Subcortical gray matter volumes in asthma: associations with asthma duration, control, and anxiety

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Abstract

Asthma as a chronic inflammatory disease can be expected to affect central nervous system structures but little is known about subcortical structures in asthma and their potential association with illness-specific outcomes and anxiety. A total of 40 young adults (20 with asthma and 20 gender- and age-matched controls) underwent high-resolution T1-weighted MRI scan, viewed short distressing film clips, and filled in questionnaires about anxious and depressed mood, as well as asthma history, control, and catastrophizing thoughts about asthma, for those with asthma. The structural scans were processed in FSL's FIRST program to delineate subcortical structures of interest: amygdala, hippocampus, putamen, pallidum, caudate nucleus, nucleus accumbens, and thalamus. Findings showed no general reduction in subcortical gray matter volumes in asthma compared to controls. Asthma duration, asthma control, and catastrophizing of asthma and asthma attacks were negatively associated with volumes of putamen and pallidum, and to a weaker extent thalamus and amygdala, while controlling for gender, age, and corticosteroid inhaler use. In addition, stronger anxiety in response to distressing films was associated with lower volume of the pallidum, whereas general anxious and depressed mood was unrelated to subcortical structures. Thus, although there are no subcortical structural differences between young adults with asthma and healthy controls, longer asthma history, suboptimal management, and illness-related anxiety

are reflected in lower gray matter volumes of subcortical structures, further emphasizing the importance of maintaining optimal asthma control.

Current knowledge about the brain in asthma is limited. Progress has been made in elucidating brain function related to respiratory sensations and stress in asthma (e.g., Davenport et al. 2000; Rosenkranz et al. 2016; von Leupoldt et al. 2009; Webster and Colrain 2002), however, the potential role of asthma in altering the shape of brain structure, in particular gray matter volume, remains largely unexplored. Given the central role of compromised lung function and airway inflammation in the asthmatic pathophysiology it is conceivable that longer lasting or uncontrolled disease could affect central nervous system structures and lead to accelerated degeneration. Two published studies have examined brain structures in asthma. Smaller hippocampal volumes have been found in a large sample of middle-aged asthma patients compared to matched controls (Carlson et al. 2017). In addition, one smaller study found that longer asthma duration was associated with larger periaqueductal gray volumes (von Leupoldt et al. 2011). Furthermore, reductions in gray matter volumes of a number of cortical and subcortical structures have been found in Chronic Obstructive Pulmonary Disease (COPD) in two other studies (Esser et al. 2016; Zhang et al. 2012). Both studies observed structural changes related to disease duration and one additionally found an association with patients' fear of dyspnea and exercise (Esser et al. 2016).

High comorbidity of asthma with anxiety disorders, in particular panic disorder, has been documented frequently, both cross-sectionally and longitudinally (Favreau et al. 2014; Goodwin et al. 2012; Meuret et al. 2017; Scott et al. 2007). More specifically, panic and fear related to asthma have been shown to affect asthma management, including excessive self-medication with bronchodilators and more frequent emergency room visits as well as overuse or overprescription of medication (Janssens et al. 2009). Anxious thoughts about catastrophic outcomes of asthma attacks and asthma in general have been related to elevated symptom reports in respiratory challenges (De Peuter et al. 2007, 2008) and reduced asthma control (Janssens et al. 2012). Such catastrophic cognitions are also a characteristic feature of panic disorder and a growing literature suggests that panic, fear, and anxiety disorders are associated with reduced gray matter volume in subcortical structures. In particular, reduced volumes have been observed in limbic structures such as hippocampus and amygdala (Ahmed-Leitao et al. 2016; Fisler et al. 2013; Hayano et al. 2009; Morey et al. 2012; Yoon et al. 2016; although with less consistency for the amygdala, see Cacciaglia et al. 2017; Günther et al. 2018) and in basal ganglia (Hilbert et al. 2015; Uono et al. 2017; Yoo et al. 2005).

In this study, we sought to examine subcortical structures in asthma, for which prior research has previously shown associations with emotional processes. From an evolutionary and comparative perspective, subcortical regions are viewed as more central to the generation of

affect, with cortical regions taking on a more modulatory role (e.g., Damasio and Carvalho 2013; Panksepp 2011). Amygdala and hippocampus are classically involved in negative emotion (LeDoux et al. 1988; Davis 1992) and are sensitive to effects of stress hormones (McEwen et al. 2015), but more recently have also been invoked in reward sensitivity and learning (Baxter and Murray 2002; Morrison and Salzman 2010). Similarly, basal ganglia have been implicated in both reward processing and positive emotion, but more recently also in negative states like anxiety and fear (Lago et al. 2017). In addition, the thalamus has been characterized in emotion theories as an important hub for proprioceptive and sensory afferents (Damasio and Carvalho 2013) as well as top-down modulation of affect by cortical input through the basal ganglia (Panksepp 2011).

The aims of the present study were, (1) to compare subcortical gray matter volumes between individuals with asthma and a group of age and gender-matched healthy controls, (2) to study associations of gray matter volumes in asthma with disease duration and control, and (3) to examine whether catastrophic thinking about asthma and anxious responding to distressing stimuli is related to gray matter volumes.

Materials and methods

Participants

Twenty volunteers with asthma and 20 healthy controls between the ages of 18–45 were recruited from a university campus and the community. Inclusion criteria for those with asthma were a physician-documented diagnosis of asthma. Exclusion criteria were treatment with oral corticosteroids in the previous two months, forced expiratory volume in the 1st second (FEV_1) below 70% of predicted; pregnancy in women (confirmed via urine test); presence or history of medical or neurological disorder such as angina, myocardial infarction, congestive heart failure, transient ischemic attacks, cerebrovascular accidents, uncontrolled diabetes mellitus, emphysema, or chronic obstructive pulmonary disease, seizures or head trauma, endocrine disorders or renal disease. Major psychological disorders excluded were: presence or history of schizophrenia, bipolar disorder, or dementia; current presence of major depressive disorder or blood-injection-injury phobia; current or recent history (within 1 year) of substance-related disorders, current recreational drug use or consuming more than 20 alcoholic drinks *per* week; current smoking or recent history (within 6 months) of smoking (< 6 pack years of lifetime smoking history); use of medication with sympathetic and parasympathetic effects, anxiolytics or other psychoactive drugs, or previous electroconvulsive therapy. Presence of history of orthopaedic circumstances and metallic inserts was contraindicated for magnetic resonance scanning. Persons with a lack of proficiency in English were also excluded. Asthma severity was determined by relevant guidelines (National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program 2007) on the basis of % of predicted FEV_1, symptoms, functional limitations, bronchodilator use, and exacerbations (in the past year) for those without maintenance medication use, or treatment step for those who initiated maintenance medication and whose asthma was well controlled.

All procedures were approved by institutional review boards of The University of Texas

Southwestern Medical Center (STU 082011–038) and Southern Methodist University (2015–007-RITT). All participants provided written informed consent. They received an honorarium of $50 for taking part in the imaging sessions or alternatively elected to receive course credit, in case they were undergraduate students.

Measures

FE_{NO} was measured with a handheld electrochemical analyzer (Niox mino, Aerocrine, Sweden; Alving et al. 2006) as an indicator of airway inflammation. FEV_1 (expressed as % of predicted values) was measured with an electronic spirometer (Jaeger/Tönnies AM2, Höchberg, Germany) as a common indicator of mechanical lung function. Both measures were obtained at the beginning of the session. Participants completed an ad-hoc questionnaire on demographics, asthma history, manifestation and past treatment, the Catastrophizing of Asthma Scale (CAS; De Peuter et al. 2007) with subscales for Catastrophizing of Asthma (CAS-asthma) and Catastrophizing of Asthma Attacks (CAS-attacks) with 13 items each, and the Asthma Control Questionnaire (ACQ; Juniper et al. 1999), which measures asthma control impairment in the past week (including scoring % of predicted FEV_1 as one of seven items), and the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith 1983) with subscales for anxious and depressive mood. Participants completed ratings of their mood prior to entering the scanner, after entering it, and after each film stimulus block during the scan. The anxiety rating consisted of an 11-point rating scale ranging from 0 ("*not at all*") to 10 ("*extremely*").

Procedures

Following questionnaire measures, FE_{NO}, and spirometry at the beginning of the session, participants entered the scanner and structural images were acquired. Subsequently, participants were instructed to view two blocks of three negative films and one block of three neutral films. Each film lasted 44 s followed by a 120 s recovery period. Negative films contained scenes of surgery, injection and injury, mostly from medical education material, which had been effective in eliciting airway constriction and negative affect in prior studies (Janssens et al. 2017; Ritz et al. 2010, 2011). Neutral films were extracts from a geology lecture on sedimentary rock formation. Films were rear-projected onto a screen and viewed by participants via a mirror mounted on the head coil. After each run, participants provided self-report of anxiety. At debriefing, possible residual symptoms were explored by the experimenter and spirometry was repeated to ensure patient safety.

MRI acquisition and analysis

All images were collected using a high-field 3-Tesla (3 T) Philips Achieva scanner equipped with a 32-channel head coil. High-resolution anatomical (T1) images were acquired using magnetization-prepared rapid gradient-echo sequence: TR/TE/TI = 8.2/3.8/873 ms, voxel size = $1.0 \times 1.0 \times 1.0$ mm^3, flip angle = 12°; FOV = 256×256 mm^2, 160 sagittal slices. The structural scans were then processed in FSL's FIRST program (Patenaude et al. 2011) to delineate subcortical structures. In short, FSL-FIRST method spatially normalizes the T1 images into MNI space and then restricts the local registration to subcortical structures. The variation in shape and intensity is modeled by multivariate Gaussian distribution based on 336 T1-weighted MR images where the subcortical regions were delineated manually. In our

analysis, we estimated the volumes of amygdala, hippocampus, putamen, pallidum, caudate nucleus, nucleus accumbens, and thalamus (Fig. 1). Next, we normalized the volume of each subcortical region by the intracranial volume to account for different brain sizes. Thus, the subcortical regions are reported in percent (%), which are in relation to intracranial volume.

Statistical analysis

Means or frequencies of demographic, anthropometric, and clinical variables were calculated for baseline characterization of groups. Group differences in gray matter volumes were examined by t-tests. Partial correlations controlling for age, gender, and inhaled corticosteroid intake were calculated for the association between gray matter volumes and asthma-related variables or anxiety response to negative film viewing (relative to baselines outside and inside the scanner). Log-transformation was applied for FE_{NO} and CAS-asthma because they deviated from normal distribution.

Results

Baseline sample characterization

Characteristics of the groups were largely similar in baseline characteristics, except for higher FE_{NO} in asthma (Table 1). Participants were young on average and asthma patients had predominantly mild severity and control was in an indeterminate range according to the ACQ[26]. Thirty-five percent were taking inhaled corticosteroids.

Gray matter volume differences between asthma and controls

Findings showed no general reduction in gray matter volumes in the asthma cohort compared to controls (Table 2).

Associations of gray matter volumes with asthma-relevant variables

Duration and asthma control were negatively associated with volumes of a number of subcortical areas, with significant or trend-level associations for amygdala, putamen, and pallidum while controlling for gender, age, and corticosteroid inhaler use (Table 3, Fig. 2). In addition, stronger catastrophizing of asthma attacks or asthma in general was consistently associated with lower volumes in the same structures and the thalamus. In significant associations with putamen and pallidum asthma-relevant variables accounted for 16.9–20.4% of variance beyond control variables. (See Supplemental Table 1 and 2 for associations between gray matter volumes with gender, age, and corticosteroid inhaler use).

Associations of gray matter volumes with anxiety response to distressing films and mood

In asthma, lower volumes of the pallidum correlated with greater anxiety response to the presentation of the distressing films (Table 3, Fig. 2). The anxiety response after entering the scanner explained 26.3% of volume variance in the pallidum beyond control variables. In controls, anxiety response (film viewing minus baseline before entering the scanner), correlated negatively with volumes of amygdala ($r[15] = -.55$, $p = .023$) and hippocampus ($r[15] = -.52$, $p = .027$). No significant partial correlations were observed with the HADS anxious mood ($rs = -.37$ to $.20$) for those with asthma, whereas controls showed significant

negative associations with amygdala volume (t[16] = −.52, p = .027) and a trend with caudate nucleus volume (t[16] = −.42, p = .086). No substantial associations were found for the HADS depressive mood subscale for both groups (rs = −.40 to .22).

Association of gray matter volumes with individual components of asthma control

Given the novelty of the uncovered associations for individuals with asthma we explored associations with individual items of the ACQ, which covered past-week night-time awaking by symptoms, severity of morning symptoms, shortness of breath, wheezing, functional limitations, β-adrenergic bronchodilator use, and current % of predicted FEV_1. Controlling for age, gender, and ICS use, past-week wheezing and bronchodilator use showed significantly negative associations with putamen volume, r = .54 and .49, p = .025 and .045, respectively, while severity of morning symptoms after awaking were negatively associated with volume of the pallidum, r = .50, p = .039.

Discussion

Our study showed for the first time that asthma history and clinical outcomes are associated with differences in subcortical gray matter volume in young adult individuals with asthma. Although no substantial differences in volumes were found compared to healthy controls, aspects of the disease history, control, and experience are reflected in subcortical structures that are linked to processing of emotion, in particular anxiety and fear. Pallidum and putamen were the structures that were most likely to show these associations. Associations of gray matter volumes with distress over symptoms have been observed before in COPD (Esser et al. 2016) and anxiety disorders and fear have been linked to deficits in limbic and basal ganglia structures (Ahmed-Leitao et al. 2016; Fisler et al. 2013; Hayano et al. 2009; Hilbert et al. 2015; Uono et al. 2017; Yoo et al. 2005; Yoon et al. 2016), but the relationship of asthma-related variables with subcortical structure variations has not been reported before. This relationship is substantial, accounting for up to 20% of variation in gray matter volumes.

Asthma duration and control both showed relatively consistent associations with basal ganglia structures, in particular putamen and pallidum. Although we were not able to establish directions of effects with our cross-sectional study design, the association of lower volumes with longer disease duration makes it more likely that the asthmatic disease process negatively affects CNS structures, rather than structural variations determining the asthmatic disease process. Mechanisms through which asthma could affect the CNS have not been studied well, but speculations at this point could involve a variety of pathways linked to medication or stress hormone effects, brain oxygenation, inflammation, oxidative stress, or sleep disruption. Stress-related hypothalamus-pituitary adrenal axis activity and steroid medication are likely to unfold detrimental effects on CNS structures (Brown et al. 2004; McEwen and Gianaros 2011), and both are more likely seen in asthma patients with significant anxiety, who are known to report or receive more frequent oral steroid regimens (Hyland et al. 1993; Kinsman et al. 1977; Romero-Frais et al. 2005). However, effects likely differ by brain region and glucocorticoid and mineralcorticoid receptor density (Joëls 2018; Meijer et al. 2019) and for the hippocampus, where receptor density is greatest and

glucocorticoid effects are well established (Lupien et al. 2018), we did not find associations of gray matter volume with disease outcomes and anxiety in those with asthma. Differential sensitivity of hippocampal substructures and types of neurons further complicate the interpretation of our findings as driven by corticosteroid effects (McEwen et al. 2016). The amydgala, another structure with rich glucocorticoid receptor density (Wang et al. 2014), which has shown volume reductions with corticosteroid treatment (Brown et al. 2008), only showed trend-level associations with disease outcome variables in asthma. Episodes of desaturation by exacerbations have been suspected as a major culprit (Albéri 2013), but problematic saturation levels in asthma appear to be more likely limited to severe exacerbations (Wagner et al. 1996), which may have been less typical for our sample. Associations between systemic inflammation markers (such as C-reactive protein and IL-6) and structural deterioration are well documented (Gu et al. 2017; Frodl and Amico 2014), although less is known about effects of Th_2-driven inflammation more typical for young individuals with asthma. Recently, associations have been shown between eotaxin-1, a chemokine marker of eosinophilic inflammation that can cross the blood brain barrier, and brain neurodegeneration (Huber et al. 2018). Oxidative stress is elevated in asthma (Riedl and Nel 2008) and additionally in anxiety disorders (Hassan et al. 2014), making it a candidate mechanisms explaining both effects of asthma pathophysiology and psychopathology on gray matter volumes. Finally, nighttime symptoms in asthma are associated with sleep deficits and lack of sleep has been linked to brain structural deficits (Dai et al. 2018). Our exploratory analysis of ACQ items did not directly support this assumption, although patients' emotional evaluation of morning symptom ("how bad" they felt) again was negatively associated with volume of the pallidum. However, given the lack of validation of the ACQ on the individual item level, the small number of participants, and the large number of computed correlations these findings should be treated with caution and may serve to generate hypothesis for future large-scale studies.

At this point it is difficult to determining a causal sequence of events related to anxiety. It is also possible that early insults through asthma and its treatment lead to brain atrophy with the subsequent development of anxiety. Gray matter reductions in cortical and subcortical (hippocampus) structures associated with early childhood maltreatment have been related to subsequent development of anxiety (Gorka et al. 2014). On the other hand, recent anxiety treatment studies have shown reductions rather than increases in amygdala and other subcortical gray matter volumes (Hölzel et al. 2010; Månsson et al. 2017; Schienle et al. 2014), complicating causal interpretations of the relation between asthma, brain structure, and anxiety at present.

The specificity of these findings for subcortical structures we studied is unknown. Although we found differences between the examined structures, with a majority of findings involving putamen and pallidum, associations were also found to a weaker extent with thalamus and amygdala. Whether our findings are evidence for a more general reduction in gray matter volumes across brain structures remains to be demonstrated with studies casting a wider net across brain regions. Our study was restricted to selected subcortical structures that are relevant for emotional processing and we cannot rule out that additional cortical structures, linked to emotion or wide ranges of function, might show similar associations. Prefrontal areas in particular play a role in brain networks processing and modulating affect (Berkowitz

et al. 2007) and show neuronal remodeling in chronic stress (McEwen et al. 2016). We elected to restrict our focus to subcortical regions given the primary importance of these structures for the generation of affect (Panksepp 2011; Damasio and Carvalho 2013) and for practical reasons given the limited size of our study.

The specificity of our findings for asthma could also be questioned. Deficits in gray matter volumes of limbic and basal ganglia structure have been found in many other conditions, including depression (Grieve et al. 2013), schizophrenia (Kuo and Pogue-Geile 2019) and attention deficit/hyperactivity disorder (Frodl and Skokauskas 2012), the latter in particular for pallidum and putamen. It is also possible that the associations with catastrophizing of asthma and asthma attacks are reflections of the general association between subcortical gray matter volume, anxiety, and fear. However, it should be noted that in our study associations with general anxious mood were not significant for individuals with asthma. The fact that anxious responding to the distressing films was also selectively seen for the pallidum in asthma may also speak against a more generalized effect in asthma, while a more general association of limbic structure volumes (amygdala and hippocampus) with anxiety and anxious responding was seen in our control group. The observation of the specific role of the pallidum in asthma requires further examination.

Emerging research has pointed towards reductions in hippocampal gray matter volume in asthma, specifically in older patients and in men (Carlson et al. 2017). We could not confirm this finding in the present study, although our sample was much smaller and may not have been sufficiently sensitive to detect smaller differences. It is possible that more pronounced deficits could be shown in older patients and/or with greater severity through cumulative disease burden, as also suggested by the observed association with asthma duration. Our sample also had less severe asthma, with a predominance of mild persistent cases, which may have affected our ability to show volume differences.

In addition to the aforementioned limitations, our study was obviously limited by the small sample size and the focus on a younger, mostly well-controlled population of individuals with asthma. However, given the relative consistent effects observed with asthma-relevant variables and subcortical structures it is likely that findings with older and more severe patients could be even more pronounced. Since our findings are only cross-sectional, additional longitudinal brain imaging studies are needed to better determine cause and effect in the observed associations. Although our analysis prioritized subcortical areas, lack of predefined masks in a spatially normalized space (i.e. MNI/Talairach Atlas) and concerns over clear identification of anatomical boundaries of other emotion-relevant hindbrain and mid-brain areas, such as periaqueductal gray, bed nucleus of the stria terminalis, superior colliculus, nucleus tractus solitarius, or parabrachial nucleus (Damasio and Carvalho 2013; Davis 1992; Panksepp 2011), kept us from inspecting these areas, although they would certainly be important to explore in future studies. Similarly, because modulation of emotion by cortico-limbic and cortico-striatal networks is integral part of human emotion, future studies also need to expand scrutiny to cortical gray matter. Despite these limitations, our findings provide initial support for the suspicion that deficits in a range of important clinical outcomes of the asthmatic disease process are reflected in reduced gray matter volumes of

subcortical brain structures, further emphasizing the importance of optimal control of the disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Abbreviations

ACQ	Asthma Control Questionnaire
CAS	Catastrophizing of Asthma Scale
CNS	Central nervous system
FE$_{NO}$	Fractional exhaled nitric oxide
FEV$_1$	Forced expiratory volume in the 1st second
HADS	Hospital Anxiety and Depression Scale
MRI	Magnetic resonance imaging
NHLBI/NAEPP	National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program

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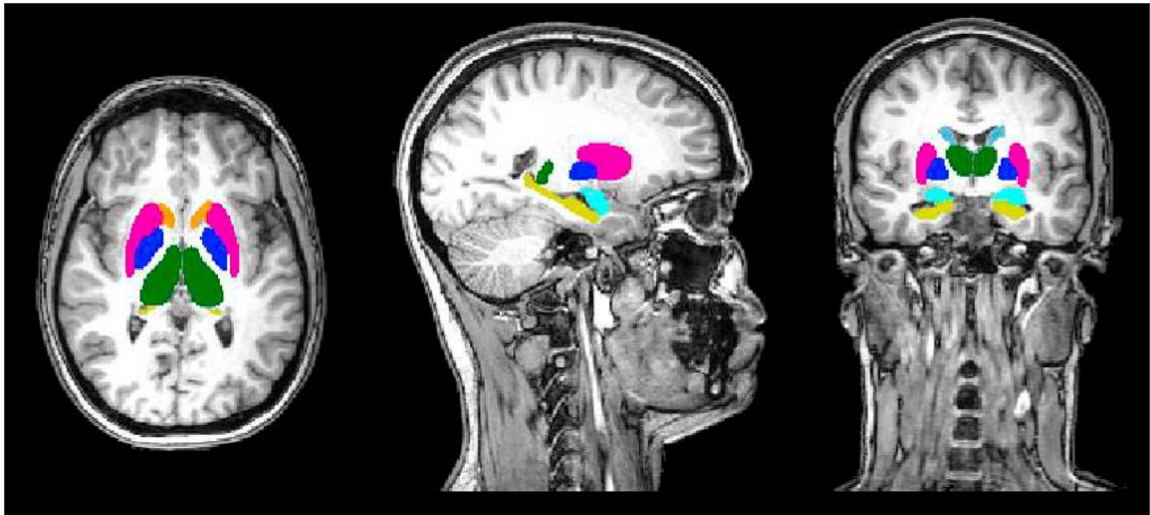
Fig. 1.
Subcortical structures analyzed for gray matter volume: pink – putamen; dark blue – pallidum; light blue – caudate nucleus; orange – nucleus accumbens; green – thalamus proper; yellow – hippocampus; teal – amygdala
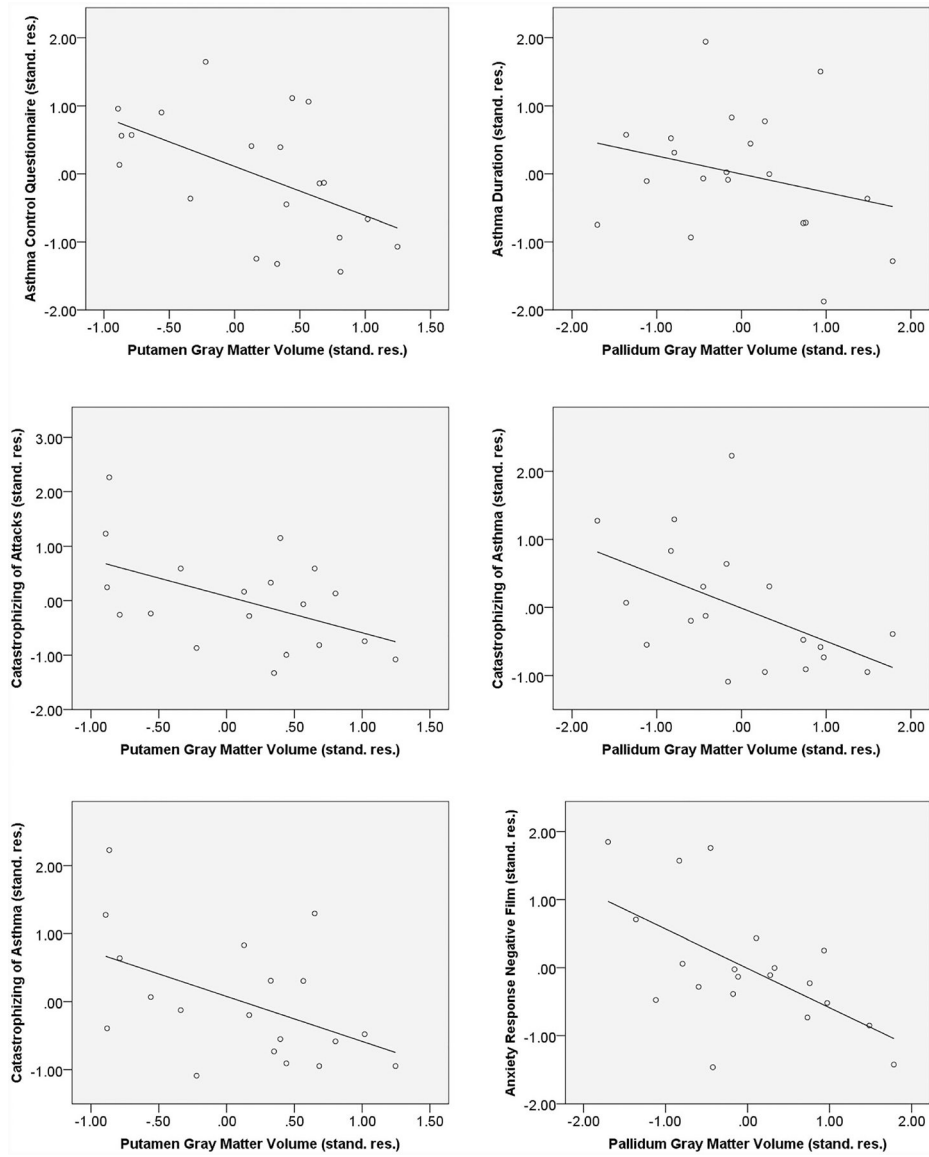
Fig. 2.
Scatter plots for selected partial correlations of putamen and pallidum gray matter volume for asthma

Table 1

Demographics for participants with asthma ($n = 20$) and healthy controls ($n = 20$)

	Asthma	Control	p
Age, M (SD)	25.3 (8.8)	25.1 (8.8)	.958
Gender, female, n (%)	10 (50.0)	10 (50.0)	1.00
Race, Non-White, n (%)	13 (59.1)	9 (40.9)	.341
Ethnicity, Hispanic n (%)[a]	4 (20.0)	4 (21.1)	1.00
BMI, M (SD)	24.5 (4.9)	26.4 (5.4)	.261
FEV_1, % of predicted, M (SD)	95.0 (10.5)	99.3 (14.5)	.280
FE_{NO}, ppb, M (SD)	51.4 (53.5)	19.5 (13.4)	.028
Asthma onset, M (SD)	8.2 (6.8)	N/A	
Asthma duration, M (SD)	17.1 (8.0)	N/A	
Asthma severity[b]			
Intermittent, n (%)	4 (22.2)	N/A	
Mild persistent, n (%)	8 (44.4)	N/A	
Moderate Persistent, n (%)	4 (22.2)	N/A	
Severe persistent, n (%)	3 (11.1)	N/A	
Asthma Control Questionnaire, M (SD)	0.99 (0.55)	N/A	
Inhaled corticosteroid use, n (%)	7 (35.0)	N/A	

Abbreviations: *BMI* body mass index, *FE_NO* fractional exhaled nitric oxide, *FEV_1* forced expiratory volume in the 1st second

[a] Missing ethnicity report for one control;

[b] according to NHLBI/NAEEP (2007), rated for those without maintenance medication or well-controlled on maintenance medication

Table 2

Comparison of subcortical gray matter volumes in percent (relative to intracranial volume) between participants with asthma and healthy controls, means (SD)

	Asthma ($n = 20$)	Control ($n = 20$)	p
Amygdala	0.16 (0.05)	0.16 (0.04)	.778
Hippocampus	0.49 (0.07)	0.46 (0.06)	.169
Caudate nucleus	0.46 (0.06)	0.46 (0.06)	.721
Putamen	0. 63 (0.05)	0. 61 (0.07)	.252
Pallidum	0.21 (0.03)	0.21 (0.02)	.731
Nucleus accumbens	0.06 (0.01)	0.06 (0.01)	.691
Thalamus	1.00 (0.06)	1.00 (0.08)	.842

Table 3

Association of subcortical gray matter volumes with asthma-related variables and anxiety response to distressing films in participants with asthma

	Amygdala	Hippocampus	Caudate N.	Putamen	Pallidum	N. accumbens	Thalamus
Asthma control (ACQ)	$-.48^†$	$-.15$	$-.22$	$-.53^*$	$-.27$	$-.22$	$-.19$
Asthma duration (yrs)	$-.46^†$	$-.08$	$.01$	$-.08$	$-.51^*$	$.28$	$-.34$
Catastrophizing of attacks (CAS-attacks)	$-.48^†$	$-.15$	$-.05$	$-.53^*$	$-.48^†$	$-.02$	$-.45^†$
Catastrophizing of asthma (lnCAS-asthma)	$-.41$	$-.12$	$-.19$	$-.52^*$	$-.52^*$	$-.22$	$-.52^*$
lnFE$_{NO}$ (ln ppb)	$-.24$	$-.17$	$-.27$	$-.18$	$-.48^†$	$-.10$	$-.06$
anxiety, relative to baseline outside scanner	$.03$	$-.01$	$-.08$	$-.05$	$-.44^†$	$-.13$	$.10$
anxiety, relative to baseline inside scanner	$-.10$	$-.28$	$-.25$	$.04$	$-.57^*$	$-.25$	$.02$

Partial rs controlling for sex, age, and inhaled corticosteroid use; note that higher ACQ values indicate lower asthma control

*
$p < .05$,

†
$p < .10$