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Decreased Central Nervous System Grey Matter Volume (GMV) in Smokers Affects Cognitive Abilities: A Systematic Review

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG **Martina Vňuková**

ABCDEG **Radek Ptáček**

DEFG **Jiří Raboch**

ABCDEFG **George B. Stefano**

Department of Psychiatry, First Faculty of Medicine Charles University in Prague and General University Hospital in Prague, Prague, Czech Republic

Corresponding Author: Radek Ptáček, e-mail: ptacek@neuro.cz

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Although cigarette smoking is a leading cause of preventable mortality, tobacco is consumed by approximately 22% of the adult population worldwide. Smoking is also a risk factor for cardiovascular disease, affects brain processing, and is a recognized risk factor for Alzheimer disease (AD). Tobacco toxins (e.g., nicotine at high levels) inhaled in smoke may cause disorders resulting in preclinical brain changes. Researchers suggest that there are differences in brain volume between smokers and non-smokers. This review examines these differences in brain grey matter volume (GMV).

In March/April 2015, MedLine, Embase, and PsycINFO were searched using the terms: "grey matter" AND "voxel-based" AND "smoking" AND "cigarette".

The 4 studies analyzed found brain GMV decreases in smokers compared to non-smokers. Furthermore, sex-specific differences were found; while the thalamus and cerebellum were affected in both sexes, decreased GMV in the olfactory gyrus was found only in male smokers. Age-group differences were also found, and these may suggest pre-existing abnormalities that lead to nicotine dependence in younger individuals. Only 1 study found a positive correlation between number of pack-years smoked and GMV.

Smoking decreases GMV in most brain areas. This decrease may be responsible for the cognitive impairment and difficulties with emotional regulation found in smokers compared with non-smokers.

MeSH Keywords: **Cognition Disorders • Neurosciences • Smoking**

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Background

Cigarette smoking is a leading cause of preventable mortality. Each day, at least 3800 adolescents in the USA try their first cigarette and 33% of teenagers that are daily smokers will die of a smoking-related condition [1]. Tobacco dependence is also the single most prevalent substance abuse disorder [2]. In 2000, 18.1% of total deaths in the USA were attributed to tobacco use, making it one of the leading causes of death, followed by poor diet and physical inactivity, which together are responsible for 15.2% of total deaths, and 3% of total deaths were alcohol-related [3]. Worldwide, tobacco is consumed by approximately 22% of the adult population. Some countries, such as England, have a decreasing tobacco-use trend, but even there, 27% of males and 24% of females reported smoking more than 20 cigarettes (1 pack) a day [4]. Approximately 90% of smokers start smoking before the age of 18 [1].

Smoking is a risk factor for many health-related diseases, including cardiovascular disease, and it also affects brain function [1,3]. It is a well-recognized risk factor for Alzheimer disease (AD); research found that smokers are twice as likely to develop AD compared to those who never smoked [5]. Adverse effects of smoking on cognition are also known [6], including a decrease in visual search speed [7]. Smoking is related to pre-clinical changes in the brain, higher risk of cognitive decline, and increased risk of dementia [8–10]. Even after the cessation of smoking, certain problems remain, such as impaired working memory [11].

These problems are probably caused by the toxins inhaled in tobacco smoke, including vinyl chloride (a risk factor for brain cancer), hydrogen cyanide, and arsenic [12]. Long-term, daily exposure to these toxins may result in altered vascular and neural processes, which probably result from tissue accumulation and/or assault. The toxicity of these smoke-related toxins may cause preclinical brain changes [11,12]. Additionally, these changes express themselves by changes in grey matter (GM) and white matter (WM) volume and brain density.

Although GMV decreases linearly with age, global white matter does not decline with age; however, local areas of relatively accelerated loss and preservation occur [13]. As the world population ages [14], it is important to determine which brain changes are attributable to normal/healthy aging and which are caused by preventable behaviors such as smoking.

A growing number of studies using the voxel-based morphometry technique have compared smokers to non-smokers in terms of the volume of white and grey matter [15–19]. This technique characterizes the tissue concentration differences in structural magnetic resonance brain images. These studies have often produced mixed and inconsistent outcomes. Kühn et al. (2012) reported no differences in WM volume between smokers and non-smokers, whereas Yu, Zhao, and Lu (2011) reported a regional WM volume increase [20,21]. As with GMV, some studies reported smokers have smaller GMV in the dorsolateral prefrontal cortex (DLPFC) [22,23], while others found a smaller volume in the anterior cingulate cortex (ACC) and thalamus [15]. A recent meta-regression analysis showed that a higher number of smoking years was correlated with more GM atrophy in the right superior frontal gyrus, and more cigarettes smoked per day was correlated with more GM atrophy in the right superior frontal gyrus and ACC, extending to the paracingulate gyrus [16]. These studies suggest that there are differences in brain volume between the 2 groups. The present review examines these differences, focusing on GMV.

Data Determination and Sources

The following databases were searched in March/April 2015: MedLine, Embase, and PsycINFO. The following string search was used: “grey matter” AND “voxel-based” AND “smoking” AND “cigarette”. Records were obtained when “grey matter” was found in the title of the article and the remaining terms were found in the abstract or in the title.

Table 1 shows results generated through our initial database search.

Table 1. Results generated by the database search.

Search term	Embase	PsycInfo	Medline	All
Grey matter	2348	942	1969	5259
Voxel based	7082	2847	5054	14983
Smoking	189041	34245	145529	368815
Cigarette	44399	9938	38351	92688
1 and 2 and 3 and 4	5	3	4	12
Remove duplicates	5	3	4	8

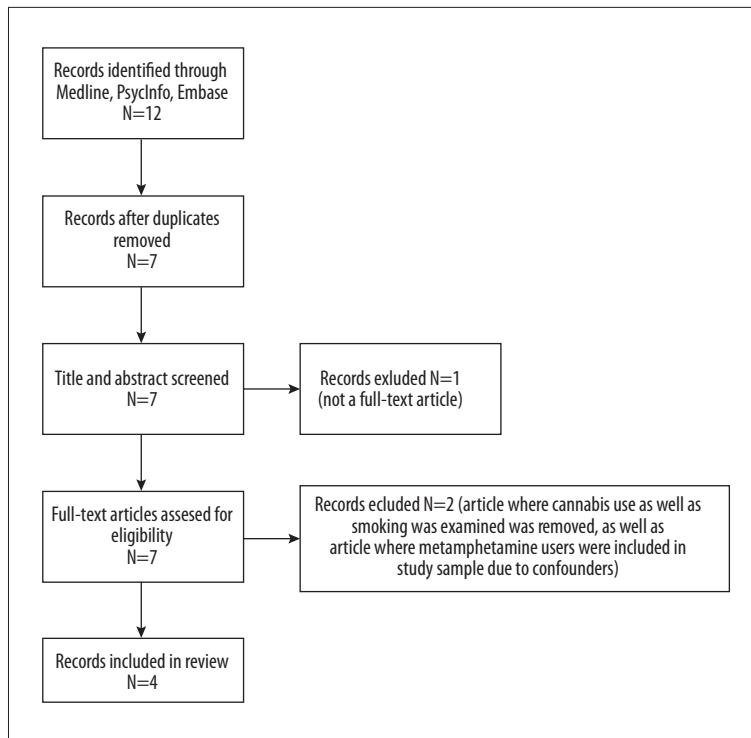


Figure 1. Representation of the inclusion and exclusion process.

Records were screened using the exclusion and inclusion criteria.

Inclusion criteria

- Male and female sample.
- Studies that measured differences in grey matter.
- Studies comparing smokers with non-smokers.
- Studies that used voxel-based morphometry.

Exclusion Criteria

- Non-human studies.
- Studies not published in English language.
- Articles that did not have full text or that could not be retrieved through our university libraries.
- Studies not relevant to the review question.
- Studies that included marijuana smoking.
- Studies that included addictions other than nicotine addiction.

The remaining records were included in this review (Figure 1).

We evaluated the quality of included articles by use of a modified version of the Effective Public Health Practice Project (EPHPP) quality assessment tool for quantitative studies. Questions about criteria unrelated to this review were excluded. Detailed component ranking is shown in Appendix 1.

Results

Tables 2–4 summarize the studies included in this review.

It is important to note that only 1 study [17] was conducted in Europe and the remaining ones [18,19,24] were in the USA. All studies used cross-sectional design and only 1 study [19] was not conducted in 2014. There were large differences in the sample sizes: Brody (2004) only included 36 participants [19], whereas Fritz (2014) had 974 [17]. None of the studies used power calculation; therefore, the results need to be interpreted with caution. Additionally, all of studies compared smokers to non-smokers, with some [18,24] adding further groups for comparison. For example, Franklin (2014) compared across sexes and Hanlon (2014) compared the differences between young and long-term smokers [18,24]. Three of the studies [18,19,24] had approximately the same number of smokers as non-smokers, but Fritz (2014) had significantly more non-smokers and significant differences in demographics of the studied population [17].

All 4 studies used voxel-based morphometry (VBM), which is a neuro-imaging analysis technique that investigates focal differences in brain anatomy [17–19,24]. Brody (2004) also included hand-drawn regions of interest (ROI) [19], which allows extraction of data for a specific structure. All images were produced by a Tesla Siemens scanner, and all studies used statistical parametric mapping (SPM), which increases the validity of conclusions because the same methodology is applied in

Table 2. Summary of included studies.

Ref	Author (date)	Name	Country	Study design
[17]	Fritz HC, Wittfeld K, Schmidt CO et al. (2014)	Current smoking and reduced gray matter volume-a voxel-based morphometry study	Germany	Cross-sectional
[18]	Franklin TR, Wetherill RR, Jagannathan K et al. (2014)	The effects of chronic cigarette smoking on gray matter volume: influence of sex	USA	Cross-sectional
[19]	Brody AL, Mandelkern MA, Jarvik ME et al. (2004)	Differences between smokers and nonsmokers in regional gray matter volumes and densities	USA	Cross-sectional
[24]	Hanlon, Colleen A, Owens et al. (2014)	Lower subcortical gray matter volume in both younger smokers and established smokers relative to non-smokers	USA	Cross-sectional

Table 3. Summary of the demographics and characteristics of the study.

Study number and reference	Sample size	Groups compared	Smokers/ nonsmokers (N)	M/F	Age smokers/ non-smokers	Cigarette/ day	Pack/ year	Started smoking	Technique	Image acquisition	Data analyses
[17] Fritz et al. (2014)	974	Smokers vs. non smokers	315/ 659	391/ 583	44.1/ 51.49	13.17	17.81	17.3	Voxel-based morphometry	1.5 Tesla Siemens MRSI scanner	SPM8
[18] Franklin et al. (2014)	160	Male smokers/ male nonsmokers/ female smokers/ female nonsmokers	80/ 80	82/ 78	(M – 35.7/ F – 31.9)/ (M – 33.2/ F – 30.9)	(M –1 6.1) (F – 13.2)	(M – 13) (F – 7)	19.8	Voxel-based morphometry	Siemens 3 – tesla trio whole body scanner	SPM8
[19] Brody et al. (2004)	36	Smokers/ non smokers	19/ 17	21/ 15	39.5/ 37.9	26.2	31	/	Voxel-based morphometry, hand drawn regions of interest	1.5 Tesla Siemens MRSI scanner	SPM99
[24] Hanlon et al. (2014)	118	Younger smokers/ younger nonsmokers/ established (older) smokers/ older nonsmokers	58/ 60	71/ 52*	(**23,9/ 40,04)/ (**23/36)	**15.3/ ***17.2	**5.2/ ***19.8	16.2	Voxel-based morphometry	Siemens 3 – tesla trio MRI scanner	SPM8

* Mistake in reports; ** younger; ***established.

each study and the results cannot be attributed to the technology or methodology used.

Quality assessment of each study was carried out using the EPHPP quality assessment tool. Studies by Fritz (2014), Franklin (2014), and Hanlon (2014) were scored as strong quality with

moderate quality in terms of representativeness of the sample [17,18,24]. Brody (2004) was graded as moderate quality after scoring weak quality in the population component of the questionnaire [19]. Table 5 shows component and global rating of quality of each study.

Table 4. Summary of the main results.

Study number and reference	Exclusion criteria	Volume loss	Volume increase	Sex difference	Other correlations
[17] Fritz et al. (2014)	Stroke, multiple sclerosis, epilepsy, Parkinson's disease, dementia, cerebral tumor, intracranial cyst, hydrocephallus	Right DLPFC, bilateral DMPFC, bilateral VLPFC, bilateral VMPFC, right ACC, inferior temporal gyrus, left insula, right olfactory gyrus	/	F – additional effect on VLPFC, M – effect on olfactory gyrus	GMV corelated negatively with pack-year
[18] Franklin et al. (2014)	Current DSM IV – Axis I diagnosis (other than ND), history of head injury, loss of consc. for longer than 3 min, alcohol & drug history	Thalamus, mOFC, bilateral cerebellum	Bilateral putamen, parahippo-campus	F – lower GMV in left cerebellum, ventral medial cortex M – lower GMV in bilateral cerebellum, greater GMV in bilateral parahippo-campus and left putamen	M – GMV in left putamen was positively correlated with # of pack years
[19] Brody et al. (2004)	History of epilepsy, seizure, stroke, head trauma, loss of consc., history of DSM IV Aixs I disorder other than ND, substance abuse	DLPFC/VLPFC,	/	/	Prefrontal cortical GMV negatively correlated with pack-year
[24] Hanlon et al. (2014)	No history of head trauma, no neurologic or psychiatric diagnosis, no history of migraine, no history of sbstance abuse or dependence (other than ND)	Younger – amygdala, left thalamus/older – insula, parahippocampal gyrus and pallidum	Older – left occipital cortex	/	Established smokers – negative correlation between pack-year and MPFC

ND – nicotine dependence.

Table 5. Quality assessment table.

	21.	22.	23.	24.
Study design	Strong	Strong	Strong	Strong
Sample	Moderate	Moderate	Weak	Moderate
Confounders	Strong	Strong	Strong	Strong
Data collection	Strong	Strong	Strong	Strong
Analyses	Strong	Strong	Strong	Strong
Global rating	Strong	Strong	Moderate	Strong

Importantly, 3 studies [17,18,24] reported significant ($p < 0.001$) differences between smokers and non-smokers in GMV, and Fritz (2014) also found a significance difference ($p < 0.05$) [16]. All studies corrected for family-wise error [17–19,24]. Decreased GMV in smokers compared to non-smokers was reported, but Franklin (2014) and Hanlon (2014) also noted increased GMV in some brain areas (Table 4) [18,24]. These studies also found further correlations between pack-years and GMV. Overall, it is clear that smoking causes decreased GMV, but variations in the specific region affected were found as well.

All 4 studies found decreased GMV in the ventrolateral prefrontal cortex of smokers [17–19,24], as well as loss of GMV in the dorsal-lateral prefrontal cortex [17,19]. Two studies found GM loss in the cerebellum of smokers [18,19]. The only study to find differences in GMV in the olfactory gyrus was by Fritz (2014) [17]. Hanlon (2014) found a decrease in GMV in the amygdala region in smokers [24]. A decrease of thalamic GMV in smokers was found by Franklin (2014) and Hanlon (2014), who also reported differences in the parahippocampal gyrus region. Interestingly, Hanlon (2014) also found decreased GMV in smokers, whereas Franklin (2014) found greater GMV in the parahippocampus in smokers [18,24]. Although contradictory results in specific areas were found, these may be attributed to the differences in samples studied. Future studies should consider differences between sexes and age groups as well as between smokers and non-smokers.

Two studies compared female and male smokers to non-smokers and found certain sex-specific differences [17,18]. One found a decrease in smokers in both sexes in the ventromedial prefrontal cortex [17], while the other found reduced GMV in the thalamus and cerebellum in smokers of both sexes [18]. Both found an additional GMV reduction in female smokers in the ventrolateral prefrontal cortex. Fritz (2014) found GMV loss in the olfactory gyrus in male smokers, and did not find any area of increased GMV, which is a unique finding [17]. Franklin (2014), on the other hand, found increased GMV in the bilateral hippocampus and the left putamen in male smokers [18]. These structures, as Franklin noted, are associated with emotional and drug memories.

Hanlon (2014) reported decreased GMV in younger smokers compared with a matched control group of non-smokers. Compared with a matched control group of non-smokers, long-term smokers had changes in the amygdala ($t = 6.03$, cluster size = 601, $P = 0.002$) and left thalamus ($t = 5.75$, cluster size = 234, $P < 0.000$). Decreased GMV in the amygdala was not reported by other investigators. Decreased GMV was found in long-term smokers in the insula, parahippocampus, and thalamus. Interestingly, when they compared long-term smokers with their non-smoking matched control group, they found decreased GMV in the same areas: the insula and parahippocampus. In

this group comparison, they also found that smokers had decreased GMV in the left occipital cortex [24]. These results suggest either that nicotine rapidly affects brain regions or that there may be pre-existing abnormalities that lead to nicotine dependence in younger individuals.

Lastly, we explored a possible correlation between GMV and age of onset of smoking, cigarettes per day, the length of time smoking, and the pack-years smoked. All 4 studies reported further correlations between GMV and pack-years. Hanlon (2014) reported a negative correlation in long-term smokers between number of pack-years and GMV in the medial prefrontal cortex [24]. Brody (2004) reported similar correlations between GMV in the prefrontal cortex and pack-years [19]. Fritz (2014) found that small clusters of reduced GMV in the middle occipital gyrus and anterior and middle cingulate cortex were correlated with number of pack-years ($r = 0.192$, $t = 3$, 45 , $p < 0.001$) [17]. Lastly, Franklin (2014) reported a positive correlation between GMV in the left putamen and number of pack-years in males ($r = .38$, $p = .018$) [18].

Overall, these studies reported similar results and all found lower GMV in certain brain areas in smokers compared to non-smokers. Some studies found sex differences [17,18] and 1 study found differences across age groups [24]. Two studies [18,24] also found brain areas where the GMV was actually higher in smokers than in non-smokers. Lastly, 2 studies [17,24] reported a negative correlation between pack-years and GMV. Only 1 study [18] found a positive correlation between number of pack-years and GMV.

Discussion

These studies found that smokers have lower GMV in multiple cortical and sub-cortical regions compared with non-smokers. Multiple atrophies in the prefrontal cortex region were also found [18,19,24]. This shows a certain neuroanatomical pattern in smokers. In this regard, nicotine and cue-induced prefrontal activation might partially explain the atrophies observed via repeated stimulation during smoking, and this is thought to be associated with lower GMV [21]. A decrease in GMV in the DLPFC may be associated with cognitive deficits in smokers [17,19]. In the abstinent state, smokers are not able to compensate higher task loads [25]. The prefrontal cortex also has a role in emotional processing (e.g., regulation) [26]. Personality-wise, smokers with lower GMV in the PFC are more likely to be impulsive and neurotic than their non-smoking counterparts [12]. The MPFC and VPFC are associated with reward and development, as well as maintenance of addiction [27]. The insula also plays a role in dysfunction of emotional regulation, as well as a general role in nicotine addiction and craving. mOFC is correlated with inhibition of

behavior; this effect is enhanced in females, explaining why they find it harder to stop smoking [18].

Importantly, 2 studies found lower GMV in the thalamus [18,24], which has the highest density of nicotine receptors of any brain region and is the prime target in long-term smoking [22]. Cigarette smoking also correlates with increased nicotine binding in the thalamus. However, controversy exists in that Fritz (2014) and Brody (2004) did not report any areas of decreased GMV in the thalamus, suggesting a role of functional abnormalities in signalling [17,19]. The thalamus is associated with memory, attention, and planning, explaining why smokers tend to have worse results on cognitive tasks, including memory [17,19].

The putamen is implicated in smoking-associated anatomical changes [18,24]. This structure is associated with habitual compulsive drug seeking and use. The severity of compulsivity was also positively correlated with increased GMV in the putamen. In 1 study, this increase was only found in males [18]. There were also differences found in the hippocampus and amygdala; these areas also are linked with emotional and drug memories [23]. However, Hanlon (2014) found differences in the amygdala only when comparing young smokers with non-smokers. Interestingly, this difference was lost in long-term smokers [24].

Despite these inconsistencies, it is clear that smoking often causes problems with emotional regulation and cognitive functions. Although all 4 studies used the same technique, certain differences may have arisen because the technique was not used at the same place and time. Also, all 4 studies were cross-sectional, so we cannot know if there were any

pre-existing structural differences in the brains of subjects. In younger smokers, nicotine either affects neural tissue volume very quickly or there are pre-existing abnormalities that predispose some individuals to smoking [24]. Further longitudinal research is needed to answer this question. Lastly, smoking is highly prevalent in people with psychiatric disorders, and smoking can be a strong confounder in brain studies of these patients.

Conclusions

Overall, smoking causes differences in GMV in various brain areas, and these differences help explain the cognitive impairment and emotional dysregulation in smokers compared with non-smokers. There are considerable differences, not only between males and females, but also between younger and older smokers, and any therapeutic treatment must take this into account. To summarize, smoking decreases GMV in most brain areas, and this decrease is believed to be responsible for the cognitive impairment and difficulties with emotional regulation in smokers. Future studies should separate physical changes of the brain from those associated with cognition, which would be useful in determining a therapeutic strategy for treating the associated pathologies of tobacco smoking. Importantly, it cannot be ignored that tobacco smoking may be a self-medicating phenomenon, which seeks to relieve a pre-existing pathology; therefore, an individualized approach to treatment is advised.

Conflicts of interest

The authors declare no competing interests.

Appendix

Appendix 1. Detailed component ranking.

		Study number and reference			
		[17] Fritz et al. (2014)	[18] Franklin et al. (2014)	[19] Brody et al. (2004)	24. Hanlon et al. (2014)
A. Study design					
Component rating	<i>Did the study address a clearly focused question/issue?</i>				
	Yes	x	x	x	x
	No				
	Unclear				
	<i>Was the study design appropriate for answering the research question?</i>				
Yes	x	x	x	x	
No					

		Study number and reference				
		[17] Fritz et al. (2014)	[18] Franklin et al. (2014)	[19] Brody et al. (2004)	24. Hanlon et al. (2014)	
Component rating	Unclear					
	Rate this section	Strong	Strong	Strong	Strong	
	B. Sample					
	<i>Was the sample of participants representative with regard to the population to which the findings will be referred?</i>					
	Very likely					
	Somewhat likely	x			x	
	Not likely			x		
	Unclear		x			
	<i>Is the method of selection of the participants clearly described?</i>					
	Yes	x	x	x	x	
	No					
	<i>What percentage of selected individuals agreed to participate?</i>					
	80–100% agreement					
	60–79% agreement					
	Less than 60% agreement					
	Not applicable					
	Unclear	x	x	x	x	
	<i>Was a power calculation reported?</i>					
	Yes					
	No	x	x	x	x	
Rate this section	moderate	moderate	weak	moderate		
C. Confounders						
<i>Were relevant confounders accounted for?</i>						
Most	x	x	x	x		
Some						
Few or none						
Unclear						
Rate this section	Strong	Strong	Strong	Strong		
D. Data collection methods						
<i>Were the measures shown to be valid?</i>						
Yes	x	x	x	x		
No						
Unclear						
<i>Were the measures shown to be reliable?</i>						
Yes	x	x	x	x		
No						
Unclear						
Rate this section	Strong	Strong	Strong	Strong		

		Study number and reference			
		[17] Fritz et al. (2014)	[18] Franklin et al. (2014)	[19] Brody et al. (2004)	24. Hanlon et al. (2014)
E. Analyses					
Component rating	<i>Are the statistical methods appropriate for the study design?</i>				
	Yes	x	x	x	x
	Somewhat				
	No				
	Unclear				
	<i>Was the statistical significance assessed?</i>				
	Yes	x	x	x	x
	No				
	Unclear				
	<i>Are confidence intervals given for the main results?</i>				
	Yes	x		x	x
	No		x		
	Unclear				
	Rate this section	Strong	Strong	Strong	Strong
	Global rating for this paper	Strong	Strong	Moderate	Strong

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