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Respirator usage protects brain white matter from welding fume exposure: a pilot magnetic resonance imaging study of welders

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Abstract

Welding fume exposure has been associated with structural brain changes and a wide variety of clinical and sub-clinical outcomes including cognitive, behavioral and motor abnormalities.

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Declaration of interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Respirator use has been shown to decrease exposure to welding fumes; however, the associations between respirator use and health outcomes, particularly neurologic health, have been understudied. In this preliminary study, we used diffusion tensor imaging (DTI) to investigate the effectiveness of respirator use in protecting workers' white matter (WM) from the harmful effects related to welding fume exposure. Fractional anisotropy (FA), a common DTI measurement of water diffusion properties, was used as a marker of WM microstructure integrity. We hypothesized that FA in brain regions involved in motor and neurocognitive functions would differ between welders reporting respirator use compared to those not using a respirator. We enrolled a pilot cohort of 19 welders from labor unions in the New York City area. All welders completed questionnaires to assess welding history and occupational health. All completed a DTI acquisition on a 3T Siemens scanner. Partial least squares discriminant analysis (PLS-DA), a bioinformatic analytical strategy, was used to model the divergence of WM microstructures in 48 regions defined by the ICBM-DTI-81 atlas between respirator users compared to non-users. This yielded an effective discrimination of respirator users from non-users, with the uncinate fasciculus, the cerebellar peduncle and the superior longitudinal fasciculus contributing most to the discrimination of these groups. These white matter tracts are involved in widespread motor and cognitive functions. To our knowledge, this study is the first to suggest a protective effect of respirator on WM microstructure, indicating that the lack of respirator may present unsafe working conditions for welders. These preliminary findings may inform a larger, longitudinal intervention study that would be more appropriate to investigate the potential protective effect of respirator usage on brain white matter in welders.

Keywords

welding; neuroimaging; respirator; diffusion tensor imaging; white matter; Partial least squares discriminant analysis

2.1. Introduction

The process of welding generates nano-sized metal particulates that can enter the body via the respiratory or olfactory tracts and lead to adverse health outcomes (Antonini, 2003). Welding fumes contain several metals that are known to be toxic to the central nervous system such as manganese (Mn), iron (Fe), cadmium (Cd), aluminum (Al) and lead (Pb) (Antonini, 2003; Flynn and Susi, 2010). Among these metals, Mn has been reported to accumulate in the basal ganglia (BG), and produce cognitive, psychiatric and motor deficits (Josephs et al., 2005). To protect workers from adverse health effects associated with exposure to welding fumes, the United States Occupational Safety and Health Administration (OSHA) established the Permissible Exposure Limit (PEL) for Mn compounds and fume is 5 mg/m^3. OSHA requires companies to maintain low exposure levels by implementing engineering controls including local exhaust ventilation, work practice controls such as adjusting the way a task is performed, and administrative controls such as minimizing the number of exposed workers. Only if these controls are not feasible, OSHA requires employers to provide workers with respirators (OSHA 2009). Studies have established the effectiveness of respirators in decreasing exposure to welding fumes and

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metals (Cho et al., 2011); however, the associations between respirator use and health outcomes, particularly neurologic health, have been understudied.

Welding fume exposure has been linked to a wide variety of clinical and sub-clinical outcomes ranging from pulmonary, cognitive, behavioral and motor outcomes (Antonini, 2003; Ja et al., 2012; O'Neal and Zheng, 2015; Santamaria et al., 2007). Clinical motor disorders such as parkinsonian-like syndrome and tremor (Bailey et al., 2018; Josephs et al., 2005; Racette et al., 2017, 2012; Sanchez-Ramos et al., 2011; Santamaria et al., 2007), and subclinical motor deficits such as decreased motor speed, movement stability and hand dexterity (Bowler et al., 2007, 2006; Chang et al., 2009; Lewis et al., 2016; Ma et al., 2018) have been associated with increasing welding fume exposure. In addition to motor deficits, neurocognitive impairments observed in welders include altered working memory, executive functions, language processing skills and increased prevalence of neuropsychiatric symptoms (Chang et al., 2010; Ellingsen et al., 2014; Opasso et al., 2016; Seo et al., 2016).

Structural brain imaging studies investigating associations between occupational exposure to welding fumes and brain abnormalities have focused primarily on the basal ganglia (BG). Several studies have reported BG abnormalities in welders, including T1 hyperintensities (Criswell et al., 2012; Pesch et al., 2018; Sen et al., 2011; Zaiyang et al., 2014), lower diffusion tensor imaging (DTI) - apparent diffusion coefficient (ADC) (Criswell et al., 2012), higher Pallidal Index (PI) (Criswell et al., 2019; Lucchini et al., 2000) and lower fractional anisotropy (FA) (Lee et al., 2016; E.-Y. Lee et al., 2018; Lewis et al., 2016).

Structural white matter (WM) abnormalities have also been described in welders. WM microstructure has been increasingly recognized in recent years as critical for human cognition and behavior (Filley and Fields, 2016). WM tracts encompass approximately half of the total brain volume and connect gray matter regions into functional networks, enabling humans to execute complex cognitive tasks (Schmahmann and N Pandya, 2006). Diffusion tensor imaging (DTI) is an MRI sequence that tracks the movement of water molecules to provide information on the integrity of WM in the brain (Mori and Zhang, 2006; Pierpaoli et al., 1996). Fractional anisotropy (FA) is a type of DTI measure that provides information on the degree to which diffusivity occurs along the fiber axis as opposed to perpendicular to it, and can be used to investigate WM microstructure (Basser and Pierpaoli, 1996). Previous DTI studies in welders demonstrated associations between changes in BG FA and both welding fume exposure, and motor dysfunctions (Lee et al., 2016; Lewis et al., 2016). Voxel-wise whole-brain analysis of FA values showed reduced FA in the corpus callosum and in the frontal WM in welders compared to controls as well as associations between motor and cognitive performance and FA in welders (Kim et al., 2011).

Although a growing body of evidence suggests a harmful effect of exposure to welding fume on WM, the efficacy of respirator use in reducing these effects has not been studied. In the present study, we used DTI-FA to investigate whether the use of a respirator protects welders WM microstructure from the harmful effects related to welding fume exposure. As welding has been associated with wide-ranging clinical manifestations, we used whole-brain data-driven methods with no a priori assumptions in regards to the brain regions affected by welding exposure. Although the most common approach for analyzing DTI-FA data

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is the generalized linear model (GLM), we expected it would be underpowered for the detection of significant results in this pilot study, due to our small sample size and the need to correct the results for a high number of comparisons. Hence, we implemented a bioinformatic analytical strategy evaluated on the basis of predictive efficacy rather than on the basis of statistical significance. Using the supervised dimensionality-reduction inherent to this approach, we evaluated the predictive efficacy of dimensions derived from welders DTI-FA profiles in discriminating between respirators users and non-users. Moreover, using the features loadings, we were able to determine which regions contribute most to the overall divergence between respirator users/non-users.

Among a pilot of occupational welders, we hypothesized that FA in brain regions involved in motor and neurocognitive functions would differ between welders reporting respirator use compared to those who did not use a respirator.

1. Methods

2.2. Participants

Nineteen New York City welders participated in this pilot study. All participants were recruited from ironworker unions and were age 35 years or older with a minimum of 5 years welding experience. All had reported welding within the previous 12 months. In addition to MRI exclusion criteria (i.e., metal implants, claustrophobia, body mass index (BMI) > 35) study exclusion criteria included a current pregnancy, a history of cerebrovascular disease and previous head trauma or injury. We obtained MRI scans of WM connectivity using DTI, and self-reported occupational histories, including respirator use, from all participants. This study was approved by the Institutional Review Board of the Icahn School of Medicine at Mount Sinai. Written informed consent was obtained from all participants. We screened 23 volunteers for the study. From these, two welders exceeded a BMI of 35, and two welders screened positive for metal in or near the eyes. Quality MRI scans and occupational exposure data were available for all 19 subjects included in this analysis.

2.3. Occupational Questionnaire

All participants completed a questionnaire informing on occupational exposure validated in a population of boilermakers (Wong et al., 2014), including smoking history, BMI, welding history and respirator use. Welding history was reported as the cumulative number of lifetime years welding and as the type of welding. Respirator use in the last 12 months was reported as dichotomous yes/no variable. Welders reporting respirator use were asked to describe the type of respirator used: paper respirator, half face respirator or full-face respirator and estimate the time the respirator was used during welding activities.

2.4. MRI acquisition

All images were acquired on a Siemens 3T PET/MR located at the Translational and Molecular Imaging Institute (TMII). The following protocols were acquired: a short dual-echo sequence was obtained to screen for incidental abnormalities. An anatomical T1-weighted scan was obtained using an MPRage sequence (TR/TE=1900/2.5ms, FOV=23cm, Matrix 256x256, slice thickness 1.0mm). A DTI sequence was obtained using a

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Pulsed-Gradient Spin Echo sequence with 33 gradient directions (TR/TE=7800ms/101ms, FOV=23cm, Matrix = 128x128, slice thickness 3mm, b-value=1200s/mm2, 33 directions).

2.5. Image Analysis

DTI were reprocessed using FMRIB Software Library v6.0 (FSL) (www.fmrib.ox.ac.uk/fsl). First, images were eddy-current-corrected using eddy correct from the FDT diffusion toolbox (version 3.0). Next, we preformed brain extraction using BET (threshold of 0.3) and fitted diffusion tensors using DTIFIT from the FDT diffusion toolbox, creating single fractional anisotropy (FA) images for each subject. Co-registered FA images in Montreal Neurological Institute (MNI) brain space were computed using the Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006) workflow. The procedure involves skeletonization of the FA images to obtain centers of white matter tracts, thresholding (FA >0.2) of the FA skeletonized image to suppress areas of low mean FA and/or high inter-subject variability and projecting each subject's FA image onto the skeleton. The Johns Hopkins University ICBM-DTI-81 WM labels atlas was used to locate anatomical regions in MNI152 space (Mori, 2005). Mean FA was calculated for each atlas-defined region on each participant's co-registered MNI FA image computed from TBSS.

2.6. Statistical analyses

To test associations between self-reported respirator use defined as a dichotomous yes/no variable and brain WM mean FA in 48 regions, we pursued a bioinformatic analytical strategy appropriate for the simultaneous assessment of associations between respirator use and WM microstructure. Using respirator-use as our outcome variable, we implemented partial least squares discriminant analysis (PLS-DA) (Brereton, 2000; Brereton and Lloyd, 2014; L. C. Lee et al., 2018) to model the divergence of WM microstructures in respirator users and non-users. Using the mean FA values from the 48 regions as inputs, this supervised dimensionality-reduction technique constructs a lower-dimensional subspace that maximizes the separation between respirator users and non-users. In contrast to traditional linear modeling strategies, which are evaluated on the basis of statistical significance, the utility of this approach is evaluated on the basis of predictive efficacy; that is, how well do derived dimensions discriminate between respirators users/non-users. A receiver operating characteristic (ROC) curve was generated to predict respirator use from the first discriminant axis with varying classification thresholds. To quantify uncertainty in the ROC curve and discriminant prediction, a confidence interval of the ROC curve was computed using 2000 stratified bootstrap replicates. Further, per the method of Mason & Graham (Mason and Graham, 2002), we implemented a rank-based statistical test to determine if the performance of our classification algorithm was significantly better than a classification made at random. P-values derived from this method should be interpreted in the context of the model's overall predictive performance, rather than indicative of any individual feature. Finally, the loadings of each region on a given dimensional subscale were evaluated to determine which regions contribute most to the overall divergence between respirator users/non-users. PLS-DA models were implemented in R (v3.4) with the mixOmics package (Rohart et al., 2017).

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2. Results

2.1. Descriptive statistics

Sociodemographic and exposure characteristics of participants are summarized in Table 1. Among the 19 welders participating in this study, 11 reported wearing a respirator and 8 reported not wearing a respirator in the last 12 months. Due to very small variability in the types of respirator used (10 out of 11 welders reporting wearing non-disposable half-face respirator), respirator type was not considered in further analyses. Results show no significant differences between groups in age, BMI, number of years welding, smoking or race.

2.2. Partial least squares discriminant analysis (PLS-DA)

The PLS-DA analysis revealed a clear separation between respirator users and non-users, with two factors explaining 44% of the variance, as shown in Figure 1. These results indicate that underlying differences in the FA profiles of respirator users and non-users yield a sufficient signature to separate the two groups. A receiver operating characteristic (ROC) curve illustrating the sensitivity and specificity for predicting respirator use from the first discriminant axis, yield an area-under-the-curve (AUC) of 0.864 (0.685-1.00) (Figure 1B). Along discriminant axis 1, mean FA in both the left and right uncinate fasciculus, the right cerebellar peduncle, the cerebral peduncle, and the right external capsule had the highest loads and therefore contribute most to the differentiation of FA profiles of respirator users and non-users (Figures 2A & 3A). Along discriminant axis 2, mean FA in the left superior longitudinal fasciculus, the left and right sagittal stratum, the left fornix and the retro-lenticular part of the right internal capsule had the highest loads and therefore, contribute most to the differentiation of these groups (Figures 2B & 3B).

3. Discussion

In the present study, we provide preliminary evidence that respirator use among welders is predictive of WM microstructure integrity. In contrast to traditional linear modeling strategies, which are evaluated on the basis of statistical significance, we used PLS-DA analysis, evaluated on the basis of predictive efficacy, to discriminate FA profiles between respirators users and non-users. This supervised dimensionality-reduction approach showed a clear separation between FA profiles of respirator users and non-users. White matter tracts identified as high contributors to differentiating between FA profiles of the two groups are involved in widespread motor and cognitive functions including the uncinate fasciculus, the cerebellar peduncle and the superior longitudinal fasciculus.

The uncinate fasciculus (UF) had the largest contributions to component 1 of the PLS-DA analysis. The UF is a bidirectional long-range WM tract that connects lateral orbitofrontal cortex with the anterior temporal lobes and is considered to be part of the limbic system (Petrides and Pandya, 2007; Von Der Heide et al., 2013). Abnormalities in the UF have been associated with several psychiatric and progressive neurological conditions including aphasias (Galantucci et al., 2011), Alzheimer's disease (Kljajevic et al., 2016), dementia (Mc et al., 2009), anxiety (Phan et al., 2009) and psychopathy (Serra et al., 2012). Previous

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studies suggest it plays a role in episodic memory (Diehl et al., 2008), language (Papagno, 2011) and emotional processing (Coad et al., 2017). Interestingly, the UF is one of the latest developing tracts and is the only brain region that continues to develop beyond the age of 30 years (Hasan et al., 2007; Lebel et al.,2012). Hence, it can be hypothesized that a protective effect of respirator use on UF WM microstructure may imply a positive effect in regards to possible effects of exposure to welding fume.

The superior longitudinal fasciculus (SLF) had the largest contributions to component 2 of the PLS-DA analysis. The SLF is a bundle of fibers connecting the frontal cortex with the parietal, occipital and temporal lobes (Schmahmann et al., 2008; Yeterian et al., 2012). Similar to the UF, the SLF is part of the neural network enabling core processes such as attention, memory, emotions, and language (Kamali et al., 2014) and is thought to have a slow axonal and myelin maturation. SLF abnormalities have been associated with psychosis (Szeszko et al., 2018), depression (Ota et al., 2015) and inhibitory control (Urger et al., 2015). Our findings indicating an association between respirator use and WM in the SLF suggest that respirator use could protect neurocognitive functions in welders.

Other tracts identified as high contributors to differentiating respirator users and non-users are involved in motor functions. For example the right superior cerebellar peduncle (SCP) which carries information between the deep cerebellar nuclei (dentate nuclei) and the thalamus (Mori et al., 2008) consists mainly of efferent fibers and its primary functions involve motor adaptation. Another tract identified as high contributor is the cerebral peduncle which contains important fibers including the cerebral peduncular loop, the corticospinal tract and the corticobulbar tract. These numerous nerve tracts projecting from motor areas of the brain to various thalamic nuclei convey motor information to and from the brain to the rest of the body (Johns, 2014). The association between respirator use and WM in these motor tracts may, therefore, point to lower risk of motor Parkinson-like symptoms associated with exposure to welding.

In addition to DTI images, we acquired T1-weighted MRI sequence in this study. These images allowed us to calculate the pallidal index (PI), a semi-quantitative index of Mn accumulation in the brain (Li et al., 2014). We did not detect PI differences between respirator users and non-users. The reason for this finding may be related to the fact that welding fumes are a complex mixture composed of different metals containing a small percentage of Mn, but also aluminum, titanium, nickel, zinc, cadmium, copper, lead, fluorides, silicon, barium, calcium, and tin (Antonini et al., 2006; Balkhyour and Goknil, 2010). Thus, the effect of respirator use on welders WM microstructure may be related to the joint effect of multiple metals rather than the effect of Mn alone.

Overall, our results suggest associations between respirator use and FA in numerous brain WM tracts. These associations may indicate a protective effect of respirator use. Thus, it can be hypothesized that the use of respirator may mitigate the harmful effects of exposure to welding fume on welders' motor and cognitive functions. Importantly, detecting these associations within a sample size of only 19 welders, highlights the importance of our pilot findings. OSHA requires maintenance of safe and healthy working conditions and our findings suggest that the lack of respirator may present unsafe working conditions for welders. These preliminary findings may inform a larger, longitudinal intervention study that would be more appropriate to investigate the potential protective effect of respirator usage on brain white matter in welders. Similar to the WELDOX intervention study, in which the implementation of various protective measures on welders exposure led to a significant reduction of blood Mn concentration (Lehnert et al., 2014), a future study could use multidimensional exposure assessment to predict WM microstructure in relation to respirator usage. If confirmed, these findings may have implications for occupational safety regulations and policies.

Limitations

Further research is needed to address several limitations of this study. First, our small sample size prohibited a cross validation, limiting the generalization of our findings to other populations. A larger sample size may also provide more statistical power which could identify additional tracts associated with exposure to welding fume. In addition, our sample contained almost only males (one female out of 19), however this sex ratio is representative of the welders population. The collection of occupational history data on previous periods, including the type of welding performed and the type of respirator used, would have enabled us to detect welding activities that may present high risk health effects. Finally, our study lacked personal or ambient air exposure metrics that could inform regulatory standards. In addition to the PEL established by OSHA, \the American Conference of Governmental Industrial Hygienists (ACGIH) set the Threshold Limit Value (TLV) at 0.02 mg/m^3 and the National Institute for Occupational Safety and Health (NIOSH) determined the Recommended Exposure Limit (REL) for Mn is 1 mg/m^3 ST 3 mg/m^3 (NIOSH Federal Respiratory Regulations 42 CFR Part 84). Notably, guidelines are commonly based on exposure to single chemicals. The combined effect of exposure to multiple chemicals is considered by OSHA as the sum of the individual effects (OSHA, 1970). Future studies should be designed as longitudinal exposure reduction intervention studies and include multidimensional exposure assessments to address mixtures, data on the precise type of respirator used, personal and ambient biomarkers of exposure as well as data on neurocognitive functions.

4. Conclusion

To our knowledge, this study is the first to propose a protective effect of respirator on WM microstructure, suggesting that the lack of respirator may present unsafe working conditions for welders. Our findings show a protective effect of respirator usage on widespread WM tracts involved in both motor and neurocognitive processes. These preliminary findings may inform a larger, longitudinal intervention study that would be more appropriate to investigate the potential protective effect of respirator usage on brain white matter in welders.

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References

Antonini JM. Health Effects of Welding. Critical Reviews in Toxicology 2003;33:61–103. 10.1080/713611032. [PubMed: 12585507]

Antonini JM, Santamaria AB, Jenkins NT, Albini E, Lucchini R. Fate of manganese associated with the inhalation of welding fumes: Potential neurological effects. NeuroToxicology 2006;27:304–10. 10.1016/j.neuro.2005.09.001. [PubMed: 16219356]

Bailey LA, Kerper LE, Goodman JE. Derivation of an occupational exposure level for manganese in welding fumes. NeuroToxicology 2018;64:166–76. 10.1016/j.neuro.2017.06.009. [PubMed: 28624528]

Balkhyour MA, Goknil MK. Total Fume and Metal Concentrations during Welding in Selected Factories in Jeddah, Saudi Arabia. Int J Environ Res Public Health 2010;7:2978–87. 10.3390/ijerph7072978. [PubMed: 20717553]

Basser PJ, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. J Magn Reson B 1996; 111 :209–19. [PubMed: 8661285]

Bowler RM, Gysens S, Diamond E, Nakagawa S, Drezgic M, Roels HA. Manganese exposure: Neuropsychological and neurological symptoms and effects in welders. NeuroToxicology 2006;27:315–26. 10.1016/j.neuro.2005.10.007. [PubMed: 16343629]

Bowler RM, Roels HA, Nakagawa S, Drezgic M, Diamond E, Park R, et al. Dose–effect relationships between manganese exposure and neurological, neuropsychological and pulmonary function in confined space bridge welders. Occupational and Environmental Medicine 2007;64:167–77. 10.1136/oem.2006.028761. [PubMed: 17018581]

Brereton RG. Introduction to multivariate calibration in analyticalchemistry. Analyst 2000;125:2125–54. 10.1039/B003805I.

Brereton RG, Lloyd GR. Partial least squares discriminant analysis: taking the magic away. Journal of Chemometrics 2014;28:213–25. 10.1002/cem.2609.

Chang Y, Kim Y, Woo S-T, Song H-J, Kim SH, Lee H, et al. High signal intensity on magnetic resonance imaging is a better predictor of neurobehavioral performances than blood manganese in asymptomatic welders. NeuroToxicology 2009;30:555–63. 10.1016/j.neuro.2009.04.002. [PubMed: 19376157]

Chang Y, Lee J-J, Seo J-H, Song H-J, Kim J-H, Bae S-J, et al. Altered working memory process in the manganese-exposed brain. NeuroImage 2010;53:1279–85. 10.1016/j.neuroimage.2010.07.001. [PubMed: 20620213]

Cho H, Yoon C-S, Lee J-H, Lee S, Viner A, Johnson EW. Comparison of Pressure Drop and Filtration Efficiency of Particulate Respirators using Welding Fumes and Sodium Chloride. Ann Occup Hyg 2011;55:666–80. 10.1093/annhyg/mer032. [PubMed: 21742627]

Coad BM, Postans M, Hodgetts CJ, Muhlert N, Graham KS, Lawrence AD. Structural connections support emotional connections: Uncinate Fasciculus microstructure is related to the ability to decode facial emotion expressions. Neuropsychologia 2017. 10.1016/j.neuropsychologia.2017.ll.006.

Criswell SR, Nielsen SS, Warden MN, Flores HP, Lenox-Krug J, Racette S, et al. MRI Signal Intensity and Parkinsonism in Manganese-Exposed Workers. J Occup Environ Med 2019;61:641–5. 10.1097/JOM.0000000000001634. [PubMed: 31348423]

Criswell SR, Perlmutter JS, Huang JL, Golchin N, Flores HP, Hobson A, et al. Basal ganglia intensity indices and diffusion weighted imaging in manganese-exposed welders. Occup Environ Med 2012;69:437–43. 10.1136/oemed-2011-100119. [PubMed: 22447645]

Diehl B, Busch RM, Duncan JS, Piao Z, Tkach J, Lüders HO. Abnormalities in diffusion tensor imaging of the uncinate fasciculus relate to reduced memory in temporal lobe epilepsy. Epilepsia 2008;49:1409–18. 10.1111/j.1528-1167.2008.01596.x. [PubMed: 18397294]

Ellingsen DG, Kusraeva Z, Bast-Pettersen R, Zibarev E, Chashchin M, Thomassen Y, et al. The interaction between manganese exposure and alcohol on neurobehavioral outcomes in welders. Neurotoxicology and Teratology 2014;41:8–15. 10.1016/j.ntt.2013.ll.004. [PubMed: 24263125]

Filley CM, Fields RD. White matter and cognition: making the connection. J Neurophysiol 2016;116:2093–104. 10.1152/jn.00221.2016. [PubMed: 27512019]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Flynn MR, Susi P. Manganese, iron, and total particulate exposures to welders. J Occup Environ Hyg 2010;7:115–26. 10.1080/15459620903454600. [PubMed: 20013450]

Galantucci S, Tartaglia MC, Wilson SM, Henry ML, Filippi M, Agosta F, et al. White matter damage in primary progressive aphasias: a diffusion tensor tractography study. Brain 2011;134:3011–29. 10.1093/brain/awr099. [PubMed: 21666264]

Hasan KM, Sankar A, Halphen C, Kramer LA, Brandt ME, Juranek J, et al. Development and organization of the human brain tissue compartments across the lifespan using diffusion tensor imaging. Neuroreport 2007;18:1735–9. 10.1097/WNR.0b013e3282f0d40c. [PubMed: 17921878]

Ja M, Ar B, Lm N. Associations of Welding and Manganese Exposure With Parkinson Disease: Review and Meta-Analysis. Neurology 2012. 10.1212/WNL.0b013e3182698ced.

Johns P Chapter 3 - Functional neuroanatomy. In: Johns P, editor. Clinical Neuroscience, Churchill Livingstone; 2014, p. 27–47. 10.1016/B978-0-443-10321-6.00003-5.

Josephs KA, Ahlskog JE, Klos KJ, Kumar N, Fealey RD, Trenerry MR, et al. Neurologic manifestations in welders with pallidal MRI T1 hyperintensity. Neurology 2005;64:2033–9. 10.1212/01.WNL.0000167411.93483.Al. [PubMed: 15888601]

Kamali A, Flanders AE, Brody J, Hunter JV, Hasan KM. Tracing Superior Longitudinal Fasciculus Connectivity in the Human Brain using High Resolution Diffusion Tensor Tractography. Brain Struct Funct 2014;219. 10.1007/s00429-012-0498-y.

Kim Y, Jeong KS, Song H-J, Lee J-J, Seo J-H, Kim G-C, et al. Altered white matter microstructural integrity revealed by voxel-wise analysis of diffusion tensor imaging in welders with manganese exposure. NeuroToxicology 2011;32:100–9. 10.1016/j.neuro.2010.11.004. [PubMed: 21111757]

Kljajevic V, Dyrba M, Kasper E, Teipel S. Is the left uncinate fasciculus associated with verbal fluency decline in mild Alzheimer's disease? Translational Neuroscience 2016;7:89–91. 10.1515/tnsci-2016-0014. [PubMed: 28123827]

Lebel C, Gee M, Camicioli R, Wieler M, Martin W, Beaulieu C. Diffusion tensor imaging of white matter tract evolution over the lifespan. Neuroimage 2012;60:340–52. 10.1016/j.neuroimage.2011.11.094. [PubMed: 22178809]

Lee E-Y, Flynn MR, Du G, Lewis MM, Herring AH, Van Buren E, et al. Editor's Highlight: Lower Fractional Anisotropy in the Globus Pallidus of Asymptomatic Welders, a Marker for Long-Term Welding Exposure. Toxicol Sci 2016;153:165–73. 10.1093/toxsci/kfwll6. [PubMed: 27466214]

Lee E-Y, Flynn MR, Lewis MM, Mailman RB, Huang X. Welding-related brain and functional changes in welders with chronic and low-level exposure. Neurotoxicology 2018;64:50–9. 10.1016/j.neuro.2017.06.011. [PubMed: 28648949]

Lee LC, Liong C-Y, Jemain AA. Partial least squares-discriminant analysis (PLS-DA) for classification of high-dimensional (HD) data: a review of contemporary practice strategies and knowledge gaps. Analyst 2018;143:3526–39. 10.1039/C8AN00599K. [PubMed: 29947623]

Lehnert M, Weiss T, Pesch B, Lotz A, Zilch-Schöneweis S, Heinze E, et al. Reduction in welding fume and metal exposure of stainless steel welders: an example from the WELDOX study. Int Arch Occup Environ Health 2014;87:483–92. 10.1007/s00420-013-0884-7. [PubMed: 23719851]

Lewis MM, Lee E-Y, Jo HJ, Du G, Park J, Flynn MR, et al. Synergy as a new and sensitive marker of basal ganglia dysfunction: A study of asymptomatic welders. Neurotoxicology 2016;56:76–85. 10.1016/j.neuro.2016.06.016. [PubMed: 27373673]

Li S-J, Jiang L, Fu X, Huang S, Huang Y-N, Li X-R, et al. Pallidal Index as Biomarker of Manganese Brain Accumulation and Associated with Manganese Levels in Blood: A Meta-Analysis. PLoS One 2014;9. 10.1371/joumal.pone.0093900.

Lucchini R, E A, D P, R G, Mg P, G M, et al. Brain Magnetic Resonance Imaging and Manganese Exposure. Neurotoxicology 2000. https://pubmed.ncbi.nlm.nih.gov/11130281/ (accessed December 6, 2019).

Ma RE, Ward EJ, Yeh C-L, Snyder S, Long Z, Gokalp Yavuz F, et al. Thalamic GABA levels and occupational manganese neurotoxicity: Association with exposure levels and brain MRI. Neurotoxicology 2018;64:30–42. 10.1016/j.neuro.2017.08.013. [PubMed: 28873337]

Mason SJ, Graham NE. Areas beneath the relative operating characteristics (ROC) and relative operating levels (ROL) curves: Statistical significance and interpretation. Quarterly Journal of the Royal Meteorological Society 2002;128:2145–66. 10.1256/003590002320603584.

Mc C, M C, Q D, R L, E D, R K, et al. Altered Connections on the Road to Psychopathy. Molecular Psychiatry 2009. 10.1038/mp.2009.40.

Mori S, Oishi K, Jiang H, Jiang L, Li X, Akhter K, et al. Stereotaxic White Matter Atlas Based on Diffusion Tensor Imaging in an ICBM Template. Neuroimage 2008;40:570–82. 10.1016/j.neuroimage.2007.12.035. [PubMed: 18255316]

Mori S, Zhang J. Principles of diffusion tensor imaging and its applications to basic neuroscience research. Neuron 2006;51:527–39. 10.1016/j.neuron.2006.08.012. [PubMed: 16950152]

O'Neal SL, Zheng W. Manganese Toxicity Upon Overexposure: a Decade in Review. Curr Envir Health Rpt 2015;2:315–28. 10.1007/s40572-015-0056-x.

Opasso PR, Barreto S dos S, Ortiz KZ. Phonemic verbal fluency task in adults with high-level literacy. Einstein (Sao Paulo) 2016;14:398–402. 10.1590/S1679-45082016A03629. [PubMed: 27759830]

OSHA. Occupational safety and health standards: Occupational health and environmental control (Standard No. 1910.1000(d)(2)(i)). 1970.

Ota M, Noda T, Sato N, Hattori K, Hori H, Sasayama D, et al. White matter abnormalities in major depressive disorder with melancholic and atypical features: A diffusion tensor imaging study. Psychiatry and Clinical Neurosciences 2015;69:360–8. 10.llll/pcn.12255. [PubMed: 25384997]

Papagno C. Naming and the role of the uncinate fasciculus in language function. Curr Neurol Neurosci Rep 2011;11:553–9. 10.1007/s11910-011-0219-6. [PubMed: 21853238]

Pesch B, Dydak U, Lotz A, Casjens S, Quetscher C, Lehnert M, et al. Association of exposure to manganese and iron with relaxation rates R1 and R2*- magnetic resonance imaging results from the WELDOX II study. Neurotoxicology 2018;64:68–77. 10.1016/j.neuro.2017.08.008. [PubMed: 28847517]

Petrides M, Pandya DN. Efferent association pathways from the rostral prefrontal cortex in the macaque monkey. J Neurosci 2007;27:11573–86. 10.1523/JNEUROSCI.2419-07.2007. [PubMed: 17959800]

Phan KL, Orlichenko A, Boyd E, Angstadt M, Coccaro EF, Liberzon I, et al. Preliminary Evidence of White Matter Abnormality in the Uncinate Fasciculus in Generalized Social Anxiety Disorder. Biol Psychiatry 2009;66:691–4. 10.1016/j.biopsych.2009.02.028. [PubMed: 19362707]

Pierpaoli C, Jezzard P, Basser PJ, Barnett A, Di Chiro G. Diffusion tensor MR imaging of the human brain. Radiology 1996;201:637–48. 10.1148/radiology.201.3.8939209. [PubMed: 8939209]

Racette BA, Criswell SR, Lundin JI, Hobson A, Seixas N, Kotzbauer PT, et al. Increased risk of parkinsonism associated with welding exposure. Neurotoxicology 2012;33:1356–61. 10.1016/j.neuro.2012.08.011. [PubMed: 22975422]

Racette BA, Searles Nielsen S, Criswell SR, Sheppard L, Seixas N, Warden MN, et al. Dose-dependent progression of parkinsonism in manganese-exposed welders. Neurology 2017;88:344–51. 10.1212/WNL.0000000000003533. [PubMed: 28031394]

Rohart F, Gautier B, Singh A, Cao K-AL. mixOmics: An R package for 'omics feature selection and multiple data integration. PLOS Computational Biology 2017;13:e1005752. 10.1371/journal.pcbi.1005752. [PubMed: 29099853]

Sanchez-Ramos J, Reimer D, Zesiewicz T, Sullivan K, Nausieda PA. Quantitative Analysis of Tremors in Welders. Int J Environ Res Public Health 2011;8:1478–90. 10.3390/ijerph8051478. [PubMed: 21655131]

Santamaria AB, Cushing CA, Antonini JM, Finley BL, Mowat FS. State-of-the-science review: Does manganese exposure during welding pose a neurological risk? J Toxicol Environ Health B Crit Rev 2007;10:417–65. 10.1080/15287390600975004. [PubMed: 17710609]

Schmahmann J, N Pandya D. Fiber Pathways of the Brain, vol. xviii. 2006. 10.1093/acprof:oso/9780195104233.003.0014.

Schmahmann JD, Smith EE, Eichler FS, Filley CM. Cerebral white matter: neuroanatomy, clinical neurology, and neurobehavioral correlates. AnnN Y Acad Sci 2008;1142:266–309. 10.1196/annals.1444.017.

Sen S, Flynn MR, Du G, Tröster AI, An H, Huang X. Manganese Accumulation in the Olfactory Bulbs and Other Brain Regions of "Asymptomatic" Welders. Toxicol Sci 2011;121:160–7. 10.1093/toxsci/kfir033. [PubMed: 21307282]

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Seo J, Chang Y, Jang KE, Park JW, Kim Y-T, Park S-J, et al. Altered executive function in the welders: A functional magnetic resonance imaging study. Neurotoxicol Teratol 2016;56:26–34. 10.1016/j.ntt.2016.05.003. [PubMed: 27208889]

Serra L, Cercignani M, Basile B, Spanò B, Perri R, Fadda L, et al. White matter damage along the uncinate fasciculus contributes to cognitive decline in AD and DLB. Curr Alzheimer Res 2012;9:326–33. [PubMed: 22272613]

Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 2006;31:1487–505. 10.1016/j.neuroimage.2006.02.024. [PubMed: 16624579]

Szeszko PR, Tan ET, Uluğ AM, Kingsley PB, Gallego JA, Rhindress K, et al. Investigation of superior longitudinal fasciculus fiber complexity in recent onset psychosis. Prog Neuropsychopharmacol Biol Psychiatry 2018;81:114–21. 10.1016/j.pnpbp.2017.10.019. [PubMed: 29111405]

Urger SE, De Beilis MD, Hooper SR, Woolley DP, Chen SD, Provenzale J. The superior longitudinal fasciculus in typically developing children and adolescents: diffusion tensor imaging and neuropsychological correlates. J Child Neurol 2015;30:9–20. 10.1177/0883073813520503. [PubMed: 24556549]

Von Der Heide RJ, Skipper LM, Klobusicky E, Olson IR. Dissecting the uncinate fasciculus: disorders, controversies and a hypothesis. Brain 2013;136:1692–707. 10.1093/brain/awt094. [PubMed: 23649697]

Wong JYY, De Vivo I, Lin X, Grashow R, Cavallari J, Christiani DC. The Association Between Global DNA Methylation and Telomere Length in a Longitudinal Study of Boilermakers. Genet Epidemiol 2014;38:254–64. 10.1002/gepi.21796. [PubMed: 24616077]

Yeterian EH, Pandya DN, Tomaiuolo F, Petrides M. The Cortical Connectivity of the Prefrontal Cortex in the Monkey Brain. Cortex 2012;48:58–81. 10.1016/j.cortex.2011.03.004. [PubMed: 21481342]

Zaiyang L, Yue-Ming J, Xiang-Rong L, William F, Jun X, Chien-Lin Y, et al. Vulnerability of Welders to Manganese Exposure - A Neuroimaging Study. Neurotoxicology 2014;0:285–92. 10.1016/j.neuro.2014.03.007.

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Highlights

- Welding fume exposure has been associated with structural brain changes.
- Diffusion tensor imaging (DTI) is sensitive to microstructural tissue properties.
- PLS discriminant analysis (PLS-DA) differentiates welders based on DTI.
- Respirator use predicts white matter microstructure integrity.
- Affected white matter tracts are involved in motor and cognitive functions.

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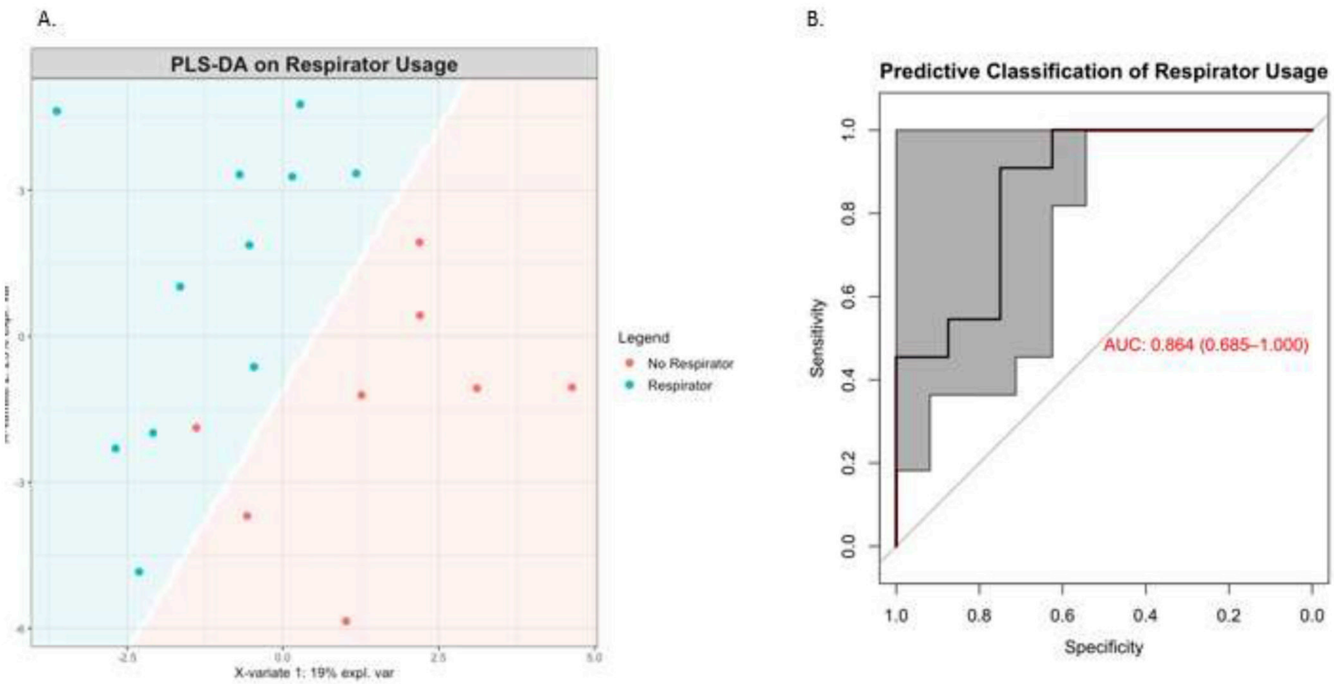

Figure 1.
Partial least squares discriminant analysis (PLS-DA)
Using the mean FA values from the 48 regions as inputs, the partial least squares discriminant analysis (PLS-DA) constructs a lower-dimensional subspace that maximizes the separation between respirator users and non-users. A. Red and blue points show individual participants scores on the first (x-axis) and second (y-axis) discriminate axes derived through PLS-DA. Separation of red and blue background (white line) illustrates the prediction area associated with each class, with subjects scoring in the blue space predicted to be respirator users, while those in red space are predicted to not be respirator users.
B. Receiver operating characteristic (ROC) curve illustrating the sensitivity and specificity for predicting respirator use from the first discriminant axis with varying classification thresholds. To quantify uncertainty in the ROC curve and discriminant prediction, a confidence interval of the ROC curve was computed using 2000 stratified bootstrap replicates, yielding an area-under-the-curve (AUC) of 0.864 (0.685-1.00).

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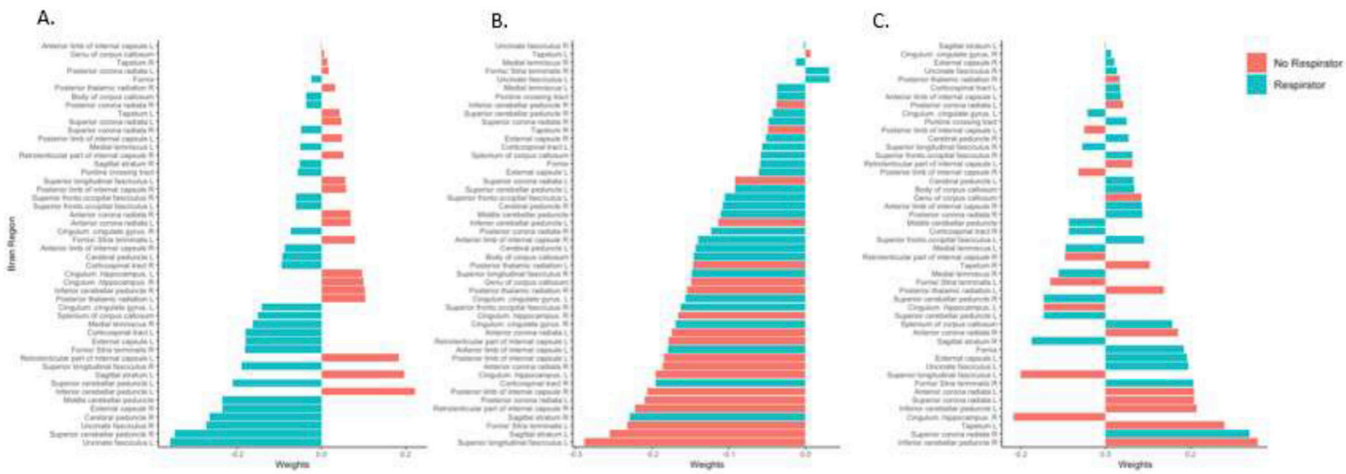

Figure 2.

Partial least squares discriminant analysis (PLS-DA) loadings.

The partial least squares discriminant analysis (PLS-DA) identifies the loadings of each region on a given dimensional subscale to determine which regions contribute most to the overall divergence between respirator users/non-users. Panels show variable loadings on the first (A), second (B), and third (C) PLS-DA discriminant axes. Loadings are color coded to indicate the group with a higher mean score on that variable, with blue lines indicating measures where respirator users had higher scores, and red lines indicating variables where respirator non-users had higher mean scores. The loadings direction (positive or negative) indicate the direction of the associations between the individual tract and respirator usage.

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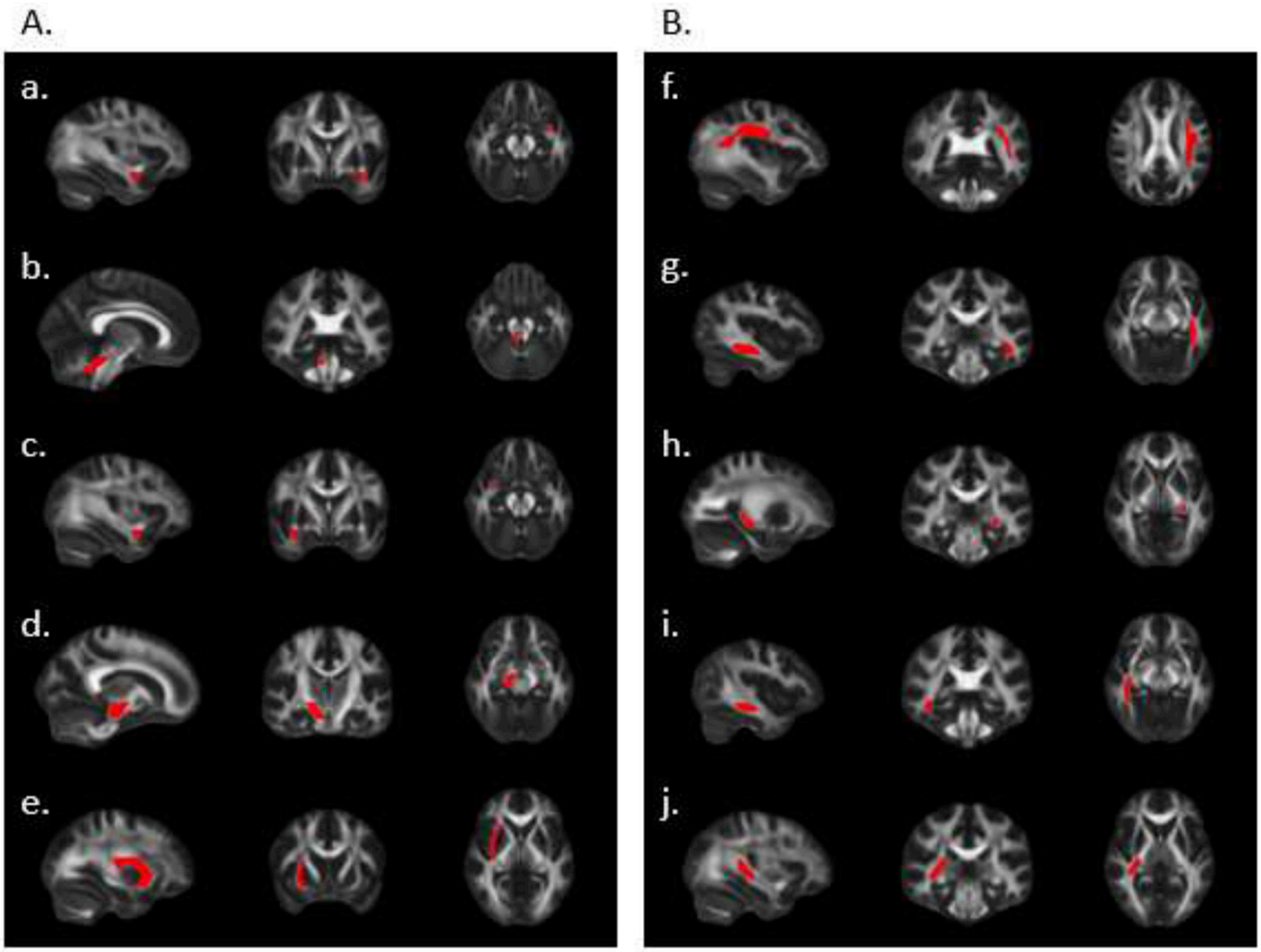

Figure 3.

White matter tracts identified as having the highest loadings in the Partial least squares discriminant analysis

Panels A and B show in red the five white matter tracts identified as having the highest loadings on the first and second PLS-DA discriminant axes, respectively. Tracts are overlaid on FMRIB58 FA 1mm standard image. (a) Left uncinate fasciculus, (b) right superior cerebellar peduncle, (c) right uncinate fasciculus, (d) right cerebral peduncle, (e) right external capsule, (f) left superior longitudinal fasciculus, (g) left sagittal stratum, (h) left Fornix/Stria terminalis, (i) right sagittal stratum, (j) right retrolenticular part of internal capsule.

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Table 1.

Sociodemographic characteristics of welders included in this pilot study (n = 19) stratified by self-reported respirator use.

Characteristic	All participants	Welders using respirator (n = 11)	Welders not using Respirator (n = 8)	p [a]
Sex; n (%)				
Male	18 (94.7)	10 (90.9)	8 (100)	Ref
Female	1 (5.3)	1 (9.1)	0 (0)	0.99
Smoking; n (%)				
No	6 (31.6)	4 (36.4)	2 (25)	Ref
Former	11 (57.9)	6 (54.5)	5 (62.5)	0.56
Yes	2 (10.5)	1 (9.1)	1 (12.5)	0.50
Race/Ethnicity; n (%)				
White	14 (73.7)	8 (72.7)	6 (75)	Ref
Black	3 (15.8)	2 (18.2)	1 (12.5)	0.71
Hispanic	2 (10.5)	1 (9.1)	1 (12.5)	0.61
Age (y);				
Mean (SD) [Range]	49.9 (8.6) [35 – 64]	50.5 (10.0) [35 – 64]	49.1 (6.7) [41 – 57]	0.71
BMI;				
Mean (SD) [Range]	30.2 (3.4) [23 – 35]	30.2 (4) [23 – 35]	30.2 (2.7) [26 – 34]	0.95
Years welding;				
Mean (SD) [Range]	19.5 (9.7) [5 – 43]	20.6 (10.6) [5 – 43]	18 (8.8) [5 – 34]	0.46
Type of welding process (%);				
Mean (SD) [Range]				
Grinding	22 (14) [0 – 50]	16 (11) [0 – 32]	29 (15) [10 – 50]	0.10 [b]
Burning	12 (11) [0 – 40]	10 (12) [0 – 40]	29 (15) [10 – 50]	0.33 [b]
Welding	66 (18) [33 – 93]	74 (13) [50 – 93]	55 (18) [33 – 86]	0.10 [b]
Type of welding tool (%);				
Mean (SD) [Range]				
Stick	60 (42) [0 – 100]	44 (45) [0 – 100]	82 (24) [50 – 100]	0.06 [b]
MIG	29 (38) [0 – 100]	37 (44) [0 – 100]	18 (24) [0 – 50]	0.24 [b]
TIG	1 (5) [0 – 20]	2 (6) [0 – 20]	0 (0) [0]	0.99 [b]
Time respirator used (%);				
Mean (SD) [Range]	n/a	76 (25) [40-100]	n/a	n/a

Note. BMI = Body Mass Index.

[a] p-values from a logistic linear regression (GLM) used to determine differences in sociodemographic characteristics between respirator users and non-users.

[b] Type of welding process and tool were reported as % of time, where all 3 types add up to 100%. Since these three variables are collinear, they were analyzed in three separate GLMs, adjusted for all the other covariates.

MIG = metal inert gas, TIG = tungsten inert gas.