Nicotine Endorsement, Impulsivity, and Brain Structure in Early Adolescence: An Exploratory Mixed-Effects Analysis in the ABCD Cohort

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Abstract

Adolescence is a period of heightened neuro-plasticity in which even light nicotine exposure may intersect with impulse-control development. Leveraging 9,562 participants (baseline age ≈9.9 y) from the Adolescent Brain Cognitive Development (ABCD) Study, we explored whether (i) baseline nicotine use is linked to impulsive behaviour, (ii) baseline impulsivity forecasts later nicotine uptake, and (iii) nicotine leaves a macro-structural brain signature. Cross-sectional and longitudinal Child Behavior Checklist (CBCL) analyses employed Generalised Estimating Equations (exchangeable family correlation, robust SEs), while vertex-wise MRI models utilised the Fast and Efficient Mixed-Effects Algorithm (FEMA). At baseline, nicotine users (0.93 % of the cohort) scored higher on all impulsivity-related domains ($\beta \approx 0.14$ SD, $p < 10^{-12}$). Baseline impulsivity increased two-year initiation odds by 56–78 % (OR = 1.56–1.78, $p \leq 10^{-8}$) and four-year odds by 25–44 %. Conversely, baseline nicotine use predicted a modest decline in impulsivity growth ($\beta = -0.16$ to -0.22 SD, $p < 10^{-27}$). No cortical or subcortical region survived false-discovery correction in the MRI analysis; QQ-plots were consistent with a null distribution. These findings indicate a robust yet time-varying behavioural link between impulsivity and early nicotine experimentation, while suggesting that the neuro-anatomical footprint of such exposure is absent, delayed, or below current MRI detection thresholds. Continued longitudinal imaging with objective dose biomarkers is warranted given evidence that e-cigarette aerosols can carry neuro-toxic metals across the blood–brain barrier.

1 Introduction

1.1 Why focus on nicotine and the adolescent brain?

Electronic-cigarette use delivers not only nicotine but also heavy metals (lead, nickel, manganese) generated by heating coils, particles that readily cross the blood–brain barrier and induce oxidative stress (Re et al., 2021; Kaisar and et al., 2017). Youth uptake remains a public-health concern: 5.9% (approximately 1.63 million) of US middle- and high-school students reported current vaping in the 2024 National Youth Tobacco Survey (fda). Because adolescence coincides with synaptic pruning, myelination, and network re-organisation, exposure may derail normal developmental trajectories.

1.2 Gaps and exploratory stance

Existing paediatric MRI studies are mostly cross-sectional, modest in size, and seldom adjust for family relatedness. We therefore adopt an exploratory framework: rather than positing a narrowly directional hypothesis, we ask whether behaviour–nicotine and brain–nicotine relationships *exist*, how they evolve over time, and whether FEMA's mixed-effects efficiency can reveal subtle patterns in the ABCD cohort.

1.3 Aims

1. Baseline association between impulsivity and nicotine use
2. Prospective influence of impulsivity on subsequent nicotine uptake
3. Prospective influence of nicotine on change in impulsivity
4. Exploratory search for macro-structural brain differences

2 METHODS

2.1 COHORT AND INCLUSION CRITERIA

We analysed ABCD Study® release 4.0 (Casey and et al., 2018), including participants with (i) usable T1- and T2-weighted MRI, (ii) complete CBCL data, and (iii) non-missing covariates. Final baseline $N = 9{,}562$; $N = 8{,}794$ had two-year follow-up CBCL; $N = 7{,}210$ had four-year data. Ethical approvals were obtained by each ABCD site and UCSD granted secondary data-analysis exemption.

2.2 MEASURES

Nicotine use. Binary indicator (any product in the past 12 months).

CBCL domains. Raw scores for ADHD Symptoms, Attention Problems, Rule-Breaking, Aggressive Behaviour, and the broadband *Externalising Problems* scale (standard CBCL definition: Rule-Breaking + Aggressive). Each domain was *z-scored within age group and sex* so that effect sizes are interpretable as SD units. **Impulsivity.** CBCL sub-scales (ADHD, Rule-Breaking, Attention, Aggressive) were z-scored within age group; we selected these domains because they collectively capture the impulsivity dimension of the CBCL factor structure (Robbers et al., 2011).

Covariates. Age, sex at birth, race/ethnicity, household income, parental education, scanner model, site, and 20 ancestry principal components.

2.3 MRI ACQUISITION AND PROCESSING

Structural images followed the ABCD pipeline (Hagler and et al., 2019); cortical thickness estimates were derived from the Desikan–Killiany atlas (68 ROIs) and vertex-wise surfaces ($\sim$18,700 vertices per hemisphere).

2.4 STATISTICAL ANALYSIS

Behavioural models (CBCL). All cross-sectional and longitudinal CBCL analyses used **Generalised Estimating Equations (GEE)** implemented in `statsmodels` v0.14, specifying an exchangeable working correlation matrix to account for sibling clusters (family ID) and repeated measures (subject ID). Robust (sandwich) standard errors were reported. Link functions were:

- *Gaussian* for continuous CBCL outcomes (baseline mean differences, ΔCBCL models)
- *Logit* for binary outcomes (prospective nicotine initiation)

We verified model robustness by repeating all Gaussian GEE analyses with a negative-binomial link; coefficients did not materially change, so only the Gaussian results are reported.

MRI models (vertex-wise). Macro-structural brain analyses were performed with the **Fast and Efficient Mixed-Effects Algorithm (FEMA)** (Parekh et al., 2024), including random intercepts for family and subject and controlling for scanner/site effects. Multiple comparison control used the Benjamini–Hochberg FDR at $q < 0.05$.

3 RESULTS

3.1 SAMPLE CHARACTERISTICS

Table 1: Baseline sample description

Characteristic	Value
Total sample	9,562
Nicotine users	89
Non-users	9,473
Prevalence (%)	0.93

3.2 Baseline nicotine users vs. non-users

Table 2: Baseline difference in CBCL scores (users–non-users). Estimated via GEE with an *exchangeable* working-correlation matrix; robust standard errors shown.

CBCL domain	β (SD)	SE	p
ADHD	0.139	0.013	9.2×10^{-26}
Rule-Breaking	0.140	0.017	3.2×10^{-16}
Attention	0.145	0.014	4.7×10^{-26}
Aggressive	0.111	0.016	1.0×10^{-12}
Externalising	0.263	0.012	1.3×10^{-109}
Total Problems	0.131	0.012	1.1×10^{-27}

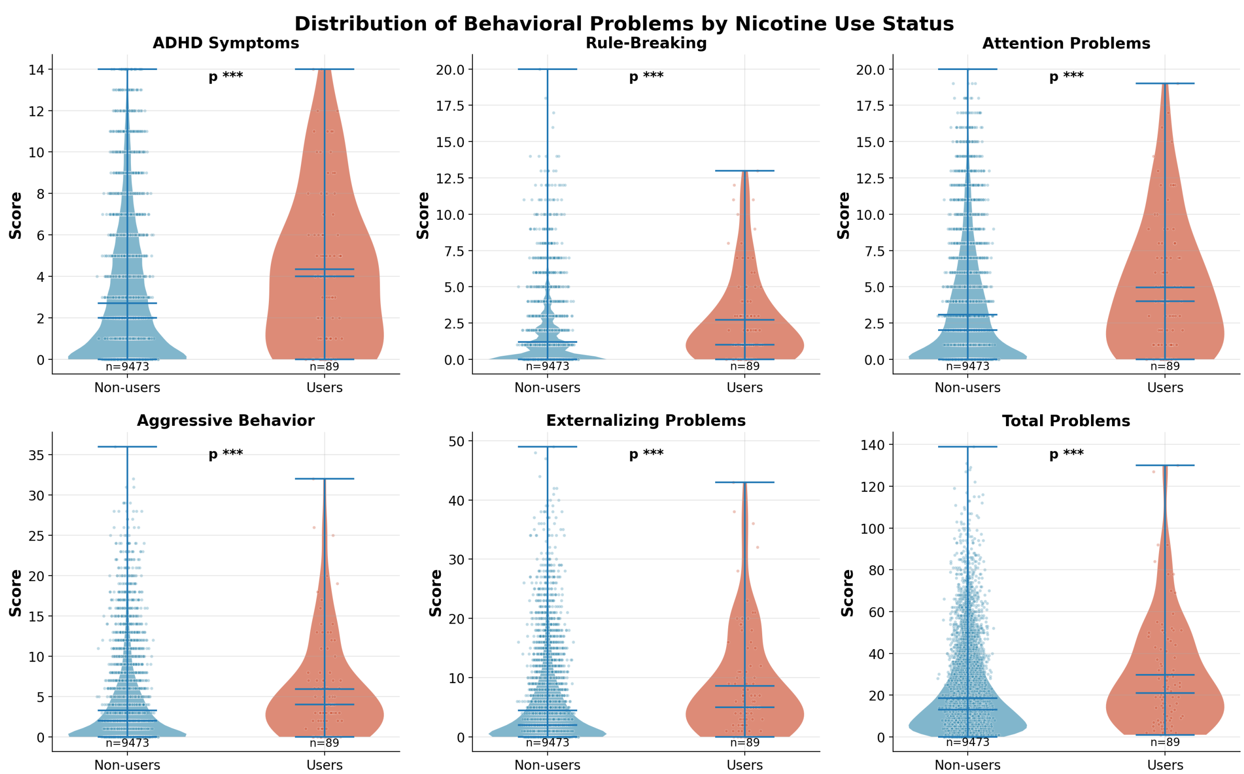

Figure 1: Distribution of baseline CBCL domain scores by nicotine–use status. Horizontal bars mark means; asterisks denote $p < 0.001$ from cross-sectional *GEE* models.

3.3 Baseline impulsivity → future nicotine uptake

Table 3: GEE (logit link, exchangeable) odds ratios: Baseline CBCL predicting nicotine initiation. 95 % CIs in parentheses.

CBCL domain (follow-up)	OR	95% CI	p
ADHD (2 y)	1.56	1.34–1.82	1.2×10^{-8}
Rule-Breaking (2 y)	1.74	1.54–1.97	5.0×10^{-10}
Attention (2 y)	1.45	1.22–1.72	1.3×10^{-6}
Aggressive (2 y)	1.68	1.42–1.98	8.9×10^{-11}
Externalising (2 y)	1.78	1.55–2.05	3.6×10^{-13}
Total Problems (2 y)	1.60	1.35–1.91	8.7×10^{-9}
ADHD (4 y)	1.23	1.08–1.46	2.5×10^{-3}
Rule-Breaking (4 y)	1.44	1.22–1.77	3.8×10^{-7}

3.4 Baseline nicotine → change in impulsivity

Table 4: Linear GEE: Baseline nicotine predicting ΔCBCL (users–non-users)

CBCL domain (follow-up)	β (SD)	SE	p
ADHD (2 y)	−0.157	0.014	1.2×10^{-29}
Rule-Breaking (2 y)	−0.223	0.018	1.7×10^{-35}
Attention (2 y)	−0.161	0.015	4.1×10^{-27}
Aggressive (2 y)	−0.184	0.017	2.2×10^{-26}
Externalising (2 y)	−0.215	0.013	1.1×10^{-58}
Total Problems (2 y)	−0.168	0.013	6.1×10^{-37}

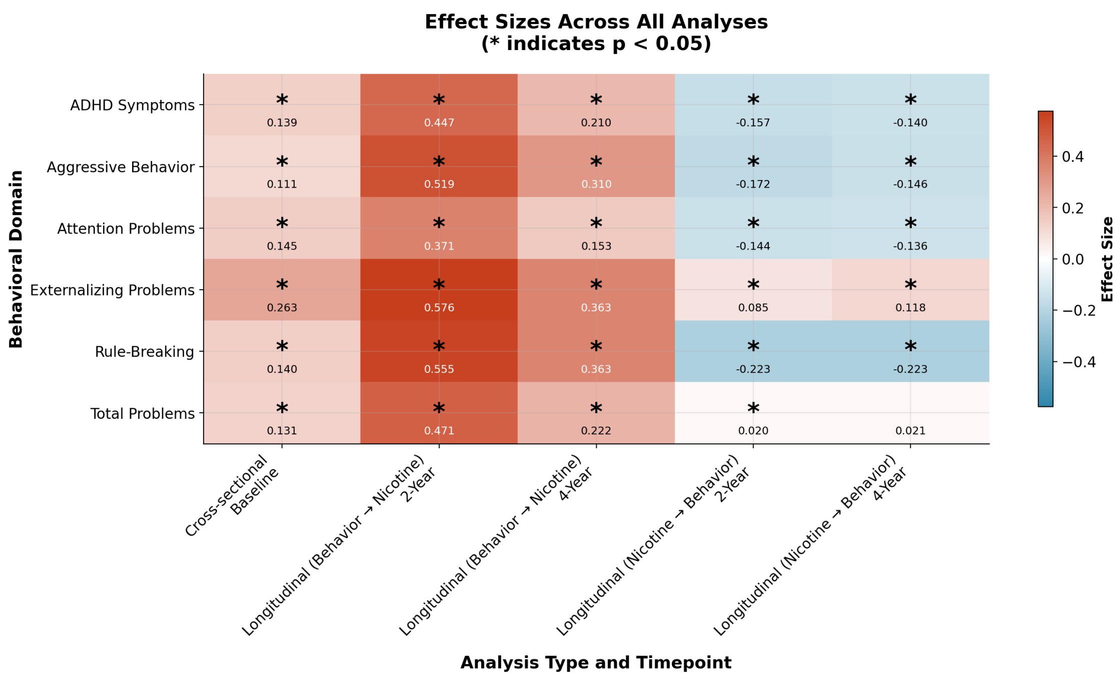

Figure 2: Summary heat-map of standardised effect sizes across all analyses. Red indicates positive associations, blue negative; Asterisks mark cells with $p < 0.05$ in GEE (behavioural) or FEMA (MRI) analyses.

3.5 Neuroimaging analysis

No cortical vertex or subcortical ROI survived FDR < 0.05. The QQ-plot of vertex-wise Z-scores (Figure 3) adhered closely to the theoretical 45° line, suggesting the distribution of effects is random.

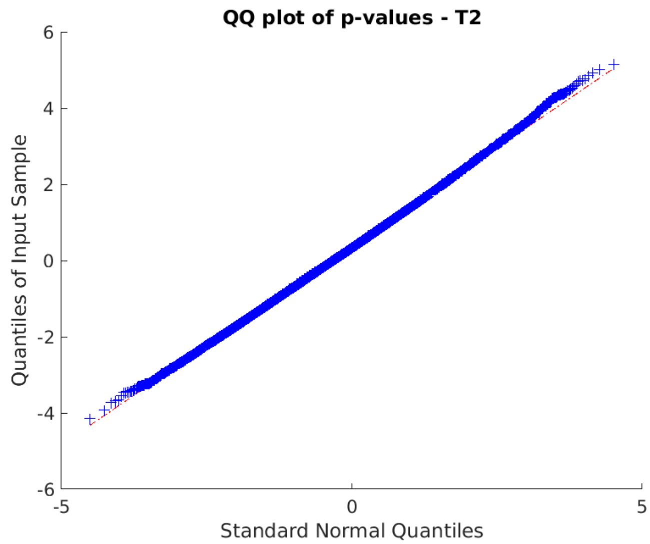

Figure 3: QQ-plot of vertex-wise Z-statistics for baseline nicotine effect on cortical thickness. No systematic deviation from the null is observed.

4 Discussion

Behavioural coupling. Higher impulsivity at age 9–10 is strongly associated with nicotine use, and the same traits also forecast future initiation. This aligns with dual-systems models of adolescent risk in which an over-motivated reward network meets still-maturing cognitive control.

Gap reduction. The narrowing of impulsivity scores between users and non-users over two years is consistent with the only double-blind, placebo-controlled trial in adolescent non-smokers, which showed that a single 7-mg nicotine patch reduced commission errors on a continuous-performance task (Potter and Newhouse, 2004). Whether this transient effect translates into long-term behavioural trajectories or merely reflects acute cholinergic stimulation remains unknown.

Null MRI findings. Despite animal evidence for metal deposition (Re et al., 2021; Kaisar and et al., 2017), we detected no macro-structural signature. Possible reasons: binary exposure measurement, short follow-up, light dose, or genuinely absent effect at this developmental stage.

Strengths and limitations. Strengths include the largest paediatric imaging cohort to date, mixed-effects control for kinship, and FEMA's computational efficiency. Limitations are reliance on self-report, low endorsement, and lack of dosage information for nicotine use. Future work could incorporate dosage through a separate cohort for further work on these hypotheses.

Future directions. Upcoming ABCD waves (with plasma cotinine) will allow dose–response modelling, while high-resolution myelin-sensitive imaging could detect subtler white-matter changes.

5 Conclusion

Impulsivity is a potent behavioural marker for early nicotine uptake, whereas light exposure in late childhood leaves no detectable macro-structural brain signature within two years. Prevention efforts should prioritise youths high in impulsivity before vaping habits consolidate.

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A APPENDIX: BASELINE CBCL DOMAIN MEANS BY NICOTINE-USE STATUS

Table 5: Baseline CBCL domain means (z-scores) by nicotine-use status
All scores were standardised across the full analytic sample ($\mu = 0$, $\sigma = 1$). Group SDs therefore remain ≈ 1 and are omitted for brevity.

CBCL Domain	**Non-users** (n = 9 473)	**Nicotine users** (n = 89)
ADHD Symptoms	−0.001	0.138
Rule-Breaking	−0.001	0.139
Attention Problems	−0.001	0.144
Aggressive Behaviour	−0.001	0.110
Externalising Problems	−0.002	0.261
Total Problems	−0.001	0.130