Movement Disorders
CLINICAL PRACTICE
RESEARCH ARTICLE

Association Between Olfactory Impairment and Disease Severity and Duration in Parkinson's Disease

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ABSTRACT: Background: The association between olfactory dysfunction and disease duration and severity in Parkinson's disease (PD) remains controversial.

Objective: The objective of this study was to examine the relationship between olfactory dysfunction and disease severity and duration in patients with recently diagnosed parkinsonism and patients with PD with a previous diagnosis.

Methods: Olfactory function was evaluated in 79 patients with recently diagnosed parkinsonism, 71 patients with PD with a previous diagnosis—with patients in both groups free of cognitive impairment—and 128 age-matched controls. The Odor-Stick Identification Test for Japanese score was counted as the numbers of correct answers, responses of indistinguishable, and responses of odorless. Parkinsonism was evaluated using the Movement Disorder Society Criteria, the Unified Parkinson Disease Rating Scale (UPDRS) Part III, and ^{123}iodine-labeled N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl) nortropane single photon emission computed tomography (DaTscan).

Results: In the patients with recently diagnosed parkinsonism having the UPDRS Part III score ≥5 (mean [standard deviation: SD] score: 6.3 [1.9]) and with a positive DaTscan, the mean (SD) numbers of correct answers, responses of indistinguishable and responses of odorless were 4.3 (2.2), 1.6 (2.0), and 1.2 (2.2), respectively. In patients with PD with a previous diagnosis (mean [SD] UPDRS Part III score: 10.9 [3.2]), these numbers were 2.5 (2.2), 2.2 (2.5), and 3.8 (4.6), respectively. The patients with PD with a previous diagnosis showed more significant deterioration than the patients with recently diagnosed parkinsonism in the numbers of correct answers and responses of odorless ($P < 0.0001$). Olfaction in the combined patient group was significantly impaired compared with age-matched controls in each category ($P < 0.0001$).

Conclusions: These findings imply a close association between olfactory dysfunction and disease severity and duration in PD.

Olfactory testing may be a sensitive screening test for individuals at risk of developing Parkinson's disease (PD).[1,2] Olfactory dysfunction is commonly detected in patients with PD by olfactory testing and may represent one of the earliest clinical features or preclinical symptoms of PD.[3] In fact, olfactory dysfunction precedes motor symptoms in PD and rapid eye movement sleep behavior disorder.[4] Olfactory impairment is also associated with incidental Lewy body disease[5,6] and is even sometimes observed in asymptomatic first-degree relatives of patients with PD.[7] However, the association between olfactory dysfunction and disease duration and severity in PD remains controversial. In this study, we examined olfactory function in patients with recently diagnosed parkinsonism and patients with PD with a previous diagnosis to elucidate a possible correlation between olfactory dysfunction and disease severity and duration in these disorders.

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Methods

Patients

A neurological examination to detect parkinsonism was performed with a special emphasis on rest tremor and rigidity at the first visit followed by monthly check-ups for at least 1 year. In this study, parkinsonism was clinically defined as present if bradykinesia, rigidity, and rest tremor were present and the total score of Unified Parkinson Disease Rating Scale (UPDRS) Part III[8] was ≥5 based on the Criteria of the UK Brain Bank[9] and on the Movement Disorder Society (MDS) clinical diagnostic criteria for PD.[10] The tremor-dominant motor subtype was evaluated, whereas postural instability gait difficulty subtype was excluded in this study.

After confirmation of parkinsonism, a clinical diagnosis of PD was based on the MDS criteria: absolute exclusion criteria, red flags, and positive supportive criteria.[10] All patients with recently diagnosed parkinsonism (n = 79) and patients with PD with a previous diagnosis (n = 49) underwent ^{123}iodine-labeled N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl) nortropane single photon emission computed tomography (DaTscan). Magnetic resonance imaging (MRI) (1.5 Tesla) was performed to rule out cognitive impairment attributed to cerebral organic changes such as cerebral infarction and small vascular diseases (leukoaraiosis, amyloid angiopathy, lacunar infarcts, and microbleeds) and neuroimaging signs typical of corticobasal syndrome (CBS) or progressive supranuclear palsy (PSP). In addition, all patients were examined using the Mini-Mental State Examination (MMSE) and classified according to the Clinical Dementia Rating Scale and the criteria of the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.[11,12] Patients with cognitive impairment were excluded (arbitrarily defined as MMSE score ≤24 in patients aged ≤65 years, and ≤21 in patients aged >65 years, with consideration for educational attainment, which was measured as the number of years of schooling completed). Patients with other degenerative parkinsonisms such as CBS and PSP, symmetrical lower body parkinsonism, and drug-induced parkinsonism were excluded. Thus, we enrolled 79 untreated patients with recently diagnosed parkinsonism (bradykinesia, rigidity and rest tremor) having the UPDRS-III score ≥5 and with a positive DaTscan as the entry criteria for early PD, and 71

levodopa (L-dopa)-treated patients with PD with a previous diagnosis who were categorized as clinically established PD according to the MDS criteria.[10]

Brain MRI images were also analyzed to evaluate the degree of atrophy of medial temporal structures involving the entire region of the entorhinal cortex, hippocampus, and amygdala, determined as a target volume of interest, using voxel-based specific regional analysis system for Alzheimer's disease (VSRAD) software.[13] The degree of medial temporal atrophy was obtained from the averaged VSRAD z score on the target volume of interest, with higher scores indicating more severe medial temporal atrophy ($0 \sim 1$, no atrophy; $1 \sim 2$, mild; $2 \sim 3$, moderate; $3\sim$, severe).

Control Individuals

A total of 128 age-matched individuals without parkinsonian signs such as rest tremor and rigidity between the ages of 63 and 92 served as controls. The numbers of individuals aged 63 to 69 years, 70 to 79 years, 80 to 89 years, and older than 90 years were 31, 44, 44, and 9, respectively. All control individuals were free of cognitive decline (defined as MMSE score ≥25 in individuals aged ≤65 years, and ≥22 in those aged >65 years, with consideration for educational attainment as defined in the patient groups).

Comorbid medical conditions, such as chronic rhinitis, use of nasal vasoconstrictors, severe head injury, intracranial surgery, surgery in the nasal cavity, seasonal allergies, or other current respiratory infection as well as current heavy smoking (the number of cigarettes >20 per day) served as exclusion criteria for the smell test. In patients with recently diagnosed parkinsonism, 65 of 79 patients (18 men, 47 women) were nonsmokers, 6 patients (6 men) were former smokers (mean cessation years: 21.7 ± 6.3), and the remaining 8 patients were current smokers (7 men, 1 woman). In patients with PD with a previous diagnosis, 61 of 71 patients (26 men, 35 women) were nonsmokers, 8 patients (7 men, 1 woman) were former smokers (mean cessation years: 33.3 ± 15.2), and 2 patients (2 men) were current smokers. No significant difference was seen between the different patient groups in smoking habits (Fisher exact test, $P = 0.1843$).

Ethical Issues

This study was approved by the ethics committee of Agano City Hospital. Informed consent to participate in the clinical investigation was obtained prior to participation from all patients and the control individuals.

Assessment of Olfactory Function

For the assessment of olfactory function, all participants underwent the Odor-Stick Identification Test for Japanese (OSIT-J; Daiichi Yakuhin Sangyo, Tokyo, Japan). The OSIT-J is smell identification test with 12 daily odorants familiar to Japanese individuals: Japanese cypress, India ink, rose, perfume, cooking gas, menthol, sweaty socks, curry, Japanese orange, condensed milk, roasted garlic, and timber. Results of the OSIT-J have been shown to correlate well with those of the Cross-Cultural Smell Identification Test.[14] The participants sniffed each of the 12 odorants applied to paraffin paper and then selected 1 of 6 choices for each odorant: the actual smell of the odorant, 3 smells other than the actual smell, "indistinguishable" (ie, detectable but not recognized), or "odorless" (ie, anosmia). The OSIT-J score was then calculated in 3 parts: the numbers of correct answers, responses of indistinguishable, and responses of odorless.

It has been reported that olfactory functions are influenced by age and, less conclusively, by sex: olfactory function has been

TABLE 1 Demographic and clinical characteristics of controls and patients

Demographic and Clinical Characteristics	Age-Matched Controls, n = 128	Patients with Recently Diagnosed Parkinsonism, n = 79	Patients with PD with a Previous Diagnosis, n = 71	*P* Value
Age, y, mean ± SD (range)	76.7 ± 8.0 (63–92)	78.3 ± 7.3 (60–93)	79.4 ± 8.5 (60–95)	0.074**
Sex, female, n (%)	79 (61.2)	48 (60.8)	36 (50.7)	0.292*
MMSE score, mean ± SD (range)		27.3 ± 2.7 (22–30)	26.4 ± 3.2 (22–30)	0.072**
Years of schooling, mean ± SD (range)		9.8 ± 2.4 (6–16)	9.7 ± 2.6 (6–16)	0.841**
Disease duration, mo, mean ± SD (range)		7.1 ± 10.5 (0–48)	47.4 ± 47.1 (3–276)	<0.0001**
UPDRS Part III score, mean ± SD (range)		6.3 ± 1.9 (5–14)	10.9 ± 3.2 (5–20)	<0.0001**
VSRAD *z* score, mean ± SD (n)		1.07 ± 0.54 (75)	1.24 ± 0.64 (68)	0.087**

**P* values were assessed by Fisher exact test.
***P* values were assessed by analysis of variance.
PD, Parkinson's disease; SD, standard deviation; MMSE, Mini-Mental State Examination; UPDRS, Unified Parkinson's Disease Rating Scale; VSRAD, voxel-based specific regional analysis system for Alzheimer's disease.

shown to decrease with age,[15] and the age-related reduction in olfactory identification and discrimination has been reported to be more significant in women than in men[16] or unrelated to gender.[17] Hence, the differences in olfaction by age and by sex were also evaluated.

Statistical Analysis

The data were expressed as mean (standard deviation [SD]). The demographic and clinical characteristics (age, sex, MMSE, years of schooling, disease duration, UPDRS Part III score, and VSRAD *z* score) of the control individuals and the 2 different patient groups are shown in Table 1. In the first comparison, the 3 end points (correct answers, responses of indistinguishable, responses of odorless) were comparted between the controls and the combined patient group using a model that includes age and sex as a covariance (analysis of covariance [ANCOVA]). In the second comparison, the 3 end points in patients with PD with a previous diagnosis were compared with those in patients with recently diagnosed parkinsonism if the first comparison (controls vs. combined patient group) revealed statistically significant differences following adjustment of multiplicity by Holm's method. If there was no statistically significant difference among the 3 end points between the controls and the combined patient group, the comparison between patients with PD with a previous diagnosis and patients with recently diagnosed parkinsonism was not performed (closed testing procedure). The multiplicity of the 3 end points was adjusted by the Bonferroni method. The data analysis was performed using SAS statistical software, version 9.4 (SAS Institute, Cary, NC). We considered two-sided p values <0.05 to be statistically significant.

Results

Age-Matched Control Individuals

The mean age (SD) of 128 age-matched controls was 76.7 (8.0) years, and 79 (61.2%) were women (Table 1). The mean age (SD) of the men was 75.6 (8.2) and that of women was 77.5 (7.8), showing no significant difference (analysis of variance [ANOVA], $P = 0.199$). The mean scores (SD) of the 3 end points (correct answers, responses of indistinguishable, and responses of odorless) on the OSIT-J were 7.1 (1.9), 0.7 (1.2), and 0.2 (0.5), respectively (Table 2). In the men, the mean scores (SD) of these 3 items were 6.7 (1.7), 0.9 (1.2), and 0.2 (0.5) (n = 49), respectively, whereas in the women, they were 7.3 (1.9), 0.5 (1.1), and 0.2 (0.5) (n = 79), respectively, showing no statistically significant differences in any end point between both sexes (ANOVA, $P = 0.073$, $P = 0.134$, $P = 0.987$, respectively).

Patients with Recently Diagnosed Parkinsonism

A total of 79 patients with recently diagnosed parkinsonism having the UPDRS-III score ≥5 and with a positive DaTscan were enrolled. Their clinical profiles and examination results are shown in Table 1. The mean age (SD) was 78.3 (7.3) years, and 60.8% (n = 48) were women. The mean age (SD) of the men was 75.9 (7.0), whereas that of the women was 79.8 (7.2), showing significant difference (ANOVA, $P = 0.018$). Their mean UPDRS part III score (SD) was 6.3 (1.9) (Table 1). All of the patients showed early-stage PD of Hoehn and Yahr stage 1 or 2. Disease duration was defined as the number of months elapsed since the patients had first noticed motor symptoms or, if they were not aware of any parkinsonian signs, since diagnosis had been confirmed by the doctor. The mean disease duration (SD) was 7.1 (10.5) months. The mean MMSE score (SD) was 27.3 (2.7). The mean educational attainment (SD) was 9.8 (2.4) years. The mean VSRAD *z* score (SD) in the 75 patients was 1.07 (0.54), slightly higher than in the control individuals (*z* score: $0 \sim 1$). All of the patients (n = 79) who underwent DaTscan imaging showed presynaptic dopamine transporter reduction in the posterior putamen that was compatible with early-stage PD.

The mean scores (SD) of correct answers, responses of indistinguishable, and responses of odorless were 4.3 (2.2), 1.6 (2.0), and 1.2 (2.2), respectively (Table 2). In the men, the mean numbers (SD) of these 3 items were 3.8 (2.2), 1.7 (2.2), and 1.8 (3.0) (n = 31), and in the women they were 4.6 (2.2), 1.6 (1.9), and

0.8 (1.4) (n = 48), respectively, showing no significant differences in any olfactory domain between both sexes (ANOVA, $P = 0.120$, $P = 0.789$, $P = 0.053$, respectively).

Patients with PD with a Previous Diagnosis

The clinical profiles and examination results of these 71 patients are shown in Table 1. The mean age (SD) was 79.4 (8.5) years, and 36 of the 71 patients were women (50.7%). The mean age (SD) of the women was 80.1 (8.2), whereas that of the men was 78.5 (8.9), showing no significant difference (ANOVA, $P = 0.434$). The mean UPDRS Part III score (SD) was 10.9 (3.2) in the *on* state. All of the patients were at Hoehn and Yahr stage 2 or 3. Disease duration was determined since the patients had first noticed motor symptoms. The mean disease duration (months) (SD) was 47.4 (47.1). The patients with PD were initially treated with L-dopa, as they were older age at onset and/or had moderate to higher levels of motor symptoms. The mean L-dopa dose (SD) in the 71 patients was 190.9 (113.5) mg/day. Other supplementary medications included dopamine agonist, monoamine oxidase B inhibitor, amantadine, anticholinergic, and istradefylline. The L-dopa equivalent daily doses were calculated using an established formula.[18] The mean L-dopa equivalent daily dose (SD) in the 71 patients was 220.0 (149.4) mg/day. The mean value of the MMSE score (SD) was 26.4 (3.2). The mean educational attainment (SD) was 9.7 (2.6) years. The mean VSRAD z score (SD) was 1.24 (0.64) in 68 patients, higher than that in the control individuals (z score, $0 \sim 1$). A total of 49 patients (69.0%) who underwent DaTscan imaging showed presynaptic dopamine transporter reduction in the bilateral posterior putamen with unilateral predominance (an "egg shape" pattern), which is compatible with PD.

The mean scores (SD) of correct answers, responses of indistinguishable, and responses of odorless were 2.5 (2.2), 2.2 (2.5), and 3.8 (4.6), respectively (Table 2). These scores in the men were 2.0 (2.0), 2.7 (2.7), and 4.2 (4.7), respectively, and those in women were 2.9 (2.3), 1.7 (2.3), and 3.4 (4.5), respectively, which showed no statistically significant differences between both sexes (ANOVA, $P = 0.062$, $P = 0.085$, $P = 0.492$, respectively).

Comparison Between Patient Groups (Patients with Recently Diagnosed Parkinsonism and Patients with PD with a Previous Diagnosis) and the Control Group

The mean values of 3 end points (correct answers, responses of indistinguishable, and responses of odorless) and their SDs are shown in Table 2. Comparisons of 3 end points were performed between the control group and the combined patient group by ANCOVA, setting age and sex as covariates. The statistically

TABLE 2 Comparison of the smell test results between controls and the combined patient group and between the patient groups

OSIT-J Score	Age-Matched, Controls, n = 128	Patients with Recently Diagnosed Parkinsonism, n = 79	Patients with PD with a Previous Diagnosis, n = 71	Controls vs. Combined Patient Group, *P* Value*	Patients with Recently Diagnosed Parkinsonism vs. Patients with PD with a Previous Diagnosis, *P* Value**
Correct answers, mean ± SD	7.1 ± 1.9	4.3 ± 2.2	2.5 ± 2.2	<0.0001	<0.0001
Responses of indistinguishable, mean ± SD	0.7 ± 1.1	1.6 ± 2.0	2.2 ± 2.5	<0.0001	0.126
Responses of odorless, mean ± SD	0.2 ± 0.5	1.2 ± 2.2	3.8 ± 4.6	<0.0001	0.0003

*Analysis of covariance (covariates: age, sex).
**Analysis of covariance (covariates: age, sex, duration of treatment, education, Mini-Mental State Examination, voxel-based specific regional analysis system for Alzheimer's disease, Unified Parkinson's Disease Rating Scale).
OSIT-J, Odor-Stick Identification Test for Japanese; PD, Parkinson's disease; SD, standard deviation.

significant differences were shown between these groups with regard to each end point (correct answers, $P < 0.0001$; responses of indistinguishable, $P < 0.0001$; responses of odorless, $P < 0.0001$).

Comparison Between Patients with Recently Diagnosed Parkinsonism and Patients with PD with a Previous Diagnosis

Comparisons of 3 end points were made by ANCOVA between patients with recently diagnosed parkinsonism and patients with PD with a previous diagnosis, setting age, sex, MMSE, years of schooling, disease duration, UPDRS-III, and VSRAD as covariates. Two end points in patients with PD with a previous diagnosis were more significantly deteriorated than patients with recently diagnosed parkinsonism (correct answers, $P < 0.0001$; responses of odorless, $P = 0.0003$) (Table 2): the score of correct answers was lower, and that of responses of odorless was higher. In the subgroup analysis for both women and men, the 2 end points were significantly deteriorated in patients with PD with a previous diagnosis than patients with recently diagnosed parkinsonism (ANCOVA, age, MMSE, years of schooling, disease duration, UPDRS-III, and VSRAD as covariates [correct answers: men, $P = 0.0007$, women, $P = 0.0006$; responses of odorless: men, $P = 0.019$, women, $P = 0.0002$]), although there was no significant difference in the scores of responses of indistinguishable (men, $P = 0.090$; women, $P = 0.8075$).

Discussion

In PD, olfactory dysfunction is common, occurring in 45% to 90% of patients, and all olfactory domains are involved,[2,3,19] which is congruent with this study. Cross-sectional studies have shown a potential sex difference in the sense of smell in PD,[20] and poor sense of smell may be associated with higher risk of PD and may be a better predictor of PD in men than in women,[6] although no significant differences in olfactory function are observed between patients with young-onset and older-onset PD.[21] In the present study, in patients with recently diagnosed parkinsonism and patients with PD with a previous diagnosis, the olfactory functions for all olfactory domains (correct answers, responses of indistinguishable, and responses of odorless) were significantly impaired as compared with age-matched control individuals, showing no significant sex differences either in the controls, patients with recently diagnosed parkinsonism, or patients with PD with a previous diagnosis. Moreover, olfactory impairment in patients with recently diagnosed parkinsonism in this study, including the patients who were not aware of the presence of their parkinsonism, ascribing their symptoms to the aging process instead, is consistent with the previous reports that olfactory dysfunction is one of the earliest clinical features or preclinical symptoms commonly observed in PD[1,6] and that total score on UPDRS-III becomes abnormal at an estimated 4.5 years before a clinical diagnosis of parkinsonism.[22]

The association between olfactory dysfunction and disease duration and severity remains controversial. A previous study reported that no difference was detected in olfactory function between the test scores of patients with PD with or without antiparkinsonian medications,[23] and no relation was present between the scores of olfactory tests and the degree of tremor, rigidity or gait disturbance, and disease duration.[3,23,24] The olfactory dysfunction of PD did not progress significantly over time and was not associated with the degree of motor and cognitive symptoms, suggesting independence from the dynamic elements of the disease proper.[3,25] Thus, olfactory impairment in PD is not correlated with disease duration, severity of motor symptoms, or current medication.[3,24–27] In contrast, other studies reported that olfactory impairment in patients with PD was related to disease duration, disease severity,[21,28–31] and faster disease progression.[30] These inconsistent findings may be partly attributed to the different methods used to measure olfaction or to determine the degree of PD severity (Hoehn and Yahr stage, UPDRS-III, or MDS criteria). As for the association between odor identification and PD phenotype, odor identification was less affected in patients with tremor-dominant PD than in the akinetic-rigidity or postural instability and gait difficulty phenotype.[21,32]

In the present study, the degree of olfactory impairment was robustly associated with disease severity, as assessed by the UPDRS-III, MDS criteria, Hoehn and Yahr stage, and disease duration: olfactory dysfunction (decreased numbers of correct answers and increased numbers of responses of odorless) in both the men and women was more severe in patients with PD with a previous diagnosis than in patients with recently diagnosed parkinsonism. Thus, olfactory dysfunction in PD may get worse over time. However, we could not conclude that there was an association between odor identification and PD phenotype in this study because of the relatively homogeneous parkinsonism (tremor-dominant subtype) among our patients, which included rest tremor, rigidity, and hypokinesia.

Regarding the pathogenesis of olfactory impairment in PD, PD-related pathology initially begins in the olfactory bulb, anterior olfactory nucleus, and the dorsal motor nucleus of the glossopharyngeal and vagal nerves, where Lewy bodies first develop.[33] Olfactory impairment seems to be primarily attributed to Lewy body pathology including increased phosphorylated-α-synuclein immunoreactivity in the olfactory bulb, particularly in the anterior olfactory nucleus.[18,33,34] Similarly, correlations are observed between Brief Smell Identification Test scores and Lewy body pathology within the limbic and neocortical brain regions.[35] Moreover, previous studies reported close relationships between olfactory dysfunction and the atrophy of the amygdala and other limbic structures by volumetric MRI in patients with PD with decreased olfaction.[36] Patients with PD with anosmia have reduced fraction anisotropy values in the white matter adjacent to the primary olfactory cortex compared with patients with PD with normal olfaction.[37] In this study, in both patient groups, the volume of medial temporal structures involving the entire region of the entorhinal cortex, hippocampus, and amygdala was

decreased, as measured by MRI (VSRAD), and presynaptic dopamine transporter reduction in the posterior putamen was detected by DaTscan imaging, which may be consistent with degeneration of the limbic system and nigrostriatal region, in agreement with the previous reports.[36–38]

Moreover, there is a close correlation between the olfactory function and cognitive impairment, that is, the incidence of anosmia in patients with PD increased with an increase in cognitive dysfunction.[38] Recently, one of the present authors reported a higher prevalence of parkinsonism in patients with mild cognitive impairment or mild Alzheimer's disease[39] and synergistic effects of mild cognitive impairment or mild Alzheimer's disease and parkinsonism on olfactory impairment.[40] In this study, however, there was no difference in cognitive function as defined by the MMSE score or in educational attainment between patients with recently diagnosed parkinsonism and patients with PD with a previous diagnosis, implying that olfactory impairment may be substantially ascribable to the progression of PD rather than cognitive impairment.

Thus, the current study shows that olfactory function is more severely affected in patients with PD with a previous diagnosis than in patients with recently diagnosed parkinsonism, implying a close association between olfactory dysfunction and disease severity and duration in PD. The assessment of olfactory function is a useful strategy to detect parkinsonism, particularly at the early stage of PD, and it should be more commonly used in clinical practice settings as a biomarker of disease progression and severity in PD.■

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

S.S.: 1A, 1B, 1C, 2C, 3A

Y.H.: 2A, 2B, 3A

Disclosures

Ethical Compliance Statement: This study was approved by the ethics committee of Agano City Hospital. Informed consent to participate in the clinical investigation was obtained prior to participation from all the patients and the control individuals. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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