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Cognitive impact of exposure to airborne particles captured by brain imaging

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1. Introduction

Moderate to severe cognitive impairment, meaning pathological dysfunction in fluid cognition, including memory, executive functioning, and verbal and category fluency can make it difficult to interact or navigate daily activities (Horn and Cattell, 1967). Such burden and loss of functioning is a major public health problem because, at present, the course of cognitive impairment (CI) is unpredictable, seemingly irreversible, and remains incurable (Adams, 2012). Cognitive impairment often represents significant losses in capabilities that are individually meaningful and are indicative of later clinical levels of pathology (Plassman et al., 2010, 2011; Ravaglia et al., 2008; Valenzuela and Sachdev, 2005). Indeed, a large body of evidence suggests that in its earliest stages, CI is commonly indicated by rapid losses in cognitive capability in the years preceding clinical pathology (Piccinin et al., 2011) and diagnosis with dementia (Jack et al., 2010). Occupational exposure to a variety of neurotoxicants causes cognitive impacts. From the early finding on carbon disulfide damage, observed in Finland by Helena Hänninen in the 1960s (Hänninen, 1966), the knowledge of neurotoxicity in the workplace has progressively been revealed throughout an impressive number of studies. Solvent-related encephalopathy, neurotoxic effects from multiple metals, pesticides, and organic compounds like PCB, dioxins, and more recently PFAS and phthalates, have been largely demonstrated as caused or exacerbated by workplace exposure. Airborne particles in the ultrafine range can impact the brain through olfactory absorption, posing the “nose-brain” connection as a relevant absorption route that can target different brain regions. The COVID-19 pandemic has further underlined the importance of the olfactory pathway in relation to neurotoxic impact from biological agents.

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Mounting evidence is accumulating that exposure to air pollutants, especially fine particulate matter, contributes to an increased risk of CI. For example, epidemiologic work by Lucchini et al. (Lucchini et al., 2012a) found memory decline and CI in children, adults and the elderly exposed to various airborne contaminants. Furthermore, imaging studies using structural magnetic resonance imaging (MRI) reported reductions in total brain volume and white matter structures after lifetime exposure (Chen et al., 2015; Wilker et al., 2015), while Aβ increases were found in animal models exposed to air pollution (Kim et al., 2012). The investigators leading these studies theorized that airborne particles may interrupt brain functioning in two ways: (1) via the circulation, through increased distribution of proinflammatory cytokines (Block and Calderón-Garcidueñas, 2009) resulting in neuroinflammation, blood–brain barrier dysfunction, and neural degeneration (Calderón-Garcidueñas et al., 2002); or (2) intranasally by direct translocation through the olfactory bulb (Bench et al., 2001). Several animal studies have shown increased brain inflammation in response to air particulate exposures (Campbell et al., 2005), signs of blood–brain barrier dysfunction, neural degeneration, cerebrovascular pathological signs, and apoptosis in glial cells (Calderón-Garcidueñas et al., 2002).

Brain imaging is rapidly improving how we understand the mechanisms of brain toxicity through a variety of anatomical and functional modalities. Functional MRI, resting states, and other techniques generate information on brain connectivity and response that can be altered by the exposure to multiple hazards and by their mixture. In this chapter, we will consider the new methodological development of brain imaging, the suitability, and the advantages of its use in occupational health when targeting the cognitive impacts of exposure to neurotoxic agents. Specific cases will be described, related to (i) the exposure to a mixture of neurotoxic agents and psychological trauma caused by the 9/11 terrorist attack, and (ii) the long-term consequences of manganese exposure among ferroalloy workers.

1.1 Brain imaging techniques

Brain imaging is used to determine the impact on the brain from exposure to neurotoxins. Functional imaging with positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are tools used to determine the damage done to the brain and the functional deficits to the brain from exposure to a neurotoxin. They also aid in evaluating the mechanisms in the brain that are involved in intoxication (de Vries et al., 2021). A brain PET scan uses a radioactive substance (a tracer) to look for disease or injury in the brain and how brain cells are working. The tracer is given intravenously (IV) or as a breathable radioactive gas. Then the tracer travels through the blood and collects in the organs and tissues helping assess specific areas or diseases. MRI as well as computed tomography (CT) scans focus on assessing the structure of the brain and on showing the blood flow to and from organs (Dougherty et al., 2004; Meyer et al., 2016).

These imaging technologies are important in evaluating chemically induced brain damage. Similarly, MR imaging and PET scans are proven effective in diagnosing Alzheimer's disease. Through MRI, we canlook at soft tissue contrast with tissue characterization from specific sections of the brain. This technology provides a three-dimensional structural distinction between cerebral gray and white matter of the brain, while PET scans can

provide functional metabolic and molecular information as well as changes and lesions in the brain. Therefore, both imaging techniques provide a more accurate diagnostic technique when used together (Barthel et al., n.d.).

2. Case study 1: Cognitive decline among the World Trade Center responders

The WTC disaster exposed tens of thousands of individuals including employees at or near the WTC site; residents of the area; and responders to a host of traumatic experiences and, at the same time, exposed many to the toxic detritus of the Towers after they collapsed. Current estimates suggest that, at midlife, a growing number of WTC responders are experiencing early CI and dementia (Clouston et al., 2016). Exposure to psychological trauma and fine particulate matter may increase the risk of dementia in traumatized populations including military veterans and WTC responders. WTC responders were exposed to neurotoxicants including metals, PCBs, dioxins, and PAHs. Ultrafine particles can reach the brain through the olfactory pathway causing oxidative stress and chronic inflammation leading to neurodegeneration. A decrement in the ability to identify odors was observed in a group of 99 WTC exposed subjects compared to 99 controls (Altman et al., 2011). Carbon nanotubes (CNT) were found in the lung biopsies of WTC responders and in samples of WTC dust (Wu et al., 2010). Furthermore, research on the role of exposures at the WTC has found elevated levels of systemic inflammation (serum C-reactive protein), indicative of accelerated systemic aging (Kazeros et al., 2015). Different exposure-related potential mechanisms of neuroinflammation leading to neurodegeneration among the 9/11 responders need further investigation (Kritikos et al., 2020).

In the Stony Brook WTC cohort, 20% of responders developed PTSD since 9/11. In 2400 responders screened with the Montreal Cognitive Assessment (MoCA), the rate of cognitive impairment (CI) (scores <20) was 2.6%, and the association with PTSD was highly significant. Given the complex exposures leading to PTSD, the etiology needs to be fully understood. Since the NIOSH CDC is mandated to pay for care for WTC-related diseases, there is a pressing need for a better understanding of the nature of this impairment, including its presentation in brain tissue, in highly exposed and traumatized WTC responders.

2.1 PTSD and CI

The first question posed by the observation of cognitive decline among the 9/11 responders is whether this is potentially a consequence of mental health disorders. In fact, PTSD has been broadly associated with a reduced cognitive functioning and an increased risk of dementia (Schuitevoerder et al., 2013; Veitch et al., 2013). PTSD involves complex memory, emotional, and behavioral processes (Lawrence-Wood et al., 2016), and encompasses distinct domains including re-experiencing, effortful avoidance, emotional numbing, and hyperarousal resulting from a traumatic event (King et al., 1998). The exact mechanisms for this association remain unclear (Pitman, 2010). Theories alternatively suggest that: posttraumatic stress may be a unique part of the causal pathway leading to cognitive aging (Greenberg et al., 2014); the association may be confounded by comorbid features that are independently associated with PTSD and dementia, such as traumatic brain injury

(McKee and Robinson, 2014). Another formulation is that symptoms indicative of PTSD, which is commonly comorbid with major depressive disorder (MDD) (Shalev et al., 2014), are also manifestations of dementia or related pathology (van Achterberg and Southwick, 2001). Moreover, consistent with these findings, structural and functional MRI have been successful in detecting associations between PTSD and neurological function. For example, structural MRI studies have highlighted hippocampus and amygdala volume (O'Doherty et al., 2015). Functional MRI studies have further noted the consistent associations found between PTSD and white matter lesions (Pitman et al., 2001) and PTSD, white matter integrity, diffusivity, and anisotropy (Daniels et al., 2013; Davenport et al., 2015). Finally, studies of neuronal function highlight the role of PTSD in modulating glucose uptake in the amygdala (Buchsbaum et al., 2015; Zhu et al., 2016) as well as generally elevated neuroinflammation (Acosta et al., 2013) and even reduced microglial activation (Seibyl, 2012).

Several other potential risk factors for CI need to be considered in addition to PTSD and massive exposure to air pollutants. They include family history, apolipoprotein ε4 allele, other early life and adult-onset extreme stress, head injury, educational attainment and childhood cognition, mid-life obesity and hypertension, smoking, lack of exercise, and excessive use of alcohol and drugs. As WTC responders age, they are increasingly faced with an aging-related disease burden, especially CI. It is, therefore, critical to understanding the role of WTC-PTSD and extreme exposure to toxic pollutants in accelerating the onset of CI in this population.

An imaging study using PET/MRI has been conducted by our group from the Stony Brook University and the Icahn School of Medicine at Mount Sinai, New York. The methodology developed in this study has included the following protocols.

2.2 MRI assessments

All imaging was performed on a Siemens 3T PET/MR. This instrument simultaneously acquires PET and MRI. Before administering the research PET/MRI protocol, a dual echo sequence was also obtained to screen for incidental abnormalities. The protocol included the following modalities: (i) anatomical T1-weighted MPRage (TR/TE = 1900/2.5ms, FOV = 23cm, Matrix 256 × 256, slice thickness 1.0mm); (ii) Diffusion Tensor Imaging using a Pulsed-Gradient Spin Echo sequence with 33 gradient directions (TR/TE = 7800ms/101ms, FOV = 23cm, Matrix = 128 × 128, slice thickness 3mm, b-value = 1200s/mm^2, 33 directions); (iii) Resting state fMRI scan (10min); (iv) Task driven fMRI performed using a working memory task (N-back letter sequences).

Images were acquired using a Gradient-Echo-EPI sequence (TR/TE = 2000ms/27ms, FOV = 23cm, Matrix 64 × 64, slice thickness 2.5mm). All visual stimuli were presented using a high-definition goggle system by Resonance Technology Inc., Northridge, CA. Stimulus presentation and subject responses were acquired using Eprime and a fiber optic response glove by Psychology Software Tools (PST Inc. Pittsburgh PA).

2.3 PET image acquisition (PET/MR)

PET/MR (3T) Siemens mMR. The 3T MR/PET is a fully integrated and capable of simultaneous whole-body PET and MRI scanning. This allows more precisely coregistered functional and structural acquisition while reducing the radiation dose in PET imaging by replacing the CT scan with an MRI scan. True simultaneous acquisition of MR and PET data by the hybrid system merges the highly sensitive PET metabolic information with the highly specific MR anatomical and functional information. Attenuation data in PET/MRI are derived from the MRI scan. For each bed position, the MRI sequence for attenuation correction (AC) purposes is acquired first. The sequence used in the integrated PET/MRI system is a 2-point Dixon volume-interpolated breath-hold examination (VIBE). This sequence is preceded by scanning preparations that include shimming to optimize the homogeneity of the magnetic field (~40s). The MRI data are then segmented to identify air, brain tissue, fatty tissue, and watery tissue as required for AC.

[^{18}F] fluorodeoxyglucose ([^{18}F]FDG) brain imaging was performed on cognitively impaired subjects in the SBU WTC cohort. To administer the [^{18}F]2-deoxyglucose, one catheter is placed in an intravenous line in an antecubital vein. Ten mCi (370MBq) of [^{18}F]2-deoxyglucose are injected. ^{18}FDG is used according to its FDA approved indication and labeling. Thirty minutes after radiotracer injection, the subject is then positioned supine in the mMR PET scanner, image acquisition period lasts 15 min. Amyloid deposition was also studied using the Amyvid tracer.

2.4 [^{18}F] amyvid PET imaging

To administer the [^{18}F] florbetapir (Amyvid™), one catheter is placed in an intravenous line in an antecubital vein. Ten mCi (370MBq) of [^{18}F] florbetapir are injected. Florbetapir is used according to its FDA approved indication and labeling. Sixty minutes after radiotracer injection, the subject is then positioned supine in the mMR-PET scanner. The imaging data acquisition lasts 15 min.

2.5 A WTC-CI neuro-phenotype

Unique brain characteristic patterns of CI among WTC responders emerged, compared to other signatures, such as AD. Hippocampal subfield volume analysis suggests reductions in specific subregions are associated with the duration of WTC exposure (Deri et al., 2021). Cortical thickness measurement from MRI provides a powerful non-invasive method for quantifying neurodegenerative disease risk including AD (Dickerson et al., 2009). Among 99 WTC responders aged 55.8 (SD = 0.52) years, 48 had CI. Compared to unimpaired responders, global means cortical thickness was reduced in CI subjects and across 21/34 cortical subregions. Surface-based analyses revealed reduced cortical thickness across frontal, temporal, and parietal lobes when adjusting for multiple comparisons (Clouston et al., 2020). Both CI and unimpaired WTC groups showed reduced cortical thickness in the entorhinal and temporal cortices compared to published normative data. An artificial neural network was also applied to accurately identify WTC responders who may be at higher risk for cognitive issues on MRI (Clouston et al., 2021). Cortical complexity can also be measured as Fractal Dimension (FD) from T1 MRI brain images and has been reported to be reduced in a variety of psychiatric and neurological conditions. Vertex clusters of complexity

were altered in WTC responders with PTSD, with marked reductions in regions within the frontal, parietal, and temporal cortices, in addition to whole-brain absolute bilateral and unilateral complexity. The magnitude of changes in regional FD severity was associated with increased PTSD symptoms (reexperiencing, avoidance, hyperarousal, negative affect) severity (Kritikos et al., 2021).

Bilateral cortical thickness resulted also in 12 cerebellar lobules of these WTC responders. Mean cerebellar cortical thickness was reduced by 0.17mm in responders with CI. Decrements in cerebellar cortical thickness were symmetric and located in the Cerebellar Crus (I and II), and in Lobules IV, VI, VIIb, VIIIa, VIIIb, and IX. Cerebellar cortical thickness was associated with episodic memory, response speed, and tandem balance. WTC responders with CI had evidence of reduced cerebellar cortical thickness that was present across lobules in a pattern unique to this cohort (Clouston et al., 2022).

Approximately 23% of World Trade Center (WTC) responders are experiencing chronic posttraumatic stress disorder (PTSD) associated with their exposures at the WTC following the terrorist attacks of 9/11/2001, which has been demonstrated to be a risk factor for CI raising concerns regarding their brain health (Kritikos et al., 2021). Diffuse brain atrophy, reduced cortical thickness, and hippocampal subfield volume analysis suggest that reductions in specific subregions are associated with the duration of WTC exposure. These findings support the hypothesis that WTC exposure to neurotoxicants is causing a long-term neurodegenerative impact. The neuro-phenotype of this impairment is different from the AD and inconsistent with signatures developed for known neurodegenerative diseases. The WTC-CI may be a WTC-specific encephalopathy with an unknown etiology characterized by widespread cortical atrophy.

3. Case study 2: Cognitive impact of occupational exposure to manganese

Manganese (Mn), one of the most abundant elements on the earth, is an essential trace element required for critical enzyme-mediated biological processes involved in development, growth, and neuronal function (Martins et al., 2019). Although necessary for life, Mn can cause health issues both in deficiency and excessive levels. Occupational settings such as mining, steel, and alloy production, welding, smelting and dry-cell battery manufacturing are among the main sources of environmental risk factors for chronic exposure to various metals (Briffa et al., 2020). Welders and smelters are among the most vulnerable groups exposed to fumes or inhaled dust types of manganese (Mn) at different levels. Different forms of Mn oxides including Mn_3O_4 and MnO_2 have been found in both welding and smelting aerosols (Cowan et al., 2009; Jiang et al., 2007; Keane et al., 2010; Long et al., 2014). A great part of respirable Mn particles is transmitted through the circulation to the brain directly and is not being involved in the process of the Mn homeostasis control of the liver. This makes occupational workers more susceptible to the neurotoxic Mn effect compared to individuals with oral exposure to Mn (Roels et al., 2012). Mn accumulates selectively in the specific parts of the brain such as globus pallidus, putamen, caudate nucleus, and cerebral cortex. The neural system and cognitive

functioning are the most relevant targets of exposure to neurotoxicants from early life to old age (Balachandran et al., 2020).

3.1 Manganese-induced cognitive impactive deficits

It is well documented that increased manganese (Mn) exposure is associated with various neurologic deficits that occur in multiple stages. Psychiatric, motor, and olfactory dysfunction and cognitive deficits (including working or visual memory and verbal disorders) have been reported in the various studies of environmental exposure to Mn in adults (Bowler et al., 2015; Lucchini et al., 1995, 2014, 2017; Zoni and Lucchini, 2013). Additionally, significant improvement in cognitive but not motor test scores has been recorded by ceasing or decreasing Mn exposure (Roels et al., 2012).

Cognitive dysfunction and structural changes in the brain regions could be implicated as important factors in contributing to Mn toxicity. Functional imaging and Mn exposure brain morphometric measurement allow analyzing cognitive function and the deleterious effects of Mn on the size, volume, and shape characteristics of different brain structures using sensitive methods such as MRI and PET scan.

A potential mechanism for Mn-induced neurotoxicity caused cognitive decline is amyloidogenesis, an increased formation of amyloid-beta (Aβ) deposition, a biomarker of cognitive dysfunction, and the main hallmark pathology in Alzheimer's disease (AD), the most common cause of dementia (DeTure and Dickson, 2019). Chronic manganese exposure may increase the risk of cognitive decline and induces amyloidogenesis mediated through whether alteration in the level of proinflammatory markers such as cytokines IL-1β and TNF-α or Amyloid Precursor Protein (APP) production. It is also shown that a high level of Mn leads to disruption Aβ degradation through down-regulation of major enzymes involved in this mechanism such as neprilysin (NEP) and insulin degrading enzyme (IDE) (Lin et al., 2020; Tong et al., 2014).

We investigated the presence of Aβ aggregation and cognitive function from a cohort of Mn-exposed workers, employed in ferroalloy plants located in different areas of the province of Brescia, Italy and historical unexposed control workers (Lucchini et al., 2022). This sample was randomly selected from the occupational cohort initiated in 1990 within the PHIME (Public Health Impact of the Metal Exposure) project, a multiage cohrt funded initially by the EY 6thFP and subsequently by NIEHS. This occupational cohort has provided numerous observations about the impact of manganese exposure on motor coordination, olfactory discrimination and cognitive decline (Lucchini et al., 1997, 1999, 2000). Workers of this cohort were originally enrolled from the company health surveillance program. They were asked to participate on a voluntary base, and were consented through a procedure approved by the Ethical Committee of Brescia. Exclusion criteria included being diagnosed with a neurological or psychiatric disorder.

Dose–response relationships were observed with cumulative exposure metrics based on the annual measurements of manganese in respirable/inhalable airborne particles in personal and stationary monitoring throughout the industrial operation (Lucchini et al., 1995). Structural MRI showed manganese deposition in the globus pallidus (Lucchini et al., 2000a,b),

providing potential interpretation of a long-term diffuse deposition of manganese in the basal ganglia after prolonged exposure to low levels throughout the working life (Lucchini et al., 2009; Lucchini and Zimmerman, 2009).

In this recent pilot study, we examined differences in the cognitive functioning and β-amyloid brain deposition in 6 ferroalloy workers (average age 64 and average Mn exposure duration 31 years) and 5 historical sex- and age-matched control workers (average age 63), not exposed to metals. The cognitive function was assessed with a battery of neuropsychological tests including the Montreal Cognitive Assessment (MOCA). Mn exposure was based on the 25-year annual assessment of workplace air monitoring and biological monitoring. A similar PET/MRI brain imaging protocol to the one utilized for the WTC responders in NYC was applied to the Italian manganese workers. In this case, the presence of β-amyloid deposition was assessed with a General Electric Discovery 690 PET-CT scanner after the injection of 185MBq of [^{18}F] flutematol (Vizamyl, GE Healthcare, Marlborough, MA, USA) through a catheter placed in an intravenous line in an antecubital vein (Vandenberghe et al., 2010). PET acquisition was carried out for 20min, starting 90min after injection.

We performed *t*-tests to compare the Mn exposed workers and the controls. β-amyloid deposition in the ferroalloy workers was more diffuse than in controls (*P*, 0.05), as shown in Fig. 1. The major regions with increased beta-amyloid uptake were the anterior and posterior cingulate, entorhinal cortex and part of hippocampus, dorso-lateral prefrontal cortices. The cognitive function testing did not differ between the two groups as shown in Table 1.

To our knowledge, this is the first study showing increased β-amyloid brain deposition in manganese exposed individuals. Further research is warranted to test the hypothesis of β-amyloid as a predictor of Mn-induced cognitive decline. Additional investigation including the analysis of blood biomarkers of signaling proteins and plasma metabolites would be effective to identify prognostic or promising diagnostic characteristics of AD and cognitive dysfunction in the Mn-exposed group. The significance of the study is the identification of the putative mechanisms contributed to chronic Mn toxicity provides new insights into the understanding of etiological, therapeutic, and preventive approaches to neurodegenerative diseases.

4. Conclusions

The two case studies of the WTC responders and the ferromanganese workers outline the utility of modern brain imaging modalities in the understanding of neurotoxicity induced by exposure to airborne pollutants. These findings underline the importance of preventive action aimed to exposure reduction in the workplaces. Given the long-term projection of cognitive impairment, protection of the brain from workplace hazards is of fundamental importance. Accelerated cognitive decline can lead to neurodegeneration, and it is imperative to act on modifiable factors to minimize the potential risk of dementia and parkinsonian disturbances in heavily exposed populations. Further studies are needed to understand the potential underlying mechanisms leading to brain amyloidosis and

neurodegeneration induced by neurotoxicants, especially when carried by small or ultrafine particles able to access the brain through the olfactory pathway (Lucchini et al., 2012b).

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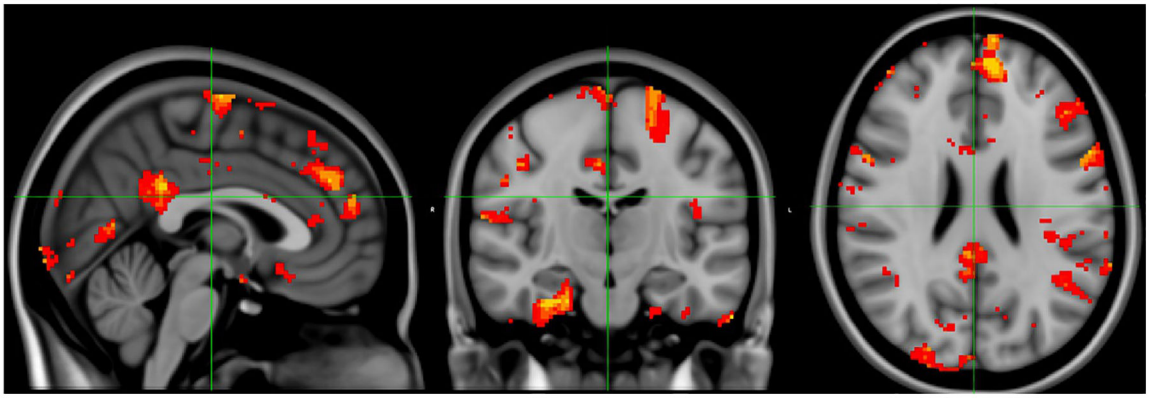

Fig. 1.

Brain β-amyloid PET scanning showed widely diffused higher β-amyloid accumulation in the ferroalloy workers. Significant voxels ($P < 0.05$) are displayed in red superimposed on a standard anatomical MRI scan.

Table 1

The cognitive function testing did not differ between the two Mn exposed and control (non-exposed) groups

	Exposed (*N* = 6)	Not Exposed (*N* = 5)	Total (*N* = 11)	*P* value
Digit Span Standard Score				0.745
Mean (SD)	9.8 (1.9)	9.5 (1.3)	9.7 (1.6)	
Median (Q1, Q3)	9.5 (9.0, 11.5)	9.5 (8.8, 10.2)	9.5 (9.0, 10.8)	
Semantic Fluency Standard Score				0.927
Mean (SD)	47.0 (8.0)	46.6 (8.7)	46.8 (7.9)	
Median (Q1, Q3)	46.8 (41.2, 49.7)	44.3 (40.3, 46.8)	44.3 (40.3, 49.6)	
Phonemic Fluency Standard Score				0.584
Mean (SD)	26.4 (8.1)	24.2 (5.0)	25.4 (6.6)	
Median (Q1, Q3)	26.4 (19.8, 32.1)	26.0 (24.0, 26.5)	26.0 (20.6, 29.7)	
Total time dominant hand				0.361
Mean (SD)	69.4 (5.3)	72.9 (4.4)	71.0 (5.0)	
Median (Q1, Q3)	70.2 (66.2, 71.7)	73.0 (69.0, 75.3)	70.7 (68.7, 74.2)	
Total time dominant hand				0.465
Mean (SD)	77.8 (8.2)	76.0 (8.5)	76.9 (7.9)	
Median (Q1, Q3)	80.4 (74.4, 83.9)	72.0 (71.6, 74.2)	74.3 (71.7, 83.0)	
MOCA score adjusted				0.454
Mean (SD)	25.0 (2.8)	24.0 (2.2)	24.5 (2.5)	
Median (Q1, Q3)	26.5 (23.0, 27.0)	24.0 (23.0, 25.0)	25.0 (22.5, 27.0)	
Standard copy score				0.522
Mean (SD)	31.9 (3.7)	32.8 (5.1)	32.3 (4.2)	
Median (Q1, Q3)	32.5 (28.7, 34.9)	34.2 (31.5, 36.2)	34.2 (29.3, 35.5)	
Standard recall score				0.584
Mean (SD)	13.5 (3.5)	13.9 (8.1)	13.7 (5.7)	
Median (Q1, Q3)	13.8 (11.9, 16.0)	10.2 (9.5, 13.4)	12.8 (9.9, 15.6)	
Standard score words immediate retrieval				1
Mean (SD)	39.2 (10.8)	38.2 (14.4)	38.8 (11.6)	
Median (Q1, Q3)	39.3 (33.8, 43.3)	35.5 (26.4, 47.3)	39.3 (27.9, 44.6)	
Standard score words delay retrieval				0.67
Mean (SD)	7.7 (3.1)	8.5 (5.3)	8.0 (3.8)	
Median (Q1, Q3)	8.5 (5.2, 10.0)	7.5 (4.3, 11.8)	8.5 (4.3, 10.6)	
Words recognition test				0.426
Mean (SD)	14.2 (1.2)	13.5 (1.7)	13.9 (1.4)	
Median (Q1, Q3)	14.5 (14.0, 15.0)	14.0 (13.2, 14.2)	14.0 (14.0, 15.0)	
Short story standard score				0.855
Mean (SD)	7.4 (2.9)	6.9 (4.6)	7.2 (3.6)	
Median (Q1, Q3)	7.5 (5.1, 9.4)	6.6 (5.2, 6.7)	6.6 (4.9, 9.1)	
Sniffin Identification Score				0.665

	Exposed (*N* = 6)	**Not Exposed (*N* = 5)**	**Total (*N* = 11)**	***P* value**
Mean (SD)	12.0 (2.1)	12.4 (1.9)	12.2 (1.9)	
Median (Q1, Q3)	12.0 (10.0, 13.0)	13.0 (13.0, 13.0)	13.0 (10.5, 13.0)	
TMT Standard score time part a				0.715
Mean (SD)	24.1 (7.9)	23.6 (10.4)	23.9 (8.6)	
Median (Q1, Q3)	25.1 (17.9, 30.3)	20.1 (19.8, 20.5)	20.5 (17.8, 28.9)	
TMT Standard score time part b				1
Mean (SD)	71.4 (60.0)	58.0 (41.7)	66.9 (52.3)	
Median (Q1, Q3)	69.5 (18.2, 115.6)	52.3 (35.9, 77.3)	52.3 (19.4, 102.2)	
TMT Standard score time part a and b				1
Mean (SD)	47.6 (55.2)	32.0 (31.0)	42.4 (47.0)	
Median (Q1, Q3)	45.6 (3.9, 84.3)	36.7 (17.8, 48.6)	36.7 (−1.1, 60.4)	