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Executive functions and bone health: a focus on cognitive impulsivity and bone mineral density

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Abstract

Background**:** It is known that cognitive impairment is associated with low bone mineral density (BMD) and that low BMD is also observed in elderly people with neurodegenerative diseases, in which executive functions (EF) could be decreased. A limited number of studies investigated the association between EF with BMD and fracture risk in elderly women.

Aims**:** The aim of this study was to explore the association between cognitive impulsivity, BMD and fall risk in a sample of postmenopausal women evaluated for osteoporosis.

Methods**:** We consecutively recruited women who obtained a score ≥ 24 at the Mini Mental State Examination (MMSE). Cognitive impulsivity was evaluated by the Stroop Colour and Word Test (SCWT). BMD was detected by dual-energy X-ray absorptiometry at lumbar spine and femoral neck.

Results: Cognitive impulsivity, as evidenced by the greater number of errors at the SCWT, was significantly related with BMD values at lumbar spine and femoral neck (r= -0.39, p= 0.01 and r= -0.43, p= 0.008; respectively), suggesting a neuropsychological impairment in patients assessed for osteoporosis. Moreover, interference effect on response time was significantly associated with higher prevalence of falls (r= 0.342; p= 0.031).

Discussion and Conclusions**:** Our findings suggested a potential involvement of cognitive impulsivity on BMD and risk of fall. This is a relevant issue in clinical practice for both clinical psychologists and physicians who evaluate postmenopausal women, to eventually predict risk of fracture.

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1. Introduction

Osteoporosis represents the most common metabolic bone disease and involves a significant social and economic burden (Brandi, 2012; Catalano et al., 2013; Martino et al., 2018a). Clinical psychological features have been associated with bone mineral density (BMD) in

postmenopausal women with osteoporosis (Mollard, Bilek, & Waltman, 2017; Catalano et al., 2018; Martino et al., 2018). Patients with osteoporosis commonly show a decreased quality of life perception and present a higher incidence of depression and anxiety symptoms (Martino et al., 2018b; Erez et al., 2012; Williams et al., 2011).

Particularly anxiety levels were recently found to be predictive of fracture risk in postmenopausal women (Catalano et al., 2018). Chronic psychological stress is a recognized risk factor for osteoporosis, leading to bone loss by inhibiting bone formation (Azuma et al., 2015).

Several lines of evidence highlighted a link between osteoporosis and cognitive impairment.

In this regard low levels of BMD have been associated with increased rates of progression from mild cognitive impairment to Alzheimer's disease and with the onset of episodic verbal learning deficit (Zhou et al., 2014; Sohrabi et al., 2015).

Moreover, recent findings from the Italian longitudinal InCHIANTI study showed that low BMD might represent an independent early marker of subsequent cognitive impairment in elderly women (Laudiso et al., 2016).

As known, EF comprehend several cognitive domains necessary for controlled and goal-directed behavior, including working memory, attentional control, planning, inhibition (Miyake et al., 2000; Royall et al., 2002; Vicario et al., 2019). The EF impairment might affect the complex activities performance, which requires goal-directed behaviors (Royall et al., 2002).

Changes in EF were also longitudinally found to be independently associated with the progressive decline of instrumental activities of daily living and they are significantly associated with higher risk of fall even in community-dwelling older adults without dementia (Overdorp et al., 2016; Tomaszewski Farias et al., 2009; Muir et al., 2013).

It is known that impulsivity is a heterogeneous construct, crucial for several cognitive and behavioral features. Spontaneous actions due to internal or external stimuli are often incompatible with long-term purpose and are usually named impulsivity (Stahl et al., 2014). Different aspects of cognitive impulsivity have been reported, comprising a lack of reflection with the inability to raise information before reaching a decision and low response inhibition, including also the inability to repress motor responses which have been made prepotent (Chamberlain & Sahakian, 2007; Whitney et al., 2012).

However, poor investigations on neuropsychological factors in subjects at risk for osteoporosis and fracture risk are available and specifically the potential impairment of executive functions (EF) remains unclear.

The aim of the current study is to investigate the relevance of EF impairment, particularly related to cognitive impulsivity, on bone health in postmenopausal women evaluated for osteoporosis, to detect a possible association between these two entities. Our hypothesis on this potential association between EF impairment and low BMD might lead to interesting development in clinical practice, allowing clinical psychologists and physicians to early identify bone fractures risk in postmenopausal women evaluated for osteoporosis.

2. Materials and methods

2.1 Study design and sample

A sample of forty Caucasian postmenopausal women, referred to our Outpatients Clinic for the Prevention and Treatment of Osteoporosis was consecutively recruited in this cross-sectional study.

We excluded women who met the following criteria: movement and neurologic disorders or psychiatric disorders, in accordance with DSM-V diagnostic criteria which could interfere with participation in the study (APA, 2013; Tay et al., 2015);

history of significant hearing or visual impairment, or significant physical disability rendering participation difficult; history of uncontrolled diabetes and abnormal thyroid function; history of cancer, heart, respiratory, kidney or liver failure; history of assuming psychotropic drugs or bone active agents.

The study was conducted in accordance with the ethical standards of our institutional research Committee and the 1964 Declaration of Helsinki and its later amendments. Participants have given written consent for their data to be used in this research.

2.2 Main outcome measures

Cognitive impulsivity was measured by the Italian version of Stroop Color and Word Test (SCWT) administration. SCWT is a neuropsychological test able to assess the ability to inhibit cognitive interference, occurring while the elaboration of a stimulus affects the concomitant processing of another attribute of the same stimulus (Stroop, 1935; Caffara et al., 2002). It is known that the words themselves have a strong influence over subject ability to say the color. The interference between what the brain receives from different informations (e.g. what the words say and what the colour of the words says) can provoke problems as time interference and error interference.

During the administration, women were required to quickly read three different tables of which two represent the "congruous condition" in which participants are required to read names of colors printed in black ink and name different colour patches. In the third table, named "incongruous condition", colour-words are printed in inconsistent colour ink (e.g. the word "red" is printed in green ink) and participants were required to name the colour of the ink instead of reading the word.

Stroop test time and error interferences were the dependent variables considered to evaluate cognitive impulsivity, reflecting EF impairment. We included only subjects with a score ≥ 24 at Mini Mental State Examination (MMSE) and to avoid cognitive bias due to the presence of depressive symptoms we administered Beck Depression Inventory Scale (BDI- II) (Folstein, Folstein, & McHugh, 1975; Beck, Steer, & Brown, 1996). To avoid confounding factors due to anxiety levels, which could affect patient SCWT response, we also administered Hamilton Anxiety Scale (HAM-A) (Hamilton, 1959). BMD was assessed by the gold-standard dual-energy X-ray absorptiometry (DXA) densitometer (Hologic Discovery) at the lumbar spine (L1-L4) in anteroposterior projection and at femoral neck. Our DXA densitometer was calibrated daily according to the instruction of the manufacturer and its coefficient of variation (CV) was 0.5% with the standard phantom**.**

In accordance with the World Health Organization recommendation, BMD was reported as T-score value, which compares the woman's BMD measurement to those of white women at an age when bone density is at its peak (WHO, 1994). We performed physical pain measurement by visual analogue scale and collected the number of self-reported falls within the last 12 months.

2.3 Statistical analysis

Statistical analyses were performed using MedCalc software (version 10.2.0.0; Mariakerke, 173 Belgium). The normal distribution of values was verified with the Kolmogorov-Smirnov test and Pearson's correlation analysis was performed to measure the degree of association between two variables. Multiple regression analysis was applied to analyze the relationship between a dependent variable and one or more explanatory variables. Values of $p < 0.05$ were considered statistically significant.

3. Results

The main demographic and clinical characteristics of the enrolled sample are shown in Table 1.

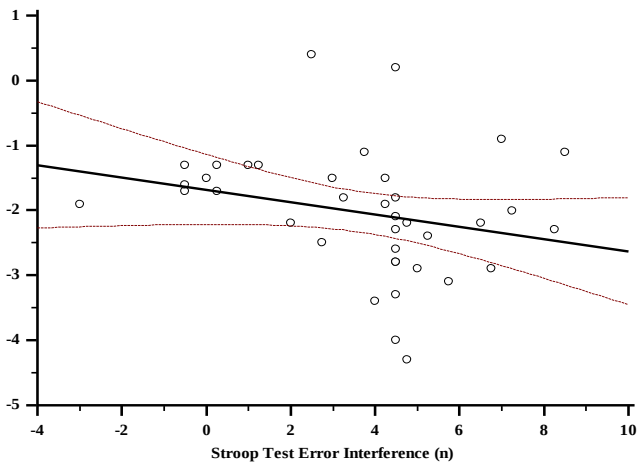
Table 1. Main clinical characteristics of participants.

Main clinical characteristics	***Patients*** *(n=40)*
Age *(yr.)*	66.7 ± 7.9
Time since menopause *(yr.)*	16.6 ± 3.6
BMI *(kg/m²)*	25.2 ± 2.8
Smoking *(n)*	8
Alcohol ≥ 3 unit/day *(n)*	0
Body pain *(score)*	1 ± 0.5
Falls in previous 12 months *(n)*	0.8 ± 1.4
Cognitive assessment	
MMSE *(score)*	27.3 ± 1.8
Stroop Test time interference *(sec)*	2.4 ± 1.5
Stroop Test error interference *(n)*	1.12 ± 1.4
DXA measurement	
L1-L4 T-score *(SD)*	-2.1 ± 0.9
Femoral neck T-score *(SD)*	-2.0 ± 0.8

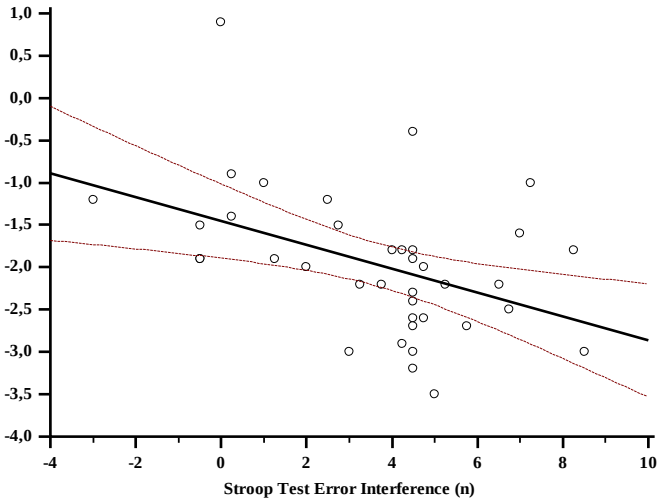
Cognitive impulsivity, as highlighted by making errors at the SCWT, was significantly and negatively associated with lumbar spine and femoral neck T-score (r= -0.39, p= 0.01 and r= -0.43, p= 0.008; respectively) as shown in Figure 1.

Figure 1. Association between Stroop Test Error Interference and T-score values at lumbar spine (**panel a**) and femoral neck (**panel b**).

Panel a



Panel b



Thus, women who committed more errors to the SCWT had lower BMD values and a greater risk of osteoporosis too. MMSE score was not significantly associated T-score values, neither at lumbar spine (r= 0.09, p= 0.5) nor at femoral neck (r= 0.2, p= 0.21); differently MMSE score was significantly and negatively related both with Stroop test error (r= -0.34, p= 0.02) and time interferences (r= -0.39, p= 0.01). Thus, women who obtained higher scores to MMSE had the best performances at SCWT.

Furthermore, time interference, was positively associated with the self-reported history of falls (r= 0.342; p= 0.031), meaning that postmenopausal women who reported more falls had higher time interference at the SCWT, as they too longer to answer. At a multiple regression analysis, considering femoral neck T-score as dependent variable and considering age, MMSE, Stroop time interference and Stroop error interference as explanatory variables, we observed that femoral T-score score was independently predicted by age (β = -0.03, p= 0.39, SE= 0.01) and by Stroop test time interference (β = -0.1255, p= 0.015, SE= 0.04).

4. Discussion

This is the first study investigating cognitive impulsivity through SCWT administration in postmenopausal women assessed for osteoporosis. The major finding of the present research is the identification of significant associations between cognitive impulsivity, BMD values and risk of fall. SCWT was previously used to measure other cognitive functions such as attention, processing speed, cognitive flexibility and working memory and it is largely used to measure the ability to inhibit cognitive interference (Jensen & Rohwer, 1996; Meyer & Kane, 2012; Mirelman et al., 2012).

SCWT allows patients to perform a less automated task (i.e., naming ink colour) while they are inhibiting the interference arising from a more automated task (i.e., reading the word).

This phenomenon in inhibiting the more automated process is known as Stroop effect (Stroop, 1935). Recently Mirelman and colleagues in a longitudinal study conducted on a setting of community living older adults, observed that the risk of fall was independently predicted by EF (Mirelman et al., 2012). This is consistent with our data, since women reporting the worst score at SCWT exhibited a higher risk of falling.

It is known that falls are more frequent in older age people and are associated with cognitive decline (Abrahamsen et al., 2014; Vind et al., 2009a; Vind et al., 2009b; Vind et al., 2010; Settineri et al., 2018). However, in elderly people EF may have a role in rewording age-associated decline of motor function, thus EF deficits could amplify the risk of fall, irrespective of global cognitive decline (Mirelman, 2012). Moreover, exclusion criteria relative to women who had MMSE < 24 allowed us not to consider those ones who had detectable cognitive decline and neurodegenerative diseases and with known higher risk of fall and bone fractures. Beyond the positive correlation between EF impairment and falls, we found a significant association between EF impairment and T-score values. As falls and T-score are known predictors of fracture risk**,** we could hypothesize that EF impairment might lead to an enhanced fracture risk in postmenopausal women referred for osteoporosis (Abrahamsen et al., 2014).

Even if in this study we did not measure the intensity and the duration of physical activity, we could speculate that the emerging association between EF impairment and low BMD could be due to a reduced physical activity in our sample of postmenopausal women. Conversely, physical exercise has been observed to significantly improve executive functions in community-dwelling older adults (Guitar et al., 2018). Moreover, postmenopausal women referred for osteoporosis usually show a poor vitamin D status, which may contribute to low BMD values and to increased risk of fall leading to bone fractures (Calvani et al., 2013; Martino et al., 2018a)**.** Furthermore, lower serum 25-hydrossivitamin D concentrations predict executive dysfunctions, especially on mental shifting, information updating and processing speed**,** nevertheless its possible role on facilitating the connection between EF impairment and low BMD needs further investigation (Annweiler et al., 2013). Regarding the BDI-II administration, it allowed us to exclude a potential confounding due to depressive symptoms which could have an impact on both MMSE (e.g. reducing attention, concentration, memory) and SCWT (error and time interferences) performances. It is also known that depressive symptoms could involve a potential poor motivation to walk, compromising muscle tropism and the habit to safe walking too (Beck, Steer, Brown, 1996; Merlo et al., 2018). For the same reason neurological and clinical psychological evaluations were necessary carried out to exclude the risk of interferences and errors at the SCWT (Annweiler et al., 2013; Mento, Merlo, & Settineri, 2017). During the clinical psychological evaluation, we collected self-reported data.

We excluded patients assuming psychopharmacological treatment for depression or anxiety disorders to avoid both confounding on timing and errors at SCWT and adverse iatrogenic effects on bone health (Langher, Caputo, & Martino, 2017; Catalano et al., 2019), frequent in several chronic diseases which even impair body masses index, body image, adherence, adaptation and related outcomes (Marchini et al., 2018; Settineri et al., 2019; Rosa et al., 2019; Martino et al., 2019). This is also in accordance with our previous data showing reduced BMD values in postmenopausal depressed women (Atteritano et al., 2013). Moreover, through HAM-A administration we excluded anxious subjects as anxiety levels could be associated with reduced BMD, higher risk of fall and could impair on time and error interference at SCWT. Patients were also free from physical disability and they did not report significant levels of physical pain as it could reduce the habit to walk increasing falls and fracture risk (Catalano et al., 2017).

We acknowledge that this study has some limitations. The cross-sectional design did not allow interference of causality because data does not hold information on it. Further studies are needed to elucidate a potential causal relationship between cognitive impulsivity, osteoporosis and falls. Other limits are the relatively small sample size consisting of only women and the absence of a control group.

Moreover, in the future perspectives, a larger sample size of participants should be tested. A selection bias of this research is represented by the exclusion of patients with MMSE < 24, which means that our sample involved of postmenopausal women who had not detectable cognitive decline.

However further prospective studies should be conducted to highlight the potential predictive role of EF impairment, even in subjects with normal score at MMSE, as early detectable sign of subclinical cognitive decline in neurodegenerative diseases.

Moreover with the HAM-A administration we excluded women who reported anxiety levels, but we didn´t make any difference between anxiety state and anxiety trait, thus we couldn't explore if anxiety trait can have an impact on EF and if it could be associated with EF impairment, low BMD, higher risk of fall and fractures.

Further studies should be conducted to evaluate whether anxiety trait, could be associated to EF impairment, BMD variation, risk of fall and bone fractures and to explore the potential difference of this association in comparison with the one relative to anxiety state.

5. Conclusions

Our preliminary data suggest a significant association between cognitive impulsivity, as specific neuropsychological correlate, BMD and fall risk. These results may prove useful for clinical psychologists and physicians, who should include psychodiagnostic evaluation into screening batteries

dedicated to postmenopausal women who refer for osteoporosis, to investigate EF and cognitive impulsivity. The specific evaluation of the association between EF impairment and low BMD in elderly women could lead to early identify patients with an increased risk of fall and bone fractures.

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