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Effect of tobacco smoking on frontal cortical thickness development: a longitudinal study in a mixed cohort of ADHD-affected and -unaffected youth

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Abstract

Smoking rates are particularly high during adolescence and young adulthood, when the brain is still undergoing significant developmental changes. Cross-sectional studies have revealed altered brain structure in smokers, such as thinner frontal cortical areas. Attention-deficit/hyperactivity disorder (ADHD) increases the risk of becoming nicotine-dependent, and has also been associated with abnormalities in frontal gray matter structure. The present study examines the relationships between smoking, cortical thickness and ADHD symptoms in a longitudinal design that compares adolescent and young adult smokers (n=44; 35 ADHD-affected) and non-smokers (n=45; 32

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Contributors

SEAA, DvR, NR, CAH, PJH, BF, MM, and JKB were responsible for the study concept and design. DvR contributed to the acquisition of MRI data in NeuroIMAGE. SEAA contributed to the acquisition of MRI data in NeuroIMAGE II. SEAA performed the analyses. DvR assisted with data analysis and interpretation of findings. SEAA drafted the manuscript. DvR, NR, CAH, PJH, BF, MM, and JKB provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved the final version for publication.

Conflict of Interest

JKB has been in the past 3 years a consultant to/member of advisory board of/and/or speaker for Janssen Cilag BV, Eli Lilly, Shire, Medice, Lundbeck, Novartis, Roche and Servier. PJH has been a member of an advisory board of Shire. BF has received educational speaking fees from Merz and Shire. These authors are neither employees of any of these companies, nor stock shareholders of any of these companies. They have no other financial or material support, including expert testimony, patents and royalties. SEAA, DvR, NR, CAH, and MM do not have any conflicts of interest to report.

ADHD-affected) on frontal cortical thickness. Average frontal cortical thickness was estimated through structural magnetic resonance imaging at two time points (mean ages 17.7 and 21.1 years), on average 3.4 years apart. Smokers had a 2.6% thinner frontal cortex than non-smokers and this effect was not explained by ADHD or other confounding factors. The rate of cortical thinning across the 3.4-year MRI measurement interval was similar in the total group of smokers compared to non-smokers. However, speeded thinning did occur in smokers who had started regular smoking more recently, in between the two measurements. These novel regular smokers did not differ significantly from the non-smokers at baseline. This suggests that the thinner frontal cortex was not a predisposing factor but rather a consequence of smoking. Although smokers had more ADHD symptoms overall, smoking did not influence the developmental course of ADHD symptoms.

Keywords

Tobacco; Smoking; Attention Deficit-Hyperactivity Disorder; Magnetic Resonance Imaging; Frontal Cortex; Longitudinal Studies

Introduction

Smoking rates are particularly high during adolescence and young adulthood, when the brain is still undergoing significant developmental changes (Lydon et al., 2014). The presence of attention-deficit/hyperactivity disorder (ADHD) increases the risk of becoming nicotine-dependent (Groenman et al., 2013; Lee et al., 2011). In the current study, we examined the interplay between tobacco smoking, brain development, and ADHD symptoms by investigating the longitudinal effect of smoking on thickness of the frontal cortex in adolescents and young adults with and without ADHD.

Several structural magnetic resonance imaging (sMRI) studies have explored links between smoking and deviations in cortical gray matter structure. A recent meta-analysis on studies using voxel-based morphometry (VBM) revealed that smokers had smaller gray matter volumes bilaterally in the frontal cortex and larger volumes in the right lingual cortex (Zhong et al., 2016). Other studies used cortical thickness (CT) as an outcome measure, which has been argued to be a more specific and sensitive measure for gray matter loss than VBM (Kühn et al., 2010). In accordance with the VBM studies, smokers exhibited lower CT in the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and insula, and also more extensively across the frontal, temporal and parietal lobes (Durazzo et al., 2013; Karama et al., 2015; Kühn et al., 2010; Li et al., 2015). Taken together, less gray matter in various brain regions has been observed in relation to smoking, but most consistently in the prefrontal cortex (Wang et al., 2015).

Due to a lack of longitudinal studies it remains unclear whether the thinner frontal gray matter in smokers represents a pre-existing difference, making individuals more prone to develop smoking habits, or is a consequence of tobacco exposure. Only three longitudinal studies have been performed to date, all in middle-aged and elderly populations. Two of these studies investigated global gray matter volume and detected no accelerated volume loss in smokers over a period of four or five years respectively (Duriez et al., 2014; Van

Haren et al., 2010). One study looked at regional volumes, demonstrating that elderly participants with a lifetime history of smoking displayed faster atrophy over two years in the OFC, middle frontal gyrus, and other frontal regions, as well as posterior and paralimbic areas (Durazzo et al., 2012). The above stresses the need for more longitudinal studies, especially in adolescence and young adulthood, the sensitive period in brain development when smoking habits are formed.

Here, we describe a study investigating longitudinal effects of smoking on the development of frontal cortex in adolescents with and without ADHD. The prefrontal cortex is among the last brain regions to mature and is thought to play a crucial role in exerting cognitive control over behaviour (Casey et al., 2005). It has been hypothesised that immature cognitive control abilities make adolescents and young adults more prone to drug use (Loth et al., 2011), and deficits in cognitive control have been associated with ADHD (Lee et al., 2011; Lipszyc and Schachar, 2010). These deficits in cognitive control coincide with the presence of smaller frontal volumes (of for example the OFC and ACC) in individuals with ADHD (Bralten et al., 2016; Frodl and Skokauskas, 2012; Valera et al., 2007). Accordingly, decreased CT in frontal areas may be a shared predisposing factor of individuals with ADHD and smokers, and may reflect immature cognitive control abilities.

To disentangle cause and consequence in the relation of smoking and CT, our first aim was to capture the progressive effect of smoking on frontal CT through adolescence and young adulthood, while controlling for ADHD as an alternative explanation.

As our second aim, we explored whether associations of smoking with frontal CT development depended on ADHD severity. We hypothesised that, considering the already vulnerable frontal cortical structure as reported in ADHD, smoking would have a larger impact on the frontal CT of individuals with more severe ADHD.

If smoking indeed speeds up thinning of the frontal cortex, this could in turn influence the development of ADHD symptoms. While smoking may have beneficial acute effects on ADHD symptoms (Gehricke et al., 2007), potentially used for self-medication purposes, it has been proposed that long-term smoking may cause amplification of impulsive behaviour (DeBry and Tiffany, 2008). Due to the lack of longitudinal studies, this hypothesis has been left largely unexplored. Therefore, our third aim was to investigate whether the developmental course of ADHD symptoms was different in smokers relative to non-smokers.

Experimental procedures

Participant selection

Participants were part of a longitudinal cohort study starting in 2003 (International Multicenter ADHD Genetics study; Müller et al., 2011), consisting of participants originally recruited with an ADHD diagnosis (probands), their affected or unaffected siblings, and healthy controls. A structural MRI scan was collected during the NeuroIMAGE follow-up study (T1; 2009–2012; von Rhein et al., 2015) and subsequently during the NeuroIMAGE II follow-up study (T2; 2013–2015). We identified smokers and non-smokers in this cohort

based on self-reported tobacco use at T2. More specifically, smokers confirmed to smoke regularly (daily or a couple of times a week) now, or to have smoked regularly in the past year. Smokers reporting quit attempts were included; only two reported to have recently quit successfully at T2. Non-smokers had to be free of any indication of present or past regular smoking (monthly or more frequently). Smokers and non-smokers groups both included probands, affected and unaffected siblings, and healthy controls. The non-smokers were matched as closely as possible to the smokers on number of ADHD-affected and -unaffected participants, gender, age, and IQ with the package MatchIT (Ho et al., 2011) in R. IQ was estimated using the vocabulary and block design subtests of the Wechsler Intelligence Scale for Children (WISC-III; Wechsler, 2002) or Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 2000), obtained during T1 and T2. Characteristics of the resulting groups of 44 smokers and 45 non-smokers are displayed in Table 1. These groups did not differ significantly in the proportion of ADHD-affected participants as established by a Chi-square test; smokers, 79.5%, non-smokers, 71.1%, $\chi^2(1, N=89)=0.85$, $p=.356$. More detailed information on participant selection and phenotypic information can be found in the Supplementary Information.

Phenotypic information

Diagnostic information—Diagnosis and symptom counts for ADHD and comorbid disorders were determined by semi-structured clinical interview at T1 and T2 (Schedule for affective disorders and schizophrenia for school-age children; Kaufman et al., 1997) and Conners' ADHD questionnaires (Conners, 1998). A diagnosis of ADHD was given if the participant had 6 or more inattention and/or 6 or more hyperactivity-impulsivity symptoms according to DSM-IV criteria. Unaffected siblings and healthy controls were allowed a maximum of 3 symptoms overall. Siblings with subthreshold ADHD, who did not meet criteria for either ADHD or unaffected status, were included in the analysis and were also labelled 'affected' for the purpose of the matching procedure as described above. Throughout the remainder of the paper symptom count was used as a continuous measure for ADHD and no group comparisons of ADHD-affected versus ADHD-unaffected were made.

Smoking information—At T1 and T2, smoking was assessed with a self-report rating scale version of the antisocial behaviour interview (Loeber et al., 1989), which includes a question on frequency of tobacco use over the past half year (never, once or a few times, monthly, weekly, daily). During T2, the Fagerström Test for Nicotine Dependence (Heatherton et al., 1991) was also obtained with additional variables that were used for our classification: "Do you smoke regularly (daily or a couple of times per week) now, or did you smoker regularly in the past year?" and "At what age did you start smoking regularly?".

Procedures

Details on ethics and procedures of the NeuroIMAGE (T1) study can be found in von Rhein et al. (2015). The procedures of NeuroIMAGE II (T2) were approved by the regional ethics committee (Centrale Commissie Mensgebonden Onderzoek: CMO RegioArnhemNijmegen; 2012/542; ABR: NL41950.091.12). Written informed consent was obtained from participants and/or their legal guardians depending on the age of the participant.

Image acquisition and processing

MPRAGE T1*weighted structural scans were acquired on a 1.5 Tesla Siemens Avanto scanner (TR=2730 ms, TE=2.95 ms, TI=1000 ms, voxel size=1×1×1 mm, FOV=256 mm, 176 slices). The same scanner and protocol was used for T1 and T2. The following steps were undertaken for these studies separately. Structural scans were processed in the automatic segmentation toolbox FreeSurfer (http://surfer.nmr.mgh.harvard.edu) to obtain estimates of regional CT and surface area. An aggregate measure of frontal CT was computed by averaging the CT estimates of the following regions (left and right), weighted by the respective surface areas of those regions: caudal anterior cingulate, rostral anterior cingulate, caudal middle frontal, rostral middle frontal, lateral orbitofrontal, medial orbitofrontal, superior frontal, pars opercularis, pars orbitalis, pars triangularis, frontal pole and insula (see Figure 1). Visual inspection was performed on all subjects' internal and external surface views for evident segmentation errors in the above regions. Following inspection, we concluded that frontal CT could be estimated correctly for all participants.

Analysis aims 1 and 2: Effect of smoking on frontal cortical thickness development

To investigate whether the development of frontal CT was different in smokers compared to non-smokers (the groups as described in Table 1), we set up a 'main model' using linear mixed-effects modelling with the lme4 package (Bates et al., 2015) in R (see supplement for details and model statement). This method was chosen, as opposed to the more traditional repeated measures analysis of variance (ANOVA), to account for the familial dependence in the data and for the fact that ADHD symptom count and diagnostic status may vary over time. With an ANOVA, fixed groups would have to be used. For the main model, we used the aforementioned composite measure of frontal CT as a within-subject dependent variable, with repeated measures at T1 and T2. To examine whether smokers differed in development of frontal CT compared to non-smokers, we specified a fixed effect for the interaction between smoking (smokers vs. non-smokers) and age (age was used as the within-subject time variable). Main effects of smoking and age were also included. These main effects captured time-independent differences between smokers and non-smokers, and general development of frontal CT, respectively. Since there is strong evidence that CT declines linearly in our age range of 9.5 to 27.6 years (Raznahan et al., 2011; Wierenga et al., 2014), we did not model quadratic effects of age. To model associations with ADHD symptoms within the main model, a fixed effect was included for symptom count (within-subject repeated measures), plus all possible interactions. All continuous predictors were mean-centred before entering the model. Random intercepts were modelled to account for within-subject dependence (repeated measures) and within-family dependence in CT. Random slopes, to capture variability in CT change over time per participant and per family, could not be modelled given that we only had 2 observations. The significance threshold was set at $p \leq .05$, and where relevant, we obtained values for adjusted means of effects and marginal pseudo R^2 (variance explained by fixed effects). In the supplement, sensitivity analyses are described, checking the robustness of the results of the main model. These concern an analysis after the removal of influential cases and analyses controlling for the potentially confounding effects of gender, estimated IQ, socio-economic status, intra-cranial volume, alcohol use, other drug use, oppositional defiant (ODD) and conduct disorder (CD) symptoms, anxiety and depressive disorders, and medication use. Finally, a supplemental

analysis was performed in ADHD-affected participants only, to see whether the effect was present within this clinically relevant subgroup and to further confirm that the effect was not driven by affected/unaffected status.

Analysis aim 3: Effect of smoking on ADHD symptom development

To examine the influence of smoking on ADHD symptom development, a model was estimated with symptom count as the within-subject dependent variable and smoking, age and smoking × age as fixed factors (see supplement for model statement). A robustness check for this analysis is detailed in the supplement. To explore whether effects on symptom count were driven by a specific symptom domain, models were also estimated for inattention symptoms and hyperactivity-impulsivity symptoms separately.

Post hoc analysis of onset of regular smoking

As a post hoc question, we were interested whether smoking onset and duration had an effect on our findings. Specifically, we were interested in separating smokers who started regular smoking before T1, from smokers who did not smoke regularly yet at T1, but started in between T1 and T2. Separating these groups sheds more light on the question whether differences in brain structure were already present before smoking onset or are more likely to be a consequence of regular smoking. To assess whether smokers who started regular smoking after T1 already had a thinner frontal cortex compared to non-smokers at that time point, we estimated a model for T1 with a fixed factor for smoking, consisting of the categories ‘non-smokers’, ‘onset before T1’, and ‘onset after T1’. We further added the following fixed effects: age, symptom count, and all two-way interactions among these fixed effects. In the event of a significant effect of the smoking onset categories, post hoc pairwise comparisons were performed with Tukey’s correction for multiple comparisons between the three groups. In addition, to test for differences between the groups in the developmental slope of frontal CT, a model including both time points was specified (similar to the abovementioned main model). For completeness, pairwise comparisons at T2 are also reported.

Post hoc analysis of regional specificity

Post hoc tests were conducted to explore whether an effect was driven by specific frontal regions, or was seen more globally across the frontal cortex. To this end, the main model was estimated for the CT obtained for each of the frontal regions separately. We also looked at the possibility of a whole-brain effect by using total CT, across the whole brain, as an outcome measure. Since this analysis concerns post hoc exploration of the magnitude of effect per region, results focus on the coefficients of the smoking effect and their standard errors. For completeness, uncorrected *p*-values are presented for the effect of smoking per region, but are not interpreted. To enable comparison of findings with two longitudinal studies described in the introduction (Duriez et al., 2014; Van Haren et al., 2010), the supplement includes an additional analysis with total gray matter volume as the outcome measure.

Results

Aims 1 and 2: The effect of smoking on frontal cortical thickness development

Smokers had a 2.6% thinner frontal cortex compared to non-smokers. This main effect of smoking was significant (F(1, 92.1)=14.2, p<.001; coef=−0.035, SE=0.009). Additionally, there was a significant main effect of age (F(1, 156.1)=69.2, p<.001; coef=−0.014, SE=0.002), with a 2.6% reduction in frontal CT per 5 years of aging. These effects are shown in Figure 2. Moreover, Figure 2 shows that smokers did not differ in the rate of frontal cortical thinning over time relative to non-smokers, i.e., the interaction between smoking and age was not significant (F(1, 155.2)=0.003, p=.955). The main effect of symptom count contributed significantly to the model (F(1, 162.4)=6.35, p=.012; coef=0.003, SE=0.001). However, it must be noted that this effect was very small; the adjusted means showed an increase of 0.006% in frontal CT per additional 5 symptoms. We therefore chose not to interpret this effect further. The following effects included in the model were not significant: smoking × symptom count (F(1, 150.0)=0.45, p=.503), age ×symptom count (F(1, 134.3)=2.96, p=.088), and smoking × age × symptom count (F(1, 135.9)=0.55, p=.461). Together, all fixed factors in the main model explained 38.6% of the variance in frontal CT (marginal pseudo R^2).

Sensitivity analyses—In the supplement, we describe sensitivity analyses in which we examined the potentially confounding effects of gender, estimated IQ, socio-economic status, intra-cranial volume, problematic alcohol use, regular other drug use, ODD and CD symptoms, anxiety and depressive disorders, and medication use. None of these variables significantly affected the reported main effect of smoking on frontal CT. Furthermore, the main effect of smoking remained significant after exclusion of influential cases and after running the model in ADHD-affected participants only.

Aim 3: Effect of smoking on symptom development

Smoking had no significant effect on the developmental course of ADHD symptom count (interaction of smoking with age; F(1, 142.6)=0.14, p=.708). Yet, smokers had on average more symptoms (adjusted mean 9.5) relative to non-smokers (adjusted mean 6.3) (main effect of smoking; F(1, 84.5)=7.86, p=.006; coef=1.58, SE=0.553). Age was also a significant predictor in the model (F(1, 140.1)=21.4, p<.001; coef=−0.42, SE=0.090); the symptom count declined with 2.1 per 5 years of aging. The main effect of smoking remained significant after exclusion of influential cases (see supplement for details). Separate models revealed that smoking significantly predicted inattention symptoms (p<.001), but not hyperactivity-impulsivity symptoms (p=.113). Aging affected both inattention symptoms (p<.001) and hyperactivity-impulsivity symptoms (p<.001). Effects are depicted in Figure 3.

Post hoc analysis of onset regular smoking

Smoking onset had an effect on CT at T1 (F(2, 72.4)=10.6, p<.001), which is depicted in Figure 4. Pairwise comparisons indicated that the ‘novel’ smokers, who started regular smoking after T1 (n =13), did not yet differ significantly from the non-smokers (n=45) at T1 (t(79.0)=0.89, p_{adj}=.646); but at that time point, they did exhibit higher frontal CT estimates relative to the ‘long-term’ smokers, that had been smoking regularly since before T1 (n=31)

(long-term smokers estimated at 5.9% thinner; $t(78.6)=2.51$, $p_{adj}=.038$). By contrast, the long-term smokers already had a significantly thinner frontal cortex compared to the non-smokers at T1 (estimated at 3.9% thinner; $t(64.5)=4.32$, $p_{adj}<.001$). In the developmental model including both time points, the interaction of the smoking onset categories with age was significant ($F(2, 125.5)=3.07$, $p=.050$). As can be seen in Figure 4, the decline in frontal CT with age seems steeper in the novel smokers compared to the other groups. At T2, the long-term smokers differed significantly ($p_{adj}=.004$) and the novel smokers non-significantly ($p_{adj}=.832$) from non-smokers, and the smoking groups did not differ from each other ($p_{adj}=.592$). Sample characteristics for novel and long-term smokers, including available information on smoking behaviour, are displayed in Supplementary Table 1. We performed additional sensitivity analyses, described in the supplement, to account for potentially confounding differences between these groups. From these sensitivity analyses, we conclude that there may be some overlap between IQ (development) and CT development in the different groups. However, we cannot make claims on the causal direction of this effect and the possibility remains that smoking affects IQ via a reduction in CT.

Post hoc analysis of regional specificity

Table 2, containing the CT results per frontal region and for the total brain, shows that the highest *t*-values were observed in the right lateral and medial orbitofrontal cortices. The results from Table 2 reveal widespread effects across the frontal cortex and also at the total brain level. An additional analysis with total gray matter volume as opposed to CT as the outcome measure can be found in the supplement and yielded no evidence for an effect of smoking.

Discussion

The current study examined the interplay between tobacco smoking, brain development, and ADHD symptoms by investigating the longitudinal effect of smoking on frontal CT in adolescents and young adults with and without ADHD. Hereby, we attempted to disentangle cause and consequence in the relation of smoking and CT. We observed that smokers had a 2.6% thinner frontal cortex than non-smokers, but we found no difference in rate of thinning across the 3.4-year MRI measurement interval. We conducted an additional analysis separating novel smokers, who started regular smoking after the baseline scan, from long-term smokers, who had been smoking since before the baseline scan. This analysis revealed that the novel smokers were not significantly different from non-smokers at baseline, whereas the long-term smokers did already have a thinner frontal cortex compared to the non-smokers. Furthermore, our results suggested accelerated thinning in the novel smokers.

Our main finding of a thinner frontal cortex in smokers is in line with previous reports describing CT and volume differences between smokers and non-smokers (Durazzo et al., 2013; Kühn et al., 2010; Li et al., 2015; Wang et al., 2015; Zhong et al., 2016). We also observed a relationship between smoking and total CT, which is in agreement with more widespread effects found in earlier studies (Wang et al., 2015). Of the frontal regions that we distinguished, the effect of smoking was strongest in the right orbitofrontal cortex (OFC). Notably, in two earlier studies, OFC volume correlated negatively with magnitude of

tobacco exposure, implying a dose-dependent effect (Kühn et al., 2010; Li et al., 2015). Smaller OFC volumes have also been linked to other forms of substance use (e.g., Lotfipour et al., 2009; Smith et al., 2015; Tanabe et al., 2009), and the role of the OFC in addiction is further substantiated by a myriad of functional neuroimaging findings showing that OFC activity varies with drug expectation, craving, and addiction severity (Goldstein and Volkow, 2011; Jasinska et al., 2014).

Results of our post-hoc analyses suggest that the reductions in frontal CT observed in smokers were not yet present before the onset of regular smoking. We could not confirm accelerated thinning across the total group of smokers in our study, but the novel smokers exhibited a steeper decline in frontal CT with age compared to long-term smokers and non-smokers. Although this result warrants replication due to the low number of novel smokers, we speculate that this difference between novel and long-term smokers could be due to one of the following reasons, or a combination thereof. First, the long-term smokers were older (mean age at T1 = 19.1 years) than the novel smokers (mean age at T1= 14.9 years), which could mean that the long-term smokers are more likely to have passed their most vulnerable period in adolescent brain development (Dwyer et al., 2009). Second, while the exact biological mechanisms by which tobacco smoke affects gray matter structure are unclear (Chang et al., 2014), these could include mechanisms (for example in the cerebrovascular system, cytoarchitecture, or synaptic functioning) that result in relatively steep changes in CT at first, but then become more stable. Our findings provide an important addition to the literature by contributing for the first time a longitudinal investigation in adolescents and young adults. This is crucial, since the neurotoxic effects of tobacco may depend on developmental stage (Dwyer et al., 2009). In one of the few previous longitudinal studies, elderly participants with a lifetime history of smoking displayed faster volume loss in several regions, among which the OFC, over two years (Durazzo et al., 2012). Two other studies, in middle-aged and elderly samples, did not observe associations of smoking with changes in global gray matter volume over periods of four and five years respectively (Duriez et al., 2014; Van Haren et al., 2010). This is perhaps not surprising, considering the fact that neurotoxic effects may vary between regions (Dwyer et al., 2009), with striatal regions often found to be unaffected or even larger in smokers (Das et al., 2012; Li et al., 2015). In agreement with this, we found no significant effect of smoking on total gray matter volume. Our results imply that CT constitutes a measure that is more sensitive to the effects of smoking than global volume.

As our second aim, we explored whether the influence of smoking on frontal CT development depended on ADHD severity. We proposed that smoking would have a larger impact on the frontal CT of individuals with more severe ADHD, as they would have, according to the literature, an already vulnerable frontal cortical structure. The results provided no support for this hypothesis, but considering the small number of ADHD-unaffected participants in our sample the power to detect such an interaction could have been limited. Smokers and non-smokers were matched on number of ADHD-cases, and in line with the previously established heightened prevalence of smoking in individuals with ADHD (Groenman et al., 2013), most of the smokers in our study were ADHD-affected participants. The matched group design optimised our ability to draw firm conclusions about the progressive effect of smoking on frontal CT, while controlling for ADHD as an

alternative explanation. Like smoking, ADHD has been related to thinner frontal cortical regions (e.g., Almeida et al., 2010; Fernández-Jaén et al., 2014; Makris et al., 2007; Silk et al., 2016), although not consistently (Dirlikov et al., 2015; Schweren et al., 2015). However, our results argue that smoking leads to accelerated thinning of the frontal cortex independent of ADHD. This underscores the importance of taking into account smoking habits when comparing individuals with ADHD, or other neuropsychiatric disorders with high smoking rates, to healthy controls.

Our third aim was to investigate whether smoking influenced the development of ADHD symptoms. We expected that if smoking speeded thinning of the frontal cortex, this could subsequently lead to exacerbation of ADHD symptoms. Although smokers had more ADHD symptoms overall, our results did not support a difference in the rate with which the number of ADHD symptoms declined in smokers relative to non-smokers. However, this seems in agreement with the fact that we did not find accelerated thinning of the frontal cortex across the whole group of smokers. It has been argued that neurobiological effects of smoking are likely to contribute to elevated levels of impulsivity seen in smokers, but due to the complexity of this research there is limited support for this theory (De Wit, 2008; DeBry and Tiffany, 2008). More prospective research is required to confirm that smokers show similar rates of ADHD remittance as non-smokers.

Our findings should be considered in the context of some strengths and limitations. First, although we could confidently capture the general contrast of regular smoking versus non-regular smoking, we had limited opportunities to explore dose-dependent effects, since the NeuroIMAGE sample did not include precise measures on amount and frequency of smoking over time. Second, although two measurements over 3.4 years can already reveal valuable information regarding the progressive effect of smoking, studies with more time points and more sophisticated smoking measures are desired. This would further elucidate the causality question and allow for more precise mapping of trajectories of tobacco exposure onto the trajectories of CT development. Nevertheless, our study adds significantly to the literature by investigating for the first time the effect of smoking on frontal CT in adolescence and young adulthood using a longitudinal design. Furthermore, our design allowed us to examine the so far unexplored effect of smoking on ADHD symptom development. An additional strength of this study is the rigorous control for potentially confounding factors including: gender, estimated IQ, socio-economic status, intra-cranial volume, other drug use, ODD/CD symptoms, anxiety and depressive disorders, and medication use.

To conclude, we confirmed previous reports of a thinner frontal cortex in smokers, and showed that although smokers had more ADHD symptoms overall, smoking did not seem to influence the developmental course of ADHD symptoms. The results did not support an acceleration of frontal cortical thinning in the total group of smokers. However, post-hoc analyses were indicative of speeded thinning in novel regular smokers, who did not differ from non-smokers at baseline. This suggests that a thinner frontal cortex was not a predisposing factor but rather a consequence of smoking.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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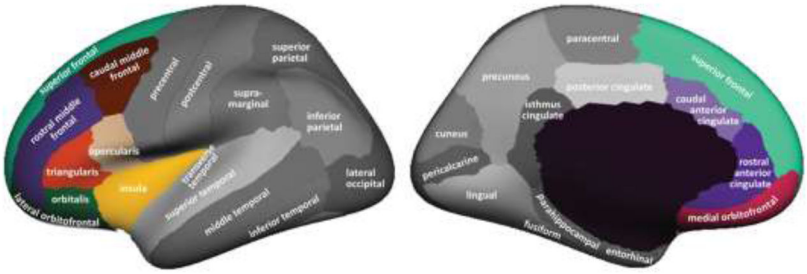

Figure 1. Regions included in the frontal cortical thickness composite measure

Note: the composite measure of frontal cortical thickness was computed by averaging the cortical thickness estimates of the coloured regions (left and right) weighted by the respective surface areas of those regions. Segmentation was based on the FreeSurfer 'Desikan-Killiany' atlas (https://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation).

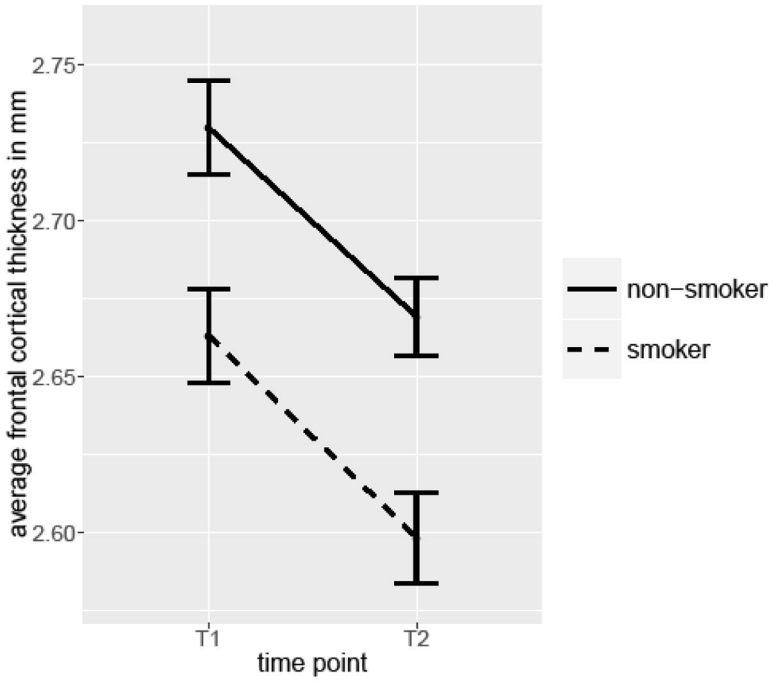

Figure 2. Development of average frontal cortical thickness in smokers and non-smokers
Note: figure displays raw means and SEs.

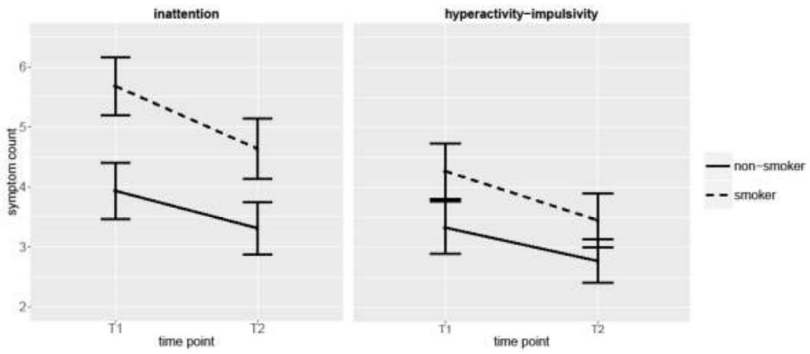

Figure 3. Development of inattention and hyperactivity-impulsivity symptoms in smokers and non-smokers

Note: figure displays raw means and SEs.

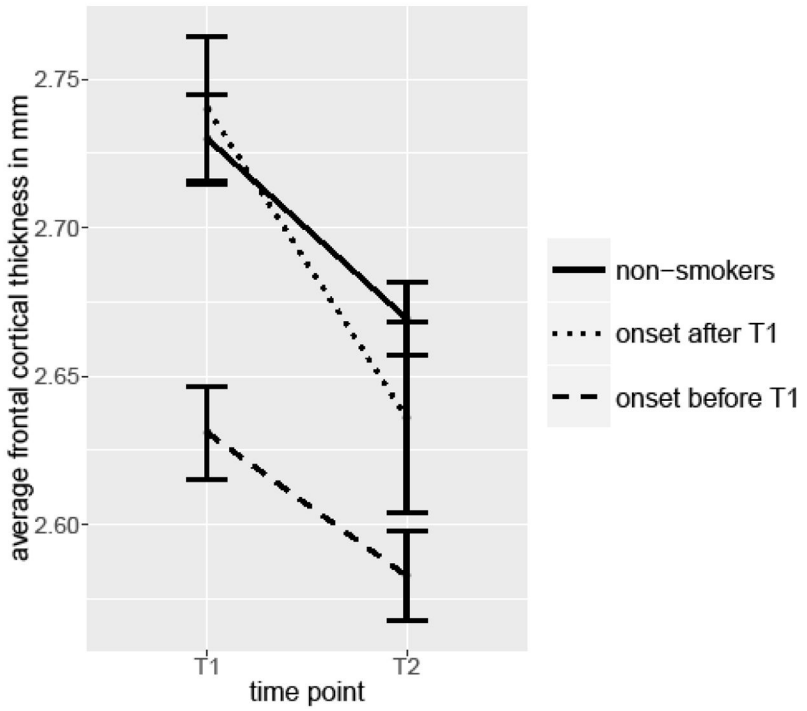

Figure 4. Development of average frontal cortical thickness in non-smokers, smokers that started regular smoking before T1 (long-term smokers), and smokers that started regular smoking after T1 (novel smokers)

Note: figure displays raw means and SEs.

Table 1

Sample characteristics.

	Smokers	Non-smokers	[1] Difference test
n	44	45	
Males, n	28	25	$\chi^2(1)=0.60$, $p=.437$
ADHD symptom count at T1, M (SD)	9.95 (5.85)	7.27 (5.60)	$t(87)=2.21$, $p=.029$
[2]**Age in years T1, M (SD)**	17.9 (2.68)	17.6 (3.51)	$t(87)=0.49$, $p=.627$
[3]**Age in years T2, M (SD)**	21.3 (2.83)	20.9 (3.52)	$t(87)=0.54$, $p=.590$
Interval in years, M(SD)	3.42 (0.79)	3.37 (0.59)	$t(87)=0.29$, $p=.769$
Estimated IQ T1, M (SD)	97.8 (15.4)	99.8(14.1)	$t(87)=0.67$, $p=.504$
Estimated IQ T2, M (SD)	94.8 (16.0)	100.8 (16.1)	$t(87)=1.78$, $p=.079$
[4]**Used ADHD medication in past 5 years, n**	20	20	$\chi^2(1)=0.04$, $p=.846$
[5]**Indication of problematic alcohol use, n**	10	6	$\chi^2(1)=1.33$, $p=.249$
[5]**Indication of regular cannabis or other drug use, n**	21	1	$\chi^2(1)=24.8$, $p<.001$
[6, 7]**ODD/CD symptom count > 5, n**	9	1	
[6, 7]**Anxiety disorder/depressive disorder, n**	3/3	2/1	

[1] Differences between smokers and non-smokers were tested by means of independent samples *t*-tests or Chi-square tests of independence.

[2] The age range at T1 was 9.5 – 24.2.

[3] The age range at T2 was 12.9 – 27.6.

[4] Reported at T2, see supplement for details.

[5] At any time point from initial inclusion, see supplement for details.

[6] Reported at T1 or T2, see supplement for details.

[7] Chi-square tests could not be performed due to cells with a minimum expected frequency < 5.

Abbreviations: ADHD – attention-deficit/hyperactivity disorder, CD – conduct disorder, ODD – oppositional defiant disorder.

Table 2

Effect of smoking on cortical thickness per frontal region and for the total brain.

Regional cortical thickness outcome	coefficient smoking	SE	*t*-value	*p*-value of smoking factor (uncorrected)
Left caudal anterior cingulate cortex	−0.013	0.023	0.58	.569
Right caudal anterior cingulate cortex	0.009	0.022	0.39	.707
Left caudal middle frontal	−0.031	0.012	2.54	**.015**
Right caudal middle frontal	−0.038	0.014	2.72	**.009**
Left lateral orbitofrontal	−0.042	0.014	2.98	**.004**
Right lateral orbitofrontal	−0.050	0.014	3.51	**< .001**
Left medial orbitofrontal	−0.048	0.016	3.03	**.004**
Right medial orbitofrontal	−0.060	0.017	3.46	**.001**
Left pars opercularis	−0.047	0.015	3.21	**.002**
Right pars opercularis	−0.048	0.016	3.08	**.003**
Left pars orbitalis	−0.050	0.018	2.75	**.008**
Right pars orbitalis	−0.030	0.020	1.52	.141
Left triangularis	−0.038	0.014	2.79	**.008**
Right triangularis	−0.042	0.015	2.88	**.006**
Left rostral anterior cingulate cortex	−0.033	0.024	1.37	.183
Right rostral anterior cingulate cortex	−0.067	0.023	2.97	**.005**
Left rostral middle frontal	−0.034	0.012	2.82	**.007**
Right rostral middle frontal	−0.030	0.011	2.82	**.007**
Left superior frontal	−0.026	0.013	2.08	**.045**
Right superior frontal	−0.037	0.012	3.15	**.003**
Left frontal pole	−0.047	0.034	1.38	.181
Right frontal pole	−0.072	0.026	2.73	**.009**
Left insula	−0.023	0.015	1.59	.123
Right insula	−0.032	0.016	2.02	.051
Total brain	−0.028	0.009	3.12	**.003**

Note: *p*-values < .05 are depicted in bold.