The connection between the triple network model and locus coeruleus integrity in those exhibiting inattentive symptoms

Joshua Neal

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Tae-Ho Lee, Chair

Rosanna Breaux

John Richey

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(Abstract)

The locus coeruleus (LC) is a nucleus within the brainstem associated with physiological arousal and attention performance, with altered structure and function previously identified in neurodegenerative disorders. Pathologies related to difficulties with attention have previously been understood within a cortical triple network model, abnormalities in which may be relate to dysfunction in either LC structure or function. To examine the possibility of LC alteration being associated with inattentive symptom report, a set of analyses have been performed. In the first analysis, LC neuromelanin contrast was regressed onto ADHD symptom report for 141 individuals across the lifespan, finding a significant negative relationship between neuromelanin in the right hemisphere of the LC and inattentive symptom report. A second analysis tested for possible mediation of the neuromelanin contrasts with structural volumes of regions associated with the salience network, which has also been previously associated with attention deficits and ADHD symptoms. These findings support the relationship between LC and attention-related behavior through both neuromelanin-sensitive and structural imaging, and observes multiple significant structural associations for cortical regions previously associated to inattention functionally.

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(GENERAL AUDIENCE ABSTRACT)

Within the brainstem is a collection of neurons called the Locus Coeruleus (LC), associated with the production of neurotransmitters associated with attention. In Magnetic Resonance Imaging (MRI) networks of brain regions associated with attention have been previously observed, with both differences in region connections and abnormalities in region composition being observed. Given the small size of the LC general volume measurement is considered difficult, but use of multi-atlas techniques and neuromelanin contrasts allow for methods of LC structure and integrity to be compared. The present study attempts to integrate the LC into this larger concept of attention processing, called the triple network model, by testing associations between structural measures of the LC, regions associated with the three triple network model networks, and attention report in 140 participants. LC contrasts were found to be significantly associated with inattention, as were structural values for the regions connected to the previously identified networks. Mediation of neuromelanin by these regions failed to produce significant results, but neuromelanin was mediated by the volume of the LC itself. The findings here support continued use of these structural techniques with regard to the LC and other applicable neural structures, as well as further work to define the relationship between the LC and the triple network model.

The connection between the triple network model and locus coeruleus integrity in those exhibiting inattentive symptoms

Attention, as the cognitive-executive process of assigning mental resources to differing thoughts, concepts, memories, or stimuli at any given time, is vital to the daily function of individuals across normal activities (Carrasco, 2011). Attention deficits are found across various psychological disorders, such as autism, anxiety, schizophrenia, and dementia (Elkins et al., 2014; Gooding, 2004; Meagher et al., 2010; Polderman et al., 2013). Beyond these, attention deficit/hyperactivity disorder (ADHD) is centrally defined by such inattention, as it stands as one of the main symptom constructs for the neurodevelopmental disorder (American Psychiatric Association, 1998, 2013). Though there are findings supporting environmental influences upon the development and severity of inattention (Johnson et al., 2019; C.-Y. Liu et al., 2019; Mikami et al., 2010; Neugebauer et al., 2015), much of the literature regarding this cognitive deficit focuses on neurological abnormalities that may produce the observed behaviors and difficulties.

The neurological differences implicated in attention deficits span different neural regions and functions. Altered Serotonergic (Quist et al., 2003; Vanicek et al., 2017; Zepf et al., 2010) and Noradrenergic (Biederman & Spencer, 1999; Russell et al., 2005; Yang et al., 2013) function have been observed in individuals displaying inattentive symptoms, with abnormalities either reducing the production of the given neurotransmitter or limiting their efficiency in synaptic transmission. Medications reducing symptoms have been observed as mainly increasing the effects of these neurotransmitters within the frontal and prefrontal cortex regions (del Campo et al., 2011; Wilens, 2008). Given findings connecting subcortical regions with neurotransmitter production and signaling (e.g., (Alcaro et al., 2007; Berridge & Waterhouse, 2003; de la Cruz et

al., 2021; Teissier et al., 2015), neural models of inattention should likely seek to integrate both subcortical and cortical function.

A Common Triple Model of Psychopathology

One of the primary models of understanding psychopathology on the neural level is the use of the triple network model (Menon, 2011; Menon & Uddin, 2010). In this conceptualization, neural level abnormalities are understood in terms of the functional relationships, most often examined through correlations of activation between different regions across a time series, called functional connectivity (FC; Ogawa et al., 1993; van den Heuvel & Hulshoff Pol, 2010). In particular, the tripe network model suggests that functional connectivity patterns or dynamics between the default mode network (DMN), the fronto-parietal network (FPN), and the salience network (SAL) are important in determining the characteristics of psychopathological process.

The DMN is understood to be a collection of brain regions that are primarily activated during internally oriented cognitive process, such as abstract thoughts or memories (Raichle et al., 2001). Within the DMN, the posterior cingulate cortex (PCC) and the medial prefrontal cortex (mPFC) have been found to be associated with the presentation of ADHD symptoms, with findings suggesting either excessive intra-network hypo- or hyper connectivity is related to symptom occurrence (Franzen et al., 2013; Picon et al., 2020; Sidlauskaite et al., 2014; Uddin et al., 2008). The FPN, alternatively labeled the central executive network (CEN) to distinguish between other networks associated with the two cortices, is understood as having higher activation during the cognitive processing of external stimuli and goal-oriented actions towards an individual's environment (Seeley et al., 2007). Within the FPN, the DLPFC has been associated with attention control processing (Li et al., 2012; Pillay et al., 2016), and broader executive deficits within ADHD (Christakou et al., 2013; Kessler et al., 2014). As the previous

descriptions indicate anticorrelations of DMN and FPN connectivity have been connected to external task performance (Kelly et al., 2008; Spreng & Schacter, 2012; Zhang et al., 2019). Finally, the SAL has been associated with the perceived importance of given stimuli in the environment (Goulden et al., 2014; Seeley et al., 2007), and positive functional connectivity between the SAL and the FPN or DMN for respectively oriented tasks has been shown to positively predict performance (Elton & Gao, 2014; Liang et al., 2016; Sidlauskaite et al., 2014). Core regions of the SAL include the insula and anterior cingulate cortex (ACC), with both having been related to the early sensory gating and conflict resolution processing respectively (Kondo et al., 2004; Uddin, 2015). The SAL is understood within the triple network model as a switch of activating neural signaling between the DMN and FPN, and abnormal activation in these networks has been previously associated with the SAL (Goulden et al., 2014).

SAL signaling may best explain DMN attention dysfunction, as presently the literature directly associating DMN and its sub-regions to attention processes suffer from mixed findings. An initial meta-analysis, tracking mainly activation patterns, found support for DMN hyperactivation (Cortese et al., 2012). In terms of functional connectivity, there has been a mixture of findings, with some supporting increased FC within and between the DMN (Gracia-Tabuenca et al., 2020; Harikumar et al., 2021; Kumar et al., 2021), and some supporting a decrease in DMN FC within ADHD populations relative to normal (Sun et al., 2012; Sutcubasi et al., 2020). Meanwhile, a major recent meta-analysis found across 30 studies with 1,978 total participants a failure to identify a significant spatial hyper-connective or hypoconnective finding for individuals with ADHD (Cortese et al., 2021). One recent study did point to a dysfunctional SAL-DMN connection, via shared regions within the insula, as a possible mechanism for the attentional deficits in ADHD (Zhao et al., 2017). Notably abnormal SAL structure and function

have been associated with increased impulsivity, an additional symptom domain within ADHD (Grodin et al., 2017; Hong et al., 2018). Altered signaling to the DMN by another network such as the SAL may explain the inconsistent individual findings of DMN function for those with ADHD.

Establishing dysfunctions in the SAL, and their connection to inattention, may also serve to clarify previous mixed findings regarding other functional connectivity networks and their roles in inattentive dysfunctions. For one, given previously detailed dysfunctions throughout the frontal lobes of individuals with attention deficits, assigning those to the DMN, the FPN, or possibly both remains a conflict to be resolved. Task-related FC for the SAL and FPN have been linked to information processing and sustained attention prior to decision making (Cai et al., 2021). Abnormal SAL signaling may be due to dysfunctions within the network itself, but may also be due to altered signaling from other regions. Given previously identified connections between attention deficits and neurotransmitter producing regions, it may be that abnormalities in one such region may be affecting the SAL, and in turn its role in switching activation of the DMN and FPN.

Inclusion of the Locus Coeruleus

One distinct possibility for altered signaling to the SAL is the locus coeruleus (LC), a brainstem nucleus understood as the main point of norepinephrine production in the brain (Nai-shin & Bloom, 1973; Nieuwenhuis et al., 2005; Redmond & Huang, 1979; Sara, 2009). While this function has been associated with broad physiological arousal in individuals, the LC has been supported as producing more specific neurological signals. Devilbiss & Waterhouse (2011) observed specific LC modulating signals to the somatosensory system in mice, while Jacobs et al. (2015) found functional connectivity between the LC and the parahippocampal gyrus to be

associated with improved memory performance. Both findings have been more directly supported through task-based fMRI (Clewett et al., 2018; Vazey et al., 2018). Lee et al. (2018) found differential effects of LC signaling for different age groups, with optimal stimuli task performance found for younger individuals exhibiting not just higher selective ROI activation, but in higher FC between the LC and FPN. In contrast older adults were found to often maintain neural arousal, but the loss of LC-FPN FC was associated with decreased ability to discriminate between salient and non-salient stimuli.

The LC is observable for alterations in structure, though due to its size instead of more traditional structural measurements such as volume, it is often assessed using a neuromelanin contrast value (Clewett et al., 2016; Sasaki et al., 2006). The unique properties of neuromelanin as normally concentrated within the region produce a significant signal intensity value during a structural MRI scan, which can then be compared to the signal intensity of another region without significant amounts of neuromelanin to estimate the integrity and function of the LC. The resulting neuromelanin contrast ratio has been associated with cognitive performance (Chowdhury et al., 2022; Clewett et al., 2016; Hämmerer et al., 2018; K. Y. Liu et al., 2020) as well as the onset and progression of neurodegenerative diseases such as Alzheimer's and Parkinson's (Olivieri et al., 2019; Putcha et al., 2023; Takahashi et al., 2015; J. Wang et al., 2018). Neuromelanin contrast has also been found to be positively associated with other structural values, such as cortical thickness, volume, and microstructure integrity (Bachman et al., 2021; Elman et al., 2022; Taniguchi et al., 2018). Asymmetries in neuromelanin sensitive regions have been previously found and connected to symptom presentation (Kuya et al., 2016; Shinde et al., 2019; Trujillo et al., 2023; J. Wang et al., 2018). This is paralleled by functional lateralization in intrinsic cortical networks (Agcaoglu et al., 2022; Markett et al., 2014). Studies

to date have utilized neuromelanin contrasts in older adult and neurodegenerative populations, where in vivo use of the contrasts can be compared to and validated by post-mortem examination (Keren et al., 2015; Sturrock & Rao, 1985). To date there have not been significant studies of LC neuromelanin contrast in neurodevelopmental disorders, but existing literature associates norepinephrine with ADHD and ASD (Keehn et al., 2021), suggesting neuromelanin contrasts for noradrenergic producing regions such as the LC may be associated with the occurrence of neurodevelopmental disorders.

In addition to structural alteration being associated with psychopathology, the functional connectivity of the LC may also significantly differ in the prevalence of disorders. Decreased LC functional connectivity to sensorimotor networks in ASD individuals has been associated with motor deficits and symptoms (Huang et al., 2021). In individuals who have experienced trauma LC signaling may mediate the prevalence of hyperresponsivity symptoms (Naegeli et al., 2018). Within older adults abnormal LC connectivity with the FPN has been associated with increased inattentive symptoms (Lee et al., 2018). In terms of normative patterns, LC functional connectivity has been found to exhibit a curvilinear pattern, increasing through adolescence and young adulthood, and declining as part of normal cognitive changes in older adults (Jacobs et al., 2018; Song et al., 2021). Song et al.'s study found that LC connectivity with sensory regions is high in early childhood and older adults but low with frontal regions such as frontal pole and the frontal medial cortex. The inverted curves of functional connectivity with the LC coincide with reduced attention performance for the respective age groups, indicating sensory overflow is prevalent for both (hypersensitivity) but attentional control is either underdeveloped in children, or has suffered degeneration in older adults.

Recently, studies suggested that a potential pathway for dysfunction through these regions and networks may include inconsistent/insufficient signaling between the LC and the SAL. This may operate through a form of bottom-up signaling, in which LC abnormalities would influence the SAL, which in turn limits the ability of the SAL to either activate the FPN/DMN or deactivate the opposing network in response to appropriate stimulus (Lee et al., 2020). On the other hand, a top-down model of neuro-regulation suggests that dysfunctions from cortical networks such as SAL and FPN could signal abnormally to the LC, affecting its performance (Unsworth & Robison, 2017). These two opposite models of LC-SAL direction are not even mutually exclusive, as neural circuits may seek both up and down regulation at different points (Aston-Jones & Cohen, 2005). While directionality in the relationship may be a point of continuing study, present findings support the importance of the LC-SAL connection. A further benefit such a model may have been that it may address connections to impulsivity symptoms in ADHD, by virtue of the SAL's connections to impulse control. The SAL, through both structural deficits (Galandra et al., 2018; Grodin et al., 2017) and limited between-network connectivity (Hobkirk et al., 2019; Navalpotro-Gomez et al., 2020) has been associated with increased impulsivity. Parsimonious models of dysfunction within those with ADHD could benefit from the network's association with multiple symptom clusters.

The distinct possibility that LC signaling dysfunctions may be responsible for cortical network abnormalities is compelling due to potentially resolving conflicting findings and by providing a common origin across several disorders. Though the evidence for a signaling pathway from the LC through the SAL and into frontal networks for attentional processes is compelling, it should be noted that alternative models of attention exist, such as those considering feedback. Unsworth and Robinson (2017) posited a model including the LC-NA

system with specific signaling connectivity to cortical networks, but with frontal networks performing positive feedback signaling through the SAL to the LC. At the same time, findings such as DMN-FPN anti-correlation being positively associated with cognitive performance (Keller et al., 2015) and regulated LC-NA signaling associated with optimal function (Aston-Jones & Cohen, 2005) suggest each network or region is vital to the overall neural performance of this potential pathway. In such a way abnormalities in the function of one network may be causative of a plurality of neural attention deficits, but not comprehensive. The possibility of heterogeneous dysfunctions within an attention networking model would appear supported by the diversity of symptom presentations in the disorder itself.

One additional aspect of a mechanistic neural model worth exploring is a possible identification of structural abnormalities related to the function of previously identified neural regions. Though frequently studied as separate modalities, structural variances have been previously associated with functional connectivity, including large-scale networks and relations to psychopathology (de Kwaasteniet et al., 2013; Greicius et al., 2009; Korponay et al., 2017; Marstaller et al., 2015). A recent study observed functional relationships between the LC, cortical networks, and attention performance (Neal et al., 2023). More specifically, the findings there included significant positive associations between the LC functional connectivity to SAL regions (including insula and dorsal ACC) and attention performance. The same analyses also observed an association between SAL functional connectivity to the right DLPFC and attention performance, further supporting previous lateralized network findings. Given previous work establishing connectivity between the LC and cortical network regions relating to attention, evaluating the possibility of structural differences that may underlie or augment connectivity differences would assist in a more holistic model.

As such, the proposed study seeks to further evaluate the potential of LC abnormalities being related to the presence of inattentive symptoms. The overall aim is to examine the present gaps in the literature regarding both the relationship between current neural effects associated with reported attention difficulties and sites of neurotransmitter production, as well as examine the possibility that neuromelanin contrast variability may explain pathology beyond neurodegenerative conditions. I propose to investigate the potential relationship of the LC to this psychopathology through both the structural measure of neuromelanin contrast, as well as through volumetric relationships with regions associated with neural networks such as the SAL.

Goal and Hypothesis

The present study conducted multiple analyses with structural and neuromelanin brain images based on a typically developed (TD) population. Consistent with the study aims, I proposed the following hypotheses:

1. Lower neuromelanin contrast of LC predicts higher inattentive symptom report
2. Cortical volumes will predict for higher inattentive symptom report
3. Cortical ROI volumes will mediate the relation between LC contrast and inattentive symptom report

Method

Participant characteristics

The 141 healthy participants were recruited and scanned as part of larger AND Lab projects (M_{age} = 25.04; *SD* = 13.53; range = 8 - 54; female = 51.77%; see Table 1 for demographic information). All participants had normal or corrected-to-normal vision and

hearing, and self-reported no history of chronic illness or cognitive impairment. 19 participants reported use of prescription medication at time of scan. All participants provided written informed consent approved by Virginia Tech Institutional Review Board.

Table 1. *Descriptive statistics of age, sex, and race for the study population*

Variable	Age (in years)	Sex	Race/ethnicity
Mean (M)	25.04		
SD	13.53		
Range	8-54		
Male		68 (48.23%)	
Female		73 (51.77%)	
White			98 (68.09%)
Black			3 (2.13%)
Asian			36 (25.53%)
Other			4 (2.84%)

MRI data acquisition

To examine the relationship between LC and attention deficits, T1w/T2w structural images and neuromelanin-sensitivity structural image were collected with 3T Siemens MRI scanners at the FBRI Biomedical Research Institute (FBRI) and the Virginia Tech Corporate Research Center (VTCRC). One neuromelanin-sensitive-weighted MRI scan was collected using a T1-weighted FSE imaging sequence (repetition time = 750 ms, echo time = 12 ms, flip angle = 120°, 1 average to increase signal-to-noise ratio (SNR), 11 axial slices, field of view = 220 mm,

bandwidth = 285 Hz/Px, slice thickness = 2.5 mm, in-plane resolution = 0.43 × 0.43 mm). We also collected a high-resolution anatomical image for each participant (T1-weighted image: repetition time = 3200 ms, echo time = 2.06 ms, flip angle = 8°, bandwidth = 220 Hz/Px, voxel resolution = 1 mm^3 isotropic; T2-weighted image: repetition time = 2,500 ms, echo time =56 ms, flip angle = 120°, bandwidth = 725 Hz/Px, voxel resolution = 1 mm^3 isotropic).

Attention Measurements

BAARS IV The Barkley Adult ADHD Rating Scale IV (BAARS-IV) is a self-report rating scale consisting of 18 items corresponding to the nine symptoms of inattention and hyperactivity/impulsivity associated with ADHD (Barkley, 2011). The overall present report value, as well as the subscales, have been found to have high internal consistency (Cronbach's alpha for current total score =.914, inattention =.902, hyperactivity=.776, impulsivity=.807), and test-retest reliability (current total score =.75, current inattention = .66, current hyperactivity =.72, current impulsivity =.76), as well as inter-rater reliability (Barkley et al., 2011). For the present sample high internal consitency was also found (Cronbach's alpha for current total score =.903, inattention =.893, hyperactivity=.724, impulsivity=.821). Each item is evaluated using a 4 item Likert scale, requesting response to each item reflecting the occurrence of the item behavior within the past six months. Responses of 3 or 4 were considered indicative of positive report for the associated ADHD symptom.

Vanderbilt Parental Rating Scale The Vanderbilt Parental Rating Scale is a parental report rating scale for behaviors consistent with DSM symptoms for ADHD (Wolraich, 2003). Report consists of 18 items responded to on a 4 item Likert scale, where responses of 3 or 4 were considered indicative of positive report of the associated ADHD symptom within the past six months. Parental report through the measure has previously demonstrated high internal

consistency (Cronbach's alpha for total score =.93), and concurrent validity (r=.79 for parental report total score with structured interview; (Wolraich, 2003). Participants aged 18 years and older completed the BAARS-IV. For children and adolescents 8-17 a parent completed the Vanderbilt Parental Rating Scale.

Neuromelanin contrast ratio analysis

Neuromelanin contrast was manually collected based on previously established methods (Clewett et al., 2016). For each individual, a T1 FSE image, previously pre-processed and registered to a standard space, was opened within FSLeyes (Jenkinson et al., 2012). Within the axial viewpoint (see figure 1) the inferior colliculus was identified, then roughly two slices inferior the left and right hemisphere LC regions were found, establishing a 3x3 voxel cross surrounding the peak intensity voxel for each LC hemisphere. A 10x10 voxel sample from the dorsal pontine tegmentum, defined as six voxels anterior to the LC crosses and equidistant between them was collected as the reference region for calculating the contrast ratio. An additional set of LC region samples was established one voxel slice inferior to the initial LC region samples. Neuromelanin contrast ratios are to be calculated for each hemisphere of the LC on the respective axial slices (see equation 1) in addition to a bilateral neuromelanin value. Hemispheric contrasts were also used in a calculation of neuromelanin contrast asymmetry (see equation 2).

$$\frac{LC_{Hemisphere} - PT}{PT} \quad \text{(equation 1)}$$

$$\frac{LC_{Left} - LC_{Right}}{PT} \quad \text{(equation 2)}$$

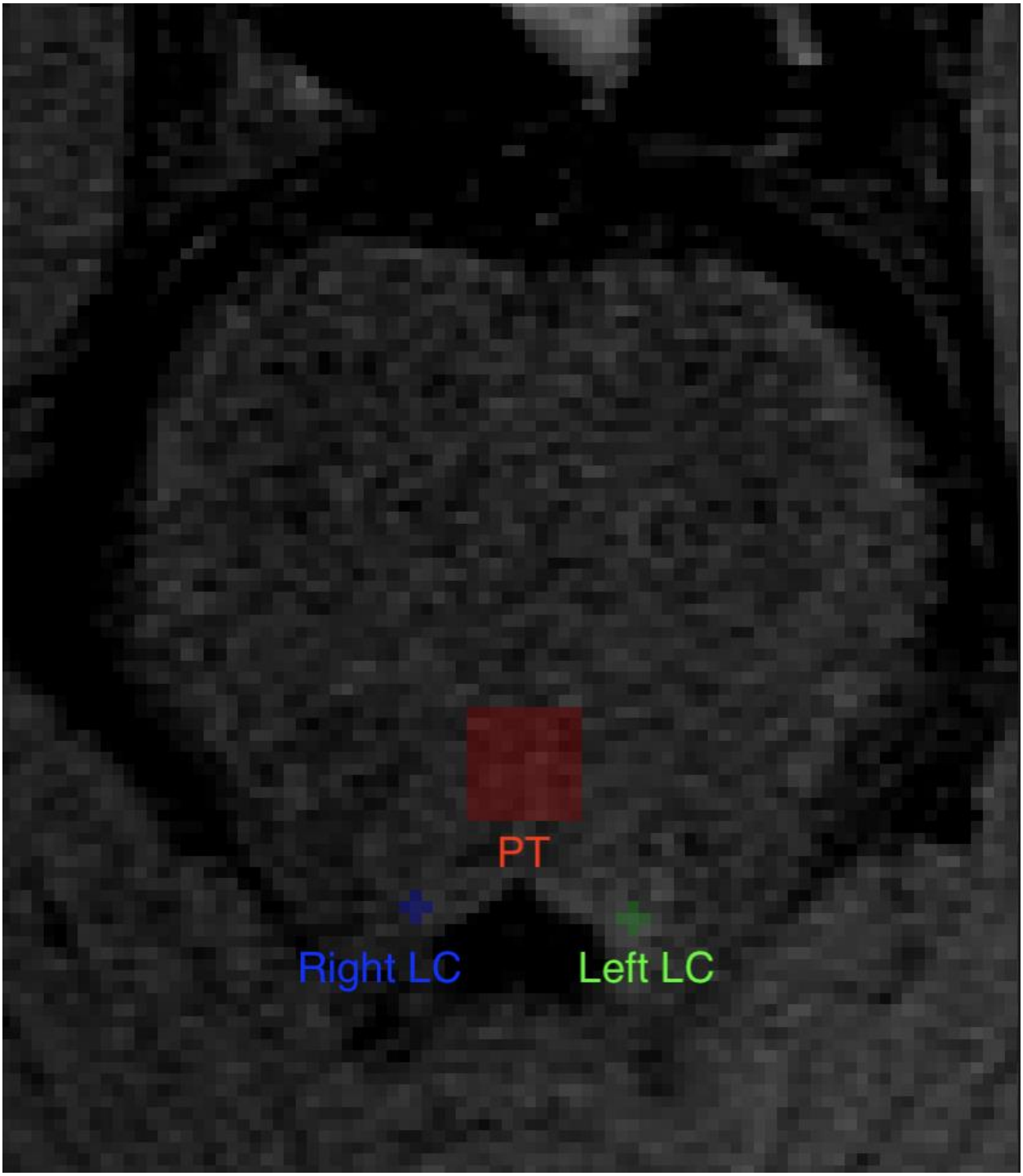

Figure 1. *Axial view of neuromelanin-sensitive MRI image and contrast masks for the left and right Locus Coeruleus, as well as the reference Pontine Tegmentum section*

Automatic atlas-based volume estimation

LC volumes: Quantification of the LC volume was achieved through the integration of neuromelanin-enhanced contrasts delineated manually and the implementation of automated contrast delineation masks. Automated LC segmentation was facilitated by the employment of multi-atlas approaches (Edlow et al., 2012; Keren et al., 2009; Liebe et al., 2020; Tona et al., 2017; Ye et al., 2021), succeeded by the application of a majority vote scheme across the warped LC annotations. To maintain congruency between the manually delineated LC masks and the automated segmentation outputs, and to rectify any discrepancies in spatial alignment, a morphological operation of one voxel dilation followed by erosion was performed. The volume was computed by multiplying of the total number of voxels in the combined integrated label with the spatial resolution.

Triple Network Related Region of Interest Volumes: For the segmentation process, tissues were classified into whole brain white matter, gray matter, and cerebro-spinal fluid compartments. Concurrently, a regional parcellation was carried out, encompassing specialized segmentations of the subcortical structures, hippocampus, and amygdala regions. This region-specific demarcation was rigorously performed in alignment with an anatomically labeled brain region of interest (ROI) template, known as the Anatomical Automatic Labeling (AAL) atlas (Tustison et al., 2010).

For this process, a multi-modal imaging approach was adopted, integrating T1-weighted (T1w) and T2-weighted (T2w) imaging data, through the application of a multi-atlas segmentation strategy. This strategy was operationalized via the MultiSegPipeline software, an in-house, open-source platform (Cherel et al., 2015). In this process multiple atlases (18 selected single atlases) were transformed into subject space through a nonlinear transformation,

specifically utilizing a cross-correlation standard symmetric normalization (SyN) with Gauss regularization [3,0], specifically tailored for diffeomorphic image registration. Gaussian smoothing was applied to account for possible errors in atlases registration. The transformation parameters were set, comprising a series of iterations and resolution levels, detailed as 50 × 25 × 15.

Subsequently the tissue probability maps, specific to each subject, were calculated through the application of localized weighted averages to co-registered atlas segmentations, ensuring that these maps were normalized to achieve a cumulative value of 1. The probability maps for white matter, grey matter, and cerebrospinal fluid were used in conjunction with the set maximal value to generate a label for extraneous tissue. Cortical regions were estimated by combining the calculated white matter, grey matter, and cerebrospinal fluid labels with the AAL atlas. Volume estimates of the DLPFC and MPFC, as core regions within the fronto-parietal network and default mode network respectively, as well as two core regions of the SAL, the insula and anterior cingulate cortex, were selected. The adjustments for overall brain size disparities were incorporated by normalizing against the total brain volume (TBV). Study population averages for the structural estimates are listed in table 2.

Table 2. *Descriptive statistics of neuromelanin contrasts, behavioral scores, and volumes for the study population*

Variable	Mean	SD	Range
Neuromelanin Asymmetry	0.052	0.070	-.116 - .254
Left Neuromelanin	0.181	0.064	.011 - .342

Right Neuromelanin	0.129	0.059	-.088 - .341
ADHD Score	30.794	8.841	18 - 61
Inattention Subscore	16.525	5.307	9 - 34
Hyperactive/Impulsive Subscore	14.270	4.485	9 - 30
TBV	1206019.17	109072.371	999483 – 1560382
Right Insula	9975.759	1339.070	6263 – 13390
Right ACC	10701.000	2499.794	4959 – 16561
Right DLPFC	14031.417	3588.743	7047 – 23179
Right MPFC	8311.083	2100.178	3886 – 13659
LC Volume	91.296	19.187	54.928 – 148.628
Left LC Volume	45.411	12.112	20.032 – 80.130
Right LC Volume	46.184	12.453	18.740 – 83.361

Regression and Mediation analyses

LC neuromelanin contrast values were regressed separately onto both the score total for the respective behavioral report as well as the number of symptoms endorsed for each participant. For these regression calculations (3) individual age, gender, and scanner type were accounted for as covariates. Structural volume estimates of the LC, as well as cortical regions of interest, were also regressed onto the inattentive symptom report score (4).

$$\text{Behavior } (Y) = \text{Intercept} + \beta_1(\text{Contrast}) + \beta_2(\text{age}) + \beta_3(\text{sex}) + \beta_4(\text{scanner}) \quad \text{(equation 3)}$$

$$\text{Behavior (Y)} = \text{Intercept} + \beta_1(\text{Volume}) + \beta_2(\text{age}) + \beta_3(\text{sex}) + \beta_4(\text{scanner}) \quad \text{(equation 4)}$$

Finally, LC neuromelanin contrast values were placed within mediation models using the TBV adjusted cortical region volumes, and their relationship with the ADHD symptom score total for the participants. Direct and indirect effects were calculated through the Lavaan package (Rosseel, 2012). Models were adjusted by age, sex, reported medication status (0 for no prescription medication reported at time of scan, 1 for medication reported) and individual scanner used.

Results

LC Neuromelanin contrast associated with ADHD symptom scores

In examining the relationship between neuromelanin asymmetry and ADHD symptom reports, we observed significant overall models for the total ADHD symptom report and the individual subscales, as detailed in table 3. For individual predictors within models neuromelanin asymmetry was positively predictive for full ADHD symptom report model (figure 2) and the report of hyperactive/impulsive symptoms, but not individually predictive of inattentive symptoms.

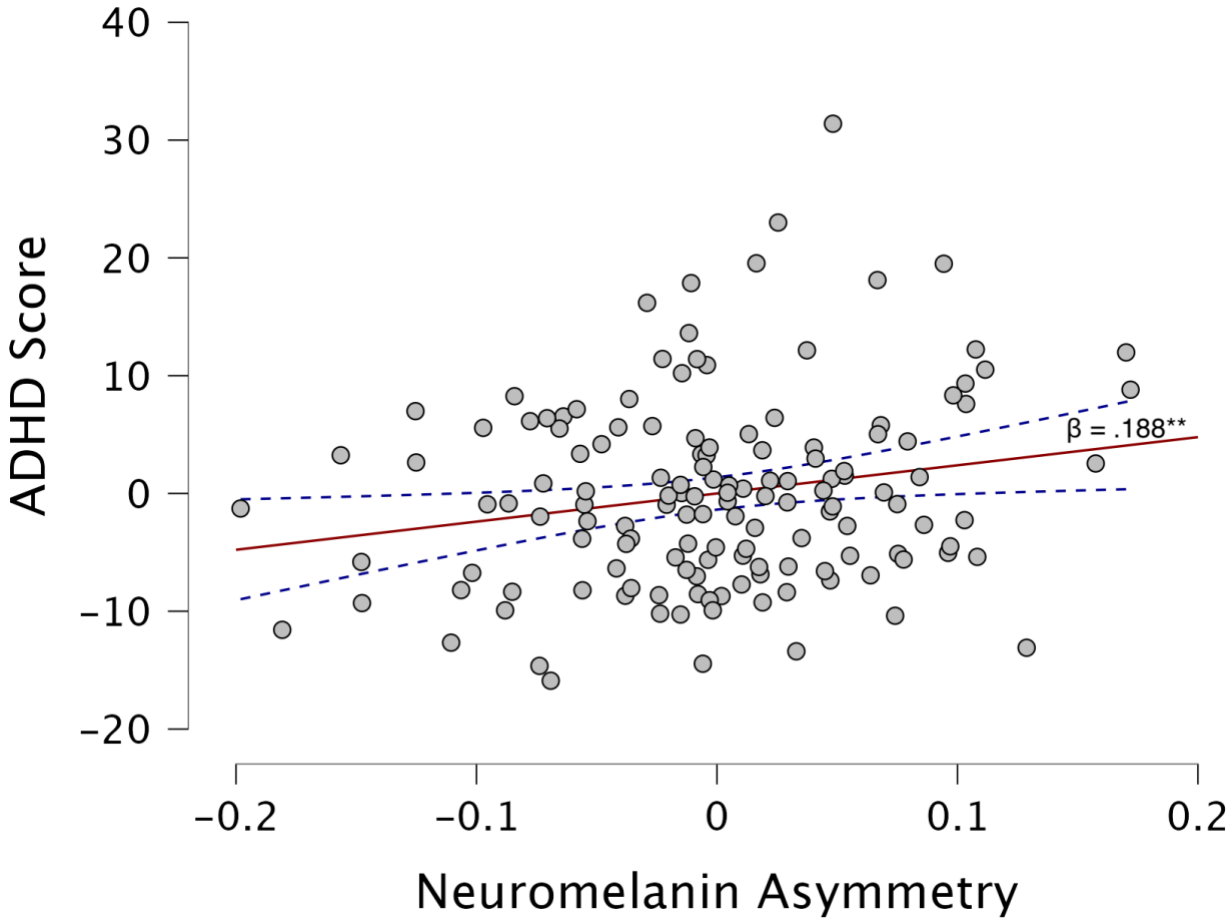

Figure 2. *Partial regression plot of neuromelanin asymmetry onto ADHD report score*

Note. The regression line for neuromelanin asymmetry onto inattentive symptom report (red) is shown across residuals, in addition to 95% confidence interval (light blue).

Table 2. *Neuromelanin contrast regressed onto ADHD symptom report scale and subscales*

Symptom Domain	R^2	F Value	Model p-value	β	Predictor p-value
ADHD	.193	6.455	<.001***	.188	.019**
Inattention	.135	4.221	.001**	.125	.127
Hyperactivity/Impulsivity	.194	6.496	<.001***	.222	.006**

*$p < .10$. **$p < .05$. ***$p < .001$

Neuromelanin Contrast by hemisphere associated with inattention symptoms

Within regressions specifically modeling the relationship of neuromelanin in each hemisphere of the LC to inattentive symptoms (table 3), the left LC neuromelanin contrast fails to produce a significant model overall or individually predict inattentive symptoms. The right LC neuromelanin contrast demonstrates both in figure 3, with increased neuromelanin in the right LC negatively predictive of inattentive symptoms.

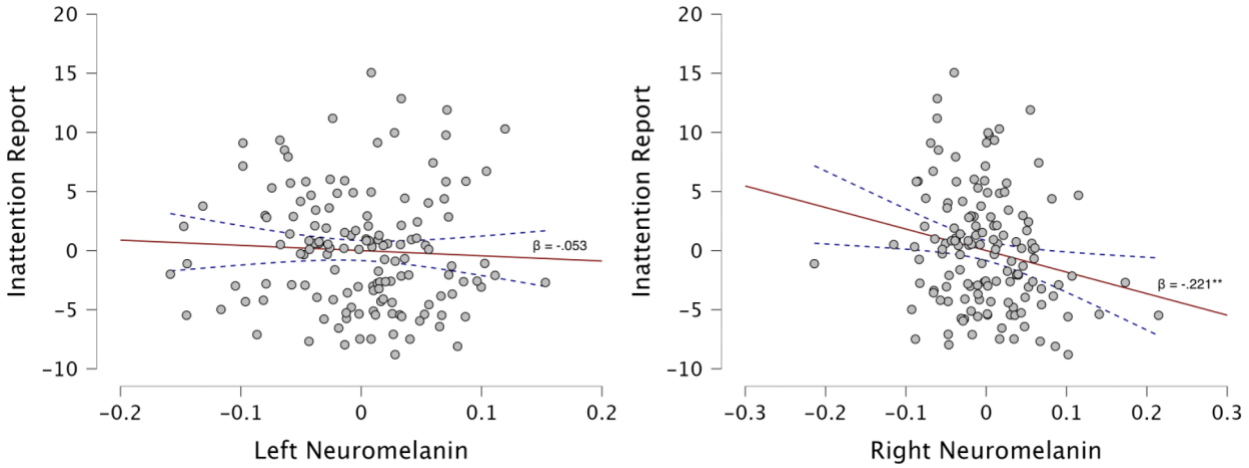

Figure 3. *Partial regression plots of neuromelanin contrast by hemisphere onto inattentive symptom report*

Table 3. *Hemispheric neuromelanin contrast regressed onto inattentive symptom report*

Hemisphere Contrast	R^2	F Value	Model p-value	β	Predictor p-value
Left LC Contrast	.123	3.771	.003**	-.053	.544

Right LC Contrast	.159	5.096	<.001***	-.204	.014**

*$p < .10$. **$p < .05$. ***$p < .001$

Volumetric estimates and their relationship to inattention symptoms

In examining structural volumes of major regions within triple network models, significant relations between the right hemispheres of these regions and inattentive symptoms were observed. Larger size of the right MPFC and right DLPFC independently predicted increased inattentive symptom report, while right ACC volume size was negatively predictive of inattentive symptoms. Increased LC volume estimates were observed to positively predict for inattentive symptoms, and when testing for LC volumetric asymmetry larger left LC volumes were negatively predictive for inattentive symptoms. Individual LC hemisphere volumes partially replicated the neuromelanin contrast findings, failing for the left LC volumes to be predictive while larger right LC volumes were positively predictive of inattentive symptom report, as seen in figure 4.

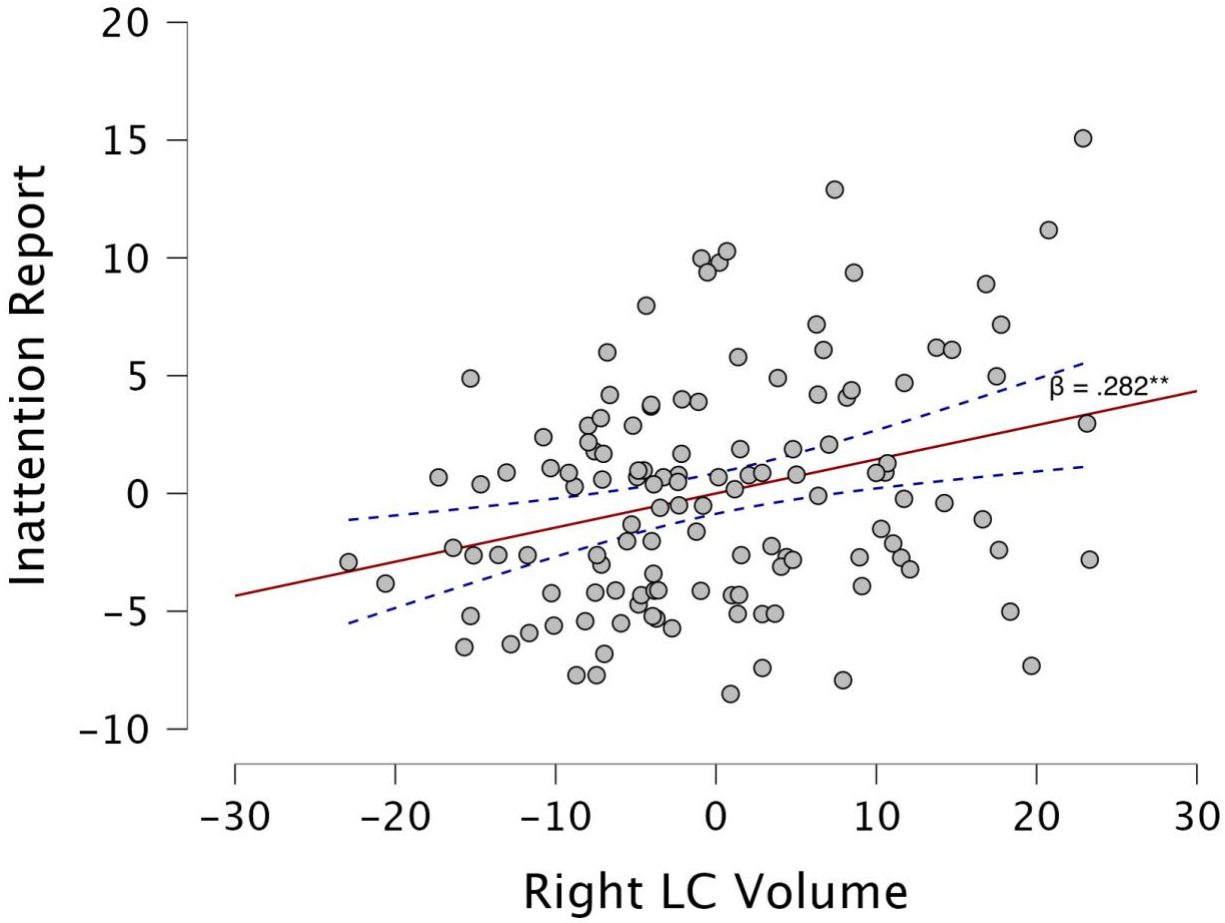

Figure 4. *Partial regression of right LC volume onto inattentive symptom report*

Table 4. *Cortical and LC volumes regressed onto inattentive symptom report*

Region Volume	R^2	F Value	Model p-value	β	Predictor p-value
RDLPFC	.181	5.572	<.001***	.234	.005**
RMPFC	.183	5.639	<.001***	.242	.004**
Right Insula	.132	3.879	.003**	-.070	.448
Right ACC	.159	4.802	<.001***	-.177	.034**
LC Bilateral	.180	5.356	<.001***	.226	.008**

LC Volume Asymmetry	.160	4.594	<.001***	-.171	.044**
Left LC Volume	.134	3.753	.003**	.059	.487
Right LC Volume	.207	6.314	<.001***	.282	<.001***

*$p < .10$. **$p < .05$. ***$p < .001$

LC and Cortical volume mediation interactions

The triple network model regions of interest established previously as having significant relations to inattentive symptom report were tested for possible mediation between the right LC neuromelanin contrast and inattention symptoms. Right MPFC, right DLPFC, and right ACC each failed to produce any significant mediation of the relation between right LC neuromelanin (RN in table 5) and inattentive symptoms. When examining LC volume for potential mediation of the right neuromelanin contrast's relation to inattentive symptoms significant mediation was found, as shown in figure 5. Finally, in exploratory analyses to examine for a possible alternative mediation path through right LC volume, right MPFC was found to have a marginally mediated indirect effect (figure 6).

Table 5. *Mediation models pertaining to neuromelanin contrasts and inattentive symptom report*

Model	Effect	β	S.E.	p-value
RN-RMPFC-IN	Indirect effect	-.013	.022	.558
	Total effect	-.204	.080	.011**
RN-RDLPFC-IN	Indirect effect	-.006	.021	.795
	Total effect	-.204	.080	.011**
RN-RACC-IN	Indirect effect	.002	.017	.902

	Total effect	-.204	.080	.011**
RN-LC-IN	Indirect effect	-.064	.031	.035**
	Total effect	-.204	.080	.011**
RMPFC-RLC-	Indirect effect	.053	.028	.058*
IN	Total effect	.251	.084	.003**

*$p < .10$. **$p < .05$. ***$p < .001$

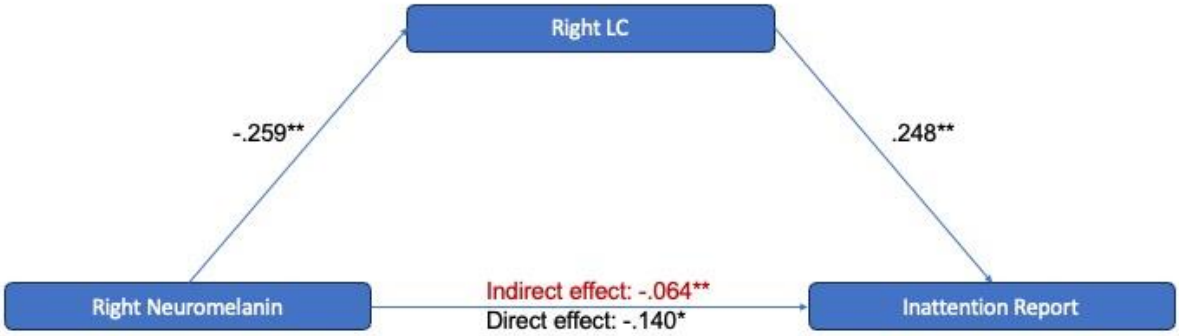

Figure 5. *Mediation model of right neuromelanin contrast, Right LC Volume, and Inattention Report (*p < .10. **p < .05)*

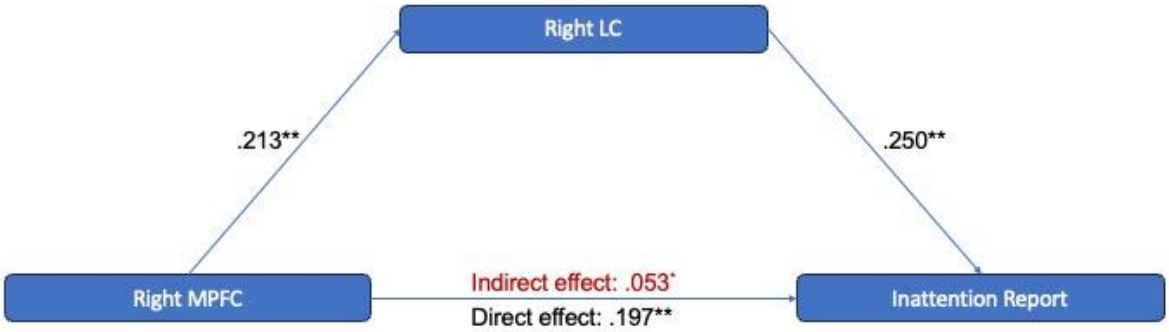

Figure 6. *Mediation model of right MPFC, Right LC Volume, and Inattention Report (*p < .10. **p < .05)*

Discussion

The present findings support a significant relation between neuromelanin and the report of inattentive symptoms within a non-clinical, non-geriatric population. This is a significant expansion for the potential use of neuromelanin imaging to investigate the relation between LC and attentional behaviors in human populations, as prior to this study there have been concerns regarding the gradual nature of neuromelanin deposit would make sensitive contrasts difficult to use beyond older adult populations.

One specific finding that stands out is the inverse relation of neuromelanin contrast to LC volume, in terms of how each predicts inattentive symptoms. Given that neuromelanin deposits are most commonly understood as a metabolic byproduct of norepinephrine production, one possible mechanistic explanation of the findings is that the density of norepinephrine-producing

neurons may itself affect the ability to either produce the neurotransmitter in sufficient quantities, or impair the ability of the locus to effectively transmit norepinephrine to cortical regions, reducing attentional performance to the point of exhibiting symptoms noticeable for report.

Another finding of the analyses worth further discussion is the extent to which LC structure and metabolic byproduct were found to be lateralized by hemisphere. Previous investigation of psychopathology and the LC have observed similar patterns (Kumano et al., 2022; Llorca-Torralba et al., 2022; Tramonti Fantozzi et al., 2021). Lateralization of differences has also been observed in cortical regions as part of pathology (Levitt et al., 2002; Lindell, 2020; Oertel et al., 2010), in addition to longstanding observations of lateralized cognitive functions (Agcaoglu et al., 2022; Desmond et al., 1995; Holland et al., 2007; Spielberg et al., 2011). Lateralized attention processing has been previously observed within the right hemisphere (Bartolomeo & Seidel Malkinson, 2019; Mengotti et al., 2020), but has been contextualized primarily within dorsal and ventral attention networks to date. Examination of right hemisphere functional connectivity within integrative networks such as the FPN or DMN may discern lateralization patterns in executive processing as part of attention. The lateralization of metabolic adjustments in the right hemisphere of the LC being associated with inattentive symptoms should be noted, as these provide insight both into cognitive connections to the LC and a more specific region of interest for possible use as a biomarker.

The findings here contribute a limited set of connections between structural measures and inattention. Cortical volume findings were found to be associated with inattention symptom report, but failed to mediate the relation between neuromelanin contrast and inattention symptom report. Both the RDLPFC and the RMPFC, as regions of the FPN and DMN respectively, demonstrated positive associations with inattentive symptom report. This is in contrast with the

right ACC, which held a negative association with such report. The larger relative size of the RDLPFC and RMPFC can be conceptualized as regions with increased numbers of neurons, and therefore an indication of higher neural activity in average function.

Taking the structural measure of these two regions as indicative of average neural activation for their representative networks, higher neural activation for the FPN and DMN being associated with inattentive symptom report would be in line with previous findings (van Rooij et al., 2015; Xuan et al., 2016). Heightened activation of the DMN or the FPN can be understood through aberrant processes of attention. (Knudsen, 2007) model of attention assigns four discrete processes: working memory, sensitivity control, competitive selection, and automatic filtering of stimuli. The DMN, as a network commonly associated with processing of abstract thoughts or memories, has activation patterns normally opposite of externalized attention tasks, such as sensitivity control and competitive selection (Buckner & Vincent, 2007). The FPN, on the other hand, has been found to be associated with central executive tasks such as top-down sensory sensitivity and selection, as well as feedback to other networks such as the SAL, itself associated with the filtering of stimuli (Fox et al., 2005). Heightened activation of the FPN, especially in the context of overactivation of the DMN, may represent executive functioning impaired by attempts to process too many stimuli, internal and external, at once (e.g., Lee et al., 2020).

FPN and DMN activation patterns are believed to be largely mediated by the SAL (Bolton et al., 2020; Elton & Gao, 2014). As such, failures in anticorrelation that result in inattentive symptom report would be expected to manifest in the form of abnormal SAL function. The present findings provide some support for this, in a negative association between the right ACC and inattentive symptom report. The insula, however, does not exhibit such a structural relationship with inattention in the analyses. This may be due to insufficient

specificity, as structural and functional differences have been observed between anterior and posterior insula (Uddin et al., 2017), with anterior predominantly connected to frontal regions. Beyond limited structural connection, the SAL's role in differential activation of other networks may place greater importance upon SAL functional connectivity, which has been previously associated with inattention (Götting et al., 2017; Lin et al., 2021).

The limited ability to model connections between either LC volume or neuromelanin and cortical networks in the context of inattention may be due to multiple factors. The small size of the LC has been known to make size estimation difficult, and therefore analyses with it may struggle to evaluate the effects of structure. As a metabolic byproduct of norepinephrine production neuromelanin may best be understood as a marker related to broad function for the LC. This may not fully capture the relation between specific neural connections of the LC to cortical networks, which may be better observed through using neuromelanin sensitive images to improve functional connectivity analysis (Mäki-Marttunen & Espeseth, 2021; Turker et al., 2021).

Beyond establishing basic associations between neuromelanin deposits and broad psychological symptoms, analyses should work to more effectively discern the implications of neuromelanin accumulation. Though a broad connection between neuromelanin deposits and norepinephrine producing neurons has been understood for some time, the precise mechanistic process still appears uncertain (Haining & Achat-Mendes, 2017; Priovoulos et al., 2020). Given that present theories as to this process are largely defined in the neurodegenerative context (Zucca et al., 2017), study of neuromelanin accumulation separately across the lifespan appears vital to properly interpret the molecule's presence in alternative contexts.

Though neuromelanin-sensitive MRI contrasts represent a substantial, if uncertain, marker of LC norepinephrine production, resting state functional connectivity can provide more direct evidence of specific neural abnormalities. These can come both by specific neural region (Huang et al., 2021), or by abnormality in signal pattern (Gong et al., 2021). In the context of feedback sensitive tasks such as selective attention, measures such as dynamic functional connectivity may represent an intrinsic LC function associable with specific cognitive actions and impairments (Damaraju et al., 2014; Fong et al., 2019; Hutchison et al., 2013). While traditionally challenged by the small size of the LC, emerging techniques such as neuromelanin contrast seeding and 7T imaging allow for improved functional connectivity analysis of the LC, such as the ability to discern differential patterns across the LC itself (Betts et al., 2017). Differential effects of LC functional connectivity have also been observed previously across the lifespan (Jacobs et al., 2018; Song et al., 2021), and expanding upon such temporal findings will further improve the context into which LC connectivity patterns are placed.

Beyond methodological refinement of neuroimaging components, future studies can and should attempt to place the observed relations here within a more robust clinical context. Previous literature regarding ADHD, a disorder of particular focus due to the centrality of neurodevelopmentally-related inattention to presentation, has observed relations between these symptoms and alterations in frontal structure or function (Almeida et al., 2010; Baving et al., 1999; Loo et al., 2009). The alterations within the frontal region in particular have been associated with deficits in executive control and attentional task performance (S. Wang et al., 2013). Thus, the degree of structural and functional alterations in the frontal region may be useful for discriminant, individual identification of those with ADHD (Cheng et al., 2012; Iannaccone et al., 2015).

The frontal cortex abnormalities are not the only observed neurological difference for attention deficits and ADHD, however. Lower levels of cortical thickness have been observed for those with the disorder (Narr et al., 2009; Silk et al., 2016). A meta-analysis of subcortical structural differences between ADHD and TD individuals found reduced volumes for those with ADHD in a number of subcortical regions, including the nucleus accumbens, amygdala, caudate, hippocampus, and putamen, as well as reduced overall intracranial volume (Hoogman et al., 2017). The functional connectivity of subcortical regions has also been identified as substantially different in those with ADHD (Costa Dias et al., 2013; Kowalczyk et al., 2022; Miller et al., 2012). Additional analysis of structural regions within a clinical population may observe a more integrated set of findings than observed presently.

ADHD also has a set of developmental theories related to neurological structure and function. One such conceptualization is the maturational delay theory, in which the core neurological dysfunction in ADHD is a set of structural and connective patterns which eventually develop, but are delayed compared to typical development. This pattern has been found in both structural and functional measure of individuals with the disorder (Shaw et al., 2007; Y. Wang et al., 2021). However, some individuals exhibit ADHD symptoms into adulthood, indicating that maturational delay is not a singular theory that explains all individuals with the disorder. For adults with continued ADHD presentation, a high degree of structural similarity with child ADHD individuals was found (Zhang-James et al., 2021), though the structural differences compared to typically developed were noted as more discriminant in children. A resting-state fMRI study noted higher functional connectivity between the DMN and limbic network as discriminant of adults with ADHD versus children with the disorder (Guo et al., 2020) suggesting that more thorough examination of the different progressions of the

disorder may also yield different relationships between abnormalities in structural regions or functional connectivity.

In addition to developmental progression, differences in functional connectivity abnormalities between ADHD presentation types (Inattentive vs Hyperactive/Impulsive vs combined) have been observed (Hart et al., 2013; Qian et al., 2019). The relation between structural differences observed in the present study may be analyzed further in the context of the additional symptom clusters. ADHD is also a highly comorbid disorder, especially with other neurodevelopmental disorders such as autism spectrum disorder (ASD). ASD-ADHD comorbidity is a particularly notable diagnosis combination, as it is estimated to represent 59% of children with ASD (Stevens et al., 2016). Expansion of a holistic cortical-subcortical neural model, either for inattention or another symptom, across pathologies may then be beneficial.

One possible method to best examine these possibilities would be a large-scale, longitudinal study examining structural and functional relationships across neurodevelopment. Extant projects, such as the ABCD study (Barch et al., 2018), provide the capacity to discern aspects of pathology such as continuous presentation from childhood or alternative mechanisms for the reported symptoms in combination with neuroimaging techniques represent an important expansion of the literature. Standardized inclusion of measures such as neuromelanin sensitive MRI in such batteries would assist in broader examination of neural relationships across pathologies and development.

The findings here progress on knowledge pertaining to cortical and subcortical substrates to inattentive symptoms, which have been suggested by previous findings within neurodegenerative structural and functional MRI. Inattentive symptom report was associated with structural values for cortical networks in addition to the LC. The absence of a concise

structural model integrating these relationships is notable, but should not be seen as undermining the important relationship between the LC and cortical networks in the context of attention.

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