-reported abstinence. A CO of $\leq$ 8 ppm

128   (Smokerlyzer, Bedfont) at both visits in the first week of instructed abstinence was

129   required to assume initial abstinence. Although twice daily CO would be necessary to

130   truly verify smoking, a recent study found daily or almost daily CO validation to be an

131   adequate substitute [33]. For the second through fourth weeks of abstinence, we added a

132   criteria that the urine cotinine test strip (Onescreen cotinine test, American Screening)

133   have a value = 0 indicating cotinine < 10 ng/ml. These CO and cotinine cutoffs detect

134   recent smoking/abstinence with high sensitivity and specificity [34]. We also required a

135   negative urine cannabis dipstick result (Discover THC dipstick, American Screening)

136   because cannabis use might mimic decreased reward sensitivity[35]. The monetary

137   reward schedule was similar to that effective in our prior studies [36, 37]. The abstinent-

138   contingent payments began at $16/visit and increased at each subsequent visit to a

139   maximum of $30/visit. In addition, participants could receive $50 - $100 bonuses

140   payments for continuous abstinence. Participants abstinent for all 4 weeks received

141     $534. Research staff provided supportive counseling at each visit (about 5 minutes)

142   consistent with the USPHS guidelines [38].

143

144   Former smokers attended lab visits once a week for 4 weeks. Tobacco and

145   cannabis abstinence were verified as with current smokers; however, we did not provide

146   extra payment for abstinence. Both current smokers and former smokers also

147 received payments for attending visits and completing measures and these payments

148 were not contingent on not smoking.

149

150 **Measures:** One primary measure was the Effort Expenditure for Rewards Task

151 (EEfRT) that examines responding as a function of response cost, reward magnitude,

152 and probability of reward [39]. The task presents participants with repeated choice tests.

153 At each test, the program presents a choice between a more difficult task in which

154 success is rewarded with more money, or a less difficult task in which success is

155 rewarded with less money. Participants had 3 seconds to choose which task to

156 undertake. The harder task required 100 button presses with the non-dominant little

157 finger in 21 seconds. The easy task required 30 presses within 7 seconds. The entire

158 session lasted 20 minutes. The payment for each test was randomly assigned to vary

159 from $0.25 - $1.05 and the probability of payment was either 12%, 50% or 88%.

160 Participants were informed on the payment and probability for each task prior to making

161 a choice. The original EEfRT also includes a second varying probability for whether

162 there is any payment for the test session. To keep the task easier to understand, we

163 deleted this last probability. Reward responsivity was measured by the proportion of

164 higher reward tasks chosen across all probabilities and then separately for the high,

165 medium and low probability choice tests. Decreased choice of the higher reward test

166 would indicate decreased reward sensitivity.   Of the 87,787 trials, we excluded 2030

167 (2.3%) because the participant did not make a choice of hard vs easy, or exclusively

168 chose hard or easy throughout the session. Performance on the EEfRT has been

169   shown to be correlated with self-report measures of anhedonia and is sensitive to the

170   effects of stimulants to increase reward seeking [39-41]

171

172   The other primary measure was the Rewarding Events Inventory, a self-report

173   measure of 54 common rewards that we developed to be a more comprehensive and

174   up-to-date measure than existing scales. The measure has excellent internal validity

175   and test-retest reliability [42]. The Inventory asked participants to rate the events

176   separately on enjoyment, with response options of "not enjoy it, enjoy it a little, enjoy it

177   some, enjoy it a lot, extremely enjoy it , and frequency, with response options of every

178   day, most days, few days, one day or no days in the last week."

179

180   To verify that participants were having withdrawal symptoms during abstinence

181   we asked participants to rate the nine DSM-5 (www.dsm5.org) withdrawal items from 0=

182   not at all to 4=severe (nb, this does not include craving), using the Minnesota Nicotine

183   Withdrawal Scale-Revised (www.uvm.edu/~hbpl) [28, 43]. The MNWS has good

184   psychometrics [28, 43]. We also included measures of constructs related to reward

185   sensitivity; i.e., anhedonia/apathy, delay discounting, and positive affect to provide

186   convergent validity tests. One measure was the 18-item Apathy Evaluation Scale (AES)

187   which asks about decreased pleasure or interest in rewards (e.g. "I am interested in

188   having new experiences") [44] with ratings from 1 = not at all to 4 = very true. The other

189   was the Temporal Experience of Pleasure Scale (TEPS) that includes a 10 item interest

190   in reward scale and an 8 item pleasure from reward scale with response options on a 6

191   point Likert scale [45]. The AES and TEPS have been tested in psychiatric, drug abuse

192   and neurological patients, and have good reliability and adequate validity [46-48]. Positive

193   affect was measured using the Positive and Negative Affect Scale (PANAS) [49]. This

194   widely used measure has excellent reliability and validity [50]. We also examined delayed

195   discounting (DD) because decreased reward sensitivity appears to be associated with

196   decreased delay discounting [51]. For this measure, participants completed a delay

197   discounting task [52] in which participants are given a series of hypothetical choice

198   situations of receiving money now vs later with varying monetary values and delay

199   periods. The amount available after the delay was always $1000 and the range of

200   delays was 1 day to 5 years. Across trials, a smaller, sooner reward was adjusted up or

201   down by 50% depending on the subject's choice (smaller, sooner choices resulted in

202   decreases; larger, delayed choices resulted in increases).

203   Results with these hypothetical choices are consistent with actual choices [53].

204   The major outcome was the k statistic which reflects the relative preference for a small,

205   immediate reward vs. a larger delayed reward and is based on a natural log

206   transformation of k [52]. A decrease in preference for the more immediate reward would

207   assumted to indicate decreased reward sensitivity. All of the above measures were

208   obtained at every lab visit.

209

210   In summary, we expected that abstinence would increase withdrawal scores,

211   decrease choice of hard response on the EEfRT, decrease enjoyment and frequency of

212   rewards on the REI, increase anhedonia scores on the AES and TEPS, decrease

213   positive affect, and decrease delay discounting.

214

215   **Data Analysis:** Since many smokers do not maintain abstinence during a withdrawal

216   study, the major issue in analysis is whom to include in the analyses[28]. If one uses all

217   participants, this reduces bias and generalizability resulting from examining only a

218   subset of participants, but it requires using withdrawal scores among those who

219   currently smoke. If one uses only those abstinent for the entire study, this avoids using

220   smokers who are smoking but can substantially reduce the sample size and allow

221   selection bias. Another option is to include all smokers and use abstinence status as a

222   time-varying covariate[54]. This option includes all smokers but some of the withdrawal

223   scores are based on short periods of abstinence.   For the primary analysis we chose to

224   use the 61 participants who were abstinent for the entire four weeks for four reasons: a)

225   this is the most commonly used option in tobacco withdrawal studies[31], b) several days

226   of abstinence may be necessary to change reward sensitivity, c) our resultant sample

227   size was still adequate for our within-participant analyses, and d) this allows a test of

228   time pattern (i.e., whether the results appear to be due to simple drug offset or to drug

229   withdrawal) that is not influenced by different participants at different timepoints. We

230   also undertook two sensitivity tests using a) the larger sample (n= 104) of participants

231   abstinent during the first week when abstinence symptoms typically peak, and b) all 211

232   participants with abstinence status as a time-varying covariate.

233

234   Our major analyses were based on within-participant ANOVAs. We used mixed

235   linear modeling to conduct longitudinal analyses of outcomes, including both restricted

236   maximum likelihood of fixed effects with a compound symmetric covariance matrix, and

237   random effects with an unstructured covariance matrix. All analyses were conducted

238   using SAS 9.4 software (SAS Institute, Cary, NC) and statistical significance across all

239   tests was defined as p < .05 (2-tailed). Our pre-specified major test among current

240   smokers was a comparison of the mean EEfRT and REI enjoyment scores during the

241   smoking-as-usual period vs the mean during the entire abstinence period. We also

242   specifically tested for an inverted U shape pattern in abstinence for all outcomes; i.e.,

243   whether any outcomes had any initial increase/decrease or during abstinence which

244   abated over time during the abstinence period via an ANOVA confined to the

245   abstinence period. We also used paired t tests to compare peak baseline score and

246   peak score during abstinence using the highest score as peak for those measures

247   expected to increase with abstinence and lowest score for those expected to decrease.

248   We next compared results between former smokers and newly abstinent smokers to

249   see if the recent abstainers had returned to the level of long-term former smokers.   To

250   do this, we tested whether the results at the 3rd and 4th visits among abstainers differed

251   from the results from the 3rd and 4th visit results among long-term former smokers, again

252   with an ANOVA.

253

254   **RESULTS**

255

256   **Initial Analyses:** About half (n=104, 52%) of participants were abstinent for $\geq$ 1 week

257   but this decreased to about a fourth (n = 61, 29%) abstinent for all 4 weeks (Figure 1;

258   Appendix, Figure 1).   As in most clinical studies, those who were able to abstain longer

259   (i.e., for 4 weeks) were older (Wilcoxon rank sum test Z = 2.0, p = .05), more educated

260   (Fisher's Exact Test, p = .004) and smoked fewer cigs/day (Wilcoxon rank sum test Z =

261   3.0, p =.003) than those who were not able to do so. Among the 61 fully abstinent

262   participants, the two baseline values did not differ from each other for any outcome,

263   indicating they represent stable baseline scores. The mean score for the MNWS score

264   during abstinence was substantially greater than the mean score during smoking

265   (+43%) indicating these 61 participants were in withdrawal during the abstinence period

266   (F=64.8, p< 0.001). For most measures, the scores for the four tests among long-

267   abstinent smokers found little change with repeated testing (< 2.5% change from one

268   time point to the next); however, preference for the harder task on the EEFRT increased

269   overtime (6.7% increase between tests). There were no significant differences

270   between the 3rd and 4th visits for long-term former smokers.

271

272   **Main Analyses**: Contrary to our hypothesis, the mean proportion of choices that were

273   for the higher-reward task on the EEfRT task during the abstinence period was greater,

274   not smaller, than the mean proportion during the smoking period (F=40.4, p < 0.001;

275   see Table 2, Figures 2 and 3).   When we looked at results at each of the three

276   probability of reward settings on the EEfRT, one showed no change and the other two

277   showed an increase, not a decrease; at probability =0.12, F=0.7, p =0.39; at

278   probability=0.50, F= 52.2, and p<0.001; at probability=0.88, F=82.3, p<0.001. In

279   contrast, consistent with our major hypothesis, abstinence decreased the rated

280   enjoyment from rewards on the REI, F=133.1, p<0.001. Also, consistent with our

281   hypotheses, abstinence decreased the frequency of rewarding events, (F=58.4, p <

282   0.001) and the delay discounting outcome, (F=22.5, p<0.0010) and increased scores on

283   the AES, F=11.4, p=0.001, and TEPS scales, (F=5.5, p=0.02), However, the

284   magnitudes of change for both our primary and secondary outcomes were small (6-

285   14%, see Table 2 and Figures 2 and 3). Using the mean score across all abstinence

286   measures as the dependent variable could have obscured a change that occurred on

287   only one or two days during abstinence. To test this, we reran the analyses comparing

288   the peak value during abstinence vs the peak value during smoking. The results were

289   very similar (Appendix Table 1).

290

291   **Time Course:** True withdrawal symptoms exhibit an inverted U time course; to test this

292   we examined whether, among the five outcomes that showed the hypothesized initial

293   change with abstinence (REI enjoyment, REI frequency, DD, TEPS and AES), whether

294   these changes scores then decreased over time (i.e., we compared scores in week 1 vs

295   the average across weeks 2-4). This was true for the REI enjoyment ($t = 2.1$, $p = 0.04$) ,

296   REI frequency ($t = -3.2$, $p = 0.002$) and DD ($t = -2.4$, $p = .02$) outcomes but not for the

297   AES or TEPS scores.   Figures 2 and 3 illustrate the magnitude of these results

298

299   **Former Smokers:**   After adjusting for subject characteristics that differed between

300   former and current smokers, recently abstinent smokers had higher MNWS scores, ($F =$

301   30.1, $p < 0.001$), and AES scores, ($F = 4.4$, $p = .04$); but lower positive affect scores, (F

302   $= 8.5$, $p < 0.004$), than former smokers. Abstinent smokers also had lower REI

303   enjoyment scores (Wilcoxon rank sum test $Z = -2.1$, $p = .03$), although we could not

304   meet ANOVA assumptions for including baseline differences in this particular test.

305   Figures 2 and 3 illustrate the magnitude of differences.

306

307   **Sensitivity Analyses**: We reran the major analysis; i.e., a comparison of mean

308   smoking vs mean abstinence score for the EEfRT and REI enjoyment but only

309   examined results from the first week of abstinence and included all participants

310   abstinent during the first week (n = 104). We also reran analyses using all participants

311   (n = 211) and using abstinent state as a time-varying covariate. In both analyses, the

312   results were very similar to that for the 61 long-abstinent smokers. The results of these

313   analyses are in Appendix Tables 2 and 3. .

314

315   **DISCUSSION**

316   Cigarette abstinence decreased self-reports of pleasure from and frequency of

317   rewards on a reward inventory, and increased scores on the two anhedonia scales.

318   That all four of these changed in the hypothesized direction suggests convergent

319   validity of results. On the other hand, the magnitude of change in these outcomes was

320   only 4-8%. Among the 21 prior studies of the effect of abstinence on reward sensitivity,

321   6 examined change in self-reports, among these, 3 found anhedonia increased but only

322   one reported the magnitude of change (+19% estimated from graph)[16] and this was

323   probably the study with the highest internal and external validity.

324   Abstinence did not decrease reward sensitivity in the behavioral test of reward

325   sensitivity - the EEfRT. Among the 15 prior studies that examined a behavioral task of

326   reward sensitivity, 7 (47%) reported abstinence decreased sensitivity. Among the six

327   studies that reported magnitude of effects, the median decrease was only 2.5%.

328   However, the study that was the most rigorous test and used a validated behavioral task

329   found abstinence completely eliminated preference for the higher magnitude reward [5].

330   One possible reason we failed to find an effect on EEfRT on the behavioral task was

331   that scores on the EEfRT appeared to increase over time, suggesting a learning effect

332   that may have obscured any decline due to abstinence. Prior studies have not

333   measured the EEfRT repeatedly over time; thus, whether learning effects are common

334   with EEfRT requires further testing. Another possible reason for different outcomes in

335   self-report vs behavioral task outcomes is that they are measuring two different aspects

336   of reward sensitivity [55]; i.e., the former is measuring hedonic response and the latter

337   motivation to pursue rewards.

338   In terms of other secondary outcomes, if abstinence decreases reward

339   sensitivity, then this should decrease delay discounting [56] which is what we found, albeit

340   the magnitude of this effect was small. Across the ten prior studies of the effect of initial

341   abstinence on delay discounting, two found abstinence decreased DD [52, 57], four found

342   it produced no change [33, 58-60] and four found abstinence increased DD [61-64]. Our

343   reading of these studies does not suggest a clear reason for these heterogeneous

344   results. It may be because the DD task and how its results are calculated differs across

345   studies. Also, studies that found abstinence increased DD, interpreted this as indicating

346   abstinence increases impulsivity, which is consistent with other studies [65]. Thus, it may

347   be that abstinence has two opposing effects on DD tasks; i.e., it decreases reward

348   sensitivity but also increases impulsivity.

349   One possible limitation of our results is that our main analysis used only the 30%

350   of our participants who were abstinent for the desired 4 week period; however, tests

351   using a larger sample of those initially abstinent and using all participants obtained

352   similar results.   Also, we did not conduct a randomized trial of abstinent vs non-

353   abstinent conditions. Instead we used a pre-post design in which participants served as

354   their own control. Although such non-randomized designs can have methodological

355   problems, in fact, most studies of tobacco withdrawal have used pre vs post designs

356   and have provided very replicable data. We did not include several measures of reward

357   sensitivity such as neuroimaging [66] or response to hedonic stimuli [19, 67] that tap other

358   aspects of reward sensitivity; e.g. reward anticipation or reward learning. Our

359   participants were more educated and more nicotine dependent than the average US

360   smoker and had no use of psychoactive drugs or current psychiatric disorder; this may

361   decrease the external validity of our study. The influence of abstinence may differ by

362   psychiatric status[5]; however, we did not collect information on past or current psychiatric

363   status. Our sample size for analysis might be thought of as small; however, our data

364   analysis was based on a within-participant comparison with multiple pre and post-

365   cessation values.

366   To our knowledge, this was the first use of the EEfRT to examine the effects of

367   smoking abstinence. Several studies have found EEfRT can detect reward sensitivity

368   changes with other drugs [39, 41, 68-71]. Our first post-cessation EEfRT measurement did

369   not occur until 3-4 days after cessation. Some prior studies suggest the effect of

370   abstinence on reward sensitivity occurs immediately after cessation [5]; thus we could

371   have missed a short-lived effect. Although one could believe such a "fleeting" effect

372   would not be clinically important, this may not be the case because over half of all

373   relapses occur in the first 3 days[72]. Finally, our contingency program to increase

374   abstinence relied on testing at only 2 visits/week and thus, some smoking could have

375   occurred between the visits and this decreased the sensitivity of our test. On the other

376   hand, the scores on the MNWS increased substantially indicating participants were in

377   withdrawal during the last 4 weeks of the study.

378

379   Compared to the prior studies of the effect of tobacco abstinence on reward

380   sensitivity, the current study had the following methodological assets: a) use of

381   smokers who are trying to quit for good, b) longer period of abstinence that included the

382   typical time periods for tobacco withdrawal, c), a sufficient time period to detect if effects

383   due to withdrawal or simple offset of direct effects, d) multiple measures during

384   smoking and abstinence periods, e) use of both objective and subjective measures, f)

385   multiple measures to allow test of convergent validity, g) abstinence verification on

386   multiple occasions, and h) experimental induction of abstinence. [28]

387   In summary, our self-report results suggest abstinence induces a small decrease

388   in reward sensitivity, but our behavioral task did not confirm this. Animal studies clearly

389   predict that smoking cessation should decrease reward sensitivity (see above). We

390   believe the small decrease in reward sensitivity we observed in a subset of the

391   measures is a weak confirmation of the applicability of animal data to smoking cessation

392   in humans. Given the heterogeneity of prior results on whether smoking abstinence

393   decreases reward sensitivity and the limitations of our own methods, further studies of

394   abstinence-induced decreased reward sensitivity using other behavioral tasks such as

395   the Progressive Ratio task [10] or the Signal Detection Task [73] that may be more sensitive

396   or reliable, concomitant with self-report measures, are needed to further clarify the

397   importance of reward sensitivity to smoking cessation.

409 **Declaration of Interests:** JRH has received consulting fees from companies that
410 develop or market products for smoking cessation or harm reduction and from non-profit
411 companies that engage in tobacco control. Other authors have nothing to disclose.
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434   Table 1.

435   Comparison of study sample with a population based sample

436

437

	Current Study			
	Current Smokers (n = 211)	Former Smokers (n = 67)	US Current Smokers with Recent Quit Attempt[a]	US Former Smokers[a]
% Women	45%	46%	46%	46%
% White/Non-Latino	86%	85%	74%	74%
Age ($M \pm SD$)	40 ± 15	47±16	40	40
% Some college or more	67%	93%	46%	57%
% Employed	62%	69%	-	-
Cigarettes per day ($M \pm SD$)	19 ± 8	-	16	-
FTCD Total ($M \pm SD$)	5.0 ± 2.1	-	4.4	-

438   [a]Based on 2007 National Health Interview Survey [74], National Epidemiological Survey
439   on Alcohol and Related Conditions [75], and Fagerstrom & Furburg [76]
440   M= mean, SD= standard deviation, FTCD= Fagerstrom Test for Cigarette Dependence
441   [32]

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445 Table 2. Baseline vs. Abstinent Scores in Participants Abstinent for Four Weeks (n=61)
446 and Among Positive Results, Whether Time Course Was Consistent With That of a
447 Withdrawal Symptom

448

449 | | Mean Baseline vs. Mean Abstinent | | | | |
|---|---|---|---|---|---|
| Variable (range) | Baseline | Abstinent | Absolute Change | Percent Change | Withdrawal Time Pattern[b] |
| EEfRT (0-1) | 0.51 | 0.58***[a] | +0.07 | +14% | No |
| REI Enjoy (1-5) | 3.7 | 3.5*** | -0.2 | -5% | Yes |
| REI Frequency (1-5) | 2.6 | 2.4*** | -0.2 | -8% | Yes |
| AES (18-72) | 29.2 | 30.9*** | +1.7 | +6% | No |
| TEPS (18-108) | 41.7 | 43.5* | +1.8 | +4% | |
| PANAS PA (10-50) | 33.8 | 33.3 | -0.5 | -2% | |
| Delay discounting (ln k) | -6.4 | -6.8*** | +0.4 | +6% | Yes |

450 [a]Note opposite to hypothesized change
451 * $p < .05$
452 ** $p < .01$
453 *** $p < .001$
454 AES = Apathy Evaluation Scale, EEfRT = Effort Expenditure for Rewards Task, K = test
455 statistic for degree of discounting, ln = natural log, NA = Negative Affect, PA = Positive
456 Affect, PANAS = Positive and Negative Affect Scale, REI = Rewarding Events
457 Inventory, TEPS = Temporal Experience of Pleasure Scale
458 [b]Withdrawal pattern defined as first post-cessation value greater than remaining post-
459 cessation values

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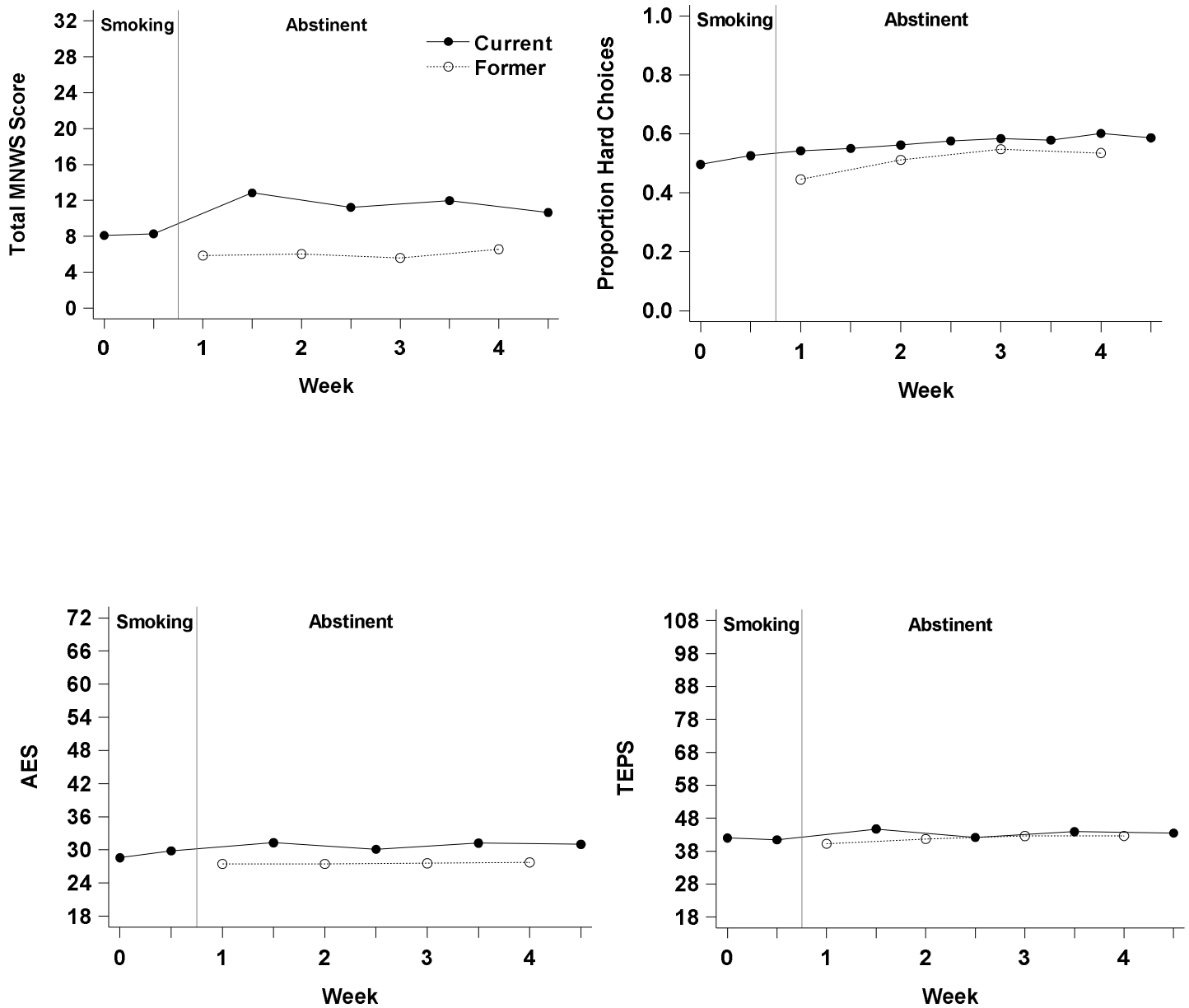671   2008;103:841-845.
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Figure 1. Participant flowchart

Current Smokers
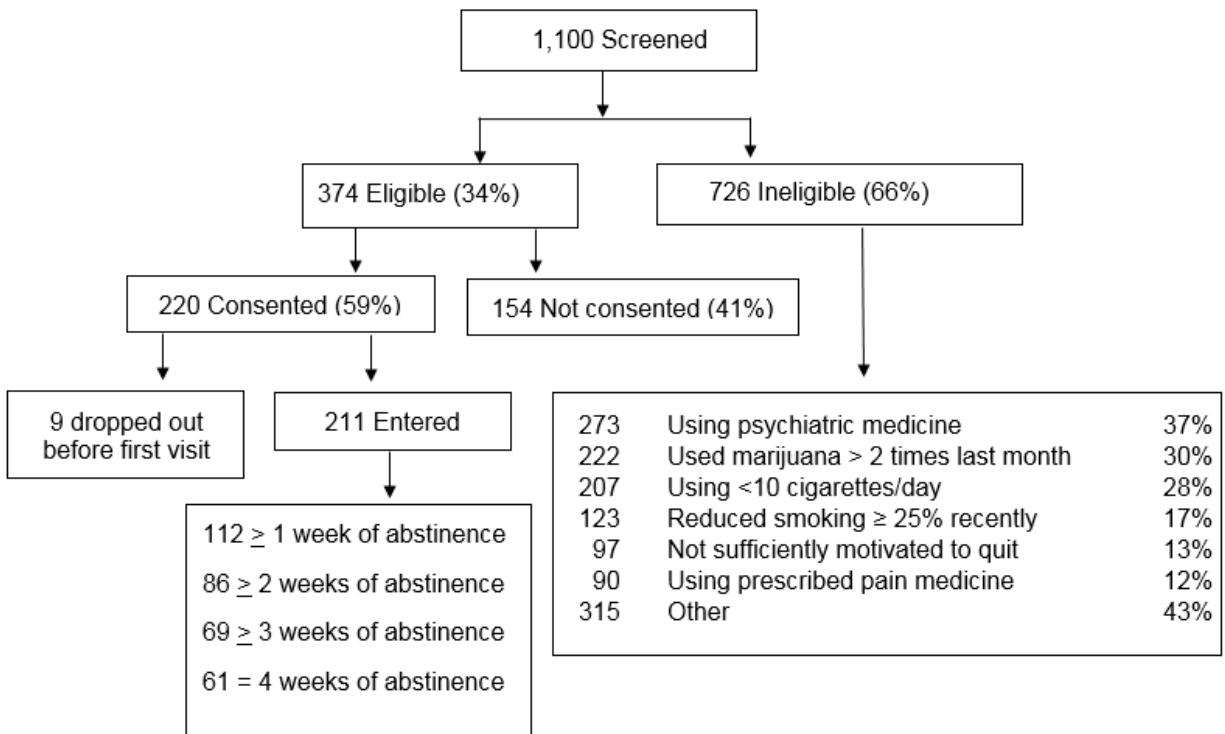
All percents are of the number in box above. Rx = prescription

Figure 2. Time course for selected outcomes.

Solid line = current smokers. Dotted line = former smokers. AES = Apathy Evaluation Scale, MNWS = Minnesota Nicotine Withdrawal Scale, TEPS = Temporal Evaluation of Pleasure Scale

Figure 3. Time course for selected outcomes
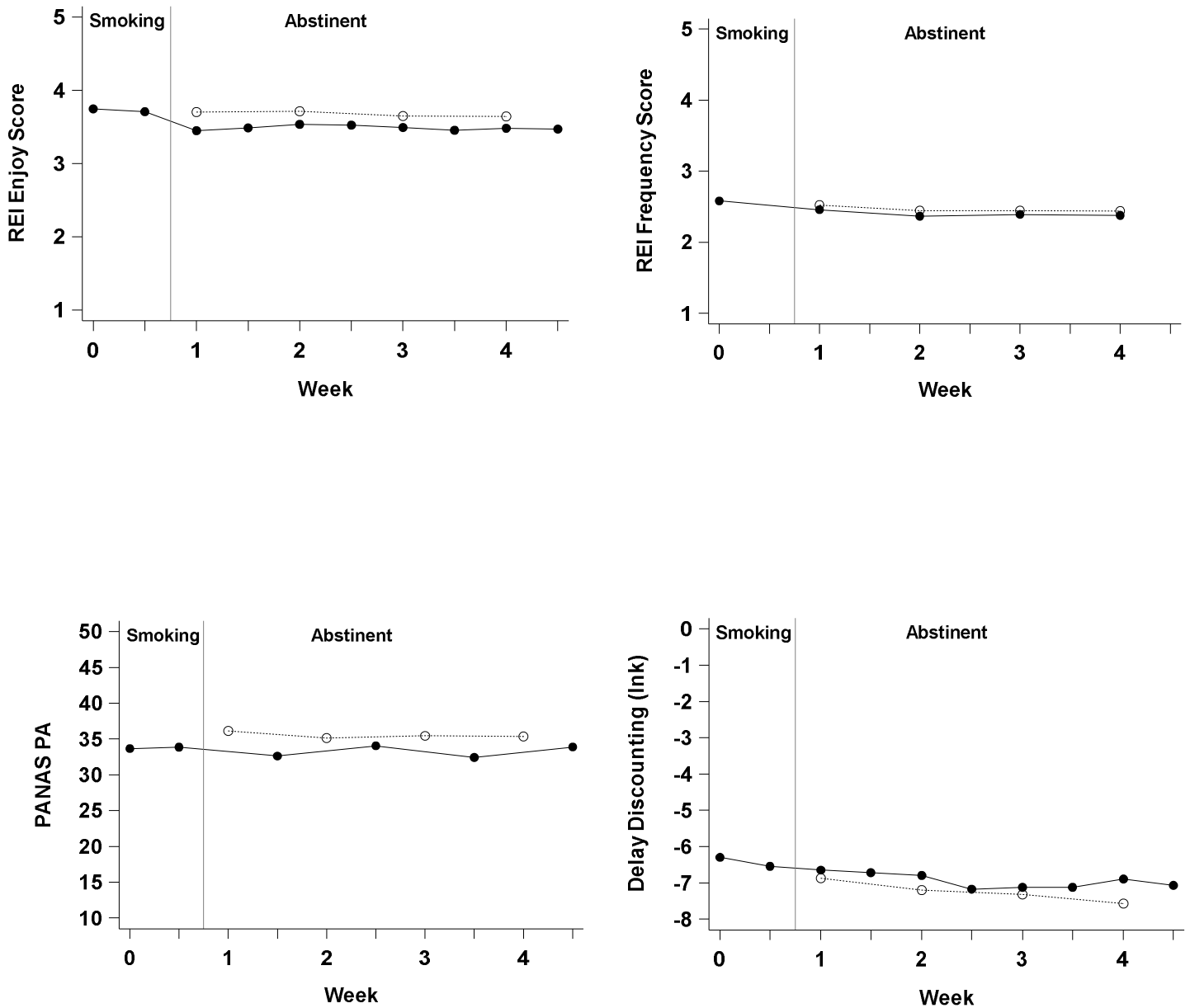
Solid line = current smokers. Dotted line = former smokers. PANAS = Positive Affect and Negative Affect Scale, REI = Rewarding Events Inventory