Structural Abnormality of Substantia Nigra Induced by Methamphetamine Abuse

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ABSTRACT

Background: Methamphetamine abuse has been linked to an increased risk of Parkinson's disease.

Objective: The objective of this study was to investigate structural abnormality of the substantia nigra in past methamphetamine users using transcranial sonography.

Methods: In a cross-sectional, observational study, echogenicity of the substantia nigra was assessed in 59 past methamphetamine users and 59 matched controls. The frequencies of an abnormal spatial extension of the substantia nigra as well as the average sizes of left and right substantia nigra were evaluated.

Results: The average echogenic size of the substantia nigra was larger in methamphetamine users ($0.22 \pm 0.06\,cm^2$) when compared with controls ($0.17 \pm 0.05\,cm^2$, $P<.001$). Furthermore, the frequency of enlarged, echogenic substantia nigra was increased in methamphetamine users (42% vs 12% in controls, $P<.001$). Partial correlation analysis revealed an association of echogenic substantia nigra size with estimated total lifetime intake of methamphetamine ($r_{55} = 0.395$, $P = .002$).

Conclusions: Current data link methamphetamine abuse in humans to injury of substantia nigra neurons and an increased risk of Parkinson's disease. © 2017 International Parkinson and Movement Disorder Society

Key Words: transcranial sonography; methamphetamine; substantia nigra hyperechogenicity

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Abuse of the psychostimulant methamphetamine has increased dramatically during recent years to develop into a worldwide epidemic. From 2009 to 2014, the amount of confiscated methamphetamine increased from 34 to 108 tons worldwide, which illustrates the rapid expansion of the global methamphetamine market.[1] Upon uptake, methamphetamine promotes the excess release of dopamine from dopaminergic neurons in the substantia nigra (SN) to the striatum.[2] Chronic methamphetamine abuse in humans, however, appears to result in a lasting striatal dopaminergic deficit.[3-8] Several epidemiologic studies suggest that Parkinson's disease (PD) risk is increased in methamphetamine users,[9-11] raising the possibility of structural, as opposed to merely functional, methamphetamine-induced injury to dopaminergic neurons. Although the degeneration of dopaminergic neurons in the SN has not been shown in human methamphetamine users, direct evidence has been demonstrated in mice for the degeneration of dopaminergic cell bodies in the SN after methamphetamine exposure.[12] This body of evidence suggests that methamphetamines may also kill dopaminergic neurons in humans.

Transcranial sonography (TCS) is a noninvasive method to detect structural abnormalities of brain stem structures, including the SN.[13] The abnormal expansion of the echogenic area of the SN (SN+) is considered a trait marker that indicates increased vulnerability of dopaminergic neurons.[13] However, the echogenic area of the SN was also found to be sensitive to ongoing degeneration of dopaminergic neurons[14-16] and may thus be interpreted as a state marker of dopaminergic neurodegeneration. Considering the increased PD risk derived from epidemiologic studies and the evidence of methamphetamine-induced dopaminergic neurotoxicity, we aimed to investigate how echogenic SN size relates to methamphetamine abuse in humans.

Methods

The study protocol conformed to the principles of the Declaration of Helsinki and was approved by the local ethics committee of the medical faculty at the University of Leipzig (Leipzig, Germany). Written informed consent was obtained from all participants prior to inclusion in the study.

Participants

Between December 2014 and November 2015, 2 groups of participants were examined: 59 participants (57 tobacco smokers) with a history of chronic methamphetamine abuse and 59 age- and gender-matched controls (57 tobacco smokers) who had never used illicit stimulants. Participants in the methamphetamine group were recruited from outpatient and inpatient drug rehabilitation programs. As a prerequisite for participation in these programs, the participants had to be abstinent from illicit drugs and alcohol. Participants in the control

TABLE 1. Demographic information for methamphetamine users and control group

Participant characteristics	METH group, n = 59	Control group, n = 59
Age (years), mean ± SD	27.6 ± 5.3	26.9 ± 5.8
Gender, men/women	42/17	38/21
UPDRS-III score, mean ± SD	0.4 ± 1.1	0.1 ± 0.4
BDI-II score, mean ± SD	9.3 ± 6.6	6.1 ± 7.0*
History of depression, n (%)	8 (13)	1 (2)*
Tobacco smokers, n (%)	57 (97)	57 (97)
Pack years, mean ± SD	10.9 ± 7.1	5.5 ± 5.9*
History of harmful alcohol use/abuse, n (%)	24 (41)	2 (3)*
History of cannabis use, n (%)	54 (92)	15 (25)*
History of methylphenidate use, n (%)	1 (2)	–
History of drug-induced psychosis, n (%)	5 (8)	–
Current neuroleptic medication, n (%)	8 (13)	–
History of METH use, n (%)	59 (100)	–
Duration of METH use, months ± SD	93 ± 61	–
Cumulative lifetime METH intake, grams ± SD	1402 ± 1367	–
Interval since last METH use, months ± SD	15 ± 18	–
Method of intake (oral; nasal; smoking; iv), %	15; 98; 36; 2	–
History of amphetamine abuse, n (%)	2 (3)	–
History of cocaine abuse, n (%)	30 (51)	–
History of ecstasy (MDMA) abuse, n (%)	37 (63)	–
History of LSD abuse, n (%)	14 (24)	–
History of opioid abuse, n (%)	9 (15)	–
History of benzodiazepine abuse, n (%)	2 (3)	–
History of "magic mushroom" (psilocybin) abuse, n (%)	19 (32)	–
Other[a]	9 (15)	–

Group differences were assessed using one-factor analysis of variance or chi-square tests as applicable (*$P < .05$). SD = standard deviation; UPDRS-III = Unified Parkinson's disease rating scale part III (motor part); BDI = Beck Depression Inventory; METH = methamphetamine; iv = intravenous; MDMA = 3,4-methylenedioxymethamphetamine; LSD = lysergic acid diethylamide.
[a]"Other" encompasses lidocaine, ketamine, neuroleptics, gammahydroxybutyric acid, and nitrous oxide.

group were recruited from hospital staff and students of the University of Leipzig. Methamphetamine history was assessed by a questionnaire that included duration of use, form of application (oral/nasal/intravenous/smoked), and average daily/weekly/monthly doses (as applicable) to estimate lifetime methamphetamine intake. A history of other illicit drugs used (>3 times) as well as tobacco and alcohol abuse were assessed. All participants received a neurological examination, including the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS-III).[17] The participants were also screened for depression using the Beck Depression Inventory.[18]

Transcranial Sonography

TCS (Acuson Antares, Siemens, Erlangen, Germany) was performed according to consensus criteria for standardized planimetric assessment of echogenic SN area.[13] For the purpose of quality control, offline analyses of images were independently performed by both investigators (J-J.R. & J.A.) who were blinded to the identity and group affiliation of the participants. Blinding of the investigators during the assessment of TCS images was not feasible because of recruitment procedures. We found high interrater agreement for echogenic SN area as represented by intraclass correlation coefficient of 0.920 (95% confidence interval 0.896-0.938) and a Spearman rank correlation coefficient of 0.825 ($P < .001$). In case of an insufficient temporal bone window on one side (1 participant in the methamphetamine group and 1 in the control group), the echogenic SN area size of the other side was entered for statistical analysis.

Results

Detailed demographic information on methamphetamine users and control participants is shown in Table 1. The groups differed significantly because of the higher exposure in the methamphetamine group with respect to recent symptoms of depression, history of a formal diagnosis of depression, lifetime cigarette consumption, and history of harmful alcohol and cannabis use. Furthermore, the groups tended to differ with respect to parkinsonian motor symptoms, showing numerically higher UPDRS-III scores in the methamphetamine users. However, this trend was driven by only 7 participants in the methamphetamine group versus 3 control participants who showed slight abnormalities.

The average echogenic area (mean of the right and left SN, $SN_{R,L}$) amounted to $0.22 \pm 0.06\,cm^2$ in methamphetamine users versus $0.17 \pm 0.05\,cm^2$ in the control participants and differed significantly between

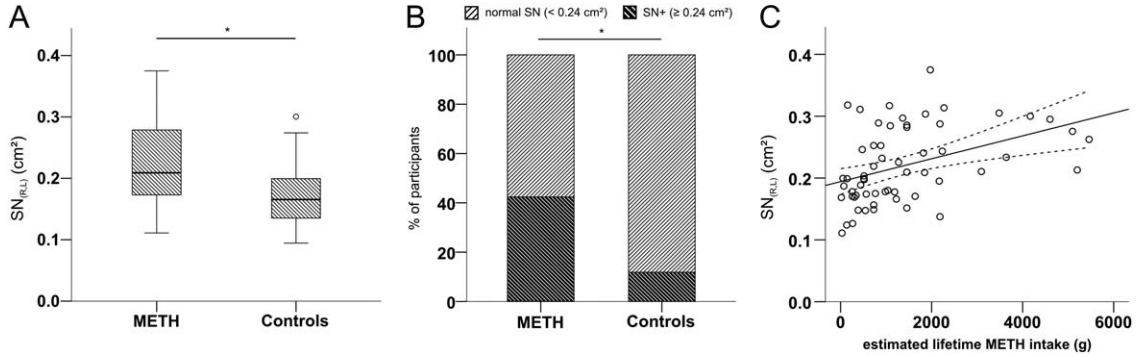

FIG. 1. (**A**) Average echogenic SN area ($SN_{R,L}$) in methamphetamine users (METH) and controls. (**B**) Frequency of normal echogenic SN area and abnormally extended echogenic SN area (SN+) in methamphetamine users and controls (*P<.05). (**C**) Correlation of estimated individual lifetime methamphetamine intake and average echogenic SN size ($SN_{R,L}$).

groups (Mann–Whitney U test: $P < .001$; Fig. 1A). With respect to the SN side (right or left), there was no significant difference of echogenic area in the methamphetamine users (Wilcoxon rank sum test, $P = .659$) nor in the controls ($P = .937$).

Individual echogenic SN area measures of both sides were dichotomized as either enlarged (SN+, $\geq 0.24\,cm^2$) or normal ($<0.24\,cm^2$) as established at our laboratory[19] and as demonstrated to optimally differentiate between PD and controls for the ultrasound machine employed.[20] Using this cut-off, the prevalence of SN + (on the right or left or on both sides) was significantly increased in methamphetamine users when compared with controls (methamphetamine users, 42%; controls, 12%; $\chi^2 = 13.892$, $P < .001$; Fig.1B).

Within the methamphetamine group, we found a significant positive correlation of $SN_{R,L}$ with the duration of methamphetamine use (Spearman $\rho = 0.343$, $P = .008$) and estimated total lifetime intake of methamphetamine ($\rho = 0.479$, $P < .001$; Fig.1C). Of note, there was no significant correlation of $SN_{R,L}$ with the interval since last methamphetamine use ($\rho = 0.125$, $P = .347$) or the UPDRS-III score ($\rho = 0.128$, $P = .166$). For all participants, $SN_{R,L}$ was also positively correlated with the factors age ($\rho = 0.257$, $P = .005$) and cigarette pack years ($\rho = 0.300$, $P = .001$). Using these factors as control variables, a partial correlation analysis revealed that correlation of estimated cumulative lifetime methamphetamine intake and $SN_{R,L}$ remained significant ($r_{55} = 0.395$, $P = .002$), whereas statistical significance of the correlation of duration of methamphetamine use and $SN_{R,L}$ was lost ($r_{55} = 0.235$, $P = 0.079$).

Discussion

This study provides evidence of a dose-dependent association between methamphetamine abuse in humans and structural alterations of the SN. A recent study[21] demonstrated an enlarged echogenic SN area in methamphetamine users when compared with nondrug, ecstasy, and cannabis users. Although our study is in line with this observation, dose dependency of alterations of SN echogenicity has potential implications for the pathogenesis of dopaminergic neuronal injury.

Although by far the strongest association of SN + is with PD,[13] SN + has been noted in several cohorts without a parkinsonian phenotype known to be at increased risk of developing PD.[22-24] Furthermore, in a prospective population-based study of participants without PD, SN + was shown to be associated with a substantially higher incidence of developing PD.[25] Therefore, the increased frequency of SN + in methamphetamine users corresponds to recent epidemiological evidence of increased PD risk in methamphetamine users.[9-11] The age of controls was matched to methamphetamine users to avoid confounding the between-group comparison by the age-dependent enlargement of echogenic SN area as found by some investigators.[26] Perhaps avoidance of age-related bias allowed us to detect the correlation between echogenic SN area and cumulative lifetime methamphetamine intake in our sample, a finding that differs from the results obtained by Todd and colleagues.[21] The correlation should only be taken to be qualitative, as cumulative methamphetamine intake was estimated retrospectively by self-report.

However, important implications arise from the finding that alterations of SN echogenicity were dose-dependent. First, because there is substantial mutual comorbidity between illicit drug abuse and attention deficit hyperactivity disorder,[27] it may be asked whether enhanced prevalence of attention deficit hyperactivity disorder in the methamphetamine group might explain enhanced prevalence of SN+.[28] This hypothesis can be refuted because it would imply independence between the amount of methamphetamine consumption and alterations of echogenic SN. Second, a dose-dependent structural abnormality in methamphetamine users may provide hints to the pathogenesis of PD. The fact that SN + clearly can be demonstrated in PD patients before they develop the motor phenotype[25] would be compatible with the alternative ideas that expansion of echogenic SN area corresponds to

either subclinical parkinsonian pathology or a state of increased nigrostriatal vulnerability that is either acquired or inherited, but in any case unrelated to parkinsonian pathology. Dose-dependent echogenicity suggests that the expansion of echogenic SN area may indeed represent an acquired structural abnormality. Although we cannot rule out that concurrent use of other illicit drugs, a limitation inevitably associated with investigations of illicit drug abusers, contributed to structural SN alterations, our evidence supports that methamphetamine has a strong potential to induce neurotoxic processes in the SN that lead to structural changes detectable by TCS.

Therefore, the question arises how methamphetamine may affect SN echogenicity. In PD, the accumulation of iron has been suggested as an important substrate of extended SN echogenicity.[29] Evidence of persisting iron accumulation was found in the SN of vervet monkeys after methamphetamine exposure.[30] However, there is no direct evidence of iron accumulation in the SN of human methamphetamine users. Another mechanism may be microglial activation (MA),[31] which was demonstrated in midbrain specimens from PD patients[32] and was related to enhanced SN echogenicity in a PD rat model[33] and postmortem PD patients.[31] MA has been repeatedly demonstrated in animals exposed to methamphetamine and may indicate an inflammatory response capable of causing neuronal damage.[34]

Although other authors did not find an association between SN echogenicity and the stage of PD,[35,36] several reports,[15,16] including results from our laboratory,[14] suggest that the echogenic SN area is also associated with the degree of dopaminergic degeneration. This would indicate that echogenic SN area is sensitive to progression of pathological changes during the course of the clinically manifest disease. A correlation with MA would be consistent with this idea because an increasing microglial response has been shown during PD progression.[37] However, contrary to the observations in the living human brain[38] and direct evidence in animal studies,[39] marked MA was unexpectedly not found in autopsy material from chronic methamphetamine users,[8,40] which leaves its connection to alterations of SN echogenicity inconclusive.

Another mechanism potentially underlying methamphetamine-induced neurotoxicity is linked to the excessive release of dopamine and inhibition of monoamine oxidase activity causing increased synaptic and intracellular dopamine levels.[2] Enhanced intracellular dopamine may then lead to oxidative stress through formation of reactive oxygen species and dopamine quinones, causing the destruction of dopaminergic SN neurons.[41,42] The release of neuromelanin from dying dopaminergic cells may also exacerbate neuroinflammatory and neurodegenerative processes by MA and the release of toxic compounds and redox-active metals, including iron.[42] However, although damage of striatal dopaminergic nerve terminals and persisting depletion of striatal dopamine has been unequivocally demonstrated in methamphetamine users,[6-8] direct evidence of the degeneration of dopaminergic neurons has not yet been demonstrated.[43]

Future longitudinal studies will likely have to combine multiple imaging modalities to be able to differentiate MA from iron deposition, gliotic scar formation, oxidative stress, and other pathological processes. If the link between consumption of methamphetamine, SN echogenicity, and specific noxious processes in the SN were strengthened by further evidence, SN sonography may guide identification and enrichment of cohorts for therapeutic trials. ■

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