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CHRONIC EFFECTS OF SHIFT WORK ON COGNITION: FINDINGS FROM THE VISAT LONGITUDINAL STUDY

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Abstract

Objectives. Shift work, like chronic jet-lag, is known to disrupt workers' normal circadian rhythms and social life, and to be associated with increased health problems (e.g., ulcers, cardiovascular disease, metabolic syndrome, breast cancer, reproductive difficulties) and with acute effects on safety and productivity. However, very little is known about the long-term consequences of shift work on cognitive abilities. The aim of this study was to assess the chronicity and reversibility of the effects of shift work on cognition.

Method. We conducted a prospective cohort study of 3232 employed and retired workers (participation rate: 76%) who were 32, 42, 52 and 62 years old at the time of the first measurement (t1, 1996), and who were seen again five (t2) and ten (t3) years later. 1484 of them had shift work experience at baseline (current or past) and 1635 had not. The main outcome measures were tests of speed and memory, assessed at all three measurement times.

Results. Shift work was associated with impaired cognition. The association was stronger for exposure durations exceeding 10 years (dose effect; cognitive loss equivalent to 6.5 years of age-related decline in the current cohort). The recovery of cognitive functioning after having left shift work took at least 5 years (reversibility).

Conclusions. Shift work chronically impairs cognition, with potentially important safety consequences not only for the individuals concerned, but also for society.

Introduction

Several studies have demonstrated the acute deleterious effects that non-standard working hours have on alertness and cognitive efficiency during night shifts and the following days[e.g., 1-7]. However, only four studies have examined whether there may also be a chronic impact of abnormal work schedules on cognitive abilities (i.e. effects that last for several weeks, months or years). Cho, Ennaceur, Cole, and Suh[8] showed cognitive performance deficits and higher cortisol levels in airline cabin crew who had experienced repeated exposure to jet-lag for more than 3 years, compared to ground crew working for the same company. There were no such effects in aircrew who had been exposed for 3 years or less. Subsequently, Cho[9] found that chronic exposure to short recovery periods (≤ 5 days) from jet-lag were associated with lower cognitive performance, higher salivary cortisol and a smaller volume of the right temporal lobe. These findings were interpreted as showing a cumulative effect of chronic exposure to circadian disruption on cerebral structures and cognitive function.

A subsequent cross sectional study[10] also revealed cognitive deficits in male industrial workers who had been exposed to shift work relative to those that had not, and a decrease in memory performance with increasing exposure to shift work. These effects were independent of age and self-reported sleep quality and are similar to those of Cho and colleagues[8 9], in that they appear to reflect chronic exposure to circadian disturbances.

Most recently, a prospective cohort study of nurses found limited evidence of cognitive impairment in later life (≥ 70 years of age) being associated with history of exposure to rotating night-shift work, as reported in midlife (i.e. at the age of 58-68 years).[11] Participants with ≥ 20 years exposure demonstrated modest impairments in a test of general cognition. However, there were no associations between shift work history and composite measures of general cognition and verbal memory, or between shift work history and cognitive decline.

Given the potentially detrimental impact of shiftwork-related cognitive decline on job performance and quality of life, the current study examines the effect of shift work on cognition in a large sample of workers followed over ten years. The first set of analyses seeks to determine whether having experience of shift work affects cognition, by comparing workers who are either currently working shifts or who have prior experience of shift working with workers who have never worked shifts. The second set of analyses examines the effects of duration of exposure to shift work, by comparing three groups of workers: those with no experience of shift work, those with up to 10 years of exposure and those with more than 10 years of exposure. The third set of analyses examines whether there is a chronic effect of shift work that persists after exiting shift work, by comparing four groups of workers: those currently working shifts, former shift workers who left shift work within the previous five years, former shift workers who left shift work more than five years previously and those who have never worked shifts. No previously published studies have examined whether such chronic effects of shift work on cognition are reversed following the cessation of shift work.

Methods

Participants and procedure. The data were taken from the VISAT study[12]. The initial sample was composed of 3232 present and former wage earners covering a wide range of occupations and economic sectors. The overall distribution by gender and socioeconomic position was very close to that observed at the national level by the French national institute for statistics and economic studies (Insee). Participants were exactly 32-, 42-, 52- and 62-years old at the time of the first data collection (1996, t1). In the older age cohort 83% were retirees at t1. Participants were randomly drawn from the patient list of 94 occupational physicians in three southern regions of France and were volunteers (participation rate: 76%). These lists comprised all the salaried workers in the region, as all workers in France have a mandatory annual medical assessment of their aptitude to work. Data were collected through questionnaires and clinical examination by occupational physicians especially trained for the purpose of the study, during this annual assessment. Two subsequent data collections took place in 2001 (t2) and 2006 (t3). All those who participated at t1 were invited to participate at t2 and again at t3, irrespective of whether they were still in work. Data for the current study were available for 3119 participants at t1. Of these, 2183 were seen again at t2, and 1253 at t3. A total of 1197 were seen on all three occasions (56 participants who were not seen again at t2 were seen again at t3).

Shift work. The shift work measures used in the present study were taken from the ESTEV cohort study[e.g.13] and correspond to accepted national and international definitions of nightwork[14]. At each measurement occasion, the participants were asked whether, for more than 50 days per year, their work schedule (i) involved rotating shift work (e.g., alternating morning, afternoon, and night shifts), or (ii) did not allow them to go to bed before midnight, or (iii) resulted in them having to get up before 5 a.m., or (iv) prevented them sleeping during the night (night work). Possible responses for each question were: "yes, currently" (current), "not now, but yes in the past" (past), or "never" (never). Note that this operationalization means that the "never" category, which serves as a control group in subsequent analyses, may include participants with a small amount of shift work exposure (≤50 days per year). Thus any observed effect of shift work on cognition runs the risk of being underestimated in this context. At baseline, the percentage of each response category (current, past, never) was, respectively, 18.5%, 17.9%, 63.6% for rotating shift work, 8.0%, 12.5%, 79.5% for the second work schedule ("midnight"), 11.8%, 15.4%, 72.8% for the third one ("5 a.m."), and 7.2%, 11.5%, 81.3% for the fourth one ("night"). For each of the four questions, information was collected on cumulative exposure duration and how many years had elapsed since they had stopped working such a schedule. In the present paper those who answered "yes currently" or "in the past" to any of these four questions at t1 were considered to be working, or to have previously been working, on some form of shift system at t1. Those with no experience of shift work are defined as "day workers". We could not calculate the total exposure to all types of atypical work schedules by summing the exposures to each, since they were not mutually exclusive. For example, if a participant reported 1 year of exposure to each type of atypical work schedule, their total exposure to any type of atypical work schedule could be anything between 1 and 4 years, depending on the degree of overlap. For this reason, analyses of exposure duration were confined to rotating shift work (which was the most commonly reported of the four types of atypical work schedule).

Cognitive tests. Participants undertook three sets of cognitive tests on each measurement occasion: (1) a verbal episodic memory test adapted from the Rey Verbal Learning Test[15], including immediate and delayed retrieval tests. The participant was read the same list of 16 words three times, and was immediately asked to recall the words after each time. After a delay of 15 minutes, filled with other tests, the participant undertook a delayed free recall test, followed by a delayed recognition test. In the latter, the participant was required to locate the 16 previously learned words that were randomly mixed in with 32 new words. Five memory measures were thus recorded: 3 immediate free recalls, 1 delayed free recall and 1 delayed recognition measure; (2) the Digit-Symbol Substitution subtest of the Wechsler Adult Intelligence Scale[16], a test mainly reflecting processing speed[17]; and (3) a selective attention test derived from the Sternberg test[18] which was composed of two subtests. The first was a task consisting of looking as quickly as possible through a line of

58 alphabetic characters to find a target letter shown in the margin. This task was repeated six times, on six lines with a different target each time. The second subtest also had six lines of 58 alphabetic characters, but this time the memory load was greater because the target to be located was one of four letters shown in the margin. No time constraint was imposed for memory tests, while for the other tests, participants were instructed that speed was an important aspect of the task.

In order to summarize information from the 8 cognitive tests, a Principal Component Analysis (PCA) was performed. The first two axes accounted for 53.4% and 14.8% of the total variance respectively. The first axis was a general performance axis that separated subjects who obtained high scores in every test from subjects who obtained low scores. The second axis ranked individuals in terms of the difference between their scores on the 5 memory orientated tests and their scores on the 3 speed orientated tests. The remaining 5 axes obtained with the PCA had no straightforward interpretation in term of type of tests or ability, and were thus deemed to be of little interest.

A performance variable was constructed from this PCA, based on the factorial scores on the first axis and was treated as a global cognitive performance score. Given the structure of the second axis, we decided to examine the possible differential impact of shift work on memory and speed performances. As it was not possible to extract memory and speed scores directly from axis 2 of the PCA, we performed two ancillary PCAs based respectively on the 5 memory oriented tests and on the 3 speed oriented tests. The first axis of the memory PCA accounted for 72.0% of the total variance and the first axis of the speed PCA accounted for 61.0% of the total variance. The factorial scores of the first axis of the memory PCA were thus used to create a memory performance variable while those of the first axis of the speed PCA were used to create a speed performance variable. We used factorial scores instead of (standardized) means in order to maximize the variance summarized by the factorial axes.

The three cognitive variables (global cognitive performance, memory performance, and speed performance) were continuous and normally distributed and could thus be used as dependent variables in linear mixed models. In order to ease interpretation of the results, all three variables were transformed so as to have scores in the range 0-100, with 100 indicating higher performance.

Controlled variables. Several potential confounds of the relationship between shift work and cognition were statistically controlled in the analyses. Participants had to rate on a 4-point scale (never, seldom, sometimes, often) the frequency in the last month of five symptoms associated with sleep problems: (1) difficulty falling asleep, (2) difficulty maintaining sleep, (3) difficulty getting back to sleep, (4) premature awakening, (5) hypnotic medication use. A sleep difficulty score was computed by summing the ratings (range: 5-20, with 20 indicating the highest sleep difficulties; Cronbach's alpha = .74). Perceived stress during the last month was assessed by means of the perceived-stress scale of Cohen, Kamarck, and Mermelstein[19] (score range: 4 to 20, with 20 indicating maximum stress; Cronbach's alpha = .70). Other variables that were used as covariates were: age (at t1), gender, socioeconomic position (executive, i.e. executives and high rank intellectual occupations, technicians and supervisors, *vs.* non-executive, i.e., office staff and blue-collar workers), alcohol use (every day *vs.* not every day), and tobacco intake (current or in the past *vs.* never). Measurement occasion (t1, t2, t3) was also incorporated in the statistical models. No attempt was made to control for retirement status, as this was highly positively correlated with age.

See Tables 1 and 2 for characteristics of the sample, shift work experience, and cognitive performance.

Statistical analyses. Mixed linear models were used to analyse the data in this study[20]. A correction for the regression to the mean was applied to the cognitive scores at t1 (for the method and the rationale see [21]). Statistical analyses were performed using Stata V11.2.

Three sets of analyses were conducted which examined the effects on cognitive performance at all three measurement occasions (t1, t2, t3) of (i) shift work, (ii) shift work exposure duration, and (iii) time elapsed (at t1) since having left shift work. Each analyses comprised two stages. In the first step, an initial model was implemented with the shift work variable, measurement occasion and the following covariates: age, gender, socioeconomic position, sleep problem score, alcohol use, tobacco use, perceived stress. In the second step of the analysis, a full model was implemented that incorporated the significant predictors identified in the first step, together with a set of interaction terms based on combinations of the significant predictors identified in the first step that were relevant for the purposes of the current enquiry. At both steps, backward selection was used to identify the significant predictors of cognitive performance.

Results[1]

Chronic Impairment. Our first analyses examined whether experience of any type of atypical work schedule (i.e. shift work) at t1 (never vs. current or past) affected global cognitive performance scores at t1, t2, and t3. The preliminary model (main effects) indicated that lower scores were predicted by "current or past" shift work experience. Four significant interactions were kept in the final model (with interactions), but none involved shift work. Poorer global cognitive performance scores were again observed for "current or past" shift workers as compared with those who had only ever worked as day workers (ß = -

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[1] Tables of the full set of results relating to all independent variables are available on request from the first author.

1.62 +/-0.367, $P < .0001$; see Fig. 1). The effect of shift work can be compared to the differences in global cognitive performance scores observed at baseline between the age cohorts. In the final model, the effect of age was ß = -11.40 ($P < .0001$) for the 62 year cohort when compared to the 32 year cohort (i.e. a decline in global cognitive performance score of 0.38 for each year). Thus the cognitive impairment due to shift work was equivalent to 4.3 years of age-related cognitive decline, based on the comparison between 62 year olds and 32 year olds. The lack of a significant interaction involving shift work suggests that the effects of shift work were not influenced by any of the covariates or by measurement occasion. The same analyses were also conducted for the memory and speed sub-scores of performance and revealed the same result: poorer scores for "current or past" shift workers as compared with those who had only ever worked as day workers (ß = -1.33 +/-0.37, $P < .0001$ and ß = -1.36 +/-0.30, $P < .0001$, respectively for memory and speed performance). No interactions involving shift work were observed. It should be noted that, since some individuals who had "never" worked shift work at t1 may have become "current", and then perhaps even "past" shift workers at t2 and t3 (7 possible scenarios over the 3 measurement occasions) our results may have underestimated the magnitude of the performance deficits.

Exposure Duration. Our next analyses focused on rotating shift work (see Shift Work subsection of Methods section for more details) and were conducted to examine the effects of shift work exposure duration. Participants were classified into three levels of exposure at baseline, namely: never worked rotating shifts ('no exposure' group); 10 years or less ('≤10 year exposure' group); more than 10 years ('>10 year exposure' group). The preliminary mixed linear analysis indicated that lower global cognitive performance was predicted by rotating shift work duration. The full model revealed three significant interactions, but again none involved shift work duration. Compared to those who were never exposed, rotating shift workers with over 10 years of experience had poorer cognitive scores (ß = -2.46 +/- 0.51, *P* < .0001), while those with 10 years or less of shift work experience showed the same, but non-significant, trend (ß = -0.91 +/- 0.49, *P* = 0.06; see Fig. 2). This was equivalent to 6.5 years of age-related cognitive decline for > 10 years of exposure. Analyses of the sub-dimensions of the global score, revealed the same result for memory scores, with poorer scores in the >10 year exposure group as compared to the no exposure group (ß = -2.12 +/-0.52, *P* < .0001), while the difference between the ≤10 year exposure group and the no exposure group was not significant (ß = -0.82 +/-0.50, *P =.102*, respectively). For speed scores, no significant difference was observed between the no exposure group and either the >10 year exposure group (ß = -0.68 +/-0.56, *P =.22*) or the ≤10 year exposure group (ß = 0.09 +/-0.55, *P =.87*). However there was an interaction between shift work exposure and the socioeconomic position indicating greater differences for the executive participants than for the non-executive participants in the comparisons between participants with no exposure and participants with >10 years exposure (ß = -1.75 +/-0.86, *P* < .05), and between those with no exposure and those with ≤10 years exposure (ß = -1.71 +/-0.80, *P* < .05). An interaction between exposure duration and the measurement occasion was also found, with participants who had >10 years exposure showing a significant decrease in the speed score between t1 and t2 (ß = -1.81 +/-0.51, *P* < .0001), while no such decline was observed in the other two exposure groups.

Reversibility and Recency. We then examined the possible reversibility of the chronic effect of shift work on cognition, by comparing performance differences between participants who had the following shift work statuses at t1: currently working rotating shifts (n=568), former shift worker, having left rotating shift work within the last 5 years (n=176), former shift worker, having left rotating shift work more than 5 years ago (n=350), and never worked any sort of shift system (n=1635). This is subsequently referred to as the effect of 'recency'. The first model revealed a significant effect of recency of rotating shift work. In the subsequent model, three significant interactions were found, but none involved recency. Compared to participants who had never worked any sort of shift system, significantly poorer global cognitive performance scores were exhibited by those who were currently working rotating shifts (ß = -2.30 +/- 0.50, $P < .0001$) and by those who had left rotating shift work within the last 5 years (ß = -2.74 +/- 0.80, $P < .001$). The loss was equivalent to 5.8 years of age-related cognitive decline in our model for the current shift workers, and to 6.9 years for those who had left rotating shift work within the last 5 years. In contrast, those who had left rotating shift work more than 5 years previously did not differ significantly from those who had never worked any sort of shift system (ß = -0.42 +/- 0.60, $P = .48$). The same results were obtained in analyses based on the memory scores, with ß coefficients in the same range as for the global cognitive performance score: ß = -2.02 +/- 0.51, $P < .0001$ for those currently working rotating shifts, ß = -2.68 +/- 0.82, $P < .001$ for those who had left shift work within the last 5 years, and ß = -0.17 +/- 0.62, $P = .79$ for those who had left shift work more than 5 years ago. For the speed score, results showed the same trend though they did not reach significance: ß = -0.97 +/- 0.50, $P = .054$ for the current rotating shift workers, ß = -1.56 +/- 0.85, $P = .07$ for those who had left shift work within the last 5 years, and ß = 0.62 +/- 0.66, $P = .35$, for those who had left shift work more than 5 years ago. An interaction was observed between recency and the socioeconomic position. Non-executive participants showed no effects of recency. However, among the executive participants, lower speed scores (relative to those who had never worked shifts) were observed among both current rotating shift workers (ß = -1.88 +/- 0.87, $P < .05$) and those who had left rotating shift work more than 5 years ago (ß = -2.72 +/- 0.98, $P < .01$).

As a check on the generality of the effects of recency of rotating shift work, we examined the effect of recency with respect to any of the 4 types of atypical work schedule i.e. participants were grouped with respect to the length of time that had elapsed since they ceased working any sort of shift system. The first model indicated that those who were currently working shifts (ß = -2.67 +/- 0.58, $P < .0001$) or who had left shift work within the last five years (ß = -2.11 +/- 0.55, $P < .0001$) exhibited significantly lower global cognitive performance scores, compared to those who had never worked shifts (see Fig. 3). The deficit was equivalent to 6.7 years of age-related decline for the current shift workers and to 5.3 years for those who had left shift work within the last 5 years. Again, those who had left shift work more than 5 years ago did not differ significantly from those who had never worked any sort of shift system (ß = 0.04 +/- 0.64, $P = .95$), and there were no significant interactions involving recency. Similar results were obtained from the analyses based on memory scores: ß = -2.29 +/- 0.60, $P < .0001$ for the current shift workers, ß = -1.93 +/- 0.57, $P < .001$ for those who had left shift work within the last 5 years, and ß = 0.10 +/- 0.66, $P = .89$ for those who had left shift work more than 5 years ago. For the speed score, a main effect of recency was not observed: ß = -0.88 +/- 0.57, $P = .12$ for those who had left shift work within the last 5 years, and ß = 0.84 +/- 0.72, $P = .24$ for those who had left shift work more than 5 years ago, as compared with those who had never worked any sort of shift system. Only current shift workers significantly differed from those who had never worked any sort of shift system (ß = -1.22 +/- 0.59, $P < .05$). An interaction was found for speed scores between recency and socioeconomic position. While there were no effects of recency among non-executive participants, executive participants who were either currently exposed (ß = -2.23 +/- 1.02, $P <$ 05) or who had left shift work more than 5 years ago (ß = -2.25 +/- 1.05, $P <$ 05), had lower scores compared with those who had never been exposed.

Attrition effects. Finally, in order to assess the possible influence of sample attrition during the course of the study, we compared (Fisher or Kruskal-Wallis test) the global cognitive performance scores at baseline of those individuals who where only present at t1 (i.e. dropouts) with those who were also included in the analyses at t2 or t3. This was conducted separately for all relevant groups used in the analyses reported above ("never" and current or past shift work, ≤ 10-years and >10-years exposure duration, current or ≤ 5 years recency and > 5 years recency). In all groups, those who had participated only at t1 showed systematically lower cognitive performance than those who were seen again at t2 or t3, (*P* range from .02 to .11), mainly because the dropouts were also a little older and less educated (*P*s <0.0001). It thus seems unlikely that attrition biased our conclusions since the dropout effect impacted in the same direction all the groups that were compared to each other.

Discussion

The current results indicated that (i) exposure to shift work was associated with a chronic impairment of cognition, (ii) the association was highly significant for exposures to rotating shiftwork exceeding 10 years (with the exception of the speed scores among non-executive participants), and (iii) the recovery of cognitive functioning after having ceased any form of shift work took at least 5 years (with the exception of speed scores).

The findings may reflect the disruption of the individuals' circadian rhythms resulting in physiological stress, which has been shown to have an impact on brain structures involved in cognition and mental health over the lifespan[22]. The apparent reversibility of the cognitive impairment found in the present study is consistent with the "stress - cortisol - atrophy of the hippocampus - cognitive impairment" pattern observed in people submitted to repeated jet-lag, because the hippocampus is a brain structure whose tissues seem to be able to regenerate through neurogenesis[23]. Greater evidence was obtained of the effects of shift work in the memory scores than in the speed scores, especially in the analyses examining the persistence of the shift work effect after leaving shift work. This also provides support for the hippocampus hypothesis, as the hippocampus is known to be highly involved in memory processes. An alternative interpretation of the present results reflects the fact that shift workers show an increased incidence of metabolic syndrome[24] which has, in turn, been associated with impaired cognitive functioning[25]. The current study lacked statistical power to satisfactorily assess the possible mediating role of the metabolic syndrome in the observed effects on performance. It has also been suggested that shift workers may be more prone to vitamin D deficiency because of their reduced exposure to daylight, and vitamin D deficiency has also been linked to impaired cognitive functioning[26].

Unlike the study of acute effects, the direct study of the long term consequences of atypical work schedules on the brain and cognitive functioning is complicated because of the great variability in the worker's history of atypical work schedules (possible multiple changes during the occupational life over a wide set of different shift systems). Hence one limitation of the current study was that we were unable to conduct separate analyses on each type of atypical work schedule, thus obliging us to group them in some of the analyses. Thus it was not possible to isolate which aspects of the atypical schedules were driving the observed effects on cognition. Conversely, the analysis of exposure duration focused exclusively on rotating shift work and hence those results cannot necessarily be extrapolated to other forms of shift work. Another limitation was that some participants in the "never" control group might have had minimal experience of shift work, insofar as the threshold for declaring experience of shift work had been placed at 50 days per year. However, if our control group was possibly slightly contaminated by shiftwork, this would suggest that, if anything, the current study underestimated the effects of shift work. Finally, although a causal effect of shift work on cognition seems highly plausible in light of the long-term effects already observed on a variety of biological parameters, the reverse causal relationship cannot be excluded, at least for some participants. Indeed it may be that those who quit shift work a long time ago may have had higher cognitive abilities and were thus better able to move into non-shift working jobs at an earlier stage in their career.

The cognitive impairment observed in the present study may have important safety consequences not only for the individuals concerned, but also for society as a whole given the increasing number of jobs in high hazard situations that are performed at night. It may also affect shift workers' quality of life, with respect to daily life activities that are highly dependent on the availability of cognitive resources. The current findings highlight the importance of maintaining medical surveillance of shift workers, especially of those who have remained in shift work for 10 years or more.

End Notes

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Contributors. J-C. M. designed the VISAT program, supervised data collection and managed the database. He contributed to the conception and design of the current study, advised on statistical aspects, interpreted the data and wrote several parts of the manuscript. P. T. conducted preliminary analyses, advised on statistical aspects and contributed to writing of the method section, to the interpretation of the data and to the preparation of the manuscript. S. F. contributed to the analysis and interpretation of the results, and to the preparation of the manuscript for publication. C. G. performed statistical analyses and participated in writing the method sections. D. A. participated to data collection and analyses, and to the formatting of the article. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. All authors gave final approval of the version to be published.

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Competing interest. All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisation that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval. The VISAT project was approved by the French National Committee for Computer Data and Individual Liberties, and all procedures were compatible with the international standards pertaining to human research. Participants were volunteers and gave informed consent.

What this paper adds

- Shift work, like chronic jet-lag, is known to disrupt workers' normal circadian rhythms and social life, and to be associated with increased health problems and with acute effects on safety and productivity. However, very little is known about the long-term consequences of shift work on cognitive abilities.

- Our prospective study shows an association between shift work and chronic cognitive impairment that is a function of length of exposure. We also show that recovery of cognitive function occurs some years after returning to normal day work.
- Measures should be considered that mitigate the impact that prolonged exposure to shiftwork has upon cognitive abilities, including switching to normal day work.

References

1. Folkard S, Tucker P. Shift work, safety and productivity. *Occupational Medicine* 2003;53:95-101.
2. Ansiau D, Wild P, Niezborala M, *et al*. Effects of working conditions and sleep of the previous day on cognitive performance. *Applied Ergonomics* 2007;39:99-106.
3. Folkard S. Effects on performance efficiency. In *Shift work: Problems and Solutions* (eds. Colquhoun W P, Costa G, Folkard S, Knauth P), 65–87 (Peter Lang, 1996).
4. Meijman T, van der Meer O., van Dormolen M. The after-effects of night work on short-term memory performance. *Ergonomics* 1993;36:37-42.
5. Vidacek S, Kaliterna L, Radosevic-Vidacek B, *et al*. Productivity on a weekly rotating shift system: circadian adjustment and sleep deprivation effects? *Ergonomics* 1986;29:1583–90.
6. Smith L, Folkard S, Poole CJM. Increased injuries on night shift. *The Lancet* 1994;344:1137-9.
7. Tucker P, Folkard S, Macdonald I. Rest breaks and accident risk. *The Lancet* 2003;361:680.
8. Cho K, Ennaceur A, Cole JC, *et al*. Chronic ‘‘jet lag’’ produces cognitive deficits. *Journal of Neuroscience* 2000;20:1–5.

9. Cho K. Chronic 'jet lag' produces temporal lobe atrophy and spatial cognitive deficits. *Nature Neurosciences* 2001;4:567–8.

10. Rouch I, Wild P, Ansiau D, *et al*. Shift work experience, age and cognitive performance. *Ergonomics* 2005;48:1282–93.

11. Devore EE, Grodstein F, Schernhammer ES. Shift work and cognition in the Nurses' Health Study. *American Journal of Epidemiology* 2013;178:1296-1300.

12. Marquié JC, Jansou P, Baracat B, *et al.* The VISAT (ageing, health, & work) prospective study: overview and methodology. *Le Travail Humain [Human Work]* 2002;65*:*243-60.

13. Ribet C, Derriennic F. Age, working conditions, and sleep disorders: A longitudinal analysis in the french cohort E.S.T.E.V. *Sleep* 1999;*22*:491-504.

14. Kubo T. International comparison of the definition of night work - Promoting health care of shift workers. *Journal-Uoeh* 2013;35:163-8.

15. Rey A. *L'examen Clinique en Psychologie [Clinical Tests in Psychology]* (Paris: Presses Univ. de France, 1964).

16. Wechsler D. *Wechsler Adult Intelligence Scale Manual* (New York: Psychological corporation, 1955).

17. Salthouse TA. What do adult age differences in the Digit Symbol Substitution test reflect? *Journal of Gerontology* 1992;47:121-8.

18. Sternberg S. Memory scanning: new findings and current controversies. *Quarterly Journal of Experimental Psychology* 1975;27:1-32.

19. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *Journal of Health and Social Behavior* 1983;24:385-96.

20. Rabe-Hesketh S, Skrondal A. *Multilevel and Longitudinal Modeling Using Stata* (College Station: Stata Press, 2008-2nd ed).

21. Marquié JC, Rico-Duarte L, Bessières P, *et al.* Higher mental stimulation at work is associated with improved cognitive functioning in both young and older workers. *Ergonomics* 2010;53:1287-301.

22. Lupien SJ, McEwen BS, Gunnar MR, *et al.* Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience* 2009;10:434-45.

23. Ming GL, Song H. Adult neurogenesis in the mammalian brain: significant answers and significant questions. *Neuron* 2011;70:687-702.

24. Tucker P, Marquié JC, Folkard S, *et al*. Shift work and metabolic dysfunction. *Chronobiol Int* 2012;29:549-55.

25. Hao Z, Wu, B, Wang D, *et al*. Association between metabolic syndrome and cognitive decline: a systematic review of prospective population-based studies. *Acta Neuropsychiatric,* 2011;23:69-74.

26. Wilkins CH, Sheline YI, Roe CM, *et al.* Vitamin D deficiency is associated with low mood and worse cognitive performance in older adults. *Am J Geriatr Psychiatry* 2006;14:1032-40.

Table 1: Participants' characteristics at baseline for the whole sample and the subsample used for rotating shift work analyses, and their relationship with cognitive performances (factorial scores).

		Total (N=3119)	Rotating Shiftwork (N= 2752)	Cognitive performance Global (M & SD)	Memory (M & SD)	Speed (M & SD)
Age (years)	32	867	761	59.59 (9.87)	53.95 (10.28)	81.16 (7.33)
	42	942	865	56.59 (9.56)	51.15 (9.89)	79.29 (7.56)
	52	856	736	51.51 (10.21)	46.88 (10.07)	75.16 (8.86)
	62	454	390	47.75 (10.01)	44.05 (9.56)	71.34 (10.11)
		ns	***	***	***	***
Gender	Male (0)	1595	1 344	52.65 (10.69)	47.61 (10.42)	76.62 (9.34)
	Female (1)	1524	1 408	56.94 (10.34)	51.94 (10.34)	78.46 (8.45)
		***	***	***	***	***
Socioeconomic position	Non executive (0)	1854	1620	51.95 (10.81)	47.23 (10.46)	75.53 (9.53)
	Executive (1)	1265	1132	58.84 (9.21)	53.37 (9.72)	80.44 (7.11)
		***	***	***	***	***
Sleep problem	Low	1104	969	54,87 (10.93)	49,71 (10.80)	77,88 (8.85)
	Medium	1014	905	55,10 (10.36)	49,90 (10.29)	78,07 (8.72)
	High	1001	878	54,24 (10.87)	49,55 (10.71)	76,56 (9.25)
		***	***	*ns*	*ns*	***
Perceived stress	Low	1308	1163	54,68 (10.84)	49,60 (10.60)	77,62 (9.09)
	Medium	1035	920	55,49 (10.22)	50,30 (10.23)	78,22 (8.53)
	High	776	669	53,86 (11.15)	49,15 (11.06)	76,41 (9.20)
		ns	*ns*	**	*ns*	***
Alcohol	Everyday (0)	2236	1985	52.19 (10.70)	47.34 (10.44)	75.96 (9.28)
	Not everyday (1)	883	767	55.75 (10.59)	50.66 (10.52)	78.13 (8.76)
		ns	*ns*	***	***	***
Tobacco	Never (0)	1207	1088	54.32 (10.74)	49.45 (10.48)	76.95 (9.16)
	Current or past (1)	1912	1664	55.01 (10.73)	49.89 (10.68)	77.88 (8.82)
		***	***	*ns*	*ns*	***

Note. *** ≤ 0.001, ** ≤ 0.01, *ns* = non significant. Statistical significances are from Chi Square tests in the first two columns (distribution of people who never worked any sort of shift system *vs* those who are current or former shift workers), and from ANOVAs in the other three columns.

Table 2: Shift work experience and cognitive performances (factorial scores) at baseline (unadjusted means)

			Cognitive performance		
		N	Global	Memory	Speed
		(3119)	(M & SD)	(M & SD))	(M & SD)
Shift work experience	Never	1635	56.0 (10.71)	50.8 (10.61)	78.5 (8.77)
	Shift work (current or in past)	1484	53.3 (10.60)	48.5 (10.46)	76.5 (9.05)
			***	***	***
Rotating shift work (current or in past)	1-10 years	583	55.4 (10.08)	50.3 (10.33)	78.1 (8.20)
	> 10 years	534	51.8 (10.49)	47.0 (10.23)	75.6 (8.84)
			***	***	***
Rotating shift work recency	Current	568	54.4 (10.44)	49.2 (10.55)	77.6 (8.08)
	≤ 5 years	176	51.8 (10.42)	47.0 (9.67)	75.7 (9.91)
	> 5 years	350	53.3 (10.31)	48.6 (10.43)	76.1 (8.68)
			***	***	***
Shift work recency	Current	381	53.0 (10.35)	48.0 (10.45)	76.6 (8.29)
	≤ 5 years	417	54.3 (10.45)	49.2 (10.18)	77.5 (8.86)
	> 5 years	295	53.5 (10.44)	48.8 (10.62)	76.2 (8.66)
			***	***	***

Note. *** ≤ 0.001. Statistical significances are from ANOVAs.

Figure legends

- **Figure 1:** The relationship between shift work experience and global cognitive performance score, obtained after adjustment for age, gender, socioeconomic position, sleep problems, perceived stress, alcohol and tobacco consumption, and measurement occasion.
- **Figure 2:** The relationship between duration of exposure to rotating shift work and global cognitive performance score, obtained after adjustment for age, gender, socioeconomic position, sleep problems, perceived stress, alcohol and tobacco consumption, and measurement occasion.
- **Figure 3:** The relationship between time since leaving any form of shift work (‘recency’) and global cognitive performance score, obtained after adjustment for age, gender, socioeconomic position, sleep problems, perceived stress, alcohol and tobacco consumption, and measurement occasion.

Figure 1

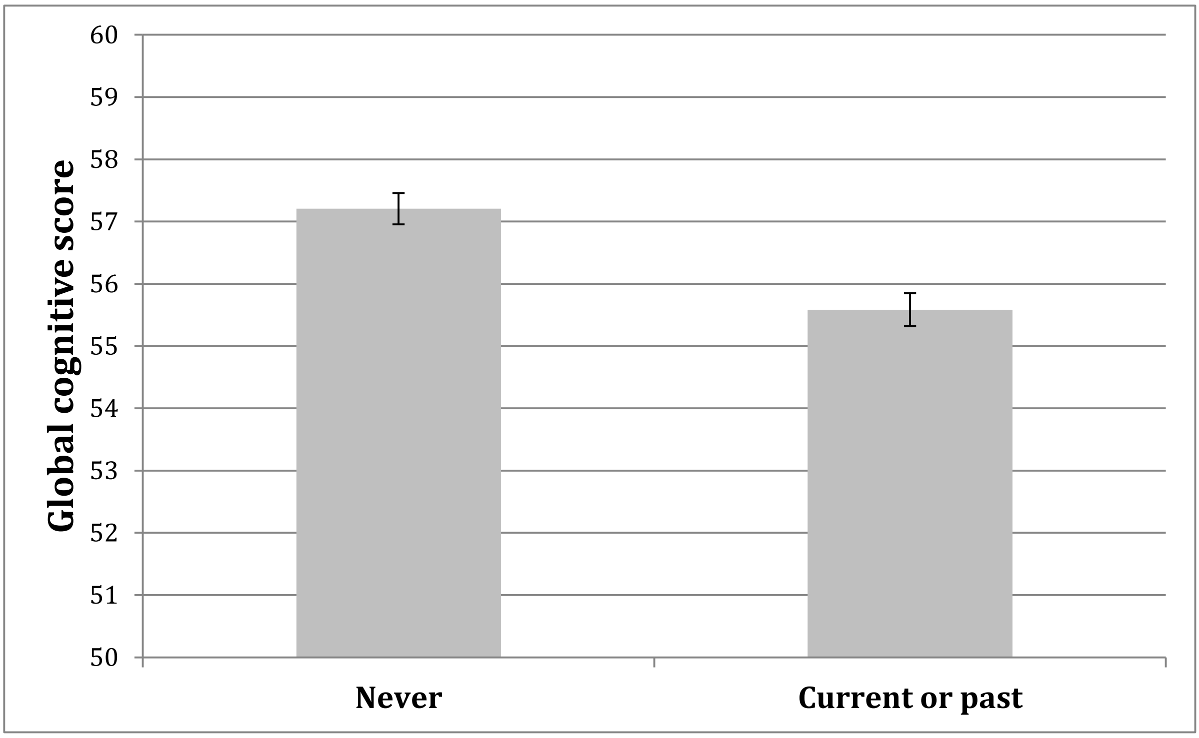


Figure 2

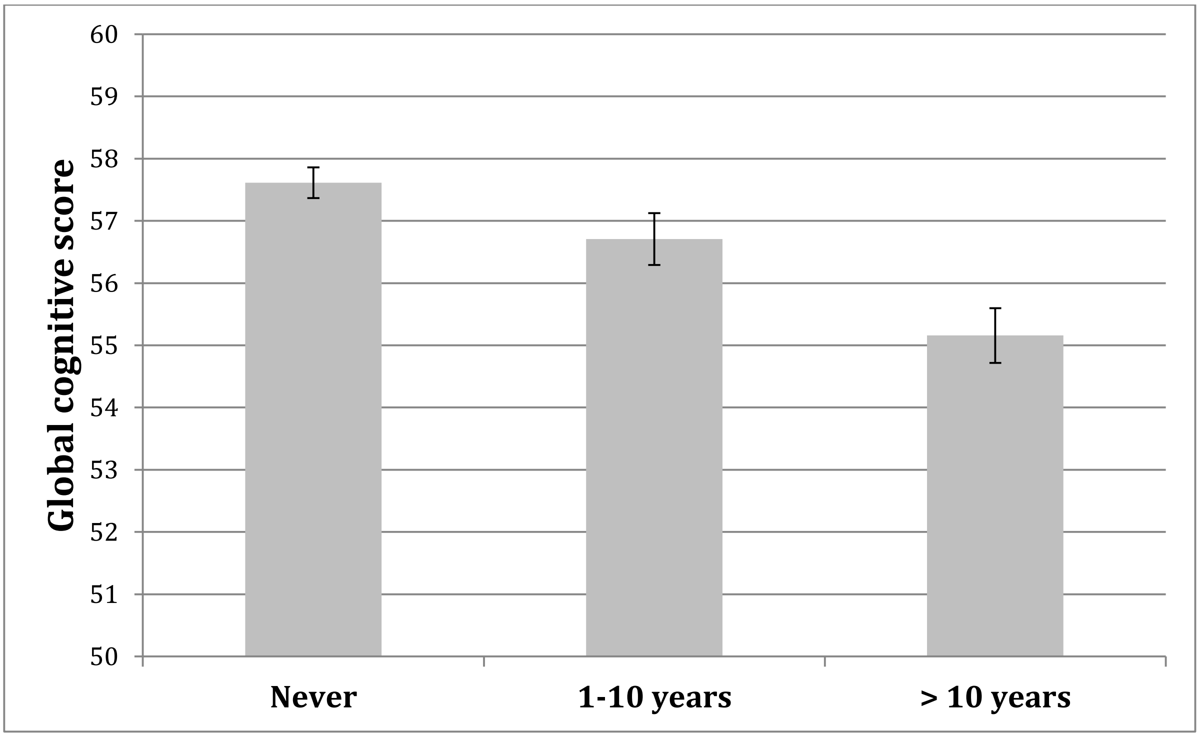
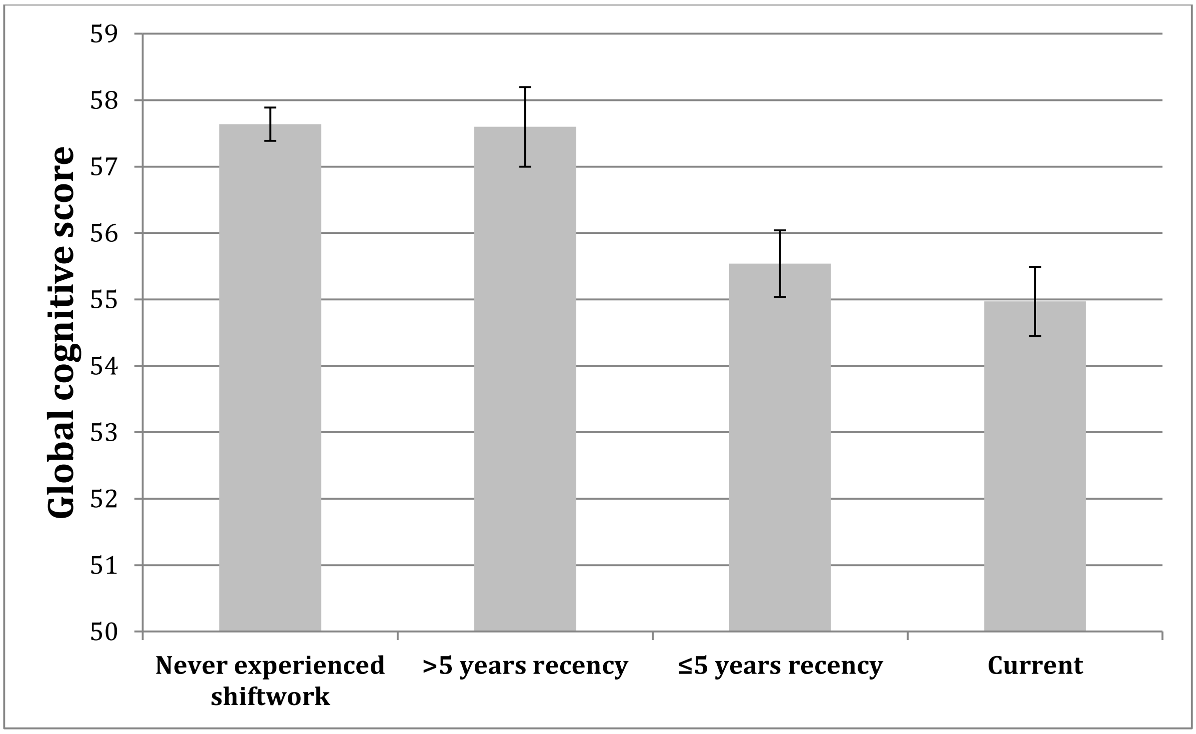


Figure 3


Global cognitive score
59
58
57
56
55
54
53
52
51
50
Never experienced shiftwork
>5 years recency
≤5 years recency
Current