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Exercise increases the dynamics of diurnal cortisol secretion and executive functionin people wiht MCI.

Tortosa-Martínez, J., Clow, A., Caus-Pertegaz, N., González-Caballero, G., Abellán-Miralles, I. and Saenz, M.J.

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Exercise increases the dynamics of diurnal cortisol secretion and executive function in people with amnestic Mild Cognitive Impairment

Summary:

Regular physical activity is protective against and beneficial for Mild Cognitive Impairment (MCI), dementia, and Alzheimer´s disease. The mechanisms underlying these benefits remain unknown although it has been suggested that exercise-induced changes in the circadian pattern of cortisol secretion may be implicated. Fitness, salivary cortisol levels (0 and 30 mins post awakening, midday, 5pm and 9pm) and cognitive function were determined in a group of amnestic MCI patients (n=39) before and after a three-month exercise program (n=19) or usual care (n=20). At base fitness measures were positively correlated with peak levels of cortisol and a greater fall in cortisol concentration from peak levels to midday. The exercise intervention successfully increased fitness and resulted in a greater fall in cortisol concentration from peak to midday, compared to the control group. The exercise intervention enhanced indices of executive function, although memory, mood, and functionality were not affected.

Key words: Mild cognitive impairment, Alzheimer´s disease, exercise, cortisol, stress.

1. INTRODUCTION

There is evidence showing that physical activity can have restorative effects on the stress neuroendocrine system from both human (Salmon, 2001; Traustadóttir, Bosch, Cantu, & Matt, 2004; Rimmele et al., 2007; Rimmele, Seiler, Marti, Wirtz, Ehlert, & Heinrichs, 2009) and animal studies (Greenwood, Strong, Dorey, & Fleshner, 2007; Droste, Collins, Lightman, Linthorst, & Reul, 2009; Hill, Droste, Nutt, Linthorst, & Reul, 2010; Kannangara et al., 2011). However, there are some inconsistencies in the literature (humans: see meta-analysis by Jackson & Dishman, 2006; rodents: Moraska, Deak, Spencer, Roth, & Fleshner, 2000; Fediuc, Campbell, & Riddell, 2006). In people with Mild Cognitive Impairment (MCI), Baker et al. (2010) recently showed an effect of aerobic exercise on cortisol secretion, where morning plasma cortisol values significantly decreased for women and increased for men after a six-month high intensity aerobic exercise program. The intervention also resulted in a significant improvement in executive function, which was more pronounced for women than for men. However, this study used a one time-point measurement of cortisol (ranging from 8:00 to 10:00) and did not control for time of awakening, which might not be the most accurate measure (Edwards, Evans, Hucklebridge, & Clow, 2001). The fact that studies looking at the effects of exercise programs on cortisol secretion have consistently not considered the dynamics of the diurnal cycle may partially be responsible for the inconsistencies in the results.

There is a growing body of evidence showing that regular physical activity has protective effects against MCI, dementia, and Alzheimer´s disease (AD) (Hamer & Chida, 2009; Geda, Roberts, Knopman, Christianson, Pankrats, & Ivnik, 2010). Exercise seems to improve memory and executive function, especially in older adults (Colcombe & Kramer, 2003; Erickson et al., 2011). Furthermore, a variety of physical activity programs have shown

positive outcomes for people with AD and other dementias (for a review see Blankevoort et al., 2010) as well as for people with MCI (Lautenschlager et al., 2008; Baker et al., 2010; Nagamatsu et al., 2013; for a meta-analysis see Gates, Fiatorone-Singh, Sachev, & Valenzuela, 2013).

However, the mechanism of action of these positive effects is currently unknown. Tortosa-Martínez and Clow (2012) recently suggested that it is possible that the benefits of physical activity may be at least partially mediated by effects on the neuroendocrine stress system. Chronic stress and aging can lead to dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis, leading to aberrant circadian patterns of cortisol secretion and a cascade of negative downstream events (McEwen, 2008). This cascade of events is considered a major risk factor for the development of AD, with evidence showing that it exacerbates cognitive deficits and causes increased levels of amyloid-b plaques and protein tau “tangles”, the neuropathological hallmarks of AD (see Rothman and Mattson, 2010, for a review).

Furthermore, the importance of the diurnal cycle of cortisol and the cortisol awakening response (CAR), defined as the rise from awakening to 30 min after, and the subsequent steep fall in cortisol level over the rest of the day, for health and cognition has recently received increased attention in the literature. In a cross-sectional study, Evans et al. (2011) showed that better overall cognitive performance was associated with a greater post-awakening cortisol rise and a consequent steeper fall (from 30 minutes to 3 hours post awakening) in healthy older adults, although the correlation with the CAR proved insignificant when controlling for age. However in the same population of healthy older adults, there was a significant positive correlation between better executive function, as shown in the Trail Making Test B (TMTB), and a greater magnitude of the CAR(β=.38; t=2.51; p<.016) (Evans, Hucklebridge, Loveday, & Clow, 2012). In addition, Beluche,

Carrière, Ritchie, & Ancelin, (2010) using a longitudinal design showed that an attenuated diurnal rhythm (flatter slope) predicted a decline over 4 years for men in TMTB performance (OR 7.7, p=0.03), and in visual memory (OR 4.1, p=0.03) as shown in the Benton Memory task. For women an attenuated diurnal rhythm was associated with a decline in verbal fluency (OR 6.0, p=0.01). These studies suggest that alterations in the magnitude of the CAR and the diurnal cortisol slope could predict cognitive decline, and that interventions targeting this pathway may provide new therapeutic options to prevent or delay this cognitive decline. Therefore, the first aim of this study was to examine the relationship between levels of fitness and the diurnal pattern of cortisol secretion in a group of older MCI patients. Secondly the impact of an exercise intervention on the diurnal pattern of cortisol secretion and cognitive function in a sample of older people with amnestic MCI was investigated. We hypothesized that increased levels of fitness would result in a more dynamic diurnal pattern of cortisol secretion and better cognitive performance in this population.

2. MATERIALS AND METHODOLOGY:

2.1. Participants:

Forty-three people diagnosed by trained neurologists with amnestic Mild Cognitive Impairment (simple or multiple domain), according to Petersen (2004) criteria, were recruited from the Neurology Unit of the Hospital de San Vicente del Raspeig (Spain). Participants were divided into an experimental group (exercise program), and a control group (followed routine care). Those who were able to attend to the program for geographical proximity were included in the experimental group (21) and the rest were allocated in the control group (22). Two women from the experimental group dropped out the program prior to the three-month assessment, one of them due to a broken bone caused by a domestic fall, and the other one because of a crisis of anxiety during the duration of program. Two men from the control

group dropped out the study after the pre-test for personal reasons. These four participants were thus not considered in the analysis.

Inclusion criteria comprised having a diagnosis of Amnestic Mild Cognitive Impairment; geographic proximity with the Hospital of San Vicente del Raspeig and the University of Alicante; and being able and willing to attend to the exercise program and/or the pre and post testing procedures. Exclusion criteria included non-compliance with testing procedures; physical, cardiovascular or sensorial limitations for doing exercise safely; severe apathy, delirium or agitation; or reporting being currently engaged in a similar exercise program as the intervention of the study.

The study followed the principles outlined in the Declaration of Helsinki of 1975. The protocol was approved by an ethics committee, both in the University of Alicante and the Hospital of San Vicente del Raspeig. All participants gave written informed consent to the protocol and were advised that the refusal of participation in the study would not affect future treatment.

2.2. Measurements

2.2.1. Fitness

The six minute walk test (6MWT)

The six minute walk test (Enright and Sherrill, 1998) is a submaximal test measuring levels of aerobic fitness. The test is known to reflect the functional exercise level during daily physical activities. It is a suitable test for elderly people and has also been used in populations with dementia (Williams & Tappen, 2007). Participants were requested to walk as fast as possible for 6 minutes, without running or jogging, through a circuit of a rectangular shape

marked with cones separated five meters each one for a total of 50 meters each complete lap. Participants were allowed to stop if they needed to during the test. A research assistant timed the walk and recorded the distance traveled by participants to the nearest cone.

Timed Get Up & Go Test (TGUG)

This test is aimed to assess agility and dynamic balance and has been previously used in people with mild cognitive impairment (Shumway-Cook, Brauer, & Woollacott, 2000). The test requires a participant to stand up from a chair, walk 2.44 meters to a cone, turn, walk back, and sit down. Time taken to complete the test is strongly correlated to level of functional mobility. The participant was requested to: "Sit with your back against the chair. At the command `go,' stand upright, then walk as fast as possible to the cone in front of you, turn around, return to the chair, and sit down." The stopwatch was started on the word `go' and stopped when the subject returned to the starting position.

2.2.2. Salivary cortisol measurement.

A 1-day saliva sampling protocol was chosen as the diurnal rhythm of cortisol has been shown to display relative intraindividual stability between days (Edwards et al., 2001). Each participant was provided with a saliva sampling pack of five salivette tubes (Salivettes Sarstedt) labelled with the sampling times, which were immediately upon awakening, 30 min post awakening, and then at 12:00, 17:00 and 21:00. Participants and their caregivers were both briefed about the collection procedures and the importance of adherence to the specified sampling times in face to face sessions. Participants were asked not to eat, drink (except water), smoke, or brush their teeth 30 minutes prior to each sample. At each sampling time participants placed the salivette dental swab into their mouths and gently chewed for 1 min to collect saliva. The swab was returned to the salivette and stored in the participant’s

refrigerator until collection. Salivettes were then taken into the laboratory of the Alicante Hospital and centrifuged at 1000g per 2 minutes, and stored at -20º until further analysis. To measure cortisol concentration, a modification of the solid-phase radioimmunoassay (RIA; Coat-A-Count, Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA) was used, and the tubes were counted on a Packard Cobra Auto Gamma Counter (Auto-Gamma 5000 series, Cobra 5005, Packard Instruments Company, Meriden, CT, USA). A minimum of 0.4 ml of saliva was required for the duplicate assay. Intra and interassay coefficients of variance were below 10%.

To assess adherence to the sampling regime, all participants were given a diary to record awakening time, the times their samples were supposed to be collected, and the time when they actually took them. In this diary, they also reported the time they went to bed the night prior to collection. At pre-test, saliva sampling was completed on the day before the fitness and cognitive tests were performed . At post-test, cortisol was measured five days after the last exercise session of the program, in order to avoid possible confounding acute effects of exercise on hormone levels.

Adherence to the saliva sampling protocol seemed to be excellent. According to patients´ reports, no sampling time deviated more than 5 minutes from the requested saliva collection times relative to reported awakening (Smyth, Clow, Hucklebridge, Thorn, & Evans, 2013).

We calculated the magnitude of the CAR and the subsequent steep fall by computing the difference between the 30 minute peak sample and the sample collected at awakening and 12:00 noon respectively. We also calculated the mean day cortisol by summing the values of samples collected at 12:00 noon, 17:00 and 21:00, and dividing the resulting number by three.

The area under the curve (AUC) with respect to ground was computed according to Pruessner Kirschbaum, Meinlschmid & Hellhammer (2003) methods.

2.2.3. Cognition

Mini-Mental State Examination (MMSE)

The MMSE is a popular measure to screen for cognitive impairment, to track cognitive changes that occur with time, and to assess the effects of potential therapeutic agents on cognitive functioning. It is brief, easily administered and easily scored.

The items were formalized by Folstein (1975) to distinguish neurological form psychiatric patients .The items were designed to assess orientation to time and place, attention and calculation, language and immediate and delayed recall.

Cognitive section of the Alzheimer’s Disease Assessment Scale (ADAS-Cog)

The Alzheimer's Disease Assessment Scale (ADAS) is a standardized assessment of cognitive function and non-cognitive features (Rosen, 1984). The cognitive section of the scale (ADAS-Cog) is the gold standard for measuring change in cognitive function in drug trials. The cognitive domains include components of memory, language and praxis.

CERAD word list memory

The Consortium to Establish a Registry for Alzheimer Disease (CERAD) consists of a test battery for examining memory (Morris, 1993). It is a procedure incorporated in the Alzheimer’s Disease Assessment Scale (ADAS). The patient reads the words printed in large letters on cards, bypassing the hearing problems common to this age group and ensuring

registration of each word. Poor free recall distinguishes Mild Cognitive Impairment from healthy older adults (Woodard, Dorsett, Cooper, Hermann & Sager, 2005).

Verbal fluency

Verbal fluency is a basic language capacity (the ability to produce fluent speech) characteristically compromised by brain damage in and near the vicinity of Broca's area in the left hemisphere. Thurstone's Word Fluency Test (Thurstone and Thurstone, 1947) was developed to assess more "executive" aspects of verbal behaviour. This test provides an excellent means of finding out whether and how well subjects organize their thinking and, indirectly, examine short-term memory to keep track of what words have already been said.

Trail Making Test (TMT) A and B

The TMT provides information on visual search, scanning, speed of processing, mental flexibility, and executive functions (Tombaugh, 2004). For the TMTA, subjects participants were requested to draw lines to connect sequentially in ascending order 25 encircled numbers randomly placed on a sheet of paper. In the more difficult condition (TMTB), subjects alternately tracked letter and numbers (e.g., 1, A, 2, B, 3, C, etc.) while performing the task. The time taken to complete the task was recorded separately for both tests. The number of errors was also recorded.

2.2.4. Mood and functionality

Geriatric Depression Scale (GDS)

The GDS (Yesavage et al., 1983) is a 30-item self-report assessment of depression in the elderly including questions such as: are you basically satisfied with your life?; do you feel that your situation is hopeless?; do you enjoy getting up in the morning?; etc. The GDS

questions are answered "yes" or "no", with one point assigned to each answer and the cumulative score is rated on a scoring grid. The grid sets a range of 0-9 as "normal", 10-19 as "mildly depressed", and 20-30 as "severely depressed".

Hamilton Anxiety rating scale (HAM-A)

The scale consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Each item is scored on a scale of 0 (not present) to 4 (severe), with a total score range of 0–56, where <17 indicates mild severity, 18–24 mild to moderate severity and 25–30 moderate to severe (Maier, Buller, Philipp, & Heuser, 1988).

Disability Assessment for Dementia (DAD).

The DAD Scale measures functional abilities in activities of daily living (ADL) in individuals with cognitive impairments such as dementia (Gélinas, Gauthier, McIntyre, & Gauthier, 1999). Functional disability is measured with the DAD Scale through the assessment of basic, instrumental and leisure activities observed over the past two weeks previous to the time of the interview. The DAD is administered through an interview with the caregiver. Each item can be scored: 1 point = YES, 0 point = NO or non applicable = N/A. A total score is computed by adding the rating for each question and converting this total score out of 100. The final score will represent a percentage which provides an appreciation of global function in ADL, with higher scores representing less disability in ADL and lower scores indicating more dysfunction.

2.3. Intervention protocols

The group exercise program was conducted in the sports facilities of the University of Alicante under the supervision of trained sports science professionals. The participants carried out the exercise routine 3 d/wk for 60 minutes per session for 3 months. All sessions included a warm-up, main phase, and a cool-down. Aerobic exercises were the main component of the program, including walking, stationary bicycle, and step aerobics. Some light strength, balance and flexibility exercises were also included usually for either the warm-up or the cool-down. Aerobic exercises were performed at approximately 60 to 75% of the maximum heart rate. The intensity started at as low as 40% and was progressively increased up to the target training zone during the first four weeks of the program. This intensity was then maintained for the study's duration. All participants were monitored with Polar Heart Rate monitors in order to control the intensity and the adaptation to the exercise. Attendance was recorded daily, which was used to calculate compliance (i.e. percentage of total classes attended). Subjects who missed two consecutive workouts would receive a call from the study coordinator to ensure compliance.

2.4. Statistical analysis:

Statistical analysis was performed using the SPSS statistical package version (SPSS 19.0. for Windows). Descriptive baseline characteristics were tabulated as mean (±SD) for continuous variables or as percentages for categorical ones (Table 1).

Data distribution was checked by looking at the curtosis and skewness of each variable, and by the Shapiro-Wilk test. Cortisol measures were distributed with highly significant degrees of skewness. For that reason, a square root transformation was applied and data were winsorised to two standard deviations to reduce the impact of outliers (3%). Where possible, in order to benefit from the incomplete data sets interpolation was carried out

(0.5%). Interpolation did not take place with missing values in the awakening and 30 min. post-awakening values.

Group differences analysis between the experimental group and the control group at baseline was conducted using unpaired *t* test for normally distributed variables and the Mann-Whitney U-test for non-normally distributed variables. Chi-square was used in the case of categorical variables such as gender.

Correlations at baseline were analysed for the fitness tests and cortisol values in order to establish a baseline relationship between fitness and the diurnal cortisol secretion pattern. Pearson correlation was used followed by partial correlations controlling for age and gender.

In order to assess the main effects of the program on the different variables, a repeated measures procedure was used in an analysis of covariance (ANCOVA). Two time points (effect over time) were considered as the within-participants factor, and the differences between the intervention group (exercise) and the control group (routine care) were treated as a between-participants factor. In light of reports suggesting a sex bias in cognitive and cortisol response to exercise (Baker et al., 2010), we included sex as a between-participants factor. Age, education, sex, the MMSE, and the 6MWT were included as covariates in the multivariate model. All reported P values are two-sided and the significance level was set at 0.05.

3. RESULTS:

3.1. Baseline characteristics of the sample

The final sample was comprised of 39 people with MCI (19 in the experimental group and 20 in the control group), with a mean age of 75.64 (±7.18) years-old. The average

attendance rate for the exercise program was 87%. Table 1 shows the main characteristics of the sample considering group differences. At baseline, there were no significant differences between the experimental group and the control group in regards to age, blood pressure and gender, although a higher percentage of women were present in the control group compared to the experimental group.

There were also no significant differences between the two groups in regards to the neuropsychological, functionality, and fitness tests. Cortisol values were not significantly different at baseline either. The average time of awakening for the day when cortisol was collected was not significantly different between the experimental and the control group, and between pre and post tests.

Some of the patients were taking omeprazole medication for controlling cholesterol or for lowering blood pressure. The number of people taking this type of medication was similar within both groups and there were no reports of significant changes in the medication type or doses over the course of the study.

…….INSERT TABLE 1 ABOUT HERE…….

3.2. Partial correlations at baseline, controlling for age and gender, between fitness levels and the cortisol secretion diurnal pattern, and between fitness and cognition.

After controlling for age and gender, the 6MWT showed a significant positive correlation with the peak of cortisol at 30 minutes and for the drop from this peak to cortisol values at 12:00, as well as a negative correlation with cortisol values at 21:00 (Table 2). The correlation between the 6MWT and the mean day cortisol values showed only a tendency. No correlations were found with the AUC. The TGUG showed a significant negative correlation

with the peak of cortisol at 30 minutes post-awakening, and also with the drop from this peak to cortisol values at 12:00. No correlations were found between the TGUG test and the AUC. This values reflect that people with MCI showing higher values in the 6MWT (indicating better cardiovascular fitness) at baseline had lower day cortisol levels and a higher drop from the peak of cortisol at 30 minutes post-awakening to cortisol values at 12:00, representing a more dynamic cortisol secretion pattern. The values in the TGUG test show that those who performed the test faster (indicating better performance) had a higher peak of cortisol at 30 minutes and a subsequent higher drop from that peak to 12:00 values, also indicating a more dynamic cortisol secretion pattern.

We also tested the correlations between the fitness tests and the cognitive measurements. After controlling for age and gender, no correlations with any of the cognitive tests proved significant for neither the TGUG test nor the 6MWT, with only the 6MWT showing a tendency for a negative correlation with the number of errors in the TMTB.

…….INSERT TABLE 2 ABOUT HERE…….

3.3. Main effects of the exercise program

3.3.1. Fitness

Three months of controlled exercise compared to routine care resulted in a significant improvement in fitness levels (Table 3). Participants in the experimental group improved significantly their performance in the Timed Get Up and Go Test ($F=12,541$; $p = 0,002$), and the 6-minute walk test ($F=19,851$; $p = 0,000$) compared to the control group.

…….INSERT TABLE 3 ABOUT HERE…….

3.3.2. Cortisol

After the intervention, the experimental group showed a tendency for an increased peak of cortisol at 30 minutes after awakening (F=3.829; p=0.068) and an increase in the magnitude of the CAR (F=3.925; p=0.069), and a significant increase in the drop between the peak of cortisol at 30 minutes (cortisol sample 2) and the cortisol values at 12:00 (cortisol sample 3) (F=6.064; p=0.026), compared to the control group (Figure 1).

…….INSERT FIGURE 1 ABOUT HERE…….

3.3.3. Cognition

Three months of controlled exercise improved executive control processes but not memory. Favorable effects of exercise were apparent for the performance in the time taken to complete the TMTB (F=5.160; P=0.046) relative to baseline, with a 27% improvement for the exercise group (from an average of 329±190 seconds in the pre-test to an average of 239±120 seconds).The number of errors remained unchanged. The time taken to complete the TMTA, which examines mainly cognitive processing speed, was unaffected by the exercise manipulation although the number of errors during the test decreased significantly (F=5.756; P=0.024). There was also a trend for an improvement in the TMTB/A ratio (F=4.287; P=0.068). When sex was included as a predictor variable in the model (group X sex), there was not a significant interaction indicating that the treatment effect did not differ significantly between men and women.

Memory and visual memory as measured by the ADAS-Cog and the Visual Memory test (CERAD) were unaffected. Verbal fluency remained also unchanged.

3.3.4. Mood and functionality

Three months of controlled exercise did not have any apparent effect on depression (Geriatric Depression Scale) or anxiety (Hamilton Anxiety rating scale) levels of the participants in the study. Functionality slightly increased for the experimental group and decreased for the control group but differences proved not significant.

4. DISCUSSION

The current study showed, for the first time, relationships between levels of fitness and the dynamics of the diurnal pattern of cortisol secretion in older adults diagnosed with MCI. Furthermore a 3-month aerobic exercise training program, that increased fitness, enhanced those same aspects of the diurnal cortisol profile found to be related to fitness at baseline: a steeper fall from peak levels 30 minutes after awakening to midday and nearly significant increase in the magnitude of the CAR.

Dysfunction of the HPA axis has been associated with cognitive functioning (Seeman, McEwen, Singer, Albert, & Rowe, 1997; Karlamangla, Singer, Greendale, & Seeman, 2005), Mild Cognitive Impairment (Wolf, Convit, Thorn, & de Leon, 2002; Arsenault-Lapierre, Chertkow, & Lupien, 2010) and Alzheimer´s disease (Rothman & Mattson, 2010). A dysfunction of the HPA axis causes, among other things, aberrant patterns of cortisol secretion (Nader, Chrousos, & Kino, 2010) and typically excessive levels of basal circulating cortisol (Lupien & Lepage, 2001), which over time produces accumulative wear and tear on the body and brain (McEwen, 2008). Elevated levels of cortisol have been linked to impaired memory in healthy participants (Seeman et al., 1997) and in patients with MCI (Wolf et al., 2002; Arsenault-Lapierre et al., 2010). In addition, Evans et al. (2011; 2012) found recently a relationship between the magnitude of the CAR, and executive functioning, in healthy older adults. They found that the higher the magnitude of the CAR the better performance in the

Trail Making Test B for executive function. They also found that a subsequent steeper fall in cortisol levels was correlated with better overall cognitive performance.

A greater CAR and a subsequent steeper fall have been also recently associated with greater brain plasticity in healthy adults (Clow et al., 2014). Thus, although some previous studies have suggested that the CAR could be a stress response (Chida & Steptoe, 2008), emerging evidence may show that attenuated CARs and blunted cortisol secretion patterns are indicative of a range of impaired function in older adults (Clow et al., 2014; Evans et al. 2011,2012; Johar et al 2014), which is consistent with our results.

There is increasing evidence of the benefits of exercise to cope with stress, although the literature shows inconsistencies (Tortosa-Martínez & Clow, 2012). To our knowledge, the only study that had previously linked exercise with cortisol levels in people with MCI, was the study of Baker and colleagues (2010) who reported an increase in basal morning cortisol for men and a decrease for women after six months of aerobic exercise, suggesting a positive adaptation to exercise for women and negative for men. However, cortisol was collected in blood in just one point of time with differences between participants, ranging from 8:00 to 10:00, and not controlling for the time of awakening. Considering that cortisol levels normally rise significantly from awakening to 30 minutes after awakening (the CAR) and then they start to descend, a one point measure without controlling for awakening time most likely gives inaccurate results. In our study, we did not find lower cortisol levels neither in the awakening sample nor in the total cortisol diurnal levels after the intervention. Considering that longer periods of training have resulted in better performance in executive function and memory in other studies, it is possible that a longer exercise program could result in total lower levels of diurnal cortisol.

The exercise program also resulted in positive effects in executive function processes (the Trails B time and Trails A number of errors, and a trend for the TMTB/A ratio), but not memory.The exercise group improved the TMTB performance from being below the 10th percentile at baseline, to being between the 10th and the 25th percentiles after the exercise intervention (Fromm-Auch & Yeudall, 1983). Although both performances are below normality, this represents a 27% improvement after the exercise program. Exercise has been previously shown to improve executive control processes including selective attention, planning, organizing, multitasking, inhibition, and working memory in healthy older adults (for a meta-analyses see Colcombe & Kramer, 2003) and people with Mild Cognitive Impairment (Baker et al., 2010). Baker and colleagues randomized 33 individuals with MCI into a 6-month high intensity aerobic exercise or stretching control group. Individuals in the aerobic exercise group engaged on a 4d/wk routine of 45-60 minutes each session, at a 75-85% of their heart rate reserve. The aerobic intervention resulted in improved executive control processes of multitasking, cognitive flexibility, information processing efficiency, and selective attention (Symbol-Digit Modalities, Verbal Fluency, Stroop, Trails B, and Task Switching; MANOVA, $F5,19=3.05$; $P=.04$). The treatment effect differed for men and women, with more favourable effects for women than for men except for the Trails B, where men and women improved in a similar way. Unlike the study of Baker et al. (2010), no differences were found between men and women. We did not measure the Symbol-Digit Modalities, the Stroop or the Task Switching tests, but we did use a Semantic Verbal Fluency test which proved unaffected by the intervention. The positive results and the gender differences found in the verbal fluency test in the Baker et al. (2010) study at 6 months could be attributed to the longer period of training and the higher frequency and intensity of the aerobic program. Additionally, our study participants were older and had lower baseline MMSE scores. In a randomized controlled trial with people with MCI, Lautenschlager et al.

(2008) found benefits of a 12-month exercise program for memory and language but not executive function. Nagamatsu et al. (2013) also found that aerobic exercise performed twice a week for six months significantly improved verbal memory and learning, although they did not find any improvements after three months. In our study, memory was unaffected by the intervention which again could be due to the shorter duration of the exercise program. Hence, it is possible that benefits of exercise for memory in people with MCI require longer periods of training.

The mechanisms underlying the relationship between exercise and the diurnal cortisol secretion pattern found in this study remain unclear and deserve further research, but could be related to the effects of exercise on the hippocampus and prefrontal brain areas. Evidence from brain imaging studies suggest that increased aerobic fitness in healthy older adults is associated with reduced age-related atrophy and increased blood flow in regions responsible for executive control and memory processes (Colcombe & Kramer, 2003). In parallel, there is evidence suggesting that HPA activity and its feedback mechanisms are associated with brain areas in which we can find a high number of glucocorticoid receptors such as the hippocampus (de Kloet, Joëls, & Holsboer, 2005), an important structure for memory processes and implicated in the neuropathology of Alzheimer´s disease (Rothman & Mattson, 2010), but also the prefrontal cortex which is responsible for executive function processes (Fries, Dettenborn, & Kirschbaum, 2009), also affected by Azheimer´s disease (Dubois et al., 2010).

Some limitations of the study should also be acknowledged. The sample size and the lack of randomization are the main limitations of this research. We did not control for APOE4 carriers either. The use of a one-day measurement of cortisol is also a limitation, but was deemed necessary in order to reduce burden on the participants. There is a need for future

similar studies including larger samples, using randomized designs, and studying the effects of longer periods of exercise training (at least 6 months). The use of objective methods for verification of waking and sampling time should also be considered.

In summary, a three month aerobic exercise program improved executive function and resulted in a more dynamic diurnal pattern of cortisol secretion in older people with Mild Cognitive Impairment. The effects of exercise on the HPA axis on this study could lead to new research directions in the field of physical activity and cognition.

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TABLES

Table 1.

Baseline characteristics of the sample

	Experimental group	*Control group*
N	*19*	*20*
Age *(years)*	*75.5(±7.23)*	*76.2 (±7.07)*
Sex		
Women	47.3%	70%
Men	52.6%	30%
Systolic BP (mm Hg)	136.0 *(±14,77)*	133.1 *(±11,92)*
Diastolic BP (mm Hg)	*71.5 (±9.52)*	71.8 *(±10.02)*
TGUG test (sec)	*8.2 (±1.74)*	*9.5 (±4,48)*
6MWT, distance (m)	*431.8 (±56.79)*	*401.0 (±109.77)*
Cortisol Awk (S1) (nmol/l)	*11.9 (±5.42)*	*13.1 (±5.86)*
Time of awakening	8:10 (±36min.)	8:04 (±31min.)
Cortisol 30 min post Awk (S2) (nmol/l)	*14.8 (±7.05)*	*17.6 (±8.66)*
Cortisol 12:00 (S3) (nmol/l)	*8.1 (±2.93)*	*6.6 (±2.97)*
Cortisol 17:00 (S4) (nmol/l)	*4.5 (±2.00)*	*5.3 (±2.16)*
Cortisol 21:00 (S5) (nmol/l)	*2.9(±1.33)*	*3.1 (±1.63)*
CAR S2-S1 (nmol/l)	*3.8 (±5.44)*	*5.0 (±7.86)*
Cortisol S2-S3 (nmol/l)	*8.5 (±5.25)*	*11.0 (±8.23)*
Mean day cortisol (nmol/l)	*4.3 (±0.97)*	*5.0 (±1.88)*
Area under the curve (AUG) with respect to ground (nmol/l)	*4729,5 (±1567,5)*	*5934,9 (±1903,0)*
MMSE score	*25.3 (±3.80)*	*23.0 (±4.29)*
Adas-Cog score	*16.2 (±4.89)*	*17.4 (±5.00)*
Visual memory score	*4.3 (±3.62)*	*3.40 (±3.61)*
Semantic Verbal Fluency score	*10.6 (±2.96)*	*11.55 (±4.03)*
TMTA (sec)	*100.6 (±53.20)*	*108.89 (±58.45)*
TMTB (sec)	*329.5 (±190.9)*	*276.0 (±149.4)*
GDS (depression) score	*4.0 (±2.64)*	*3.8 (±2.16)*
HAM-A (anxiety) score	*8.2 (±4.74)*	*10.7 (±7.16)*
DAD % (functionality)	*87.5 (±10.91)*	*86.7 (±13.14)*

Abbreviations: TGUG=Timed Get Up and Go test; ; 6MWT = Six Minute Walk Test; MMSE = Mini-Mental State Examination; Adas-Cog = Cognitive section of the Alzheimer's Disease Assessment Scale; TMTA and TMTB = Trail Making Test A and B; GDS = Geriatric Depression Scale; HAM-A = Hamilton Anxiety rating scale; DAD= Disability Assessment for Dementia

Table 2.

Partial correlations, controlling for age and gender, between fitness tests cortisol values.

	AWK	30 min	12:00	17:00	21:00	CAR	C2-C3	Meandaycort
TGUG	-.268	**-.486****	.267	.158	.169	-.273	**-.595*****	.245
6MWT	.025	**.388***	-.176	-.357□	**-.430***	**.376** □	**.456****	**-.363** □

Abbreviations: TGUG = Timed Get Up and Go test; 6MWT = Six Minute Walk Test; AWK = Awakening time; CAR = Cortisol Awakening Response; C2-C3 = cortisol sample at 30 min post awakening minus cortisol sample at 12:00; Meandaycort = the sum of cortisol samples at 12:00, 17:00 and 21:00 divided by three.
For coefficients in bold: *** p <.001; ** p<.01; * p<.05; □ p<.10.

Table 3.

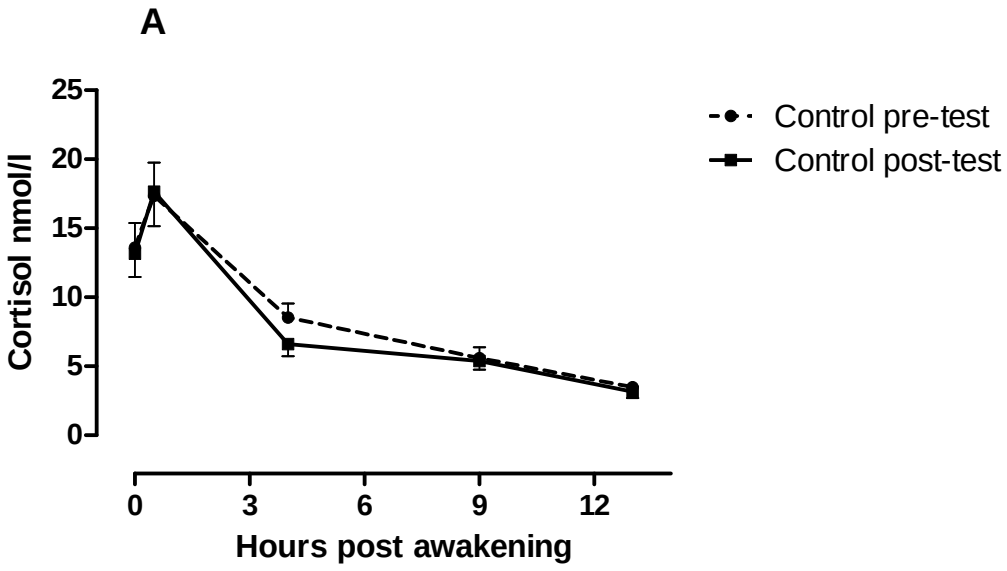
Pre-post fitness tests values for the experimental and the control group.

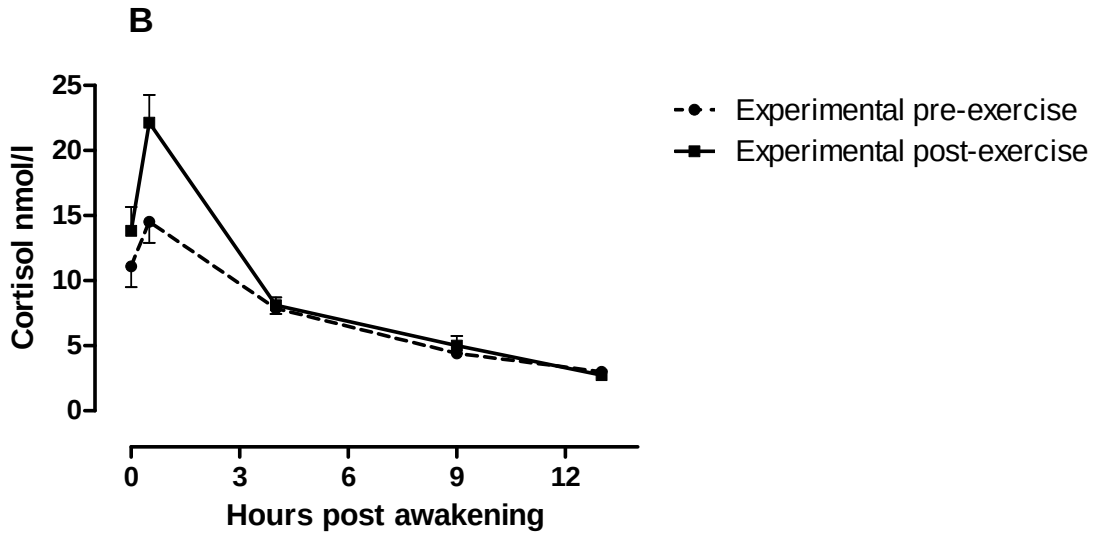
	Experimental group pretest	*Experimental group posttest*	*Control group pretest*	*Control group posttest*
TGUG test (sec)	*8.23 (±1.74)*	***6.33 (±0.84)******	*9.52 (±4,48)*	*9.40 (±4.72)*
6MWT, distance (m)	*431.84 (±56.79)*	***493,88 (±31.22)******	*401.05 (±109.77)*	*399,66 (±87.00)*

Abbreviations: TGUG = Timed Get Up and Go test; 6MWT = Six Minute Walk Test
For coefficients in bold: *** p <.001; ** p<.01; * p<.05; □ p<.10.

FIGURES

Figure 1. The diurnal pattern of cortisol secretion in the control and experimental groups pre and post 3 months of exercise or routine care. Results are expressed by Means plus and minus the Standard Error of the Mean (SEM).




B
Cortisol nmol/l
25
20
15
10
5
0
0
3
6
9
12
Hours post awakening
Experimental pre-exercise
Experimental post-exercise

1