No Evidence of Structural Abnormality of the Substantia Nigra in Adult Attention-Deficit/Hyperactivity Disorder: A Cross-Sectional Cohort Study

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Abstract

Background

Attention-deficit/hyperactivity disorder (ADHD) is a common neuropsychiatric disorder that has recently been associated with an increased risk of developing movement disorders such as Parkinson's disease (PD), particularly in individuals treated with psychostimulants. Abnormal expansion of the echogenic area of the substantia nigra (SN), a trait marker for PD, is also commonly found in children with ADHD, in whom this feature was attributed to maturational delay of the dopaminergic system. Here, we investigated the structural integrity of the SN in adults with ADHD and its relationship to symptomatic treatment with psychostimulants.

Methods

In this cross-sectional cohort study, we performed transcranial sonography of the SN in 30 adults (mean age 33.3 ± 7.6 years, 11 females) diagnosed with ADHD according to DSM-V criteria. The cumulative dose of methylphenidate was extrapolated based on the treating physicians' documentation and patient's reports.

Results

The mean echogenic SN area in our cohort amounted to 0.17 ± 0.04 cm² (mean ± standard deviation), which is well within the normal range of echogenic SN area according to consensus criteria and did not significantly differ from the mean echogenic SN area observed in two independent control groups previously collected at our site (all $p \geq 0.297$). Importantly, we observed no significant treatment-associated changes of SN echogenicity with respect to the extrapolated cumulative dose of methylphenidate derivates ($r=-0.261$, $p = 0.163$).

Conclusions

Our results indicate that expansion of the echogenic SN area is, unlike evidence in children with ADHD, not useful as an ADHD biomarker in adults. The current results, furthermore, challenge the view that abnormal expansion of the echogenic SN in ADHD may reflect maturational delay of the dopaminergic system, at least it does not persist into adulthood. Therefore, if there is an intrinsic link between ADHD and PD, it is not reflected by structural alterations of SN echogenicity. Importantly, we found no evidence of treatment-associated changes in structural SN integrity mitigating concerns about a possible causal relationship between therapeutic psychostimulant use in ADHD and an increased risk of PD.

Background

Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent neuropsychiatric disorder in which symptoms first appear in childhood [1]. However, many individuals with a history of ADHD in childhood continue to be affected by symptoms of the disease beyond adolescence and require ongoing

symptomatic treatment including amphetamine-type psychostimulants [2]. Interestingly, a recent large cohort study reported that individuals with ADHD are at 2.4 times increased risk for movement disorders including Parkinson's disease (PD) [3]. Moreover, the increased risk of developing PD was even six times higher in individuals with ADHD who had received psychostimulants [3]. Concerns about a possible causal relationship between the use of amphetamine-type stimulants and increased risk of PD may be supported by epidemiologic studies reporting an increased risk of PD particularly in individuals with illicit methamphetamine use [4–6].

Transcranial sonography (TCS) is a noninvasive imaging technique for detecting structural abnormalities of midbrain structures including the substantia nigra (SN). In PD, abnormal echogenic SN area expansion (SN+) is considered a trait marker that can be found in up to 90% of patients [7, 8]. In adults without PD, SN + may indicate increased vulnerability or even injury of dopaminergic neurons [9, 10]. SN + has also been noted in children with ADHD and, in this context, was interpreted as evidence of dysfunction of the dopaminergic system, possibly caused by developmental delay but unrelated to symptomatic treatment [11, 12]. However, increased prevalence of SN + in adults with methamphetamine abuse [13–15] may suggest that amphetamine-type psychostimulants could cause injury to nigral dopaminergic neurons. Here, we used TCS to investigate the structural integrity of the SN in adults with ADHD and its relationship to symptomatic treatment.

Methods

We included 30 adults with ADHD according to DSM-V criteria who were recruited from the outpatient clinic at the Department of Psychiatry and Psychotherapy at Leipzig University Medical Center between June 2019 and March 2022 (with interruptions due to the SARS-CoV-2 pandemic). Participants were screened for psychiatric co-morbidity (Structured Clinical Interview for DSM-V: clinician version, SCID-5-CV) [16, 17], completed retrospective symptom acquisition questionnaires for hyperkinetic disorders (Wender-Utah-Rating-Scale short version, WURS-K) [18, 19], Conners’ Adult ADHD Rating Scales (CAARS) [20] and the ADHD Self-Report Scale (ASRS-v1.1) [21]. Exclusion criteria encompassed history of structural brain lesions, PD and other basal ganglia or cerebellar disorders, current severe depressive, manic, or psychotic symptoms, acute suicidality, current abuse of illicit drugs and alcohol.

Transcranial sonography

In each participant, TCS (Acuson S2000, Siemens, Erlangen, Germany) was performed according to consensus criteria [7, 8] by two experienced ultrasound raters separately. The echogenic SN area in each image was determined offline by manually encircling the outline of the echogenic SN. For the purpose of internal quality control, one of the raters (P.M.) was blinded for the study objective and diagnosis of participants. To reduce intra-rater variability mean values of three assessments each of the left and right echogenic SN were entered in the analysis.

Statistical analysis

Statistical analysis was performed using SigmaPlot (Systat Software, Erkrath, Germany). We applied paired or unpaired student's t-tests for within- and between-cohort comparisons (or Mann-Whitney rank sum test in case of non-normally distributed values). Pearson correlation was used to test for linear correlations of SN echogenicity with demographic characteristics. The alpha-level was set to 0.05. Since there was no systematic error for echogenic SN assessments between the blinded and unblinded rater (right/left, average; all $p \geq 0.287$), we used the assessments of the blinded rater for final analysis.

Results

For detailed demographic information see Table 1. The mean area of right and left echogenic SN ($SN_{R/L}$) amounted to 0.17 ± 0.04 cm² (mean ± standard deviation), and was, thus, well below consensus cut-off values for moderate or marked SN+ (i.e., ≥ 0.20/≥0.25 cm^2, [7]) and the cut-off value for SN + established at our site (≥ 0.24 cm², [22]), which has also been considered by others to be optimal for distinguishing PD from controls [23]. There was no significant difference of echogenic SN expansion in terms of side (left/right, $p = 0.706$), or sex ($p = 0.697$). Furthermore, $SN_{R/L}$ was not significantly different from that of two independent healthy cohorts from previous studies at our site ([24]: n = 116, 51 female, mean age 27.4 ± 4.9, $SN_{R/L}$ 0.18 ± 0.06 cm², $p = 0.297$; [13]: n = 59, 21 female, mean age 26.9 ± 5.8, $SN_{R/L}$ 0.17 ± 0.05 cm², $p = 0.990$, Fig. 1A). Prevalence of SN+ (≥ 0.24 cm^2 on either side) in the adult ADHD cohort was 13.3% and, thus, did not deviate from the range of SN + prevalence (~ 10–20 %) in several cohots without PD [25, 9, 26, 24, 13]. Correlation analysis revealed no relevant association of $SN_{R/L}$ with cumulative intake of methylphenidate derivates ($r=-0.261$, $p = 0.163$), age ($r = 0.037$, $p = 0.847$), nor with clinical features of ADHD (all $p \geq 0.192$, except for self-reported frequency of potentially disease-related symptoms, ASRSv1.1 part B, $r = 0.414$, $p = 0.040$; see Fig. 1B-F). Participants with a history of methamphetamine abuse (n = 5) showed a numerically larger, but not significantly increased, echogenic SN area compared to participants without former methamphetamine use (0.19 ± 0.04 cm² vs. 0.17 ± 0.04 cm², $p = 0.352$).

Table 1

Clinical and demographic details of the ADHD cohort (n = 30). Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ASRS-v1.1 = ADHD Self-Report Scale v1.1; CAARS = Conners' Adult ADHD Rating Scale; DSM (-G, -IA, - HYI) = Diagnostic and Statistical Manual of Mental Disorders (-global, -inattention, -hyperactivity/impulsiveness); SD = strandard deviation; WURS-K, short version of the Wender-Utah Rating-Scale

Age in years (mean ± SD; range)	**33.3 ± 7.6; 24–57**
Sex (male/female, n)	19/11
Duration of ADHD symptoms in years (mean ± SD; range)	27.3 ± 7.8; 14–50
Interval since time of initial ADHD diagnosis in months (mean ± SD; range)	66 ± 106; 1–408
Symptomatic pharmacologic therapy for ADHD (%/n)	83.3/25 (%/n)
Duration of symptomatic pharmacologic therapy in months (mean ± SD; range)	31.8 ± 53; 0–264
Use of amphetamine derivates (methylphenidate, lisdexamfetamine; %/n)	76.6/23
Use of other stimulating agents as monotherapy (atomoxetine; %/n)	6.6/2
Amphetamine derivative dosage equivalents in mg/day (mean ± SD; range)	39.4 ± 12.8; 20–50
Cumulative dose of amphetamine derivatives in g (mean ± SD; range)	38.0 ± 64.6; 2.4–288.9
Positive illicit drug history (%/n)	60/18
Tetrahydrocannabinol use (%/n)	43.3/13
(Meth)Amphetamine use (%/n)	16.7/5
Diagnosed psychiatric comorbidity (%/n)	70/23
Diagnosed recurrent depressive disorder (%/n)	40/12
WURS-K, sum score (mean ± SD; range)	37.2 ± 14.8; 9–69
ASRS-v1.1 part A, sum score, (mean ± SD, range)	16.8 ± 2.1; 13–21
ASRS-v1.1 part A, cut-off (mean ± SD; range)	4.9 ± 0.9; 3–6
ASRS-v1.1 part B, sum score (mean ± SD; range)	31.4 ± 4.8; 23–41
ASRS-v1.1 part B, cut-off (mean ± SD; range)	8.8 ± 2.0; 5–12
CAARS, total score (mean ± SD; range)	117.9 ± 18.7; 84–162
DSM-G, T-score (mean ± SD; range)	78.6 ± 8.0; 61–90
DSM-IA, T-score (mean ± SD; range)	82.8 ± 6.8; 64–90
DSM-HYI, T-score (mean ± SD; range)	66.4 ± 11.7; 64–90
ADHD-index, T-score (mean ± SD; range)	77.7 ± 7.7; 65–90

Discussion

The current study showed that structural integrity of the SN, as assessed by TCS, was intact in adults with ADHD. This contrasts with previous findings in children with ADHD, in whom a markedly enlarged echogenic SN area was reported and discussed as a potential biomarker for dysfunction of the dopaminergic system [12, 11]. Specifically, the observation of a physiological postnatal *decrease* of the echogenic SN area across the first decade of life[27] led to the interpretation that SN + in children with ADHD may be related to maturational delay of the dopaminergic system [12]. However, others [25] reported an almost linear *increase* in echogenic SN area across infancy to adulthood. Given these contradictory observations, it is uncertain whether the hypothesis that SN + in children with ADHD is linked to developmental delay can be sustained. Our current results suggest that if SN + in ADHD was indicative of a maturational delay of the dopaminergic system, it does not persist into adulthood despite ongoing symptoms. This is compatible with studies that question dopamine dysregulation as the primary cause for ongoing ADHD symptoms in adults [28]. The persisting efficacy of amphetamine-type stimulants in adult ADHD, on the other hand, suggests that dysfunction of the dopaminergic system continues to be clinically relevant. Therefore, if there is dysfunction within the dopaminergic system in adult ADHD, it is not driven or reflected by structural alterations of the SN (at least none that can be detected with TCS).

In adults, SN + is by far most closely associated with PD, in which this trait is present in some 90% of patients [7]. However, SN + can also be found in at least 10% of individuals without PD and may signal increased vulnerability or even injury of dopaminergic neurons [29, 10]. Increased prevalence of SN + in cohorts without Parkinsonian motor symptoms but non-motor prodromal PD symptoms [30–32] appear to suggest that SN + represents a risk marker of PD. If SN + was indicative of an increased PD risk in ADHD and considering the association of ADHD and PD observed in a recent study [3], one would expect an increased frequency of SN + in adults with ADHD as well. However, in addition to the normal average echogenic SN extension, the prevalence of SN + in our ADHD cohort fell well within the range observed in healthy controls [24, 13, 26, 9, 25]. Thus, if there is a pathophysiologic link between ADHD and PD, it is not reflected by alterations of the echogenic SN. However, given our relatively young cohort this does not exclude development of echogenic SN alterations in the future.

Reports of an increased frequency of SN + in individuals with methamphetamine abuse [13–15], who were found to be at increased PD risk [4–6], and the observation of a potential methamphetamine dose-dependent expansion of the echogenic SN [13] suggests that the echogenic SN may be sensitive to alterations induced by amphetamine-type stimulants. Here, we showed that the expansion of the echogenic SN in adults with ADHD was not associated with the cumulative intake of amphetamine derivates. Again, if there is an intrinsic association between ADHD and PD, the current results do not suggest that this association is related to, or even caused by, psychostimulant-induced injury of SN neurons. Of note, none of our participants received symptomatic treatment with methamphetamine (not approved in Germany). However, consistent with previous research [13–15], we found a numerically (however not statistically significant) larger echogenic SN expansion in participants with former

methamphetamine abuse which supports that illicit methamphetamine use may induce injury to SN neurons.

Conclusion

In conclusion, our results show that the expansion of the echogenic SN area is, unlike evidence in children with ADHD, not useful as an ADHD biomarker in adults. Moreover, the current results challenge the view that SN + in ADHD may reflect maturational delay of the dopaminergic system, at least it does not persist into adulthood. Our results further suggest, that if there is an intrinsic link between ADHD and PD, it is not reflected by structural alterations of the SN as assessed by TCS. Importantly, we found no evidence of treatment-associated changes in structural SN integrity that would link therapeutic use of psychostimulants to increased PD risk in ADHD.

Abbreviations

ADHD Attention-deficit/hyperactivity disorder

ASRS-v1.1 Attention-deficit/hyperactivity disorder Self-Report Scale

CAARS Conners' Adult ADHD Rating Scales

DSM-V Diagnostic and Statistical Manual of Mental Disorders No. 5

PD Parkinson's disease

SARS-CoV 2 Severe acute respiratory syndrome coronavirus type 2

SCID-5-CV Structured Clinical Interview for DSM-V: clinician version

SN Substantia nigra

SN + Enlarged echogenic area of substantia nigra

$SN_{R/L}$ Right/left substantia nigra

TCS Transcranial sonography

WURS-K Wender-Utah-Rating-Scale short version

Declarations

Ethics approval and consent to participate

The study was approved by the local ethics committee of the University and the Medical Faculty of Leipzig (Reg. no.: 048/19-ek) in accordance with the 1964 Declaration of Helsinki and its later

amendments. All participants provided written informed consent before any study-related procedures.

Consent for publication

Not applicable.

Availability of data and materials

Data privacy statements signed by all subjects protect personal data. The data will be made available upon specific request taking into account the opinion of the local data privacy board.

The datasets used and analysed during the current study are available from the sorresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests – neither financial nor non-financial.

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Author's contributions

JJR, MS and DK designed and conceptualized the study. DW screened and recruited the participants of the study. IF and DK performed the neurologic clinical examinations. IF and PM performed the transcranial sonography. NM and JH screened for psychiatric comorbidities and collected the psychiatric scores. IF, MS and JJR analysed and interpreted the data. IF wrote the first draft of manuscript. All authors read, revised and approved the final manuscript.

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Figures

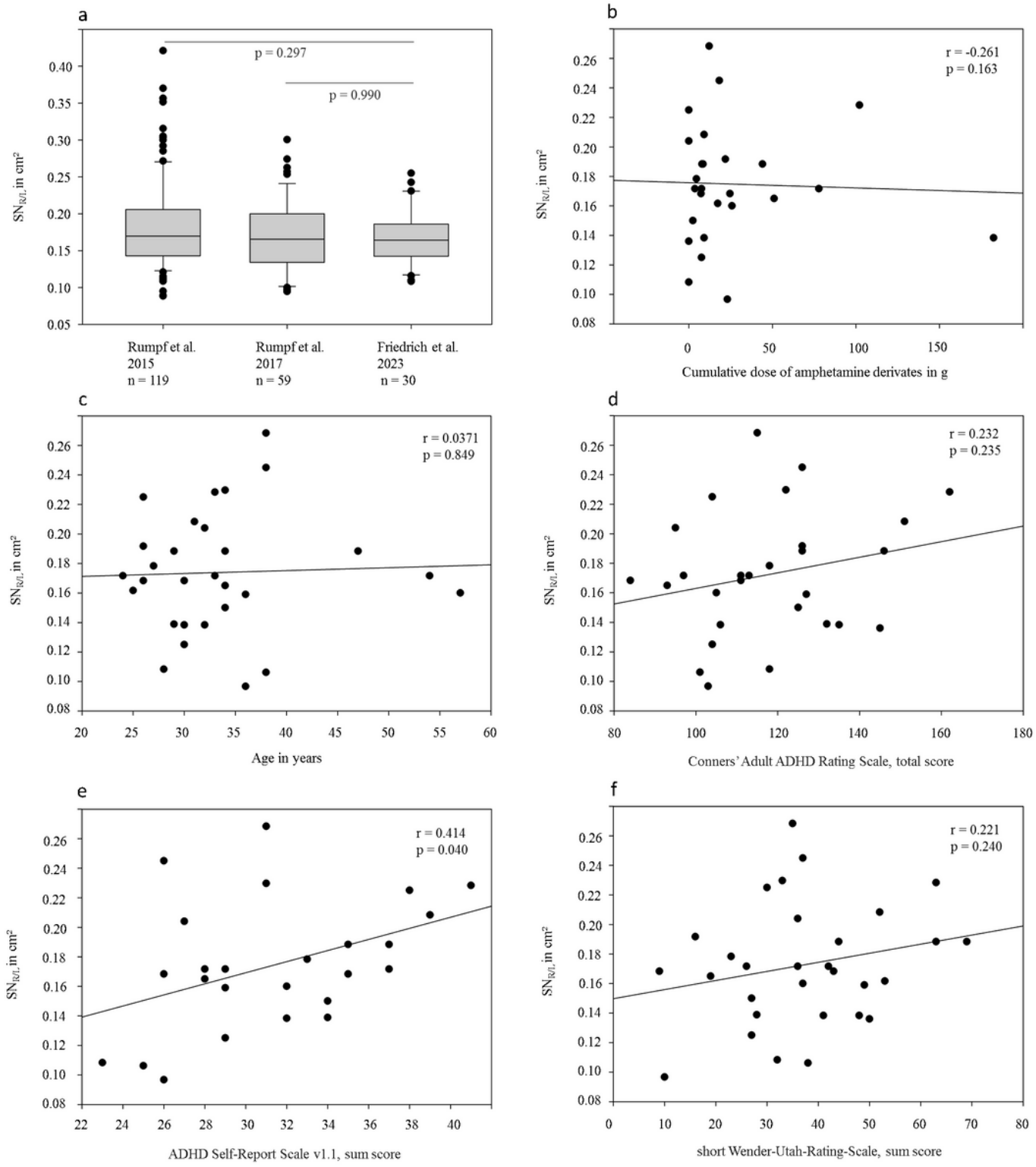

Figure 1

Representation and association of the size of the echogenic SN with selected demographic and clinical variables. (*a*) Average echogenic SN area ($SN_{R/L}$) of the current ADHD cohort compared to independently recruited healthy (control) cohorts from previous studies at our side ([23, 13]). (*b*)-(*f*): $SN_{R/L}$ area shown as a function of (*b*) the approximated cumulative dose of methylphenidate derivates, (*c*) age, (*d*) scores in

Conners' Adult ADHD Rating Scale, (*e*) scores in ADHD Self-Report Scale v1.1 part B and (*f*) scores in Wender-Utah-Rating-Scale (short version)