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Environmental exposure to manganese in air: Tremor, motor and cognitive symptom profiles

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Abstract

Background: Excessive exposure to manganese (Mn) may cause parkinsonian-like motor and tremor symptoms and adverse cognitive effects, including problems with executive functioning (EF), resembling those found in later-stage Parkinson's disease (PD). Studies seeking to differentiate PD patients into subgroups with associated cognitive and functional outcomes using motor and tremor symptoms identified tremor-dominant (TD) and non-tremor dominant (NTD) subtypes. It is unclear whether differing patterns of pathophysiology and symptoms exist in Mn neurotoxicity, as they do in PD.

Methods: Residents of East Liverpool (n=83) and Marietta, OH (n=99) exposed to chronic (>10 years) environmental Mn through industrial pollution were administered neuropsychological measures and a physician-rated scale of movement-disorder symptoms. Two-step cluster analysis was used to group residents based on tremor symptoms, bradykinesia/rigidity symptoms, gait disturbance, and executive function. Cluster membership was validated using modeled air-Mn exposure and a computerized tremor measure.

Results: Elevated tremor and motor symptoms and executive dysfunction were observed, and TD and NTD symptom clusters were identified. Two additional clusters were also identified:

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ESK conceived of the study with input from RMB and SCL. Study data were archival and drawn from a larger study conducted by RMB, and contributed to be DLT and MAC. RMC, DTL, and MAC participated in implementation/data collection for the larger study. ESK conducted the statistical analyses with assistance from SLC. All authors reviewed and approved the final manuscript

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Executive Dysfunction and Normal Functioning. The NTD residents, with elevated levels of gait disturbance and other movement disorder symptoms, did not evidence EF impairment, as predicted. Instead, residents with EF impairment formed their own cluster, and were relatively free of movement disorder symptoms.

Conclusions: Results resemble reports in the PD literature with TD and NTD clusters identified, but executive dysfunction did not cluster with NTD symptoms. PD and Mn exposure likely have differing pathophysiology and developmental courses, and therefore different symptom patterns, even when similar symptoms are present.

Keywords

Manganese; Executive Function; Neurotoxicology; Tremor

1. INTRODUCTION

Manganese (Mn) is an essential nutrient found in the human body, and consumption of trace amounts daily in food is required to maintain health [1]. However, humans exposed to high concentrations of Mn have been found to experience Parkinsonian-like motor and tremor symptoms [2] and cognitive impairment, especially deficits in executive functioning (EF). Bowler et al. [3–4] previously identified motor and cognitive dysfunction associated with a sample of residents environmentally exposed to Mn.

1.1 Neuropathology and clinical presentation of Mn toxicity and PD

Neuropathologically, deterioration in both Mn neurotoxicity and Parkinson's disease (PD) targets the basal ganglia, and at levels of exposure above normal dietary intake Mn appears to be associated with aggregation of protein a-synuclein, one of the neuropathological agents implicated in PD [5]. Both diseases have similar clinical presentations, and result in motor, cognitive, and mood dysfunction [6]. Deficits in EF, the higher-level cognitive processes that coordinate lower level cerebral functions to allow an individual to interact effectively with his or her environment and other individuals, are a key feature of both PD and Mn neurotoxicity [6]. In fact, it is not unusual for those with excessive Mn exposure to be misdiagnosed with PD, even by experienced neurologists [7].

The two illnesses are distinguished by different types of tremors: patients with Mn neurotoxicity usually display an intention tremor, whereas patients with PD show a resting tremor [2]. Patients with Mn neurotoxicity also have earlier ages of onset of symptoms [8]. Furthermore, Mn toxicity targets the globus pallidus and striatum of the basal ganglia, whereas PD primarily degenerates the substantia nigra [5]. Mn does not appear to cause degeneration of midbrain dopaminergic neurons, as does PD, and thus does not respond to L-Dopa, an amino acid supplement used in the treatment of PD [8–10]. Finally, Mn toxicity is not associated with an accumulation of Lewy bodies, as is PD [11]. In spite of these important distinctions, both pathologies are similar in location of neurodegenerative processes, symptoms, functional outcome, and variation of presentation, and an investigation of whether predictive relationships between clinical presentation and outcomes exist in Mn neurotoxicity, as they do in PD, is warranted.

1.2 Symptom Profiles in PD

Cluster analyses of symptom profiles have been conducted with patients diagnosed with PD in order to better understand and treat the illness through the identification of subtypes [12–13], although the validity of such classification has recently been questioned [14]. Seeking to differentiate PD patients into subgroups with associated outcomes based on motor and tremor symptoms, such studies have identified tremor-dominant (hereafter referred to as Tremor) and non-tremor dominant (No Tremor) subtypes [12–13]. Tremor presents with the classic Parkinsonian pill-rolling tremor, but may also feature other movement abnormalities. No Tremor patients may have symptoms including bradykinesia, rigidity, postural instability and gait disturbance [13], and are more likely to have impairment in EF when compared to Tremor patients [12, 15–16].

1.3 Heterogeneity in Mn toxicity

MRI studies have identified pathophysiology for humans with Mn toxicity (see Guilarte[8,17]). Guilarte [17] suggests that the cognitive and motor deficits found in Mn toxicity result primarily from damage to the striatal pathway connecting the caudate, putamen, internal globus pallidus, and substantia nigra pars compacta of the basal ganglia. As basal ganglia structures are interconnected by complex neuroanatomical and neurochemical pathways, however, damage to only one structure may not remain confined to that structure over time. [7,17]. Moreover, Guilarte [9] and Mergler et al. [18] postulate that adverse effects of Mn exposure on brain function likely occur on a continuum, and the dose and duration of Mn exposure required to reach a critical threshold at which brain damage occurs varies among individuals [7]. In addition, neuropathological consequences of Mn exposure can occur at lower levels of exposure than previously recognized [17], including the chronic, low dose exposure seen in residents exposed environmentally to Mn (see Bowler et al. [3–4, 19]). Finally, the effect of Mn exposure on the brain differs based on iron exposure, subclinical liver dysfunction, and other individual factors [7]. Thus, the available evidence strongly suggests heterogeneity in the neurodegenerative processes of the disease and a need to identify any existing subtypes and prognostic indicators. Though distinct areas of functioning, including pathophysiology, symptoms, and associated outcomes have been studied independently in humans who are Mn-exposed (primarily occupationally-exposed), the possible presence of such symptom profiles to assist clinicians with accurate diagnosis and treatment planning have not yet been explored.

1.4 The Current Study

Analyzing a sample of Mn-exposed residents from Marietta and East Liverpool, Ohio, this study aimed to determine whether 1) clusters or subtypes of Tremor and No Tremor symptoms exist in Mn neurotoxicity as they do in PD, and 2) to the extent subtypes exist, whether the clustering of No Tremor symptoms and EF impairment resembles the clustering seen in samples of PD patients [12,16]. At the outset of the study, we postulated that one of the clusters would be composed of participants with severe tremor symptoms along with a low level of bradykinesia/rigidity and postural instability (indicating presence of a Tremor motor-symptom subtype) and no EF impairment. Further, we postulated that another cluster would be composed of residents with mild tremor symptoms, severe bradykinesia/rigidity

symptoms, and severe postural instability symptoms (indicating presence of a No Tremor motor symptom subtype) in addition to EF impairment.

2. METHODS

2.1 Participants

Participants were part of a sample recruited for a larger study funded by the U.S. Environmental Protection Agency (U.S.EPA) to examine the effects of environmental Mn exposure on adult residents of Marietta and East Liverpool, Ohio (*N*=186). Four residents from the original sample were excluded from the cluster analysis due to missing data on one or more of the clustering variables, for a total sample size of 182. Participants excluded from the analysis did not differ significantly from the included participants on town of residence, Mn exposure, or any other demographic, clustering, or validation variables.

The study residents were individuals who lived in an area where Mn exposures have been occurring over at least a 10-year period. Participants were identified using tax records by the proximity of their residence to the Mn sources in Marietta and East Liverpool and their length of residence at that address. Adults aged 30–75 living in households located in zones with 10 or greater micrograms per cubic meter air Mn concentration (as measured by EPA air monitoring devices) were eligible for study participation. Participants were recruited within two air miles of the Mn source in East Liverpool (due to large Mn particle size and reduced dispersion range of Mn emissions in East Liverpool) and within 12 air miles of the Mn source in Marietta. Potential participants with idiopathic PD, as well as other neurological, severe medical and psychiatric disorders, were excluded *a priori* from participation in the study (see Bowler et al. [19]).

Data were collected on neurological, neuropsychological, physiological, mood, and health measures administered in 2009 (Marietta) and in 2011 (East Liverpool). All study procedures were approved by San Francisco State University Institutional Review Board, US EPA Human Subjects Research Review Office, and the local governments. A cross-sectional, epidemiological design was used. Identical recruitment procedures and data collection methods were used in both towns and were reported in detail in Bowler et al. [19].

2.2 Measures

Manganese exposure.—Ambient air exposure to Mn over 10 years was modeled for each participant using a site-surface area emissions method which uses the US EPA's AERMOD dispersion model calibrated with air measurements from EPA approved air monitors that are part of the Ohio monitoring network.[20]. Briefly, air monitors were set up at different sites throughout the exposed towns. Residue from those monitors was examined and levels of air Mn were thereby measured over a 10-year period in order to create a precise model of exposure based on location. This measure takes into account topographic features of the landscape, weather over the 10 years studied, Mn particle size, and distance from the Mn source in both towns. The modeled air-Mn exposure variable allows for direct comparison of exposure between Marietta and East Liverpool residents. Mn exposures were generally in the form of spherical Mn oxide particles, and from industrial sources in both

towns (a ferro-Mn smelter in Marietta and an open-air Mn storage and packaging facility in East Liverpool). Refer to Colledge et al. [20] for more details. Mean modeled air-Mn exposures ranged from 0.03–1.61 μg/m^3 for Marietta and 0.01–6.32 μg/m^3 for East Liverpool.

2.2.1 Motor symptoms—The Unified Parkinson's Disease Rating Scale (UPDRS) [21] measured motor symptoms using data from patient reports and clinical observations. The UPDRS is comprised of four scales which measure the effects of PD symptoms on non-motor activities of daily living. Only Scale III, the Motor Examination subscale, was used, resulting in evaluations of motor symptoms conducted exclusively by trained raters. Standardized motor symptom scores (for tremor, bradykinesia/rigidity, and postural instability/gait disturbance) were derived from scores on the Motor Examination scale of the UPDRS using a technique described by Rejinders and colleagues [13].

2.2.2 Tremor—The CATSYS (Coordination Ability Test System) tremor test [22] is a computerized measure of both essential and resting tremor. Healthy individuals may evidence some degree of tremor on the CATSYS; "normal tremor," as measured by the CATSYS, is characterized by variability [23]. With higher blood Mn levels, tremor is more regular [22]. CATSYS tremor scores have value as validation variables because they allow for the removal of some degree of human subjectivity.

2.2.3 Executive functioning—Five separate measures of EF (see table 1) were included here to (a) reflect the diverse cognitive abilities associated with EF, (b) maintain consistency with previous research on EF in PD and Mn neurotoxicity, and (c) acknowledge the findings that Mn exposure and PD are associated with problems in set shifting, planning, working memory, response inhibition, and verbal initiation/fluency, aspects of EF [24]. For the main analysis, each participant was considered to have EF impairment if he or she scored in the impaired range (z score below −1.5) on two of the five measures of EF (measures that produce T scores were converted to Z scores prior to analysis).

2.3 Data Analysis

Two-step cluster analyses (CA) were used for the main analyses. Participants were grouped based on standardized measures of tremor symptoms, bradykinesia/rigidity symptoms, gait disturbance symptoms, and dichotomous EF impairment status. In order to facilitate comparison between the current study results with previous research on Tremor and No Tremor symptom profiles in PD [25], we used an iterative approach. Two-step cluster analysis was used to allow for the presence of a dichotomous EF impairment variable in the model. The number of final clusters is determined by using a measure of model fit (i.e., Bayes Information Criterion [BIC]) to identify the optimum number of clusters [26]. After cluster membership was established, the cluster solution was validated by comparing clusters on variables not included in the cluster analyses, such as CATSYS tremor score and modeled air Mn exposure. Cluster validation was accomplished via comparison on levels of variables known to be associated with Mn exposure but not used as clustering variables (i.e., tremor and Mn exposure) using ANOVAs and Bonferroni pairwise comparisons and

nonparametric One Way ANOVAs by Rank following the methods documented by Lewis and colleagues [12]. All analyses were conducted using IBM SPSS 22 [27].

3. RESULTS

The Mn-exposed residents were primarily white (95%) and female (59%), with an average age of 55 years. On average, they had some college education and more than four decades of residence in their respective towns (Table 2). Descriptive statistics for clustering and validation variables are presented in Table 2. Correlations among clustering variables were consistent with expected relationships among the clustering variables and none were large enough to warrant a factor analysis to establish superordinate variables [26].

3.1 Cluster Analysis

3.1.1 Cluster identification—Four distinct symptom clusters were identified in this sample: Non-Impaired, Tremor, Executive Dysfunction, and No Tremor. A four-cluster solution fit the data best; use of different starting points and a set number of clusters did not provide better cluster solutions (data not shown). For the four-cluster solution, Bayes Information Criterion (BIC) was 331.47, BIC change was −31.97, ratio of BIC changes was .18, and ratio of distance measures was 2.78. Cluster quality measures of cohesion and separation fell in the good range (0.5–1.0 [28]).

The largest identified group (Cluster 1: Non-Impaired) contained 60% of the sample and was characterized by average scores (within one standard deviation of the overall sample mean) on measures of gait disturbance, bradykinesia/rigidity, and tremor, and the absence of EF impairment. The second-largest group (Cluster 3: Executive Dysfunction) contained 20% of the sample and consisted of average scores on measures of tremor, gait disturbance and bradykinesia/rigidity, but all members met criteria for EF impairment. The third-largest group (Cluster 2: Tremor) contained 11% of the sample and was characterized by high tremor and average bradykinesia and rigidity. The smallest group (Cluster 4: No Tremor) contained 7% of the sample and had high levels of gait disturbance and bradykinesia/rigidity with relatively lower levels of tremor. Three members of the No Tremor group (23%) met criteria for EF impairment.

3.1.2 Cluster differences in demographic characteristics—One-way ANOVAs indicated that clusters did not differ based on participant age or years of residence, though differences emerged with regard to years of education (Table 3).

Bonferroni comparisons indicated that Normal Function cluster members had significantly more years of education than Executive Dysfunction cluster members and No Tremor cluster members. Members of the Tremor cluster did not differ significantly on years of education compared to members of other clusters. Clusters did not differ on town of residence, but did differ significantly on sex, race, household income, and employment status (Table 4).

Examination of cell-specific standardized residuals revealed that women were under-represented in the Tremor cluster, and men were over-represented in that cluster. For race, clusters differed significantly such that non-white participants were over-represented in the

No Tremor cluster, although concerns about sample size and the small number of non-white participants in this sample render this comparison less meaningful. Clusters differed on household income, with members of the lowest $10,000-$29,999 income range under-represented in the Non-Impaired subsample. Clusters differed significantly on employment status, such that unemployed residents were under-represented in the Non-Impaired cluster and over-represented in the No Tremor cluster.

3.1.3 Cluster differences in validation variables—In order to evaluate whether cluster group membership was related to differences in objectively-measured tremor and Mn exposure, subgroup differences in those variables were examined using ANOVAs and Bonferroni pairwise comparisons and nonparametric One Way ANOVAs by Rank. Clusters did not differ significantly on Mn exposure (subgroup means shown in Table 2; p=.058), although a trend towards higher exposure in the Executive Dysfunction and No Tremor subsamples was noted. On CATSYS tremor variables, a nonparametric Kruskal-Wallace one-way ANOVA by rank revealed that the four clusters differed significantly on right hand tremor harmonic index [*test statistic*=10.36, df=3,182, p=0.02]. The Tremor subsample had the highest harmonic index and differed from all the other clusters (*mean rank*=102.9); the Non-Impaired subsample (*mean rank* = 98.46) and Executive Dysfunction subsample (*mean rank* = 70.3) differed significantly. The four clusters did not differ significantly on the other CATSYS tremor variables: right hand center frequency (*test statistic*=7.12, p=0.07), left hand center frequency (*test statistic*=4.11,p=0.25), right hand tremor intensity (*test statistic*=4.97, p=0.17), left hand tremor intensity (*test statistic*=6.65, p=0.08), and left hand harmonic index (*test statistic*=5.56, p=0.14). It is important to note that the tremor cluster has the values indicative of most dysfunction for each tremor variable, and p values for other tremor variables approach significance. Therefore, the pattern is consistent with expectations and the lack of significant findings may represent a sample size issue.

In examining the cluster scores on the validation variables, trends emerged: although cluster mean differences were not significant (p=.058), the No Tremor cluster had the highest mean Mn exposure and the Executive Dysfunction cluster had the second-highest exposure scores, while exposure levels for the Non-Impaired and Tremor subsamples was relatively lower (Table 2). Similarly, CATSYS variables were highest for the Tremor cluster, with the exception of the center frequency variables, which were highest for the Executive Dysfunction subsample and for which high values indicate less severe tremor (Table 2).

4. DISCUSSION

This study is the first to attempt to fit an existing classification of Parkinson's Disease (PD) symptoms (e.g., movement disorder symptoms, executive dysfunction) to a sample of residents who were exposed to Manganese (Mn) through industrial air pollution and who were hypothesized to have symptoms of movement disorder and executive dysfunction. Cluster analysis of data from 182 Mn-exposed residents of two towns was used to group residents with similar scores on measures of 1) tremor, 2) non-tremor movement disorder symptoms, and 3) EF. Cluster membership was then validated through comparing subsamples on variables not used in the cluster grouping (i.e., Mn exposure level and a

computerized measure of tremor). The current results contrast with findings from individuals with PD [12–13], as discussed below.

Four distinct, homogenous symptom clusters were identified: Non-Impaired, Tremor, Executive Dysfunction, and No Tremor. Our resulting clusters partially resemble previous early findings of patients with beginning stage PD [25], in that tremor- and non-tremor subsamples were detected. However, unlike reports of symptom clustering in early PD patients, most Mn-exposed participants with executive dysfunction were clustered into their own subsample, defined primarily by the presence of symptoms of executive dysfunction, and not the co-occurrence of executive dysfunction and non-tremor symptoms. Cluster membership was not associated with the validation variables in the pattern hypothesized, except for tremor (i.e., No Tremor motor symptoms and deficits in EF did not cluster together). However, the Executive Dysfunction cluster and the No Tremor cluster qualitatively resembled each other, with higher levels of modeled air Mn exposure and less severe or absent tremor, as assessed by the CATSYS computerized tremor measurements of intensity and center frequency variables.

Consistent with recent neuroimaging research in this domain [e.g., 17], our findings suggest that the neurodegenerative patterns of Mn toxicity and PD are distinct. The overall results of this study also suggest the possibility of a shared pathophysiology of movement disorder symptoms between Mn toxicity and PD, perhaps a problem with release of motor inhibition as governed by the frontal-subcortical dorsolateral pathway, but a difference in the pathophysiology and manifestation of deficits in EF. Indeed, whereas most existing research on impaired executive function in Mn exposure has focused on the basal ganglia due to the known similarities to PD, recent imaging research on this topic has moved beyond the basal ganglia and has begun to target areas of cortex, especially the frontal lobes, in an effort to better elucidate the cognitive dysfunction seen in Mn exposure [15]. Approaches in those studies represent a departure from the current models of cognitive dysfunction in later-stage PD and are examples of a growing recognition of the distinctness of neurocognitive dysfunction in Mn overexposure and PD. Differences in pathophysiological processes (i.e., the absence in Mn toxicity of widely distributed cortical and subcortical Lewy bodies that are thought to significantly contribute to cognitive dysfunction in PD [5,11] and variously disturbed functional neuroanatomical connectivity) may lead to distinct clinical symptom presentations and symptoms associated in Mn neurotoxicity compared to PD via the contrasting effects on frontal-subcortical networks such as the dorsolateral and striatal pathways.

Although both disease processes produce neurological and cognitive impairments that can be used to cluster patients into distinct subsamples, the symptom presentations, and likely the associated outcomes, of the clusters are different. The literature on symptom clusters and outcomes in PD provides a useful starting point for research in those over-exposed to Mn. However, more research on the distinct subsamples that occur in Mn over-exposed groups is needed to further elucidate the mechanisms that explain differences and to explore-related social, psychological, and occupational outcomes associated with each distinct presentation of the disorder.

When considered in the context of the literature on occupational exposure to subclinical levels of Mn, our results are intriguing. Low-dose occupationally-exposed individuals who are asymptomatic (i.e., without obvious neurological impairment) demonstrate MRI abnormalities that are consistent with motor, not cognitive, deficits [29]. Our identification of a subsample with motor dysfunction and low levels of executive function impairment (No Tremor) is consistent with these findings; the presence of executive dysfunction without motor or tremor disturbance in our sample (Executive Dysfunction subsample) is not. However, Guilarte posits that low-dose exposures result in damage to the frontal lobe rather than the midbrain as seen in high-level occupational exposures because the frontal lobe has a lower threshold for susceptibility to Mn-induced neurotoxicity than subcortical brain regions, resulting in cognitive impairment without tremor/motor dysfunction [17]. Our findings of executive dysfunction in the absence of motor/tremor symptoms are consistent with this theory. Furthermore, occupational exposures tend to involve inhalation of Mn during work hours, whereas environmental exposures involve inhalation as well as ingestion via contaminated food and water supplies over entire lifetimes. Finally, our findings of both motor dysfunction (No Tremor) and Executive Dysfunction in separate subsamples, and the consideration that our sample may contain more occupational, educational, sex, and age diversity than samples in the occupationally-exposed literature, raise the possibility that interindividual variation may explain at least some of our discordant results.

4.1 Limitations

Clusters are likely more complex than results indicate, and although an attempt was made to control for the effects of variables that were hypothesized to impact the clustering solution, cluster membership may be importantly affected by variables not included in this analysis. Although findings from the Mn-exposed samples in Marietta and East Liverpool were compared to findings in the PD literature, no PD sample was available as a comparison group for the current study. Functional imaging data comparing Mn-exposed residents to PD patients may further clarify the presence or absence of the symptom patterns in question in the current study. There may be an effect of selection bias, which was, however, minimized by our stringent recruitment procedures, which were non-coercive and followed strict epidemiological methodology. Participants ranged in age from 30 to 74 years, and all were residing for at least 10 years in the two Ohio towns which both had a major source of airborne environmental Mn. Thus, results may not be completely generalizable to other geographical areas.

4.2 Strengths

The current study is one of the first studies to examine the relationship between tremor and movement disorder symptoms and symptoms of executive dysfunction, and to investigate EF measures across different domains, in environmental Mn exposure. The study design and recruitment procedures were methodologically strong, with data collection conducted by trained examiners resulting in high-quality clinical data. Using a measure of the modeled air Mn exposure over 10 years for each participant provides an additional methodological strength. The results of this study add to the understanding of the cognitive and motor effects of low dose, chronic environmental Mn exposure.

4.3 Conclusion

The hypothesis that the variability of symptoms and the complexity of pathophysiology in Mn toxicity would result in distinct symptom profiles was confirmed. This finding supports the utility of neuropsychological assessment in identifying cognitive (especially executive skills) dysfunction in Mn-exposed individuals. Important clinical implications exist for detecting patients who may benefit from cognitive rehabilitation as a result of that dysfunction.

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Table 1

Executive function measures

Executive Function	Measure	Score
Verbal initiation, semantic verbal fluency, cognitive flexibility	Animal Naming[a] (AN)	T score
Response inhibition, set shifting	Stroop Color Word Task[b] (Stroop)	T score
Visual tracking, sequencing, & set shifting	Trail Making Test B[c] (TMT B)	T score
Visual Planning	Rey Osterrith Complex Figure Test, Copy Trial[d] (Rey-O)	Z score
Working memory, divided attention	Auditory Consonant Trigrams[e] (ACT)	Z score

[a] Lezak et al., 2012);

[b] Golden, 1978);

[c] Strauss, Sherman, & Spreen, 2006;

[d] Rey, 1941;

[e] Boone, Miller, Lesser, Hill, & D'Elia, 1990; Lezak et al., 2012

Table 2

Key variables by cluster

	Total Sample (n=182)	Non-Impaired (n=111)	Tremor (n=21)	Executive Dysfunction (n=37)	No Tremor (n=13)	p
Clustering Measure *Mean (SD)*						
Tremor raw	0.06 (.14)	0.008 (.031)	0.328 (.197)	0.074 (.129)	0.087 (.130)	<0.01 *
Bradykinesia/rigidity raw	0.04 (.13)	0.081 (.061)	0.008 (.036)	0.023 (.058)	0.333 (.319)	<0.01 *
Gait disturbance raw	0.10 (.21)	0.029 (.081)	0.143 (.143)	0.103 (.146)	0.667 (.368)	<0.01 *
Executive function impairment %	22%	0%	0%	100%	23%	<0.01 *
Demographic Variable *Mean (SD)*						
Age	55.07(10.91)	53.94 (10.85)	55.62 (10.30)	56.51 (11.02)	59.77 (11.55)	0.21
Years of residence	40.90(16.99)	38.50 (16.54)	41.00 (18.30)	46.14 (16.89)	46.38 (16.30)	0.07
Years of Education	13.77 (2.60)	14.49 (2.48)	13.67 (2.61)	12.38 (2.06)	11.85 (2.58)	<0.01 *
Demographic Variable %						
Sex[1]	58.2%	64.9%	23.8%	56.8%	61.5%	0.01 *
Employment Status[2]	58.8%	67.6%	47.6%	48.6%	30.8%	0.02 *
Race[3]	93.9%	95.5%	95.2%	94.6%	84.6%	0.03 *
Cluster validation measure *Mean (SD)*						
Mn exposure (μg/m^3)	0.53 (0.92)	0.44 (0.79)	0.39 (0.59)	0.72 (0.93)	0.91 (1.85)	0.14
CATSYS mean tremor intensity: right hand[4]	0.13 (0.07)	0.12 (0.07)	0.16 (0.09)	0.12 (0.04)	0.13 (0.04)	0.17
CATSYS mean tremor intensity, left hand[4]	0.13 (0.08)	0.12 (0.07)	0.17 (0.09)	0.12 (0.04)	0.19 (0.18)	0.08
CATSYS mean center frequency, right hand Hz	5.97 (2.82)	5.58 (2.89)	6.32 (2.79)	0.76 (2.59)	6.55 (2.65)	0.07
CATSYS mean center frequency, left hand Hz	5.93 (2.96)	5.61 (3.06)	6.26 (2.29)	0.55 (2.65)	6.30 (3.22)	0.25
CATSYS harmonic index, right hand[5]	0.90 (0.08)	0.90 (0.07)	0.92 (0.06)	0.86 (0.08)	0.88 (0.07)	0.02
CATSYS harmonic index, right hand[5]	0.90 (0.08)	0.90 (0.07)	0.92 (0.06)	0.86 (0.08)	0.88 (0.07)	0.02

[1] Percentage of female participants, vs. male

[2] Percentage of employed or student participants, vs. unemployed

[3] Percentage of white participants, vs. nonwhite

[4] Values represent the root mean square of acceleration recorded in the .9–15 Hz band

[5] Comparison of tremor frequency pattern to pattern of a single harmonic oscillation, which has a value of 1.00; value decreases when oscillations are more frequent

[*] Differs significantly

Table 3

Results of One-way ANOVAs Comparing Age, Years of Residence, and Education by Cluster

	Df	F	p
Age	3,182	1.45	0.213
Years of Residence	3,182	2.417	0.068
Education	3,182	10.03	<0.001

*Note.** Significant at the p< 0.01 level.. Partial η^2=0.145

Note: Omnibus tests only; results of planned comparisons not shown

Table 4

Distributions of key categorical variables by cluster and measures of association across four identified clusters

	Cluster				Pearson Chi Square	df	Asymp. Sig (2-sided)	ϕ
	Non-Impaired	Tremor	Executive Dysfunction	No Tremor				
Executive Function Impairment	N (Std. Residual)	N (Std. Residual)	N (Std. Residual)	N (Std Residual)	.168.54	3	<0.01**	0.96
No	111 (2.6)	21 (1.1)	0.0 (−5.4)	10 (0.0)				
Yes	0 (−4.9)	0 (−2.1)	37 (10.1)	3 (0.1)				
Participant Town					6.07	3	0.11	0.18
East Liverpool	45 (−0.8)	8 (−.5)	23 (1.5)	7 (0.4)				
Marietta	66 (0.7)	13 (.5)	14 (−1.4)	6 (−0.4)				
Sex					12.33	3	0.01**	0.26
Male	39 (−1.1)	16 (2.4)	16 (0.1)	5 (−0.2)				
Female	72 (0.9)	5 (−2.1)	21 (−0.1)	8 (0.2)				
Race					8.97*	3	0.03*	0.30
White	63 (0.1)	13 (.2)	13 (0.0)	4 (−0.7)				
Nonwhite	3 (−0.5)	0 (−.9)	1 (.2)	2 (2.7)				
Employment Status					10.40	3	0.02*	0.24
Employed/Student	75 (1.2)	10 (−0.7)	18 (−.8)	4 (−1.3)				
Unemployed	36 (−1.4)	11 (0.8)	19 (1.0)	9 (1.6)				
Marital Status					17.10	3	0.15	0.31
Single	7 (−0.1)	1 (−0.3)	4 (1.0)	0 (−0.9)				
Married	82 (0.2)	14 (−0.3)	26 (−.2)	10 (0.2)				
Divorced	14 (0.3)	5 (1.7)	2 (−1.1)	0 (−1.2)				
Widowed	5 (−0.7)	0 (−1.1)	3 (0.5)	3 (2.5)				
Cohabiting	3 (−0.3)	1 (0.4)	2 (0.7)	0 (−0.7)				
Household Income					29.99	15	0.01*	0.42
$0–19,999	9 (−2.4)	6 (1.0)	13 (2.2)	5 (1.9)				
$20,000–39,999	27 (−0.3)	6 (0.1)	12 (0.5)	3 (−0.1)				
$40,000–59,999	19 (0.7)	3 (−0.1)	5 (−0.3)	0 (−1.3)				
$60,000–79,999	18 (0.8)	2 (−0.6)	2 (−1.5)	3 (1.1)				

		Cluster			Pearson Chi Square	df	Asymp. Sig (2-sided)	ϕ
$80,000–99,999	10 (0.6)	1 (−1.5)	3 (0.0)	0 (−1.0)				
$100,000 plus	17 (1.5)	2 (−0.3)	1 (−1.6)	0 (−1.1)				

*Note. Significant at the p<.05 level.

**Significant at the p<.01 level