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Association between shift work history and performance on the trail making test in middle-aged and elderly humans: the EpiHealth study

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Shift work has been proposed to promote cognitive disturbances in humans; however, conflicting evidence is also present. By using data from 7143 middle-aged and elderly humans (45–75 years) who participated in the Swedish EpiHealth cohort study, the present analysis sought to investigate whether self-reported shift work history would be associated with performance on the trail making test (TMT). The TMT has been proposed to be a useful neuropsychological tool to evaluate humans' executive cognitive function, which is known to decrease with age. After adjustment for potential confounders (e.g., age, education, and sleep duration), it was observed that current and recent former shift workers (worked shifts during the past 5 years) performed worse on the TMT than nonshift workers. In contrast, performance on the TMT did not differ between past shift workers (off from shift work for more than 5 years) and nonshift workers. Collectively, our results indicate that shift work history is linked to poorer performance on the TMT in a cohort of middle-aged and elderly humans.

1. Introduction

Multiple factors have been proposed either to curb or accelerate the rate of cognitive impairment across lifespan, such as duration and quality of sleep (Yaffe et al., 2014), engagement in regular physical activities (Benedict et al., 2013; Ruscheweyh et al., 2011), alcohol consumption (Stampfer et al., 2005), and educational level (Foubert-Samier et al., 2012; Steffener et al., 2016). In recent years, a handful of studies found that shift work may independently associate with cognitive functions in humans (Ansiau et al., 2008; Hart et al., 2006; Marquie et al., 2015). For instance, in a French prospective study on aging, health, and work (named VISAT), it was shown that night work (i.e., at least part of the work activity had taken place before 6 a.m. or after 10 p.m.) correlated with poorer performances on verbal memory and selective attention tests the next day (Ansiau et al., 2008). In a separate analysis using data from the VISAT population, it was further demonstrated that shift work (including rotating and night shifts) were linked to lower global cognitive test scores in those with a shift work history of more than 10 years (Marquie et al., 2015). Moreover, recovery of cognitive functions was seen among shift workers who reported to have left shift work for at least 5 years (Marquie et al., 2015). In line with these observational findings, short periods of experimentally simulated night shift work have also been shown to impair cognitive performance in humans, such as vigilance and inhibitory control (Hart et al., 2006).

The question is: why may shift workers run an increased risk for impaired cognitive performance compared with nonshift workers? One explanation could be that shift work has for example been associated with smoking, chronically poor sleep patterns, and psychological stress (Lindholm et al., 2012; Nea et al., 2015; Ramin et al., 2015). These factors have been implicated in accelerated cognitive aging (Cedernaes et al., 2016; Marshall et al., 2015; Ott et al., 1998). Moreover, disrupted circadian rhythms—a well-known consequence of atypical work schedules—have been

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linked to neurodegeneration (Kondratova and Kondratov, 2012; Wulff et al., 2010). For instance, deletion of the master clock gene Bmal1 in the mouse brain has been shown to increase neuronal oxidative damage (Musiek et al., 2013).

Contrary to the results previously described, there are however studies that did not find associations between shift work and cognitive performance in humans. For instance, using data from the United States Nurses' Health Study, no association between shift work history and composite measures of general cognition and verbal memory in later life was observed (Devore et al., 2013). With this in mind, additional large-scale studies are required to examine how shift work history may relate to cognitive performance in humans.

Thus, in the present study involving 7143 adults in the age range between 45 and 75 years, we sought to investigate if self-reported shift work history is associated with performance on the trail making test (TMT; Bowie and Harvey, 2006). Results from previous studies suggest that the TMT may have clinical utility as a measure of neurological deficits (Reitan and Wolfson, 1994) and cognitive impairment (Ashendorf et al., 2008). Given that shift work history has recently been associated with lowers scores on a global cognitive test (Marquie et al., 2015), we hypothesized that shift workers, compared with nonshift workers, would need more time to complete the TMT-A and TMT-B subtests and would obtain higher values for the ratio TMT-B/TMT-A. The present study was based on a post hoc stratification of data deriving from the Swedish EpiHealth cohort study.

2. Methods

2.1. Study population

The present study used data from the Swedish EpiHealth cohort study (started in 2011), www.epihealth.se (Lind et al., 2013). The primary objective of EpiHealth is to study how interactions between genotypes and lifestyle factors contribute to the development of common disorders in humans, such as cardiovascular diseases, cancer, and dementia. To this aim, participants in the age between 45 and 75 years voluntarily fill out an internet-based questionnaire, as well as visit 1 of 2 Swedish test centers (located in Malmö or Uppsala, Sweden). An invitation letter was sent to a random sample of participants who were resident in the municipalities and within the selected age limits using the Swedish Population Registry.

Variables used in the present study were extracted in March 2015 by the Karolinska Institute Biobank, Sweden. After exclusions because of missing data, 7143 were considered eligible for the present analysis (Table 1). Note that excluded participants may have had missing data on more than 1 parameter. Furthermore, as specified in Table 1, it must also be borne in mind that participants who were for instance unemployed, retired, or students at time of data collection were not presented job-related questions (including those on shift work history) during the computerized survey, and as such could not be entered into the present analysis.

The study was approved by the Ethics Committee of Uppsala University, and all participants gave written informed consent to participate.

2.2. Primary exposure variable—shift work history

When filling out the internet-based questionnaire, EpiHealth participants indicated whether they have performed shift work within the last 5 years or not. Participants could select 1 out of 4 possible responses: "*yes, currently*", "*yes, in the past*", "*no*", or "*don't know/don't want to answer*". The answer "*don't know/don't want to answer*" was treated as missing value (n = 33). In addition, in a separate question, participants indicated if they have ever worked at night or not. The possible responses were: "*no*", "*less than 1 year*", "*1 to 2 years*", "*3 to 5 years*", "*6 to 10 years*", "*11 to 20 years*", or "*more than 20 years*". Based on participants' responses at the time of the survey, the following shift work groups were constructed for the present study:

- Nonshift workers—answered both questions with no;
- Past shift workers—answered that they did not work shift during the past 5 years, but that they had worked night shifts more than 5 years ago.
- Recent former shift workers—stated that they performed shift work during the past 5 years but not at the time of data collection;
- Current shift workers—performed shift work at time of data collection.

Data on duration of shifts and shift plans (e.g., 3-day shift plans vs. 4-day shift plans, and so forth) were not collected in the EpiHealth study.

Table 1
Subject exclusionary criteria and sample sizes

Reason for exclusion	No. of exclusions	No. of available subjects
Initial sample size		19,135
Participant's performance on the trail making test was not available	−325	18,810
Participant did not answer questions related to shift work history[a]	−8312	10,498
Data on participant's responses to the psychological stress scale were not available	−495	10,003
No data available to calculate participant's cumulative sleep disturbance score	−265	9738
Participant's educational status was not specified	−3	9735
Data on participant's leisure physical activity were not available	−4	9731
No information on participant's current smoking status	−2430	7301
Participant's alcohol consumption was not specified	−128	7173
No data on participant's sleep duration	−9	7164
Participant's age more than 4 SD apart from the population mean	−1	7163
No data on participants' night shift work history[b]	−20	7143
Participants who were eligible for the main analysis		7143

Data were extracted by the Karolinska Institute Biobank, Sweden in March 2015.
Key: SD, standard deviation.
[a] Participants who were for instance unemployed, retired, or students at time of data collection. They were not presented job-related questions (including those on shift work history) during the computerized survey, and as such could not be entered into the present analysis.
[b] Only among those who stated at time of the internet-based survey that they have not worked shift within the last 5 y.

2.3. Primary outcome variable

A computerized version of the TMT was administered when participants were visiting 1 of 2 Swedish test centers. This cognitive test consists of 2 parts, TMT-A and TMT-B. The TMT-A determines cognitive processing speed, whereas the TMT-B measures executive functions (Bowie and Harvey, 2006). In TMT-A, participants were requested to connect circles labeled with numbers 1–25 in an ascending order. In TMT-B, participants must alternate between numbers (1–13) and letters (A–L) in an ascending order (i.e., 1-A-2-B and so forth). The instruction was to complete these subtests as quickly as possible.

During this computerized TMT, a computer mouse was used to join the symbols on the computer screen. To ensure that participants would understand the task procedure, they were provided computer-based instructions how to perform the TMT before the start of this test (including short test trials). An erroneously chosen path (e.g., 1-2-4) was immediately indicated by changing its color to red.

The variable of interest for the present study was the total time needed to connect correctly all symbols during each subtest, which included the time to correct erroneously chosen paths. In addition, the ratio between TMT-B and TMT-A was calculated (named TMT ratio in the following), as it has been proposed to be a more accurate measure of executive functions (Hester et al., 2005).

2.4. Confounders

Participants' educational status, physical activity (PA) during leisure time, alcohol consumption, and smoking habits (nonsmokers vs. smokers at the time of data collection) were assessed by the internet-based questionnaire. Participants' educational status was defined as follows: primary and elementary school (up to 9 years of formal schooling) versus upper secondary school (up to 12 years of formal schooling) versus university versus other (e.g., further training). PA during leisure time was measured on a scale ranging from 1 to 5 (1 = "mostly sedentary", 3 = "walking for 30 minutes per day", and 5 = "vigorous activity 60 minutes per day"). Based on their responses, participants were divided into 3 PA level groups: low (score range = 1–2), intermediate (score range = 3–4), and high (score range = 5). Alcohol consumption during the last 12 months was categorized as "never/seldom", "2–3 times a month", "1 time/week", "2–3 times a week", "4 times a week or more often", yielding a 5-level ordinal variable. Body mass index (BMI) was measured when participants visited 1 of 2 test centers.

To assess participants' perceived stress during the last month, the Perceived Stress Scale (PSS-10, scores range from 0 to 40) was administered (Cohen et al., 1983). The Cronbach's alpha of the 10 stress items used by this psychometric tool was 0.812.

Self-reported sleep disturbances were assessed by 6 symptoms: difficulties to stay awake during the day; difficulties getting back to sleep after nighttime awakenings; difficulties falling asleep; early awakenings; disturbed sleep; and feel not rested after sleep. The Cronbach's alpha was 0.77. Participants ratings (never/seldom, 1 to 3 times a month, 1 to 3 times a week, 4 or more times a week) were used to construct a cumulative sleep disturbance score (range 0–18, with 18 indicating the highest sleep difficulties). Participants were also asked to indicate how many hours per day they usually sleep. In light of previous findings suggesting that sleep duration is associated with health outcome parameters in a U-shaped fashion (e.g., mortality; Cappuccio et al., 2010), sleep duration was treated as ternary variable in our analysis, that is, <7 hours per day, 7–8 hours per day, and >8 hours per day.

Participants also provided a free text response concerning their main occupation and workplace during the last 5 years. The International Standard Classification of Occupation-08 released by the International Labor Organization (available at http://www.ilo.org/public/english/bureau/stat/isco/) and Swedish Standard Classification of Occupations (2012), which is based on The International Standard Classification of Occupation-08 (http://www.scb.se/sv_/Hitta-statistik/Publiceringskalender/Visa-detaljerad-information/?Publobjid=18597),were used to assign participants into white collar workers (managers; professionals; technicians and associate professionals; clerical support workers; and service and sales workers), blue collar workers (skilled agricultural, forestry and fishery workers; craft and related trades workers; plant and machine operators, and assemblers; and elementary occupations), and others. Note that participants were assigned to the occupational category "others" in case if there was insufficient information to identify the work category. Participants of the armed forces occupations class were assigned to the group "others" in the present analysis, as it only included 19 individuals.

2.5. Statistical analysis

All statistical analyses were performed using SPSS, version 22.0 (SPSS Inc, Chicago, IL, USA). Descriptive data are presented as means (standard deviation), unless otherwise specified. The chi-square test was used to analyze group differences for categorical variables. Numerical data were analyzed with univariate analyses of variance. In case of non-normally distributed variables, the nonparametric Kruskal-Wallis test was applied.

A generalized linear model was chosen as main statistical method to examine associations between shift work history and TMT outcomes. For all generalized linear models, the gamma distribution and log link function were chosen to account for non-normal distributions of TMT outcomes. Two models were applied: (1) a basic model including gender and shift work history as categorical factors and age as covariate; (2) a fully adjusted model treating gender, shift work history, educational status, physical activity level, alcohol consumption, smoking status, sleep duration, and occupational status as categorical factors, whereas age, perceived stress, cumulative sleep disturbance score, and BMI were entered as covariates into the analysis. Estimated marginal means (standard error of the mean) and parameter estimates of unstandardized β (95% confidence interval) using nonshift workers as reference category are reported. Interactions between shift work history and potential confounders were not modeled. Overall, a 2-sided p value of less than 0.05 was considered as statistically significant.

3. Results

3.1. Descriptive

Cohort characteristics, stratified by shift work history, are shown in Table 2. Compared with the nonshift worker group, individuals with shift work history were generally younger, less educated, had a higher prevalence of current smoking, felt more stressed, exhibited a higher BMI, more often reported to sleep less than 7 hours per day, and had a higher cumulative sleep disturbance score. In contrast, recent former and current shift workers reported to drink less alcohol than nonshift workers and past shift workers. Compared with the nonshift worker and past shift worker groups, there was a greater proportion of blue collar workers among recent former and current shift workers. No difference in leisure time physical activity was found between the shift work history groups. No difference in errors on TMT-A was observed. Total errors on TMT-B were more common among recent former and current shift workers.

Overall, participants needed more time to complete the TMT-A and TMT-B with increasing age (Spearman's r = 0.38 and r = 0.34 respectively, both $p < 0.0001$; Fig. 1).

3.2. Association between shift work history and performance on the TMT

Raw mean values ± standard deviation on the performance on both TMT subtests and TMT ratio, stratified by shift work history, are shown in Fig. 2.

Table 2
Participants' characteristics, stratified by self-reported shift work history

Parameter	Non-SW	Past SW	Recent former SW	Current SW	*p* value
Total participants, n	4611	1531	358	643	—
Age, y, mean (SD)	56.2 (6.5)	55.5 (6.2)	55.0 (6.2)	54.6 (5.8)	0.000[a]
Females, n (%)	2854 (61.9)	828 (54.1)	181 (50.6)	392 (61.0)	0.000[b]
Educational status, n (%)					
Primary/elementary school	411 (8.9)	131 (8.6)	50 (14.0)	93 (14.5)	0.000[b]
Upper secondary school	1301 (28.2)	391 (25.5)	124 (34.6)	297 (46.2)	
University	2560 (55.5)	872 (57.0)	139 (38.8)	189 (29.4)	
Other	339 (7.4)	137 (8.9)	45 (12.6)	64 (10.0)	
Leisure PA level, n (%)					
Low	1392 (30.2)	459 (30.0)	100 (27.9)	180 (28.0)	0.412[b]
Medium	2986 (64.8)	994 (64.9)	232 (64.8)	422 (65.6)	
High	233 (5.1)	78 (5.1)	26 (7.3)	41 (6.4)	
Current smoker, n (%)					
No	4226 (91.7)	1372 (89.6)	295 (82.4)	560 (87.1)	0.000[b]
Yes	385 (8.3)	159 (10.4)	63 (17.6)	83 (12.9)	
Perceived stress score, mean (SD)	12.59 (5.72)	12.67 (5.52)	13.11 (5.28)	13.45 (6.04)	0.002[c]
Alcohol consumption, n (%)					
Never/seldom	795 (17.2)	275 (18.0)	87 (24.3)	192 (29.9)	0.000[b]
2–3 times/month	851 (18.5)	311 (20.3)	87 (24.3)	181 (28.1)	
1 time/wk	1004 (21.8)	327 (21.4)	85 (23.7)	116 (18.0)	
2–3 times/wk	1623 (35.2)	507 (33.1)	83 (23.2)	131 (20.4)	
≥4 times/wk	338 (7.3)	111 (7.3)	16 (4.5)	23 (3.6)	
BMI, kg/m^2, mean (SD)	25.99 (3.84)	26.37 (3.89)	27.13 (4.41)	26.89 (3.94)	0.000[a]
Sleep duration per day, n (%)					
<7 h	1519 (32.9)	556 (36.3)	134 (37.4)	254 (39.5)	0.002[b]
7–8 h	3005 (65.2)	949 (62.0)	219 (61.2)	370 (57.5)	
>8 h	87 (1.9)	26 (1.7)	5 (1.4)	19 (3.0)	
Cumulative sleep disturbance score, mean (SD)	5.41 (3.74)	5.32 (3.72)	5.50 (3.83)	6.01 (3.91)	0.001[a]
Occupational status, n (%)					
White collar	4094 (88.8)	1350 (88.2)	275 (76.8)	504 (78.4)	0.000[b]
Blue collar	339 (7.4)	126 (8.2)	66 (18.4)	132 (20.5)	
Others	175 (3.8)	55 (3.6)	17 (4.7)	7 (1.1)	
TMT-A errors, n (%)					
No errors	2037 (44.2)	672 (43.9)	150 (41.9)	291 (45.3)	0.718[b]
1 error	1406 (30.5)	444 (29.0)	108 (30.2)	187 (29.1)	
≥2 errors	1168 (25.3)	415 (27.1)	100 (27.9)	165 (25.7)	
TMT-B errors, n (%)					
No errors	2447 (53.1)	803 (52.4)	166 (46.4)	317 (49.3)	0.001[b]
1 error	1025 (22.2)	365 (23.8)	78 (21.8)	140 (21.8)	
≥2 errors	1139 (24.7)	363 (23.7)	114 (31.8)	186 (28.9)	

A *p*-value smaller than 0.05 was considered as statistically significant.
Key: BMI, body mass index; PA, physical activity; SD, standard deviation; SW, shift workers; TMT, trail making test.
Analysis was based on.
[a] Kruskal-Wallis test.
[b] Pearson chi-square test.
[c] 1-way ANOVA.

Both current and recent former shift workers required more time to complete the TMT-A than nonshift workers in the basic model (Table 3). In contrast, no difference in the performance on this TMT subtest was found between past shift workers and nonshift workers. No statistically significant shift work group differences for the time to complete the TMT-A were however found in the fully adjusted model (Table 3).

With regards to the TMT-B, both the basic and fully adjusted model demonstrated that current and recent former shift workers required more time to join the letters and numbers on the computer screen (Table 3). Again, no differences in the performance on this TMT subtest were found between past shift workers and nonshift workers (Table 3).

The TMT ratio significantly differed between shift work history groups in all statistical models (Table 3). Compared with the nonshift worker reference group, both current and recent former shift workers exhibited a higher TMT ratio. In contrast, the TMT ratio did not differ between past shift workers and nonshift workers (Table 3).

4. Discussion

A considerably large proportion of today's workforce performs shift work, for example, up to 20% in Europe and United States. Both epidemiological and experimental studies have demonstrated that shift workers are at an increased risk for multiple diseases (Esquirol et al., 2011; Itani et al., 2011; Morris et al., 2015; Scheer et al., 2009; Vimalananda et al., 2015; Wang et al., 2015). However, knowledge regarding short- and long-term effects of shift work on parameters of brain health is still fragmentary. By using data from 7143 participants of the Swedish EpiHealth cohort study, we sought to investigate if shift work history links to the performance on the TMT. This test has been proposed to be a useful neuropsychological tool to evaluate humans' executive cognitive function, which is known to decrease with age (also seen in our study, see Fig. 1). Our analysis revealed that current and recent former shift workers (worked shifts during the past 5 years) performed worse, albeit with varying strength, on TMT outcomes than nonshift workers. No obvious group differences in

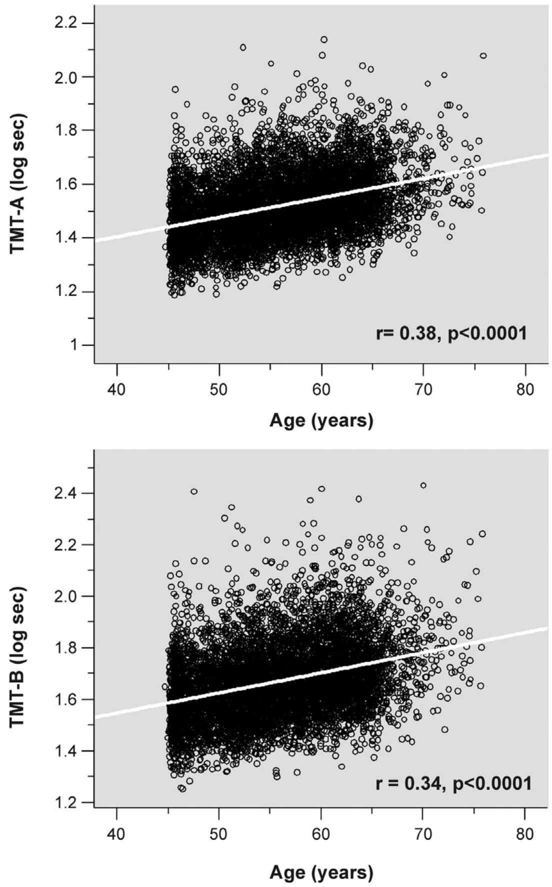

Fig. 1. Association between the performance on the trail making test and age in the Swedish EpiHealth cohort study. A Spearman correlation analysis was used to examine the association between performance on the trail making test (TMT, comprising subtests TMT-A and TMT-B) and age. Higher values indicate poorer performance on the TMT.

the performance on the TMT were, however, found between past shift workers and nonshift workers.

There is some preliminary evidence that shift work may adversely influence cognitive functions in humans (Ansiau et al., 2008; Machi et al., 2012; Marquie et al., 2015). For instance, working before 6 a.m. or after 10 p.m. has been linked to impaired performance on verbal memory and selective attention tests the day after (Ansiau et al., 2008). Moreover, shift work has been linked to lower scores on a global cognitive test in employed and retired humans (Marquie et al., 2015). Short periods of experimentally simulated night shift work have further been tied to impaired working memory performance (Hart et al., 2006). Collectively, these studies suggest that shift work impairs a variety of cognitive functions, both in the short and long term. In line with these results, we show that current and recent former shift workers required more time to complete the TMT, than nonshift workers. Importantly, no difference in performance on TMT was observed between nonshift workers and past shift workers, that is, those who had quit shift work more than 5 years ago at time of data collection. This could suggest that it may take at least 5 years of time-out for shift workers to perform equally well as nonshift workers on this neuropsychological test. A similar time span has previously been reported for restoring the performance on a global cognitive test in shift workers (Marquie et al., 2015). However, as of yet, a mechanistic explanation as to why shift workers require at least 5 years of time-out to recover their cognitive performance is lacking, and as such warrants further investigation.

There are also several findings in the literature that do not provide conclusive evidence for an association between shift work and cognitive impairment (Devore et al., 2013; Machi et al., 2012). For instance, in a prospective cohort study in nurses (mean age = 74.3 years old), no association between history of night shift work at midlife and cognitive function in later life was found (Devore et al., 2013). In this study, the assessment of cognitive function was based on global composite scores of general cognition and verbal memory (Devore et al., 2013), contrary to the TMT used in the present study. Another study involving 13 emergency physicians did not find changes in the performance on TMT before and after daylight and overnight shifts (Machi et al., 2012). Possible explanations for these contrasting results between the present and the aforementioned study could relate to differences in the design (the present study tested associations between shift work history and TMT, whereas the previous study tested acute effects of shifts on the performance of this task), sample size, and age (the present study involved middle-aged and elderly humans, whereas the previous study involved younger participants).

Our observational study is limited as we cannot yet establish causality. There are however several potential pathways that may explain the association between shift work history and cognitive performance. For instance, human and animal studies have shown that psychological stress conditions exert multiple adverse effects on the frontal lobe of the brain, comprising diminished blood perfusion (Chung et al., 2006), reduced gray matter volume (Li et al., 2014), and compromised neural plasticity (Zheng et al., 2011). Given that frontal lobe functions play an important role for the performance on the TMT (Stuss and Levine, 2002), it could be hypothesized that stress may account for the observed association between shift work and performance on this test. In line with this

Fig. 2. Participants' performance on the trail making test, stratified by shift work history. Left panel: raw mean ± SD on the time that was needed to complete the trail making test (TMT)-A. Middle panel: raw mean ± SD on the time that was needed to complete the TMT-B. Right panel: raw mean ± SD on the ratio TMT-B/TMT-A. Abbreviation: SD, standard deviation.

Table 3
Shift work history and performance on the trail making test

Dependent variable/shift work group	Basic model			Fully adjusted model		
	Estimated marginal means (SEM)	β (95% CI)	*p* value	Estimated marginal means (SEM)	β (95% CI)	*p* value
TMT-A, s						
Non-SW[a] (n = 4611)	33.93 (0.14)	0		36.77 (0.43)	0	
Past SW (n = 1531)	33.84 (0.23)	−0.003 (−0.018 to −0.013)	0.731	36.62 (0.47)	−0.004 (−0.019 to 0.011)	0.612
Recent former SW (n = 358)	35.42 (0.50)	0.043 (0.014–0.072)	**0.003**	37.48 (0.65)	0.019 (−0.009 to 0.048)	0.190
Current SW (n = 643)	35.84 (0.38)	0.055 (0.033–0.077)	**0.000**	37.54 (0.56)	0.021 (−0.002 to 0.043)	0.069
TMT-B, s						
Non-SW[a] (n = 4611)	48.85 (0.24)	0		56.48 (0.80)	0	
Past SW (n = 1531)	48.22 (0.40)	−0.013 (−0.032 to −0.006)	0.183	55.69 (0.87)	−0.014 (−0.032 to 0.004)	0.135
Recent former SW (n = 358)	54.09 (0.94)	0.102 (0.067–0.137)	**0.000**	59.91 (1.26)	0.059 (0.025–0.093)	**0.001**
Current SW (n = 643)	54.60 (0.71)	0.111 (0.084–0.138)	**0.000**	59.60 (1.08)	0.054 (0.027–0.081)	**0.000**
TMT-B/TMT-A						
Non-SW[a] (n = 4611)	1.47 (0.01)	0		1.57 (0.02)	0	
Past SW (n = 1531)	1.46 (0.01)	−0.007 (−0.023 to 0.009)	0.401	1.56 (0.02)	−0.008 (−0.024 to 0.009)	0.351
Recent former SW (n = 358)	1.56 (0.02)	0.060 (0.030–0.091)	**0.000**	1.64 (0.03)	0.040 (0.009–0.070)	**0.011**
Current SW (n = 643)	1.55 (0.02)	0.055 (0.031–0.078)	**0.000**	1.62 (0.03)	0.029 (0.005–0.052)	**0.018**

Results are presented as estimated marginal means (SEM), parameter estimates of unstandardized (β), and 95% confidence intervals (CI) based on generalized linear models using a gamma distribution with a log link function. Basic model: adjusted for age and gender. Fully adjusted model: controlled for gender, age, educational status, physical activity level, alcohol consumption, smoking status, perceived stress, cumulative sleep disturbance score, sleep duration, BMI, and occupational status.
Significant *p*-values are indicated in bold ($p < 0.05$).
Key: SEM, standard error of the mean; SW, shift workers; TMT, trail making test.
[a] Reference group.

view, we found that shift workers reported slightly higher perceived stress levels than nonshift workers (see also Table 2). Another possible explanation for our main finding could be that living under shift work conditions disrupts circadian processes in humans, a condition that has for instance recently been shown to promote neurodegenerative processes in the brain of transgenic animal models (Musiek et al., 2013). Shift work also impairs the ability to fall and stay asleep (Lajoie et al., 2015). Because short sleep has been associated with learning and memory impairments (Killgore, 2010; Rasch and Born, 2013), it could therefore be hypothesized that short sleep duration, in combination with circadian disruption may further restrain performance on the TMT-B in shift workers.

4.1. Strengths and limitations

The major strength of the present study is its large sample size. Moreover, results were robust to adjustments for multiple potential confounders, such as participants' age and educational level. Several limitations however apply: we did not have information regarding the type of shift work, for example, daytime rotating shift work versus day-night rotating shift work. Moreover, other potential confounders, such as diseases (e.g., hypertension) and medication, have not been included in the present analysis. It must also be borne in mind that participants, who were for instance unemployed at the time of data collection, were not presented job-related questions during the computerized survey, which may have limited the power of the current analysis. We further cannot exclude that some of our participants may have had a neurodegenerative disease or its prodrome, which may have affected the performance on the TMT. For instance, it has been shown that neurodegenerative signs of preclinical Alzheimer's disease (such as central nervous system amyloid beta burden) can occur in individuals long before its clinical onset (Caselli et al., 2009). Thus, this potential bias must be taken into account when interpreting our results. Finally, the sleep disturbance score used as covariate in the present study was largely based on symptoms that are also measured by established tools such as the Pittsburgh Sleep Quality Index (Buysse et al., 1989). However, it must be kept in mind that the accuracy of the sleep disturbance score to assess sleep disturbances in the general population must be interpreted with caution as long as it has not been validated through further studies.

5. Conclusion

Our results indicate that shift work history is linked to poorer performance on a widely used neuropsychological test, the TMT, in a cohort of middle-aged and elderly humans. This test has been proposed to be a useful neuropsychological tool to evaluate humans' executive cognitive function, which is known to decrease with age. It must however be kept in mind that the observed differences in the performance on the TMT between shift work history groups were relatively small. Finally, the finding that it may at least require a 5-year off-time period of shift work until humans can restore their executive functions must be interpreted with caution, given the cross-sectional design of our study.

Disclosure statement

All authors had full access to all data in the study and take responsibility for the integrity and accuracy of the data analysis. The authors have no conflicts to disclose. The study was approved by the Ethics committee of Uppsala University, Faculty of Medicine. All participants gave their written informed consent. The study was conducted according to Declaration of Helsinki Principles. Furthermore, the institutional review board of each participating institution approved this protocol.

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References

Ansiau, D., Wild, P., Niezborala, M., Rouch, I., Marquie, J.C., 2008. Effects of working conditions and sleep of the previous day on cognitive performance. Appl. Ergon. 39, 99–106.

Ashendorf, L., Jefferson, A.L., O'Connor, M.K., Chaisson, C., Green, R.C., Stern, R.A., 2008. Trail Making Test errors in normal aging, mild cognitive impairment, and dementia. Arch. Clin. Neuropsychol. 23, 129–137.

Benedict, C., Brooks, S.J., Kullberg, J., Nordenskjold, R., Burgos, J., Le Greves, M., Kilander, L., Larsson, E.M., Johansson, L., Ahlstrom, H., Lind, L., Schioth, H.B., 2013. Association between physical activity and brain health in older adults. Neurobiol. Aging 34, 83–90.

Bowie, C.R., Harvey, P.D., 2006. Administration and interpretation of the trail making test. Nat. Protoc. 1, 2277–2281.

Buysse, D.J., Reynolds 3rd, C.F., Monk, T.H., Berman, S.R., Kupfer, D.J., 1989. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 28, 193–213.

Cappuccio, F.P., D'Elia, L., Strazzullo, P., Miller, M.A., 2010. Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. Sleep 33, 585–592.

Caselli, R.J., Dueck, A.C., Osborne, D., Sabbagh, M.N., Connor, D.J., Ahern, G.L., Baxter, L.C., Rapcsak, S.Z., Shi, J., Woodruff, B.K., Locke, D.E., Snyder, C.H., Alexander, G.E., Rademakers, R., Reiman, E.M., 2009. Longitudinal modeling of age-related memory decline and the APOE epsilon4 effect. N. Engl. J. Med. 361, 255–263.

Cedernaes, J., Osorio, R.S., Varga, A.W., Kam, K., Schiöth, H.B., Benedict, C., 2016. Candidate mechanisms underlying the association between sleep-wake disruptions and Alzheimer's disease. Sleep Med. Rev. http://dx.doi.org/10.1016/j.smrv.2016.02.002.

Chung, Y.A., Kim, S.H., Chung, S.K., Chae, J.H., Yang, D.W., Sohn, H.S., Jeong, J., 2006. Alterations in cerebral perfusion in posttraumatic stress disorder patients without re-exposure to accident-related stimuli. Clin. Neurophysiol. 117, 637–642.

Cohen, S., Kamarck, T., Mermelstein, R., 1983. A global measure of perceived stress. J. Health Soc. Behav. 24, 385–396.

Devore, E.E., Grodstein, F., Schernhammer, E.S., 2013. Shift work and cognition in the nurses' health study. Am. J. Epidemiol. 178, 1296–1300.

Esquirol, Y., Perret, B., Ruidavets, J.B., Marquie, J.C., Dienne, E., Niezborala, M., Ferrieres, J., 2011. Shift work and cardiovascular risk factors: new knowledge from the past decade. Arch. Cardiovasc. Dis. 104, 636–668.

Foubert-Samier, A., Catheline, G., Amieva, H., Dilharreguy, B., Helmer, C., Allard, M., Dartigues, J.F., 2012. Education, occupation, leisure activities, and brain reserve: a population-based study. Neurobiol. Aging 33, 423.e15–423.e25.

Hart, C.L., Haney, M., Vosburg, S.K., Comer, S.D., Gunderson, E., Foltin, R.W., 2006. Modafinil attenuates disruptions in cognitive performance during simulated night-shift work. Neuropsychopharmacology 31, 1526–1536.

Hester, R.L., Kinsella, G.J., Ong, B., McGregor, J., 2005. Demographic influences on baseline and derived scores from the trail making test in healthy older Australian adults. Clin. Neuropsychol. 19, 45–54.

Itani, O., Kaneita, Y., Murata, A., Yokoyama, E., Ohida, T., 2011. Association of onset of obesity with sleep duration and shift work among Japanese adults. Sleep Med. 12, 341–345.

Killgore, W.D., 2010. Effects of sleep deprivation on cognition. Prog. Brain Res. 185, 105–129.

Kondratova, A.A., Kondratov, R.V., 2012. The circadian clock and pathology of the ageing brain. Nat. Rev. Neurosci. 13, 325–335.

Lajoie, P., Aronson, K.J., Day, A., Tranmer, J., 2015. A cross-sectional study of shift work, sleep quality and cardiometabolic risk in female hospital employees. BMJ Open 5, e007327.

Li, L., Wu, M., Liao, Y., Ouyang, L., Du, M., Lei, D., Chen, L., Yao, L., Huang, X., Gong, Q., 2014. Grey matter reduction associated with posttraumatic stress disorder and traumatic stress. Neurosci. Biobehav. Rev. 43, 163–172.

Lind, L., Elmstahl, S., Bergman, E., Englund, M., Lindberg, E., Michaelsson, K., Nilsson, P.M., Sundstrom, J., 2013. EpiHealth: a large population-based cohort study for investigation of gene-lifestyle interactions in the pathogenesis of common diseases. Eur. J. Epidemiol. 28, 189–197.

Lindholm, H., Ahlberg, J., Sinisalo, J., Hublin, C., Hirvonen, A., Partinen, M., Sarna, S., Savolainen, A., 2012. Morning cortisol levels and perceived stress in irregular shift workers compared with regular daytime workers. Sleep Disord. 2012, 789274.

Machi, M.S., Staum, M., Callaway, C.W., Moore, C., Jeong, K., Suyama, J., Patterson, P.D., Hostler, D., 2012. The relationship between shift work, sleep, and cognition in career emergency physicians. Acad. Emerg. Med. 19, 85–91.

Marquie, J.C., Tucker, P., Folkard, S., Gentil, C., Ansiau, D., 2015. Chronic effects of shift work on cognition: findings from the VISAT longitudinal study. Occup. Environ. Med. 72, 258–264.

Marshall, A.C., Cooper, N.R., Segrave, R., Geeraert, N., 2015. The effects of long-term stress exposure on aging cognition: a behavioral and EEG investigation. Neurobiol. Aging 36, 2136–2144.

Morris, C.J., Yang, J.N., Garcia, J.I., Myers, S., Bozzi, I., Wang, W., Buxton, O.M., Shea, S.A., Scheer, F.A., 2015. Endogenous circadian system and circadian misalignment impact glucose tolerance via separate mechanisms in humans. Proc. Natl. Acad. Sci. U. S. A. 112, E2225–E2234.

Musiek, E.S., Lim, M.M., Yang, G., Bauer, A.Q., Qi, L., Lee, Y., Roh, J.H., Ortiz-Gonzalez, X., Dearborn, J.T., Culver, J.P., Herzog, E.D., Hogenesch, J.B., Wozniak, D.F., Dikranian, K., Giasson, B.I., Weaver, D.R., Holtzman, D.M., Fitzgerald, G.A., 2013. Circadian clock proteins regulate neuronal redox homeostasis and neurodegeneration. J. Clin. Invest. 123, 5389–5400.

Nea, F.M., Kearney, J., Livingstone, M.B., Pourshahidi, L.K., Corish, C.A., 2015. Dietary and lifestyle habits and the associated health risks in shift workers. Nutr. Res. Rev. 28, 143–166.

Ott, A., Slooter, A.J., Hofman, A., van Harskamp, F., Witteman, J.C., Van Broeckhoven, C., van Duijn, C.M., Breteler, M.M., 1998. Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: the Rotterdam Study. Lancet 351, 1840–1843.

Ramin, C., Devore, E.E., Wang, W., Pierre-Paul, J., Wegrzyn, L.R., Schernhammer, E.S., 2015. Night shift work at specific age ranges and chronic disease risk factors. Occup. Environ. Med. 72, 100–107.

Rasch, B., Born, J., 2013. About sleep's role in memory. Physiol. Rev. 93, 681–766.

Reitan, R.M., Wolfson, D., 1994. A selective and critical review of neuropsychological deficits and the frontal lobes. Neuropsychol. Rev 4, 161–198.

Ruscheweyh, R., Willemer, C., Kruger, K., Duning, T., Warnecke, T., Sommer, J., Volker, K., Ho, H.V., Mooren, F., Knecht, S., Floel, A., 2011. Physical activity and memory functions: an interventional study. Neurobiol. Aging 32, 1304–1319.

Scheer, F.A., Hilton, M.F., Mantzoros, C.S., Shea, S.A., 2009. Adverse metabolic and cardiovascular consequences of circadian misalignment. Proc. Natl. Acad. Sci. U. S. A. 106, 4453–4458.

Stampfer, M.J., Kang, J.H., Chen, J., Cherry, R., Grodstein, F., 2005. Effects of moderate alcohol consumption on cognitive function in women. N. Engl. J. Med. 352, 245–253.

Steffener, J., Habeck, C., O'Shea, D., Razlighi, Q., Bherer, L., Stern, Y., 2016. Differences between chronological and brain age are related to education and self-reported physical activity. Neurobiol. Aging 40, 138–144.

Stuss, D.T., Levine, B., 2002. Adult clinical neuropsychology: lessons from studies of the frontal lobes. Annu. Rev. Psychol. 53, 401–433.

Vimalananda, V.G., Palmer, J.R., Gerlovin, H., Wise, L.A., Rosenzweig, J.L., Rosenberg, L., Ruiz Narvaez, E.A., 2015. Night-shift work and incident diabetes among African-American women. Diabetologia 58, 699–706.

Wang, P., Ren, F.M., Lin, Y., Su, F.X., Jia, W.H., Su, X.F., Tang, L.Y., Ren, Z.F., 2015. Night-shift work, sleep duration, daytime napping, and breast cancer risk. Sleep Med. 16, 462–468.

Wulff, K., Gatti, S., Wettstein, J.G., Foster, R.G., 2010. Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. Nat. Rev. Neurosci. 11, 589–599.

Yaffe, K., Falvey, C.M., Hoang, T., 2014. Connections between sleep and cognition in older adults. Lancet Neurol. 13, 1017–1028.

Zheng, C., Quan, M., Yang, Z., Zhang, T., 2011. Directionality index of neural information flow as a measure of synaptic plasticity in chronic unpredictable stress rats. Neurosci. Lett. 490, 52–56.