

The association of physical activity to neural adaptability during visuo-spatial processing in healthy elderly adults: A multiscale entropy analysis

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ABSTRACT

Physical activity has been shown to benefit brain and cognition in late adulthood. However, this effect is still unexplored in terms of brain signal complexity, which reflects the level of neural adaptability and efficiency during cognitive processing that cannot be acquired via averaged neuroelectric signals. Here we employed multiscale entropy analysis (MSE) of electroencephalography (EEG), a new approach that conveys important information related to the temporal dynamics of brain signal complexity across multiple time scales, to reveal the association of physical activity with neural adaptability and efficiency in elderly adults. A between-subjects design that included 24 participants (aged 66.63 ± 1.31 years; female = 12) with high physical activity and 24 age- and gender-matched low physical activity participants (aged 67.29 ± 1.20 years) was conducted to examine differences related to physical activity in performance and MSE of EEG signals during a visuo-spatial cognition task. We observed that physically active elderly adults had better accuracy on both visuo-spatial attention and working memory conditions relative to their sedentary counterparts. Additionally, these physically active elderly adults displayed greater MSE values at larger time scales at the Fz electrode in both attention and memory conditions. The results suggest that physical activity may be beneficial for adaptability of brain systems in tasks involving visuo-spatial information. MSE thus might be a promising approach to test the effects of the benefits of exercise on cognition.

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1. Introduction

Aging and its relation to inefficiency in human brain functioning have been widely investigated (Churchill et al., 2002; Grady, 2012;

Hedden & Gabrieli, 2004). Notably, while aging might generally impact cognitive functioning, it affects certain neural systems disproportionately (Friedman, 2003; Nyberg et al., 2010). For example, visuo-spatial ability, executive control and working memory have been found to be more vulnerable to aging than other cognitive functions (Hedden & Gabrieli, 2004; Shay & Roth, 1992; West, 1996). These age-related and uneven declines in cognitive abilities are likely a consequence of non-identical regional loss in brain volume, with evidence showing prefrontal cortex or hippocampus being more affected by aging relative to other regions such as the occipital cortex (Hedden & Gabrieli, 2004). In addition, a recent

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model has reported that changes in subcortical areas such as the cerebellum, which works jointly with the frontal lobe, are also a contributing factor to the effects of aging in cognition (Hogan et al., 2011). As such, converging evidence highlights a greater decline in the frontal lobe, along with its associated cognitive functions in later adulthood.

Despite such decline during older adulthood, there is a growing body of evidence showing that exercise or physical activity can prevent or delay age-related loss of brain function (Erickson, Gildengers, & Butters, 2013; Erickson et al., 2010; Hillman, Erickson, & Kramer, 2008; Kramer et al., 1999; Voss et al., 2012) or neurodegenerative diseases (Hamer & Chida, 2009; Sofi et al., 2011). Interestingly, this beneficial effect is selectively larger for frontal-related functions such as executive control (Colcombe & Kramer, 2003; Kimura, Yasunaga, & Wang, 2012; Kramer et al., 1999; Tsai, Wang, et al., 2014), where such loss is most evident. For example, Hillman et al. (2006) reported that, in elderly adults, higher levels of physical activity are related to better task performance in tasks involving greater amounts of executive control. Similar to this, in terms of electrophysiological findings, Hillman, Belopolsky, Snook, Kramer, and McAuley (2004) observed that elderly adults that are more physically active exhibited enhanced frontal P3 amplitude selectively during a condition requiring higher amounts of executive control. These findings all suggest that physical activity may be able to compensate for the larger age-related degenerations in both cognitive and brain functions typically seen with aging.

Although numerous studies have assessed the effects of physical activity on cognition in elderly adults using analysis of mean neurophysiological (e.g., event-related potentials, ERPs) or neuroimaging signals (Erickson et al., 2010; Hillman et al., 2008; Kramer & Erickson, 2007), the investigation of within-individual brain signal complexity or variability has been limited. Signal complexity reflects some aspects of changes in magnitude from moment to moment in neurophysiological time series (Costa, Goldberger, & Peng, 2002, 2005; Garrett et al., 2013; Goldberger, Peng, & Lipsitz, 2002). This type of measure can provide information different from that acquired via mean signals (Garrett, Kovacevic, McIntosh, & Grady, 2012; Hogan et al., 2006) and is considered to reflect neural adaptability and efficiency during cognitive functioning (Garrett et al., 2013; Heisz, Shedden, & McIntosh, 2012; Hogan et al., 2012; Liang et al., 2014; Yang et al., 2013). Mounting evidence has demonstrated the utility of measuring brain signal complexity for the investigation of various physical and mental states, including developmental and aging processes (Garrett et al., 2012, 2013; O'Hara et al., 2013), diseases (Catarino, Churches, Baron-Cohen, Andrade, & Ring, 2011; Hogan et al., 2006), and cognitive performance (Liang et al., 2014). In addition, studies using analysis of brain signal variability may also provide some insight into the relationship between reduced brain complexity and aging (Garrett et al., 2013 for a review). One notable study by Garrett, Kovacevic, McIntosh, and Grady (2010), examining the standard deviations (SDs) of BOLD (blood oxygen level-dependent) signals in young and elderly adults during fixation blocks, reported that the brain signals in elderly adults were generally less varied relative to those in younger adults, possibly reflecting an age-related decrease in network complexity and integration. In addition, studies using calculation of sample entropy also support this argument (Garrett et al., 2013; Hogan et al., 2012). Sample entropy, in short, is a modification of Shannon's entropy (Shannon and Weaver, 1949) and Pincus' appropriate entropy (Pincus, 1991), which calculates the repetitions of similar sequences in a physiological time series signal (Hogan et al., 2012; Richman & Moorman, 2000). Thus, the more unpredictable the dynamic signals are, the higher the values of sample entropy would be, and vice versa. Sample entropy has also been examined

in relation to aging and declined brain functioning; Hogan et al. (2012) observed that cognitively-declined older adults tend to show lower entropy during memory encoding than do healthy elderly individual, suggesting that the sample entropy measure may reveal differences in brain complexity with regard to some subtle brain state differences between a healthy and a declined brain. These important investigations suggest that aging-related decline in cognitive function may be due, in part, to changes in the complexity of neural systems.

Is higher complexity better? Here it is important to note that complex systems are neither absolutely deterministic nor completely random (Costa et al., 2005; Tononi, Edelman, & Sporns, 1998); that is, there is no direct association between regularity and complexity (Feldman & Crutchfield, 1998). Thus, enhanced irregularity in the measure of sample entropy is not necessarily synonymous with an increase in intrinsic physiological complexity (Costa et al., 2002, 2005; Goldberger et al., 2002). In such cases, it is suggested to be better to evaluate a loss of physiological complexity by using scaling approaches or other techniques (Goldberger et al., 2002; Peng, Havin, Stanley, & Goldberger, 1995). A fractal scaling measure of physiological complexity, multiscale entropy (MSE), that calculates sample entropy across multiple coarse-grained sequences (Costa et al., 2002, 2005; Heisz et al., 2012; Liang et al., 2014), seems to better meet the criteria of a complexity measure (Tononi et al., 1998). MSE evaluates the occurrence of repetitive patterns of each timescale as an index of signal complexity. Higher MSE values thus would signify that the signal is less predictable and information rich, whereas lower MSE values would imply that the time series is more regular and less complex (Costa et al., 2002, 2005; Garrett et al., 2013; Yang et al., 2013). The time scale is defined as the length of each non-overlapping time window within which the original data are averaged to produce a coarse-grained time series. A small time scale means that the length of non-overlapping time windows is short (e.g. 1 ms) whereas a large time scale implies that the length of non-overlapping time windows is long (e.g. 20 ms). Therefore, within a 1000 ms EEG signal sampled at 1000 Hz, there are 1000 data points for the 1-ms time scale coarse-grained time series and only 50 (1000/20) data points for the 20-ms time scale coarse-grained time series. Entropy values at smaller coarse-grained time series capture short-range temporal irregularity, whereas those at larger coarse-grained time series capture long-range temporal irregularity. Therefore, MSE can provide a more comprehensive complexity measure in comparison to a single time scale (Ueno et al., 2014). In support of this argument, studies investigating cardiac interbeat activity using MSE have observed that, although healthy elderly adults exhibited lower entropy values across all time scales compared to those of healthy young adults, the smallest difference occurred at scale one (Costa et al., 2002, 2005). This finding suggested the importance of investigating age-related loss in physiological complexity over different time scales. Similarly, Takahashi et al. (2009) observed age-related differences in MSE values of participants' electroencephalographic (EEG) signals while they were viewing a photic stimulus, in particular for values at larger time scales. The lack of significant MSE modulation by photic stimuli in elderly adults may be indicative of age-related decreases in physiological complexity/functional responses to visual stimuli, and this finding also demonstrates the potential of MSE for the investigation of aging pathophysiology based upon EEG data. More importantly, they observed that, after viewing a visual stimulus, MSE values tended to increase at smaller time scales in elderly adults (e.g., scales of 1–5). For larger time scales in these elderly adults values decreased, in contrast to remaining constant in young adults (e.g., for scales of 10–20). The constant MSE pattern in young individuals may reflect a physiological complexity associated with temporal long-range correlations, while the break down

of multiscale non-linear complexity in older adults may indicate a reduction in adaptive capabilities (Goldberger et al., 2002). According to these findings, Takahashi et al. (2009) claimed that the non-linear dynamics of EEG signals might not be observable using a single scale factor for entropy calculation.

In sum, given the positive effects of physical activity on the aging brain and cognition (Colcombe & Kramer, 2003; Hillman et al., 2008), brain signal complexity is hypothesized to show differences in line with these changes in elderly adults, and MSE measures may provide further understandings of the fundamental mechanisms underlying the relationship between physical activity and brain signal complexity during cognitive functioning in elderly adults.

The aim of the current study is to further understand the relationship of physical activity to the aging brain by evaluating the complexity of brain signal via MSE analysis. Prior studies have reported that cognitive processes tapping visuo-spatial components or higher levels of executive controls are more sensitive to aging (Chen, Hale, & Myerson, 2003; Myerson, Emery, White, & Hale, 2003; West, 1996) or exercise (Hillman et al., 2008; Kramer et al., 1999; Shay & Roth, 1992) relative to other cognitive processes. We thus adopted a cognitive task (Muller & Knight, 2002) that involves visuo-spatial components with different amounts of executive control (e.g., working memory vs. attention) to address this issue. With regards to the role of physical activity in protecting against or reducing age-related cognitive loss in elderly adults, particularly in processes requiring higher levels of executive control (Hillman, Motl, et al., 2006; Hillman et al., 2004; van Uffelen, Paw, Hopman-Rock, & van Mechelen, 2008), and in light of the negative relationship between physiological complexity and aging (Costa et al., 2002, 2005; Goldberger et al., 2002; Yang et al., 2013), we hypothesized that, compared with physically inactive elderly adults, physically active ones would show better task performance and higher EEG-based MSE values. Secondly, we also expected to see a greater effect during the working memory condition, where higher frontal control is required. Testing these hypotheses may reveal whether analysis of brain signal complexity can provide additional useful information in this field by shedding new light on the relationship between physical activity and cognition, as well as the benefits of physical activity in modulating the effects of aging on behavioral performance.

2. Methods

2.1. Participants

Forty-eight healthy elderly adults were recruited from the Tainan Senior Citizen Center in Taiwan. We recruited participants aged 66–70 years due to a larger expected effect of exercise on cognition within this age range (Colcombe & Kramer, 2003). Of these, twenty-four (female = 12; aged 66.63 ± 1.31 years) were members of the senior table tennis club and engaged in physical activity (e.g., table tennis, walking) regularly, while another gender- and age-matched group (aged 67.27 ± 1.20 years) were members of other non-exercise clubs (e.g., the chess or photography club) and reported being sedentary (defined by the estimation of levels of physical activity) at the time of the study. All participants had normal or corrected-to-normal visual acuity and reported being right-handed. No individuals reported suffering from neurological disease, taking any medications that affect cognitive function, and they were screened for dementia and depression with the Mini-Mental State Examination (MMSE; >24 points) (Folstein, Folstein, & McHugh, 1975) and Beck depression inventory II (BDI-II; <14 points) (Beck, Steer, & Brown, 1996). All participants gave informed consent prior to participating and the study was approved by the local ethics committee.

2.2. Measures

2.2.1. Demographic variables

The height and weight of all participants were measured while they wore light clothing. Height was measured via a wall-mounted stadiometer based on units in centimeters (cm), and weight was measured with a digital scale based on units in kilograms (kg). We calculated BMI by dividing body weight (kg) by height (m) squared $[(\text{kg})/(\text{m})^2]$. Years of education was measured by a self-report survey.

2.2.2. Estimation of levels of physical activity

A 7-day physical activity recall questionnaire was adapted from Sallis et al. (1985), which can be utilized to estimate and quantify levels of physical activity (Maximova, O'Loughlin, Paradis, Hanley, & Lynch, 2009; Wang et al., 2013). For this questionnaire, the experimenter instructed the participants to recall their physical activity in the past 7 days, which can help estimate the time (hours) spent at different levels (e.g., light, moderate, high, intense, and sleep) of physical activity. Each level of intensity was assigned a metabolic equivalent (MET, 1 MET = 1 kcal/kg/hour): sleep = 1-MET, light = 1.5 METs [24 h – (sleep + moderate + moderate + high + intense)], moderate = 4 METs (e.g., golf, flexibility), high = 6 METs (e.g., doubles tennis, dancing), intense = 10 METs (singles tennis, swimming, jogging). The kcal expenditure was estimated using the formula: $\text{kcal/day} = \text{Total physical activity (METs)} / 7 \times \text{weight (kg)}$. Thus, this questionnaire could successfully screen unwanted participants that would potentially bias the results (Wang, Chang, Liang, Shih, et al., 2013). Both groups were screened according to the following exclusion criteria: (1) for the physically active group: those who exercised in the table tennis club for less than five hours per week; (2) for the control group, those who spent more than two hours per week exercising at the intensity of moderate or higher.

2.2.3. Non-delayed and delayed matching-to-sample tests

The current study employed a non-delayed and a delayed matching-to-sample test which consist of one visuo-spatial attention (non-delayed) condition and one visuo-spatial working memory (delayed) condition (Muller & Knight, 2002). This type of paradigm allows the investigation of differences in visuo-spatial capacity for different populations (Muller & Knight, 2002; Tsai, Chang, Hung, Tseng, & Chen, 2012).

The paradigm was programmed using STIM2 software (Neuroscan Ltd, El Paso, TX, USA). All stimuli were presented on a 21-inch cathode-ray tube display against a black background. Similar to Muller and Knight (2002)'s study, the stimuli consisted of a red dot ($0.5^\circ \times 0.5^\circ$) randomly presented within a $3.8^\circ \times 7.4^\circ$ gray rectangle, which was either in the center of the screen or 5.9° to the left or right of the central fixation point. The procedure is illustrated in Fig. 1.

2.2.3.1. Visuo-spatial attention (non-delayed) condition. In the attention condition, two rectangles were presented on the screen simultaneously: one was placed in the center and another was placed either to the left or right of the center (Fig. 1, non-delay task). The stimuli were presented for 180 ms, a duration typically shorter than voluntary saccade latency, so minimizing the possibility of unwanted eye movements affecting the results (Muller & Knight, 2002; Tsai, Chang, et al., 2012). In this condition, participants were required to discriminate whether the red dots in the two different rectangles were spatially identical or not.

2.2.3.2. Visuo-spatial working memory (delayed) condition. In the working memory condition, the first stimulus (S1) was presented for 180 ms on either the right or left of the central fixation

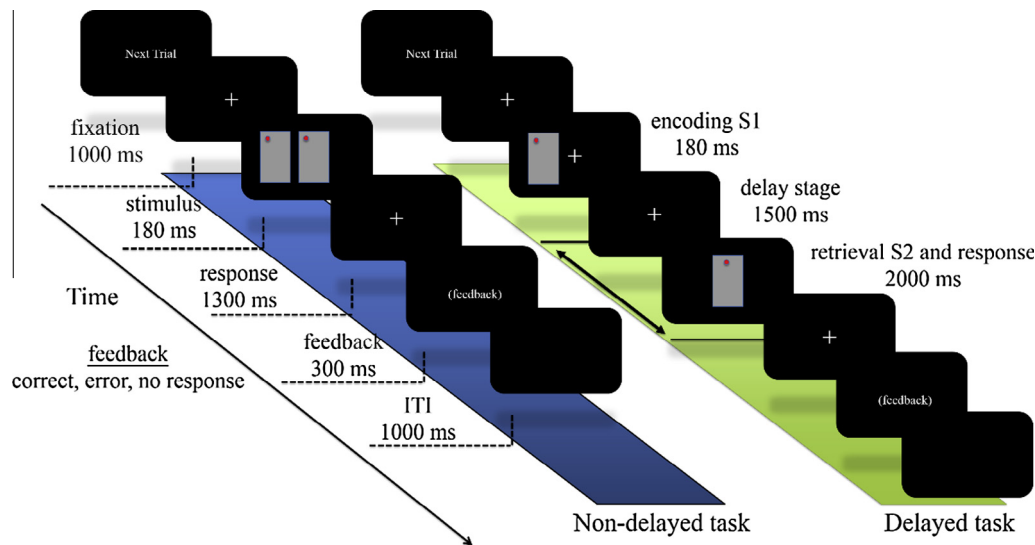


Fig. 1. Illustration of the non-delay and delayed matching-to-sample task. Two different conditions were presented using this paradigm: (1) a non-delayed (attention) condition where two stimuli were presented simultaneously (2) a delayed condition (working memory) which consisted of two stimuli with a 1.5 s delay in between. Feedback was given according to the accuracy of subjects' responses.

($0.5^\circ \times 0.5^\circ$), and the second stimulus (S2) appeared for 500 ms in the center of the screen and replaced the fixation during the 1.5s-delay (Fig. 1, Delay task). Participants were required to encode the red dot position from the first stimulus (S1), and to maintain representation of its spatial location for 1.5 s, and then to decide whether the position of the red dot in the second stimulus (S2) was the same.

Before performing the task, participants were instructed that both accuracy and speed were equally important. If the spatial positions of the stimulus seemed identical (matching), participants had to press the "K" key with their index finger, or to press the "L" key, if it they thought the stimulus was different (non-matching, 0.36° diagonal difference), using their middle finger on a computer keyboard. Feedback (correct, incorrect, no response) was provided based on their responses. A total of 216 trials were included in the whole task procedure, which was divided into three consecutive blocks of 72 trials that comprised randomized non-delayed and delayed conditions with equal probability. They were encouraged to take a 3-to-5-min break between blocks.

2.3. Procedure

Prior to the experiment, all participants were naïve regarding the purpose of the study. The experimental procedure included two phases: the first phase consisted of obtaining the demographic variables (e.g., height, weight, BMI, and education), MMSE, BDI-II, and 7-day physical activity recall questionnaire. The second phase was comprised of the cognitive task and EEG recording. Only eligible participants who passed the criterion for the questionnaires went on to perform the cognitive task. During the cognitive neurophysiological test, participants were seated in a dimly lit and soundproof room, in front of a screen positioned at eye level at a distance of approximately 100 cm. The duration of the total experimental procedure was approximately 1 h. Before the formal test, the experimenter explained the task procedure and ensured that the participants understood the task with a practice block of 16 trials consisting of both possible trial types. Additionally, participants were instructed to avoid saccades towards the laterally presented stimuli. After being familiarized with the whole procedure, participants then performed the task while behavioral and EEG data were recorded.

2.4. EEG recording

The electroencephalographic recording procedure was similar to previous studies (Tsai, Chang, et al., 2012; Tsai, Wang, & Tseng, 2012). EEG activity was recorded using a Nu-Amps EEG amplifier and the Scan 4.3 package (Neuroscan Inc., El Paso, TX, USA) with 32 electrodes mounted in an elastic cap (Quik-Cap; Compumedics, Neuroscan Inc.) designed for the International 10–20 System. Scalp locations were referred to linked mastoid electrodes and a ground electrode on the mid-forehead of the Quik-Cap. Horizontal and vertical electro-oculograms were recorded bipolarly from the superolateral right canthus, and below and lateral to the left eye and connected to the system reference allowing monitoring of eye movements. Electrode impedances were kept below 10 k Ω . Electroencephalography data were acquired with a sampling rate of 1000 Hz per channel and filtered with a Butterworth bandpass filter (0.1–50 Hz) (Catarino et al., 2011).

2.5. Data analysis

2.5.1. Participant characteristics

Means and standard deviations for all participants' descriptive characteristics (including age, height, weight, BMI, education, and estimated physical activity level) were calculated and group differences were analyzed using independent t-tests.

2.5.2. Behavioral data

A two-way [2 (groups: active and sedentary) $\times$ 2 (conditions: attention, working memory)] mixed design, factorial, repeated-measures ANOVA with a Bonferroni adjustment for multiple comparisons was conducted to analyze task performance, including accuracy and mean RTs for correct trials, neither of which violated the assumptions of the ANOVA. When appropriate, correction of the degrees of freedom was made with the Greenhouse-Geisser procedure (Vasey & Thayer, 2007). The significance level was set at $p \leq .05$. All analysis was completed using the SPSS 18.0 Software System.

2.5.3. EEG preprocessing

The offline ocular-corrected EEG data, with eye-blink peaks derived from VEOG by means of regression and correlation, were

locked to the stimulus onset, and were segmented into epochs: (1) for the attention (non-delayed) condition, –1000 to 1000 ms relative to the stimulus onset; (2) for the working memory (delayed) condition, 1000 ms before the encoding stimulus onset (S1), and lasting until 1000 ms after the retrieval stimulus (S2). Trials containing artifacts with amplitudes exceeding $\pm 150\mu\text{V}$ and EOG amplitudes $> \pm 50\mu\text{V}$ were discarded (Liang et al., 2014).

2.5.4. Multiscale entropy analysis

Brain signal complexity in different time scales was estimated by using multiscale entropy analysis (MSE) (Costa et al., 2002, 2005; Goldberger et al., 2000). Because it is suggested that visuo-spatial processing mainly involves the fronto-parietal network (Curtis, 2006; McEvoy, Pellouchoud, Smith, & Gevins, 2001) we selected the electrodes of interest to be Fz, Pz for analysis to test the effects of physical activity on EEG complexity during visuo-spatial processing across participants. The Oz electrode was selected as a control site because physical activity seems less related to age-related decrements in visual function (Hatfield, Spalding, Apparies, Haufler, & Maria, 2003). The MSE analysis was calculated in two steps and was performed from time scales 1–20 in the following time windows: (1) 0–600 ms relative to the stimulus onset in the attention condition; (2) 0–600 ms relative to encoding stimulus onset (S1) and (3) 0–800 ms for the retrieval stage (S2) in the working memory condition. This choice of time intervals for the MSE analysis was to obtain as many data points as possible and to avoid any influence from response execution. First, the algorithm progressively down-sampled the EEG post stimulus time series $\{x_1, \dots, x_i, \dots, x_N\}$ for each trial in each condition. This down-sampling procedure was defined as a coarse-grained procedure along various time scales in the MSE analysis. For timescale τ , the coarse-grained time series $Y^{(\tau)} = \{y(1), y(2), \dots, y(\tilde{N}^{(\tau)})\}$ was obtained by averaging data points within non-overlapping windows of length τ . Therefore each element of a coarse-grained time series, j , is calculated according to:

$$y(j) = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} x_i, \text{ where } 1 \leq j \leq \tilde{N}^{(\tau)}, \tilde{N}^{(\tau)} = \frac{N}{\tau}.$$

Second, the algorithm computed the sample entropy for each coarse-grained time series $Y^{(\tau)}$. Note that all the superscripts (τ) are omitted in the following to simplify the notation. There are two specified parameters for calculating the sample entropy: pattern length m and tolerance level r for similarity comparison. Given the coarse-grained time series Y , sample entropy was calculated as follows: first, construct $\tilde{N} - m + 1$ vectors

$$Y_m(i) : Y_m(i) = \{y(i+k)\}, 0 \leq k \leq m-1$$

and the distance between two vectors is defined as the absolute maximum difference between the corresponding scalar components

$$d[Y_m(i), Y_m(j)] = \max(|y(i+k) - y(j+k)|), 0 \leq k \leq m-1.$$

Given r , n_i^m is defined as the number of vectors $Y_m(j)$ falling within vector distance $r * s$ of $Y_m(i)$ without allowing self-matches, where s is the standard deviation of the original time series. Similarly, n_i^{m+1} is defined as the number of vectors $Y_{m+1}(j)$ falling within vector distance $r * s$ of $Y_{m+1}(i)$. Finally, Sample entropy was defined by the negative natural logarithm of the conditional probability that a time series of length N , having repeated itself within a tolerance $r * s$ (similarity factor) for m points pattern, will also repeat itself for $m+1$ points pattern

$$S_E(m, r, \tilde{N}) = \ln \frac{\sum_{i=1}^{\tilde{N}-m} n_i^m}{\sum_{i=1}^{\tilde{N}-m} n_i^{m+1}}.$$

Although there are no recommendations in terms of the best values for parameters for calculating sample entropy values in EEG studies, some theoretical and clinical applications have suggested setting $m = 1$ or 2 and $r = 0.1$ – 0.25 to provide a high validity for sample entropy in EEG signals (e.g., Escudero, Abasolo, Hornero, Espino, & Lopez, 2006; Takahashi et al., 2009). Here the pattern length, m , was set to 1 or 2 ; that is, one or two consecutive data points were used for pattern matching; the similarity criterion, r , was set to 0.25 , meaning that data points were considered to be indistinguishable if the absolute amplitude difference between them was $\leq 25\%$ of the time series standard deviation. To test the trial type effect (matching; nonmatching) and group effect (physically active group; sedentary control) for each electrode, a $p < .05$ with false discovery rate (FDR) correction for multiple time scales was set for the level of significance. In addition, because previous research has suggested that data lengths of 10^m to 20^m (m : pattern length) should be sufficient to estimate sample entropy (Richman & Moorman, 2000), estimation of sample entropy in the current coarse-grained EEG data (before the coarse-graining procedure, 600 ms time points in attention, 600 ms time points in memory encoding, and 800 ms time points in memory retrieval stage) may be sufficient for $m = 1$ with time scales 1–20 and for $m = 2$ with time scales 1–8. The examination of data using $m = 2$ can confirm that the results of MSE values were not only a result of stochastic dynamics, but also from the underlying chaotic deterministic dynamics in the EEG data. Moreover, the time scale indicates the length of each non-overlapping time bin within which the original data were averaged; for example, time scale 20 refers to averaging within each 20 ms window when the original sampling rate was 1000 Hz.

EEG data processing was performed using SPM8 and custom MATLAB (Math Works) scripts. The algorithm for MSE analysis can be found at <http://www.psychresearch.org/tools.html>.

3. Results

3.1. Participant demographics

Participant demographic data and their levels of physical activity are shown in Table 1. Demographic variables including age, $t(46) = -1.84$, $p = .072$, $d = -.53$, height, $t(46) = -.08$, $p = .306$, $d = .00$, and weight, $t(46) = -.32$, $p = .751$, $d = -.10$, BMI, $t(46) = -.30$, $p = .766$, $d = -.09$, MMSE, $t(46) = 1.03$, $p = .306$, $d = .30$, BDI-II, $t(46) = -.48$, $p = .632$, $d = -.14$, and education, $t(46) = -.11$, $p < .91$, $d = -.04$, did not differ between groups. However, there was a significant group difference for the levels of physical activity, $t(46) = 4.11$, $p < .001$, $d = 1.19$. This indicates the homogeneity of the two groups except for the physical activity levels.

Table 1
Demographics of Participants in Each Group.

Group	Physically active ($n = 24$)	Physically inactive ($n = 24$)
Age (year)	$M = 66.63$, $SD = 1.31$	$M = 67.29$, $SD = 1.20$
Height (m)	$M = 1.60$, $SD = 0.06$	$M = 1.60$, $SD = 0.07$
Weight (kg)	$M = 60.00$, $SD = 6.22$	$M = 61.00$, $SD = 12.05$
BMI (kg/m^2)	$M = 23.39$, $SD = 2.77$	$M = 23.66$, $SD = 3.49$
MMSE	$M = 29.00$, $SD = 0.88$	$M = 28.67$, $SD = 1.31$
BDI-II	$M = 3.08$, $SD = 2.98$	$M = 3.50$, $SD = 3.01$
Education (years)	$M = 12.58$, $SD = 2.50$	$M = 12.67$, $SD = 2.55$
Kilocalorie expenditure (kcal/d)	$M = 2408.2667$, $SD = 367.78^{***}$	$M = 1952.56$, $SD = 399.68$

*** Significantly different from controls at $p < .001$.

3.2. Behavioral performance

3.2.1. Accuracy

Accuracy was defined as the percentage of correct responses. As can be seen in Fig. 2a, the data showed a main effect for condition, $F(1,46) = 14.05$, $p < .001$, $\eta_p^2 = .23$, indicating the cognitive load may be higher in the working memory (delayed) condition relative to the attention (non-delayed) condition. Although we found a main effect for group, $F(1,46) = 16.23$, $p < .001$, $\eta_p^2 = .26$, an interaction between group and condition was not observed, $F(1,46) = 3.71$, $p = .06$, $\eta_p^2 = .08$. These findings reveal that the active group had better ability in identifying the difference in spatial locations compared to inactive controls, regardless of cognitive load.

3.2.2. Reaction time

Fig. 2b shows the mean RT for correct trials across groups and conditions. A significant main effect was observed for condition, $F(1,46) = 76.54$, $p < .001$, $\eta_p^2 = .63$, with shorter RTs for the attention condition and longer RTs for the working memory condition. However, no significant effect was found for group, $F(1,46) = .74$, $p = .395$, $\eta_p^2 = .016$ and nor was there a group by condition interaction, $F(1,46) = .09$, $p = .766$, $\eta_p^2 = .00$, suggesting the two groups had comparable processing speeds in identifying the difference in spatial locations.

3.3. Multiscale entropy

3.3.1. Attention (non-delayed) condition

For the trial type comparison, no differences between matching and non-matching trials were found across all participants or for each group for all time scales (all $p > .05$ FDR corrected), suggesting that the two trial types may have similar effects on brain signal complexity. For the results when $m = 1$, as shown in Fig. 3a, we found that the active group, relative to the inactive group, showed higher sample entropy from time scales 6–20 selectively at the Fz electrode ($p < .05$, FDR corrected) but not at the Pz or Oz electrode. However, no such effect was found for the time scales 1–5. Results from when $m = 2$ showed similar effects to those of $m = 1$. However, a group effect was only found for time scales 7 and 8 and with a significance level of $p < .05$ uncorrected (Fig. 4a).

3.3.2. Working memory (delayed) condition

No differences in MSE values between matching and non-matching were seen for any time scales across participants or for either group (all $p > .05$ FDR correction). As Figs. 3b and 4b illustrates, we did not observed any group differences in sample entropy across time scales for all electrodes using $m = 1$ or 2 during the encoding stage. However, in the memory retrieval stage

(Figs. 3c and 4c), we found that the physically active group had greater MSE at the Fz electrode than the physically inactive controls from time scales 4 to 20 when $m = 1$ ($p < .05$, FDR corrected) and from time scales 4 to 8 when $m = 2$ ($p < .05$, FDR corrected). This effect was not found at the Pz or Oz electrode.

4. Discussion

The present study used multiscale entropy (MSE) analysis to examine differences in electrophysiological signal complexity for data that was acquired during performance of a visuo-spatial cognitive task in elderly adults who either did or did not engage in physical activity. The primary results showed that physically active older adults, relative to sedentary counterparts, had better accuracy on visuo-spatial attention and working memory tasks with complementary higher values of MSE at larger time scales selectively at the electrode over the top of the frontal lobe but not for the parietal or occipital lobe. Notably, the results from $m = 2$ were similar to those from $m = 1$, suggesting that the effects of physical activity on MSE were not only due to stochastic dynamics, but also from the deterministic dynamics. These effects, however, were not statistically significant during the spatial memory encoding stage in which no comparison or motor execution was required. In sum, the present study may provide preliminary evidence demonstrating that, in aging brains, physical activity is associated with differences in brain signal complexity during cognitive functioning for longer time scales.

The neuroprotective effects of exercise or physical activity on brain functioning later in life have previously been widely reported (Erickson et al., 2010, 2013; Hamer & Chida, 2009; Hillman et al., 2008; Kimura et al., 2012; van Uffelen et al., 2008), and the positive outcomes include higher efficiency in cognitive function and spared brain volume (Erickson et al., 2010; Kramer & Erickson, 2007; Kramer, Erickson, & Colcombe, 2006). Here we further addressed this issue by testing the association of exercise with brain signal complexity during visuo-spatial processing.

4.1. The relationship between physical activity and cognitive functioning

At the behavioral level, we adopted a cognitive task (Muller & Knight, 2002) that comprises visuo-spatial processing and executive control, which are considered to be age- and exercise-sensitive. The results showed that physically active older adults had better accuracy performance for both visuo-spatial attention and working memory compared to their inactive counterparts, suggesting that physical activity may help elderly adults maintain or improve their cognitive capacity. This is in line with previous studies investigating the cognitive differences between elderly participants with dif-

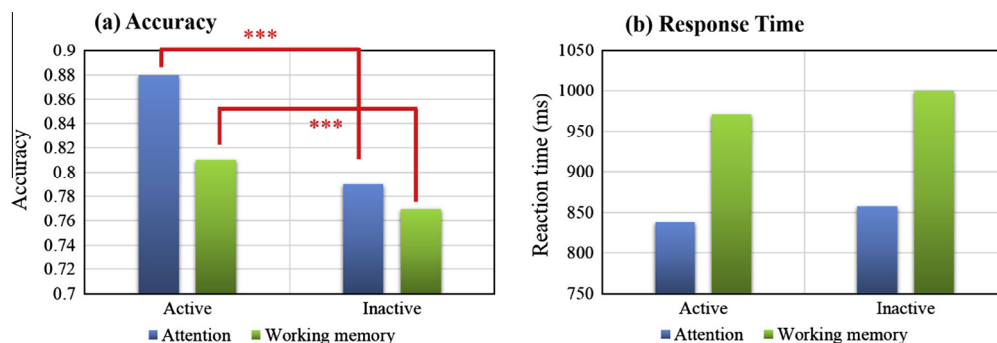


Fig. 2. Task performance including (a) accuracy and (b) reaction time for correct trials for physically active and inactive elderly adults in both the attention (non-delayed) and working memory (delayed) conditions. *** Denotes $p < .001$.

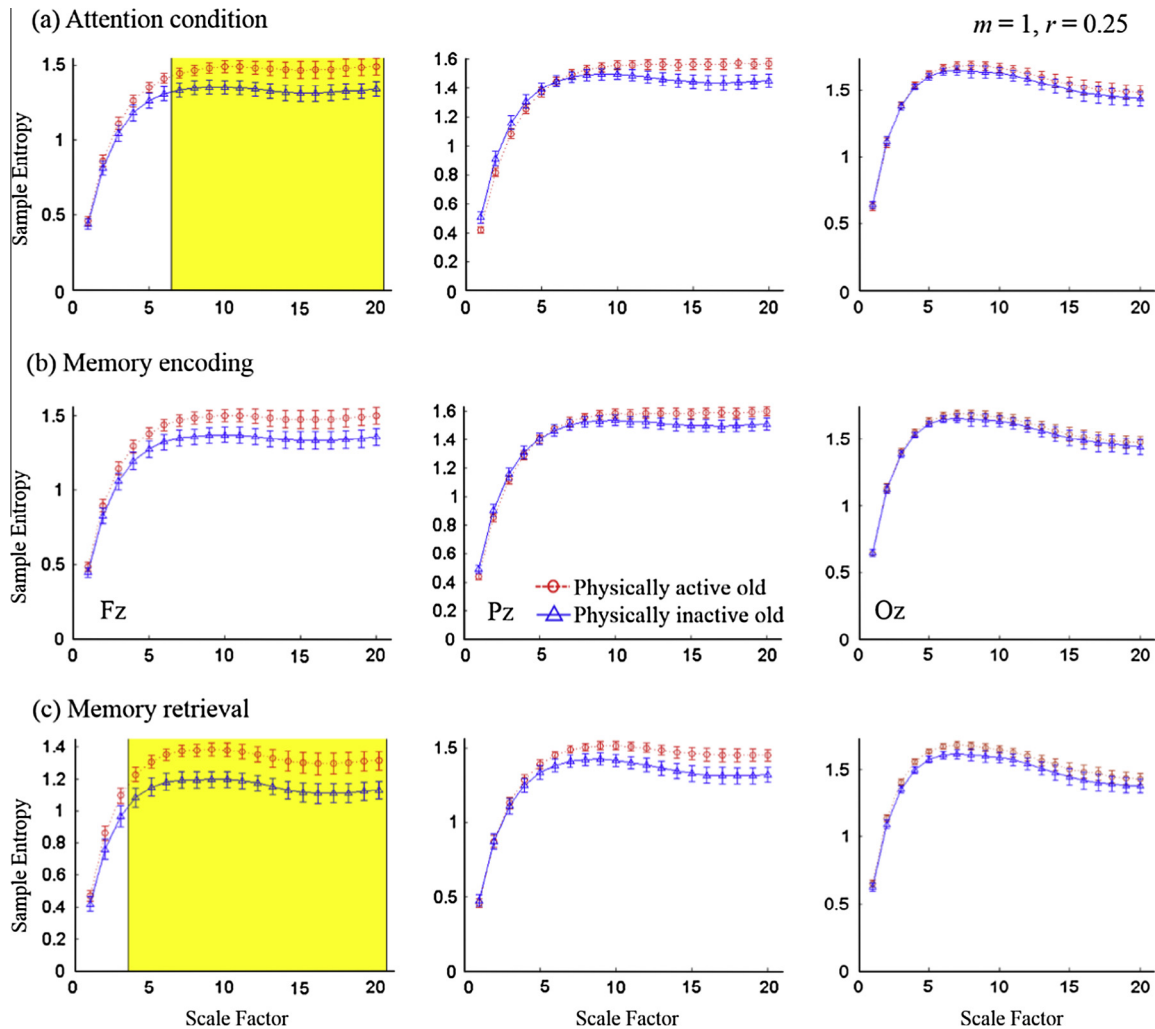


Fig. 3. Differences in EEG-based multiscale entropy ($m = 1, r = 0.25$) at Fz, Pz, and Oz electrodes for physically active and inactive elderly adults in the (a) attention (non-delayed), (b) memory encoding, and (c) memory retrieval condition. The yellow region depicts significant effects for contrasts between groups ($p < .05$, FDR corrected). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

ferent levels of physical activity (Hatta et al., 2005; Hillman, Motl, et al., 2006; Hillman et al., 2004). Hatta et al. (2005) employed a somatosensory oddball task and found that older adults who regularly engaged in a variety of physical activities (e.g., aerobic exercise, resistance training, and stretching exercise) had better performance in comparison to those who were sedentary. Likewise, Hillman, Motl, et al. (2006) used a flanker task and found that physical activity was related to faster responses in both congruent and incongruent conditions for older participants. Moreover, Hillman, Kramer, Belopolsky, and Smith (2006) observed faster overall response times for active older adults relative to sedentary elders during a task-switching paradigm. These findings suggest that physical activity may benefit or at least lower the rate of cognitive degradation late in one's lifespan. Accordingly, our findings may further support this argument into the context of visuo-spatial cognition.

Interestingly, our behavioral results were partly inconsistent with our original predictions because we found a positive effect of physical activity irrespective of the amount of executive control. Two possible reasons may help account for this finding. Firstly, task difficulty may be high enough to see the beneficial effect in both conditions. In the current task, the small dot sizes (merely 0.36° diagonal difference) seemed to be hard to discriminate for elderly adults. In support of this argument, we found 83% accuracy for the

attention and 78% accuracy for the working memory task across participants, indicating a high visuo-spatial demand in both conditions. This may be attributed to the vulnerability of visuo-spatial processing capacity to aging (Chen et al., 2003; Myerson et al., 2003), thus leaving sufficient room for improvement in this type of cognitive component (Shay & Roth, 1992; Stroth, Hille, Spitzer, & Reinhardt, 2009; Wu et al., 2014). Accordingly, tasks with suitable visuo-spatial load may be useful to examine the cognitive benefits of exercise in older adults.

Secondly, the type of physical activity may play an important role in this kind of investigation (Miller, Taler, Davidson, & Messier, 2012). In the present study, we recruited the physically active group from senior table tennis clubs. That is, the physical activities they experienced were mostly from a racket sport, a sport of a type that has been suggested to have the capacity to improve cognitive functions (Tsai, 2009; Wang, Chang, Liang, Shih, et al., 2013; Wang et al., 2013). For example, Tsai (2009), employing a visuo-spatial attention paradigm, observed that a 10-week racket sport intervention could reduce attentional costs induced by an invalid spatial cue in children with developmental coordination disorder (DCD). In addition, sports with intense cognitive demands (e.g., temporal preparation in tennis) may result in larger modulation of cognitive function relative to sports that are less demanding (Wang, Chang, Liang, Chiu, et al., 2013; Wang, Chang, Liang, Shih,

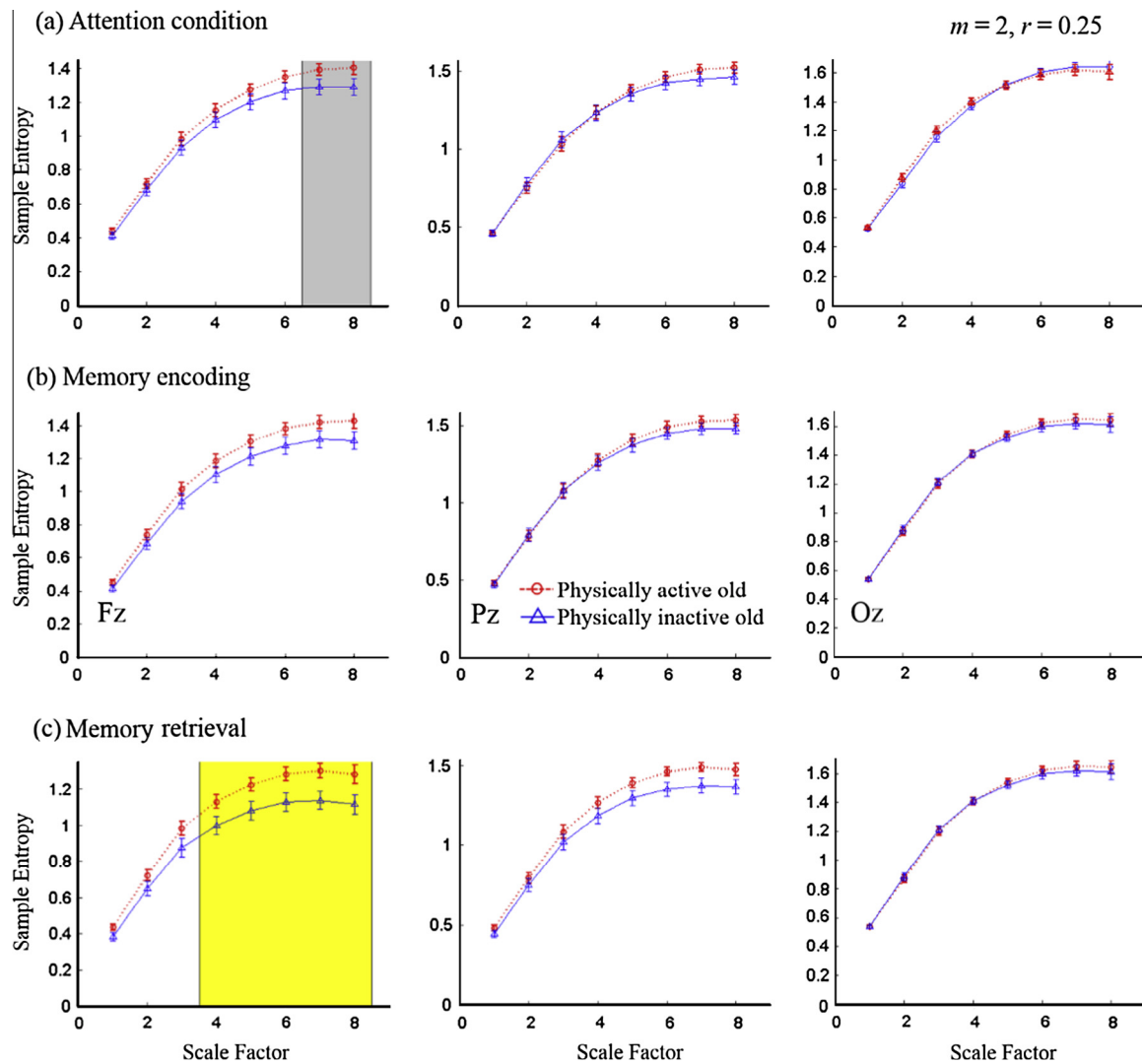


Fig. 4. Differences in EEG-based multiscale entropy ($m = 2$, $r = 0.25$) at Fz, Pz, and Oz electrodes for physically active and inactive elderly adults in the (a) attention (non-delayed), (b) memory encoding, and (c) memory retrieval condition. The yellow region depicts significant effects for contrasts between groups ($p < .05$, FDR corrected), while the gray region depicts significant effects for contrasts between groups ($p < .05$, uncorrected). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

et al., 2013). Consequently, the active group in the present study may have benefits in visuo-spatial processing as a result of the type of sport they regularly participated in, showing superior visuo-spatial cognitive performance regardless of the amount of executive control (for a similar example in cognitive control, see Wang, Chang, Liang, Chiu, et al., 2013). This idea by itself, however, would lead to the prediction that the effect of sports activity are restricted to the visual and strategic nature of the sports (i.e., no different from a video game), and therefore will not transfer to cognitive functions that are less involved. This would be at odds with the wealth of findings that demonstrate the positive effects that aerobic fitness (from exercising, running, swimming and the like) has on cognitive functioning (Kramer & Erickson, 2007; Kramer et al., 1999). As such, perhaps a combination of both factors are true here, and future studies would benefit from more specific assessment of what kinds of activity might be most beneficial for reduction of cognitive aging (Miller et al., 2012).

4.2. Frontal EEG complexity via MSE

One novel approach of the present study was the analysis of EEG signal complexity via MSE, which can provide an index of

dynamic changes in inherent brain activity (Yang et al., 2013) and “meaningful structural richness” for a biological system in terms of underlying chaotic deterministic dynamics (Costa et al., 2005; Thuraishingham & Gottwald, 2006). This may shed light on possible differences in neural activity behind the behavioral findings (Liang et al., 2014). The between-subjects results showed that the brain activity of the active group was more complex and information rich compared to the inactive group at frontal sites in both attention and working memory conditions. This suggests that physically active elderly adults may have greater ability to adapt to environmental changes in comparison to inactive ones (Costa et al., 2002, 2005; Garrett et al., 2013; Goldberger et al., 2002), thereby allowing the brain to better adapt to processing external visuo-spatial stimuli under different levels of cognitive load. In addition, we found that such an effect was particularly evident for the frontal electrodes but not for parietal or occipital electrodes, which is presumably due to the fact that the frontal areas are the first regions to suffer from aging, and thus would be more likely to receive the beneficial effects of physical activity (Hatfield et al., 2003; Hillman et al., 2004). Furthermore, in this study the between-subject effect on MSE was not observed in small-scale ranges (1–5 for attention; 1–3 for working memory). This MSE

pattern is similar to those in studies investigating the difference between young and older adults (Takahashi et al., 2009) and autistic individuals and healthy controls (Catarino et al., 2011), which also showed no group differences in MSE within smaller time scales. One possible reason accounting for this may be because random noise decreases as the time scale increases (Costa et al., 2005), thus resulting in more reliable complexity values for larger time scales. This also demonstrates the importance of measuring entropy values across multiple coarse-grained sequences (Costa et al., 2002, 2005; Ueno et al., 2014). Moreover, it might be also likely that, relative to inactive counterparts, these physically active elderly adults were better at using relatively large temporal scale neurophysiological dynamics, in order to deal with varying and unexpected visuo-spatial stimuli. Indeed, the usefulness of EEG-based MSE for exploration in aging pathophysiology has been previously suggested (Garrett, McIntosh, & Grady, 2011). The present findings thus indicate that physical activity may be associated with higher brain signal complexity related to functional and cortical responses, particularly in brain areas that are susceptible to aging (Nyberg et al., 2010).

It is noteworthy that although the EEG signal picked up at each electrode might not reflect the electrophysiological activity directly underneath the recording location, alterations in frontal EEG activity allied to aging have been proposed before (Friedman, 2003), highlighting the importance of frontal electrophysiological activity in examining aging cognition. Thus, our findings imply that a more information-rich brain activity in the frontal region is at least one candidate for better task performance in elderly adults. This partially aligns with previous EEG and imaging studies that suggest neural activity in frontal regions to be critical in the relationship between physical activity and aging cognition. For example, Kimura et al. (2012) used a task-switching paradigm and found that highly active older adults showed higher cognitive stability and task-related frontal activation than the control group, suggesting that physical activity may attenuate age-related loss in frontal and executive functioning. Similarly, Hillman et al. (2004) also observed that elderly adults with higher levels of physical activity showed increased frontal P3 amplitudes during the condition involving higher executive control, whereas this effect vanished in those with lower levels of physical activity. All of this suggests that physically active older individuals may compensate for age-related cognitive decline via recruitment of greater frontal cortical resources.

In addition, it has been previously claimed that EEG-based MSE may reflect the information processing capacity of brain systems and the repertoire size of responses induced by stimulus presentation in brain (Heisz et al., 2012). That is, the more information available, the higher the signal complexity produced by a given stimulus (Deco, Jirsa, & McIntosh, 2010). In addition, a certain amount of physiological complexity may be needed for the neural systems to adapt effectively to an uncertain situation (Seth, 1998). Hence, higher frontal EEG complexity elicited in the active group here perhaps indicates that the active participants may have gained richer visuo-spatial information from the stimulus presentation relative to the inactive group, thereby facilitating the processing of stimulus comparison and motor execution and resulted in better behavioral outcomes. Based on this finding, higher physical activity appears to be related to increased adaptation and cognitive repertoire of the aging brain, which is captured by higher neural complexity. While some may argue that greater entropy actually reflects higher neural noise, the 2005 study by Costa et al. has shown that the color-noised biological signals are more complex than uncorrelated random signals (white noise), and those white noise signals can only show high entropy within a limited number of the smallest scales. In this study, we observed higher MSE for physically active elderly in a long continuous range

of scales, thus reducing the likelihood that our observations were driven by uncorrelated noise.

Intriguingly, the effect of physical activity was absent during the memory encoding stage where only one dot position was to be processed and no other cognitive processes (e.g., dot comparison or motor execution) were involved. The data collected here therefore suggest that higher frontal MSE in the active group might not be attributed to better neural adaptability and efficiency in general or the complexity in the default mode network. Instead, such an effect might be task-dependent, in which higher MSE can only be observed for the active group when executive control was required. This is presumably because brain signal complexity was modulated by cognitive functioning, with evidence showing that greater increases in BOLD variability from fixation to tasks tapping into cognitive processes (Garrett et al., 2012). Based on this, we speculate that the beneficial effect of physical activity on brain complexity in elderly adults may be more easily seen in cognitive functions such as executive control. However, future studies are warranted to examine whether the effects of physical activity on brain signal complexity in the default mode network are related to task performance (e.g., Yang et al., 2013).

While the present findings shed light on the effects of physical activity effect on visuo-spatial processing and brain signal complexity in terms of dynamic EEG activity, there are some limitations to the interpretations that require caution. Firstly, although the usefulness of a self-reported estimation of physical activity in this type of study has been shown (Dai, Chang, Huang, & Hung, 2013; Hillman, Motl, et al., 2006; Hillman et al., 2004), it may be worth addressing this issue by using more objective measures (e.g., motion sensors, accelerometers, heart rate monitoring) (Warren et al., 2010). In addition, recent electrophysiological studies have documented an interactive effect of physical fitness and a single bout of exercise on cognitive functioning (e.g., Hogan, Kiefer, Kubesch, Collins, & Brosnan, 2013; Tsai, Chen, et al., 2014; Tsai, Wang, et al., 2014). Further studies are thus warranted to investigate how such interaction may affect brain signal complexity. Moreover, to reduce the potential influences of recalling physical activity on cognitive tasks and EEG signals, it is suggested to place the recall questionnaires after the experiments or assign different experimenters for questionnaires and cognitive task measurements separately. This may help reduce any observer-expectancy effect (e.g., a Clever Hans effect). Finally, our data is not able to show that physical activity alters brain signal complexity due to the nature of the quasi-experimental design we used. Some other confounding variables such as personality, genetic, social or other factors also prevent any causal interpretation regarding the effect of physical activity on brain signal complexity at present. Further research is necessary to experimentally manipulate people's exposure to different levels of physical activity in order to demonstrate a causal basis for the relationship between physical activity and EEG complexity that we report here.

5. Conclusions

The present study demonstrated the effectiveness of brain signal complexity in investigating the effect of physical activity on age-related cognition. We found that elderly adults with higher physical activity had better visuo-spatial processing regardless of levels of executive control. Interestingly, the highly active elderly adults showed a higher degree of EEG-based brain signal complexity than their sedentary counterparts selectively at the frontal electrode, suggesting that physical activity may be related to greater neural adaptation or efficiency in elderly adults. Our results here might suggest that physical activity could keep the brain healthy, as suggested by the greater MSE values, in late adulthood. These

findings may have important practical implication such that EEG signal complexity may be a suitable measure of cognitive functioning and a promising approach to examining the relationship between physical activity and healthy cognitive aging.

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