Smoking and the course of anxiety and depression

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CHAPTER 7

General Discussion

The adverse health risks/ consequences of smoking[1-4] and of depression and anxiety disorders[5-9] are well-documented, and these conditions frequently co-occur[10-15]. The aim of the present thesis was to further improve our understanding of the link between smoking and affective disorders and to provide an opportunity to stimulate longitudinal research on smoking-psychopathology association in order to elucidate the underlying mechanisms of this association. This may optimize smoking prevention strategies and intervention programs.

In this chapter, we will, first, summarize the findings reported in chapter 2 through chapter 6. Then we will discuss the findings within the context of the current scientific evidence, and speculate about possible mechanisms underlying the main findings. Next, we will point out some methodological issues, and address clinical implications of our findings and recommendations for future research. Finally, concluding remarks will be presented.

For chapter 2 to chapter 5, we used data from the Netherlands study of depression and anxiety (NESDA), while in chapter 6, we collected our own data using students from Leiden University.

Summary of the Findings

1. We first examined, retrospectively, an association of age at the onset of smoking with the onset age of depression and/ or an anxiety disorder (chapter 2). We selected those participants who had been diagnosed with an affective disorder (depression and/ or anxiety) after the onset of smoking (N = 1,055). Participants were grouped into early-onset (started smoking at 10 to 15 years) and late-onset (started smoking after the age of 15 years) smoker. The time period between smoking onset and the onset of depression and/or an anxiety disorder was shorter for early-onset smokers as compared to late-onset smokers. Within the first five years after starting smoking, a greater percentage of early-onset smokers than late-onset smokers had the first onset of an affective disorder. When we examined this association separately for depression

and anxiety disorders, this pattern of results was found only for anxiety disorders. The analyses were adjusted for the effects of gender, education and childhood trauma.

2. The effect of smoking and nicotine dependence on the severity and 2-year course of depressive and anxiety symptoms was investigated (chapter 3) in patients with a current (past 6 months) diagnosis of depression and/or an anxiety disorder (N = 1,725). The sample was categorized into never-smokers, former smokers, non-dependent current smokers, and nicotine-dependent current smokers. We found that the baseline symptoms of depression, general anxiety, social anxiety and agoraphobia were more severe in nicotine-dependent smokers than in non-dependent smokers, former and never-smokers. These differences remained after adjusting for covariates, except for social anxiety on which the groups did not differ when the models were adjusted for covariates. Over a two-year follow-up, nicotine-dependent smokers improved their symptoms of depression and anxiety disorders at a slower rate than the other groups, even after controlling for covariates. No differences between the groups in the course of symptoms of social anxiety and agoraphobia were observed over time. Thus, in psychiatric patients, smoking is associated with higher severity of depressive and anxiety symptoms, and with slower recovery, but only when smokers are nicotine-dependent.
3. The mechanisms underlying the well-established association of smoking and nicotine dependence with depression and anxiety disorders are unclear. In chapter 4, we investigated the interaction between the BDNF gene $Val^{66}Met$ polymorphism and smoking status with symptom severity of depression and anxiety disorders. We selected the same NESDA sample (N = 1,271), having a current diagnosis of an affective disorder, and it was stratified into never-smokers, former smokers, and current smokers with and without nicotine dependence. The results revealed that in the patients who carried the $Val^{66}Val$ genotype of the BDNF $Val^{66}Met$ polymorphism nicotine-dependent smokers had more severe symptoms of depression and anxiety than non-dependent smokers, former smokers, and never-smokers, whereas the latter three

groups were comparable on symptom severity. In Met[66] carriers, however, there were no differences among the four smoking groups on severity of depression and anxiety. Regarding the symptoms of social anxiety and agoraphobia, the BDNF genotype had no effect. Nicotine dependence was the strongest predictor of severity of symptoms only in Val[66]Val carriers. Thus, the relationship between nicotine dependence and symptom severity in patients with an affective disorder may be moderated by the BDNF Val[66]Met polymorphism.

4. Both smoking and psychopathology are associated with serum brain-derived neurotrophic factor. In an attempt to elucidate the mechanisms underlying smoking-psychopathology association, we examined, in chapter 5, the levels of serum BDNF in never-smokers, former smokers and current smokers with and without nicotine dependence (N = 2,088) while controlling for age, sex, education, alcohol use, physical activity, recent negative life events, body mass index, the use of anti-depressants, and the diagnosis of a affective disorder. We also examined the interaction of the polymorphism and smoking status with serum BDNF. We found that current smokers with and without nicotine dependence had higher levels of serum BDNF than the non-smoking groups of former and never-smokers who were comparable in their serum BDNF levels. Similarly, the two current smoking groups with and without nicotine dependence were comparable in serum BDNF. Nicotine dependence and number of cigarettes smoked per day were not significant predictors of serum BDNF. However, total smoking years was a predictor of serum BDNF. Thus, regardless of smoking severity, current smoking was associated with higher serum BDNF levels. In contrast, in NESDA un-medicated depression was weakly associated with decreased levels of serum BDNF[16]. This opposite pattern of associations for BDNF does not make it very likely that the smoking-depression association is driven by underlying BDNF mechanisms. Further, we also did not find an interaction of BDNF genotype and smoking status on serum BDNF, suggesting that BDNF Val[66]Met polymorphism did not further contribute to the smoking-serum BDNF association. In all, these results further suggest that serum BDNF may

not be a linking mechanism in the smoking-psychopathology association.

5. Attentional control, the ability to focus attention on task-relevant stimuli, and to inhibit interference from distracting stimuli, may be another potential mechanism underlying smoking-psychopathology association. To date, there is no study that investigated attentional control as a mechanism underlying smoking-psychopathology association. Previous research has been done on attentional control and threat related attentional bias, and it has been shown that anxious individuals with poor attentional control have inefficient ability to divert their attention from threat-related stimuli, and thus are unable to cope with their anxiety. The initial step to investigate the role of attentional control in smoking-psychopathology association would be to investigate the role of attentional control in attentional bias to smoking-related cues (chapter 6), as this issue has not been addressed before. Smoking-related attentional bias in both the initial orienting and in the maintenance phases of attention has been reported. Attentional control may modulate the attention-capturing effects of distracting information. In chapter 6, we investigated attentional bias across information processing phases and the role of attentional control in each of these phases using a dot-probe task with smoking-related and neutral pictures in smokers and non-smokers (N = 43; 24 smokers). The pictures were presented for 100 ms, 500 ms, and 900 ms. The main findings of the study were that smokers had higher *overall* attentional bias score than non-smokers. However, when pictures were presented for 500 ms and 100 ms, no significant group differences were observed. In longer picture-presentation duration of 900 ms, the group difference in attentional bias was a trend. These findings are suggestive of a bias in the maintenance of attention, but not in initial orienting. We did not find a moderation or interaction of attentional control on attentional bias to these stimuli. However, we did find a strong, negative correlation of attentional control with attentional bias to smoking-related stimuli presented for 100 ms and with the overall attentional bias score. Smokers with low attentional control have high overall attentional bias

and attentional bias to smoking-related pictures presented for 100 ms. This suggests that the effect of attentional control on attentional bias is more prominent when stimuli are presented briefly. Such negative correlation, though, was also found for non-smokers when stimuli were presented for 100 ms. Thus, the data indicate that in individuals with low ability to regulate attention, *involuntary* attentional capture by smoking-related cues (or any salient cues) is increased. The presence of attentional bias to smoking-related stimuli seems to depend on the phase of information processing and on attentional control.

Explaining Smoking-Psychopathology Linking Mechanisms/ Risk Factors

Research on the relationship of smoking with depression and anxiety has reported a two-way smoking-psychopathology association, such that some studies have found that depression and anxiety precedes the onset of smoking behavior[17-21], whereas other studies have reported a subsequent onset of or higher risk of depression and/ or an anxiety disorder after starting smoking[22-26]. Some longitudinal studies have found a bi-directional association in which both the conditions mutually influence each other[27-30]. These studies lead to the formulation of three theories: (i) smoking may serve as self-medication to ameliorate depressive or anxious symptoms[31, 32], (ii) smoking is a vulnerability factor in the development of depression and/or anxiety disorders[33], and (iii) both smoking and negative affect may be due to common vulnerability factors[27, 34]. These theories are not mutually exclusive; in fact all three may be true. Below we discuss some factors, from our research and from the previous investigations, which may potentially influence smoking-psychopathology association:

Age at the Time of Nicotine Exposure

Our findings suggest that the age at which an individual starts smoking may be crucial to determine whether or not an individual will experience aversive mood states later in life. In early-onset smokers, not diagnosed with depression or anxiety at the onset of smoking, the time to the onset of a disorder

after starting smoking, was shorter, than in late-onset smokers. This indicates that the brain at a younger age is probably more sensitive to the detrimental effects of nicotine which manifests in adverse health outcomes later in life. Previous animal and human studies (presented below) have shown that prenatal or early-age nicotine exposure has consequences for physical and mental health.

Animal Studies

Prenatal or early-age nicotine exposure has adverse effects on the brain and mental health later in life. For example, animal studies documented the abnormalities in neurodevelopment and neurotransmission systems due to prenatal nicotine exposure[35].

Prenatal nicotine exposure has been shown to cause morphological and neurobehavioral abnormalities in the developing brain. Significant reductions in neuronal areas of dentate gyrus and the hippocampus[36] and somatosensory cortex[37, 38] were observed following prenatal nicotine exposure, and it has been suggested that these morphological changes may delay neuronal maturation[38], and may contribute to the behavioral abnormalities[36] in cognition, learning, and memory[37].

Similarly, prenatal nicotine exposure acutely reduces and inhibits the synthesis of DNA in all brain regions, suggesting that nicotine has direct effect on cell replication[39].

It also has an effect on development and functionality of catecholamine and neurotransmitter systems. It suppresses norepinephrine and dopamine levels[40] and damages serotonergic systems[41]. Deficits in the functioning of serotonin and other catecholamine systems emerge or lasted in the brain in adulthood[40-43] suggesting that prenatal nicotine exposure does not only produce direct neurodevelopmental damage, but it leads to lasting disruption of the functionality of catecholamine and neurotransmitter systems, and these dysfunctions contribute to behavioral abnormalities. In the words of Slotkin, it "changes the trajectory of brain development, that is, it alters the program for

the establishment and functioning of circuits and connections"[35], and "permanently reprograms synaptic activity"[43], and that "even where some synaptic parameters return nearly to control values…this does not necessarily represent the restoration of completely normal function but rather can reflect adaptations to the initial damage and/or the subsequent change in the developmental trajectory of the affected circuits"[35]. Thus, damages due to prenatal nicotine exposure are irreversible, and may lead to long-term sequelae that persist even after abstinence.

Animal models of depression and anxiety have shown that early-age nicotine exposure induces more anxiety-like[44] and depression-like[45] states in adulthood than late-age nicotine exposure.

Human Studies

In humans, maternal smoking during pregnancy has adverse effects on subsequent physical and cognitive development of the child[46-49]. It is associated with specific subtypes of attention deficit hyperactivity disorder in genetically susceptible children[49-52]. It is also associated with conduct disorders[53], bipolar disorders[54], and mood disorders and nicotine dependence[49, 55] in children.

Research on age at the onset of smoking in humans indicates that exposure to nicotine early in life is associated with the development of peripheral artery disease[56], the risk of lung cancer[57], deviant or atypical smoking patterns such as inability to quit and nicotine dependence[58-67], engagement in substance use and delinquent behavior[68], drug dependence[69], alcohol abuse and dependence[60, 69] and bipolar disorder[70].

Given the previous research on adverse physical and mental health effects of prenatal and early-age nicotine exposure in animals and humans, it is probable that individuals who start smoking at a younger age, may have an increased vulnerability to subsequently experience worse mental health outcomes, such as depression and anxiety disorders, specifically that early-age

nicotine use produces functional deficits in serotonergic systems[41, 71, 72] which has been shown to be associated with affective disorders[73-80].

Nicotine Dependence

Our findings of high rates of affective symptoms in nicotine-dependent current smokers than in non-dependent, former, and never smokers, and slow recovery of symptom severity over time in dependent smokers indicate that nicotine dependence might be a predisposing factor in smoking-psychopathology association. Consistent with this, a number of studies has reported a dose-response relationship between smoking and affective disorders. Severity of depressive and anxiety symptoms has been related to regular smoking, frequency of cigarette use, and heavy smoking[22, 32, 81-85]. In an 11-year population-based study on adults; the risk of subsequent depression was higher for heavy smokers, and smoking chronicity and severity were associated with increasing risk of major depression[24]. In a 3-wave community-based prospective study, heavy smoking during adolescence was associated with an increased risk of generalized anxiety disorder, agoraphobia and panic disorder during early adulthood[86]. Similarly, current smokers with nicotine dependence had higher levels of depressive and anxiety symptoms than non-dependent smokers[87-89]. In a prospective population-based study of young adults, a history of nicotine dependence was associated with an increased risk of first-incidence of major depression than no history of nicotine dependence[27]. Similarly, nicotine-dependent smokers at baseline had an increased risk for new onset of panic attacks and disorder at 4-year follow-up period[90] and elevated rates of anxiety and depression in a 13-year population-based study[91].

Candidate Genes

We further found that only those nicotine-dependent smokers had more severe symptoms of depression and anxiety than non-dependent and non-smoking groups, when they were having the Val[66]Val genotype of BDNF Val[66]Met polymorphism. In Val[66]Met carriers, all four smoking groups, that is, never-smokers, former smokers, non-dependent current smokers and nicotine-

dependent current smokers were comparable in symptom severity**.** The smoking-psychopathology association has rarely been studied taking into account candidate genes. We found two studies that tested, from a genetic perspective, the theory of smoking as a self-medicating agent to alleviate depressive symptoms. One study (N = 231) found that self-medicating smoking practices were significantly heightened in depressed smokers with two short alleles of DRD4 gene but not in those heterozygous or homozygous for the long alleles of DRD4[92]. In another study, a cohort of 615 adolescents were followed from 9th to 11th grade, and the effects of dopamine transporter (SLC6A3) and dopamine receptor (DRD2) genetic variants on smoking progression were evaluated. The sample was grouped into never-smokers and those who had been exposed to nicotine (i.e., smoked at least a puff of a cigarette). Smokers with severe depressive symptoms were more likely to progress to a higher level of smoking only if they had DRD2 A1 allele. No effects of SLC6A3 on smoking-depression association was observed[93]. Thus, these studies suggested that genetic factors involved in dopamine transmission may be involved in the rewarding effects of smoking. The theory that smoking is a vulnerability factor in depression and anxiety has recently been investigated using the rs1051730 SNP variant located in the nicotine acetylcholine receptor gene cluster on chromosome 15. The participants were selected from a large population-based study, the Norwegian HUNT study (N= 53, 601). Self reported smoking was positively associated with the symptoms of anxiety and depression, and the polymorphism was positively associated with smoking. However, no association of the polymorphism with either anxiety or depression was found among smokers[94] suggesting that this gene variant is not a predisposing factor to link smoking with depression and anxiety. Our results are supportive of, or refine the vulnerability theory of smoking-psychopathology association (chapter 4).

We found that only those nicotine-dependent smokers who were homozygous for Val[66]Val BDNF genotype, had severe symptoms of depression and anxiety. But since, the study is cross-sectional no causal association can be established. Both these studies point to elucidate a mechanism but the association is a bit more complex.

Nicotine Acetylcholine Receptors (nAChRs)

One of the theories explaining smoking-psychopathology association is the self-medication theory. However, nicotine use is not an effective anti-depressant , given the high prevalence of depressive and anxiety symptoms in smokers. Though it has been reported that smoking alleviates negative mood, but the effect do not seem to be long-lasting. Smoking may initially improve mood, but chronic nicotine use may be associated with worsening symptoms of affective disorders. This assumption has been supported by studies showing that smoking cessation leads to reduced stress[95], and that successful quitters experience significantly less depressive symptoms than unsuccessful quitters[96].

One of the neurobiological mechanisms might be nicotine acetylcholine receptors (nAChRs) that are molecular targets of nicotine in the brain. nAChRs have been intensely studied to elucidate their pathophysiological role in mediating addiction to nicotine in tobacco[97-99]. nAChR dysfunctions are also implicated in anxiety disorders and depression[100, 101]. It has been shown that nicotine use induces hyperactivation of cholinergic signaling, and this hyperactivation may lead to depression[102]. This has been demonstrated by studies showing that the increase of acetylcholine levels in brain by administering cholinesterase antagonist physostigmine resulted in negative effects on mood[103]. From these observations, it was suggested that cholinergic hypersensitivity may be a risk factor in the onset of depression[104]. Recently, it is suggested that smoking upregulates nAChRs which may induce depressive symptoms[105].

Attentional Control

Attentional control can be defined as the ability to use executive functioning to selectively keep focus on task-relevant stimuli and to hinder interference from task-irrelevant stimuli[106]. High-anxious individuals find it difficult to inhibit processing of task-irrelevant threatening stimuli possibly because of the reduced efficiency of the inhibition function of attentional control[107]. In order to assess attentional bias to threatening stimuli and to

investigate whether attentional control moderates the relationship between attentional bias to these stimuli and anxiety symptoms, a number of studies were conducted. These studies suggested that individual variation in attentional control may determine the presence or absence of attentional threat bias. For example, individuals with high trait anxiety and poor attentional control showed enhanced processing of threat-related stimuli in a spatial-cueing task[108] and had difficulty in ignoring task-irrelevant threat-related emotional pictorial stimuli[109] as compared to those with better attentional control. Other studies also reported an association of low attentional control and attentional bias to threatening words in individuals with general anxiety symptoms[110] and attachment anxiety[111].

In our study (chapter 6), we expected that attentional control would moderate the association of attentional bias to smoking-related cues, such that smokers with low attentional control would have greater bias to smoking-related stimuli as compared to those with high attentional control. Although, we did not find a moderation of attentional control on attentional bias to smoking-related stimuli, we did find that low attentional control was correlated with high attentional bias to smoking-related pictures presented for 100 ms; however, this effect was seen for both smokers and non-smokers. Thus, the data indicate that in individuals with low ability to regulate attention, *involuntary* attentional capture by smoking-related cues (or any salient cues) is increased.

It has been suggested that the disruption of the balance between two attentional systems, the goal-driven and the stimulus-driven attentional systems, may cause this impaired attentional control[112]. In anxious individuals, the activation of the stimulus-driven attentional system is increased while the functionality of the goal-directed attentional system is decreased. This results in the processing of threat-related stimuli to a higher degree[113]. In an earlier account of attentional control, there is an involuntary posterior attentional system in which attention is, first, disengaged from one point, moved to a different point and engaged to the new point where it is facilitated and transferred to the voluntary anterior system of attention. The anterior system regulates the posterior attentional system, thus it might help reducing anxiety by

disengaging a person from threat or diverting his/her attention from it[114, 115]. It has been suggested that attentional control is related to the functioning of the voluntary anterior attentional system[108]. Thus individuals with poor attentional control who show bias in their attention to concern-related stimuli may find it difficult to inhibit processing of task-irrelevant stimuli probably because of the deficit in their voluntary attentional system.

Here, it should also be noted that the nature of the stimuli of our study and of the previous studies assessing anxious individuals is not the same. Anxious individuals may find the threat-related stimuli aversive, and thus good attentional control may allow them to shift their attention from aversive stimuli; however, smokers may find smoking-related stimuli appetitive and attractive, thus they may not shift their attention from these stimuli, and may not show attentional avoidance to such stimuli. Such attentional avoidance is the characteristic of anxiety and may occur in response to threat-related stimuli, but not to smoking-related stimuli. Thus, it is probable that attentional control may act differently for smoking-related and threat-related stimuli.

Methodological Considerations

Except for the chapter on attentional bias and attentional control in relation to smoking (chapter 6), all other chapters are based on data from NESDA. Though we have already discussed several methodological issues in different chapters, here we will point out some limitations and strengths in NESDA in general.

1. In the chapter on smoking age-onset and its association with psychopathology, we were unable to control for several potential confounding variables such as pre-existing drug and alcohol use and other confounding factors because data on age-onset of these variables were not available.
2. In NESDA, one of the exclusion criteria was a primary diagnosis of a severe addictive disorder[116], thus individuals with other addictive behaviors were excluded which might limit the generalizability of our

findings; however, at the same time, this is an advantage because our results were not 'coloured' with the effects of other substances.

3. In NESDA, nicotine dependence was assessed only at baseline, and was not assessed in former smokers.
4. NESDA may not be representative of other ethnic groups because the sample is pre-dominantly Dutch. However, for genetic studies, this is an advantage because studies have reported confounding ethnic differences in genotype and allele frequencies[117].
5. Depression and anxiety disorders are highly comorbid with other mental health problems, so the exclusion criteria of NESDA to exclude persons who have a primary severe other psychiatric disorder, such as psychotic disorder, obsessive-compulsive disorder, bipolar depression, may limit the generalizability of our findings[118]. However, again, this is a merit for our research because comorbidity of severe other psychiatric disorders could also confound the link between smoking and depression-anxiety.
6. Serum BDNF levels may not accurately reflect central BDNF levels, although previous animal research has shown a strong correlation of serum BDNF levels to cortical BDNF[119]. Moreover, results on serum BDNF cannot be generalized to the studies conducted on BDNF stored in plasma or platelets because plasma BDNF is circulated in platelets with 200 fold less concentration than serum BDNF.
7. In our project on smoking-related attentional bias and attentional control, we did not manipulate nicotine deprivation, so urge to smoke or recency of smoking may have varied across smokers. Moreover, we recruited participants who smoked 10 or more cigarettes per day, thus, not controlling for variation in smoking behavior between light and heavy smokers.

An advantage of addressing our research questions using NESDA data is that the sample size is fairly large, and we were able to control for a large number of variables/ covariates that may confound smoking-psychopathology association. Further, the sample is ethnically homogenous, and we focussed on psychiatric patients whereas most previous studies have used samples from the

general population. In psychiatric patients the prevalence of smoking is relatively high as compared to samples from general population. The NESDA's assessment of depression and anxiety disorders were made according to DSM-IV criteria, whereas most previous studies that investigated "smoking and depression-anxiety association", assessed symptoms using self-report measures.

The mechanisms underlying smoking-depression/ anxiety association can be better understood in longitudinal studies that follow healthy smokers over a span of several years.

Clinical Implications

The time to the onset of psychopathology in early-onset smokers was shorter than in late-onset smokers (chapter 2). As has been discussed already, starting smoking at a young age is associated with various adverse physical and mental health outcomes later in life. Thus, our findings and the previous research on early-onset smoking and worse health outcome, provides a reason to focus on children and adolescents in smoking prevention and cessation programs.

Our finding that nicotine-dependent smokers experience more severe affective symptoms, and slower recovery of their symptoms as compared to non-dependent smokers and non-smoking groups (chapter 3) suggests that chronic and heavy nicotine use does not help to alleviate negative affect, as is suggested by self-medication theory of addictive behaviors. This finding may be useful in educational programs for smokers who smoke in an attempt to control or self-medicate their mood. These findings also suggest to implement a screening for nicotine dependence in health prevention and intervention programs in psychiatric patients who smoke. This may be helpful to develop more effective methods for managing depression and anxiety disorders, especially for those who smoke.

In chapter 4, we found that among nicotine-dependent smokers, only those carrying the Val^{66}Val genotype of the BDNF Val^{66}Met polymorphism

have more severe symptoms of depression and anxiety as compared to non-dependent smokers and the two non-smoking groups of former and never-smokers. In Met^{66} carriers, however, no group differences in symptom severity among the four smoking groups were observed. This study implies that $Val^{66}Val$ carriers may benefit most from smoking cessation. Moreover, understanding of genetic influences on smoking-psychopathology association may be significant for guiding smoking prevention and intervention programs in identifying smokers, particularly those with nicotine-dependence who are vulnerable to adverse outcomes.

Findings of chapter 6 imply that smokers low in attentional control may have hypervigilance to smoking-related cues, and may represent a risk group for smoking relapse. These smokers may benefit more from attentional bias modification (ABM) that aimed at strengthening attentional control and may reduce attentional bias for smoking-related stimuli, thus decreasing craving in addicted smokers, who may more likely to achieve abstinence and less likely to relapse to smoking.

Future Research Directions

This thesis has yielded important insights into future research on the association of smoking with depression or anxiety disorders.

1. Our finding of an association of early-onset smoking with early onset of psychopathology (chapter 2) is consistent with the pre-clinical and clinical research on prenatal and early-age nicotine exposure. However, this was a cross-sectional study, therefore longitudinal and prospective research on the relationship of early-onset smoking with depression and anxiety disorder is needed to determine whether starting smoking early in life indeed explain the development of subsequent psychopathology. Moreover, longitudinal investigations should also focus on the underlying biological mechanisms explaining the association. Further, NESDA data on age-onset of several variables, such as pre-existing alcohol intake, drug use, or other substance use were unavailable.

Therefore, it is likely that these factors may influence the association, as research has shown that the onset of affective disorders is associated with other substance use as well[120]. Therefore, in future research on age-onset of smoking and the development of psychopathology, the role of these variables should be explored.

2. More severe symptoms of affective disorders, and slower recovery over two-year period was observed in nicotine-dependent smokers than in non-dependent, former, and never-smokers (chapter 3); and when the symptom severity was examined in the smoking groups stratified into Val^{66}Val and Val^{66}Met carriers (chapter 4), we found that only those nicotine-dependent smokers have relatively more severe symptoms of depression and anxiety who carry the Val^{66}Val genotype. In Val^{66}Met carriers, no differences in symptom severity among the smoking groups were found. Thus, these findings suggest that genetic differences are important determinants to explain worse behavioral outcome of nicotine in some individuals but not in other. It would be interesting to replicate these findings in future research, and to investigate the role of other polymorphisms in BDNF gene and in other genes and smoking status on symptom severity in order to elucidate the underlying molecular mechanisms, and to help better our understanding of the complex association. Importantly, different ethnic groups should be given consideration in future research because of the ethnic differences in genotype and allele frequencies[117].
3. In current smokers, higher levels of serum BDNF were observed than the non-smoking groups of former and never-smokers who were comparable in their serum BDNF levels. No association of smoking severity, that is, nicotine dependence and number of cigarettes smoked per day, was found with serum BDNF levels. However, total smoking years was a predictor of serum BDNF (chapter 5). Whether quitting smoking has an effect on serum BDNF levels, could be studied in a prospective way to better understand the smoking-BDNF association, because research in this area is sparse. Similarly, it would be interesting to investigate longitudinally if starting smoking has an effect on serum BDNF.

4. Our finding of a relationship of low attentional control with high overall attentional bias and attentional bias to smoking-related pictures presented for 100 ms (chapter 6), suggests that the effect of attentional control on attentional bias is more prominent when stimuli are presented briefly. This indicates that in individuals with low ability to regulate attention, *involuntary* attentional capture by smoking-related cues is increased. This research can be extended by investigating the psychopharmacological mechanisms of attentional bias, taking into account attentional control. For example, attentional bias to smoking-related stimuli had been reduced over time by attenuating dopamine levels in smokers by acute tyrosine and phenylalanine depletion[121, 122]. It would be interesting to explore the role of attentional control in this association. The brain activation associated with attentional bias to smoking-related pictures was reduced by decreasing the dopamine levels by administering the D_2/D_3 dopamine antagonist haloperidol[123]. This study can be extending by investigating group differences in the reduction or increase of attentional bias and related brain activation as a result of manipulating dopamine levels in smokers with low and high attentional control. Moreover, nicotine deprivation is associated with greater information processing bias[124]. Future research may be extended by experimentally manipulating craving to examine the effect of attentional control on the processing of these cues when there is an increased urge to smoke. However, as mentioned earlier, attentional control may function differently for appetitive stimuli, such as smoking-related cues, and aversive stimuli, such as threat-related cues. Therefore, in future research, this issue should be taken into consideration. Moreover, attentional control can further be investigated as a linking mechanism of smoking-psychopathology association.

Conclusion

To conclude, our findings provide an important insight into the complex association of smoking with affective disorders, and suggest that:

1. The age at which an individual starts smoking might be an important factor to define the association of smoking with depression/ anxiety disorders, because the exposure to nicotine early in life may have detrimental effects on brain and behavior subsequently.
2. The severity of the symptoms of an affective disorder depends on whether the smoker is nicotine-dependent.
3. Genetic factors may play a role in smoking-psychopathology association. BDNF $Val^{66}Met$ polymorphism (and other genes/ polymorphisms) might moderate smoking-psychopathology association or may effect symptom severity in smokers and non-smokers.
4. Serum BDNF may not be a possible linking mechanism underlying smoking-psychopathology association, because, on the one hand, the down-regulation of serum BDNF is associated with psychopathology, while, on the other hand, the up-regulation of serum BDNF is associated with smoking.
5. Attentional control might be a possible linking mechanism underlying the association of smoking and depression/ anxiety disorders. However, research on attentional control and attentional bias to smoking-related stimuli should be replicated with large sample size and should be extended to investigate this in the context of smoking-psychopathology association.

Our findings imply that it is crucial for smoking prevention and intervention programs to focus on children, and that public should be made aware of the detrimental effects of early-age nicotine exposure on brain and general health. This public awareness may lead to a reduction in smoking rates in children and adolescents. Further, understanding of genetic influences on smoking-depression/ anxiety association may help guide smoking prevention

and intervention programs in identifying smokers who may be more vulnerable to worse outcomes of nicotine use.

Our findings also imply that attentional bias modification may be used to reduce smoking behavior in smokers with low attentional control. Reducing smoking behavior may have important positive consequences for negative mood.

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