Psychoneuroendocrinology 91 (2018) 198–205

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Serum calcium levels and neuropsychological performance in depression and matched healthy controls: Reversal of correlation a marker of the aging cognitive clock?

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ARTICLE INFO

Keywords:
Major depressive disorder
Cognitive impairment
Neuropsychological performance
Serum biomarker
Calcium signaling
Cognitive aging

ABSTRACT

Background: Major depressive disorder (MDD) is associated with cognitive impairment, that might be related to disturbed calcium homeostasis. Calcium-related processes have also been implicated in age related cognitive decline. Since serum calcium and brain interstitial fluids maintain long-term equilibrium under normal physiological states, serum calcium levels could affect neuronal and hence cognitive function. High serum calcium has been associated with cognitive decline in geriatric populations, whereas evidence for MDD and healthy populations is less consistent.

Methods: Differences in neuropsychological (NPS) performance and their relationship with serum calcium (total, ionized, total to ionized ratio) in (partially) remitted MDD patients (n = 59) and healthy controls (HC) (n = 59) individually matched for age, gender and education (age-range 19–60 years) were examined. Modulation of study parameters and their interaction by the factor age was investigated, with subgroups young and old divided at median = 37 years. Participants provided blood samples and completed an extensive NPS test battery.

Results: MDD showed significantly poorer NPS performance compared to HC. Serum calcium associated positively with NPS performance in HC and negatively in MDD for entire age-range samples. While younger MDD and HC showed positive NPS-calcium correlations, older MDD and HC exhibited negative NPS-calcium correlations ('correlation reversal'). Age had a significant effect on cognition and ionized calcium and interacted with illness-status, with an exaggerated influence on cognition in MDD compared to HC.

Conclusions: The results place calcium 'correlation reversal' to early middle-age time window, which may be accelerated for MDD and highlight the central role of calcium pathways in normal and pathological cognitive aging.

1. Introduction

Cognitive impairments are present in the acute phase as well as remission (e.g., (Hasselbalch et al., 2011)) of Major depressive disorder (MDD). The factors modulating cognitive impairment in MDD are not well-understood. Various neurobiological alterations have been postulated to be involved in MDD's pathophysiology and related cognitive deficits (reviewed by Rot et al. (aan het Rot et al., 2009)).

Calcium (Ca) is an important element necessary for activation of various neurophysiological pathways. Abnormal neuronal Ca homeostasis and signaling have been postulated to be involved in different neurodegenerative diseases such as Alzheimer's Disease (AD) (Berridge, 2010)), and abnormal serum Ca levels have been associated with depressive symptoms and cognitive deficits (e.g., primary hyperparathyroidism (Hurst, 2010)). Literature for peripheral Ca levels in MDD is less conclusive with both higher plasma, serum or CSF Ca levels (e.g.,

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https://doi.org/10.1016/j.psyneuen.2018.03.012
Received 18 February 2018; Received in revised form 18 March 2018; Accepted 20 March 2018

(Jimerson et al., 1979)) and lower plasma Ca levels (e.g., (Bowden et al., 1988)), while some studies report no differences between serum Ca levels in MDD and healthy controls (HCs) (e.g., (Jamilian et al., 2013)).

Ca has been reported to exist in blood free in ionized form, bound to plasma protein or anions (Bushinsky and Monk, 1998). The biologically active ionized form has the highest physiological relevance for disturbances in Ca homeostasis (e.g., (Sava et al., 2005). A likely indicator of peripheral Ca homeostasis is the total to ionized Ca ratio (tCa/iCa ratio) or relative ionized Ca, so far only researched for extreme pathological conditions (Link et al., 2012). A lower tCa/iCa ratio reflects more bioactive (ionized) Ca and a higher mobilization of Ca stores (Henderson et al., 1989). Constitution of the brain interstitial fluid (ISF) has been reported to be similar to that of cerebrospinal fluid (CSF) (Subhash et al., 1991). Since CSF Ca concentration depends on both serum Ca concentration (major source) and blood brain barrier (BBB) permeability (e.g., (Joborn et al., 1991), the amount of electrolytes available in serum could influence neuronal and therefore cognitive performance. Further a proportional equilibrium between serum and CSF/ISF Ca levels has been reported (Tai et al., 1986). Although very few studies have investigated exact mechanisms of Ca transport across the BBB or blood-CSF barrier (BCSFB) under normal homeostatic conditions, the existing albeit scarce literature indicates simple passive diffusion operating across concentration gradient as the mechanism of choice under normal homeostasis (e.g., (Breschi et al., 2013)).

In the central nervous system (CNS), influx of extracellular Ca is important for neuronal processes such as vesicular neurotransmitter release at chemical synapses and NMDA (N-methyl-D-aspartate) receptor mediated neuroplasticity via long-term potentiation (LTP). Upon activation, NMDA receptors allow the entry of Ca ions into the neuron activating downstream signaling pathways: Ca enhances synaptic transmission and LTP induction via the enzyme calmodulin-dependent protein kinase II (CaMKII) (Lisman et al., 2002) but also induces long-term depression (LTD) via calcineurin (Mulkey et al., 1994). Moreover, Ca regulates gene transcription (rat models e.g., (Hardingham et al., 2001)) as that of BDNF important for synaptic plasticity (Vasquez et al., 2014). The nuclear Ca transients important for transcription may also be amplified by extracellular Ca influx (Hardingham et al., 2001). However, the quantitative relationship between the amount of peripheral, extracellular and intracellular Ca remains largely unknown.

In sum, extracellular and intracellular Ca play a crucial role in neuronal signaling pathways including learning via neuroplasticity and evidence points to direct influence of peripheral extracellular Ca on mood and cognition (e.g., (Hurst, 2010)). Only few clinical studies have examined the relationship between peripheral Ca and cognition across psychiatric and healthy populations. A recent study reported higher serum tCa levels to be associated with better neuropsychological (NPS) performance in MDD, providing first evidence for the modulation of NPS performance in MDD by peripheral Ca (Sharma et al., 2017). Another study reported higher serum ionized Ca (iCa) concentrations to correlate with better NPS performance in healthy individuals (Lam et al., 2016). Although factors affecting the modulation of cognition by Ca remained largely unexplored, age emerged as potential mediator of this relationship in one of these studies (Sharma et al., 2017). Studies examining cognitive decline in geriatric populations (age ≥75 y) have also postulated age to be an important modulator with higher serum tCa levels associated with lower baseline global cognition and rapid cognitive decline (Schram et al., 2007) and high iCa as risk factor of cognitive decline (Tilvis et al., 2004). The lack of a much younger (middle aged or earlier) comparison sample restricts the validity of these negative associations to geriatric populations.

To our knowledge, previous studies investigating NPS performance in partially remitted MDD have lacked sufficiently large matched-sample size with wide age-range (e.g., (Hammar and Ardal, 2013)), individualized matching (age, sex and education) or an extensive cognitive test battery. Studies comparing NPS performance between fully remitted MDD patients and HCs in age range 19–60 y with large sample size, they either lacked matching or a wide cognitive test-battery (e.g., (Preiss et al., 2009)).

Therefore, the aims of the current study were to:

1) Verify previously reported results of cognitive impairment in (partially) remitted MDD patients compared to HCs individually matched for age (± 2 y), gender and education.
2) Examine the validity of serum Ca measures (tCa, iCa, tCa/iCa ratio) as potential predictors of NPS performance in (partially) remitted MDD patients and matched HCs.
3) Examine differences in serum Ca measures (tCa, iCa, tCa/iCa ratio) between (partially) remitted MDD patients and matched HCs as potential mediators of group differences in NPS performance.
4) Explore the influence of age (across age-range 19–60 y) as a modulator of the correlation between serum Ca measures and NPS performance in the two study groups and to further examine its interaction individually with NPS performance, illness-status and serum Ca measures.

This is the first study to investigate the interplay of peripheral Ca measures, NPS performance and age in a large sample of (partially) remitted MDD patients and individually matched HCs, and highlights the role of Ca-related pathways that could potentially shape cognitive performance in healthy aging and in MDD pathology.

2. Materials and methods

2.1. Diagnosis and sociodemographic characteristics of study participants

(Partially) remitted MDD patients (n = 109) and HCs (n = 79) (19–60 y) were screened and recruited for the study via various sources (e.g., doctor's/psychotherapist's contact, flyer distribution, advertisements) between March 2016 and July 2017. Only patients who received a main diagnosis of MDD (296.35/36 and 296.25/26) without psychotic symptoms according to DSM-IV criteria (Saß et al., 2003) for a singular (n = 18), a recurrent depressive episode (n = 41) or additional dysthymia (F34) (n = 10) without psychotic symptoms were invited for participation. Structured clinical interview for DSM-IV (SKID-I) for past MDD (Wittchen et al., 1997) and Mini International Neuropsychiatric Interview (M.I.N.I.) (Ackenheil et al., 1999) were administered to confirm diagnosis and evaluate current psychiatric comorbidities. Exclusion criteria were: IQ < 80 according to the *Multiple Choice Vocabulary Intelligence Test* (MWT-B) (Lehrl, 2005); 24-item *Hamilton Rating Scale for Depression* (HAMD) (Guy and Bonato, 1970) (adaption of Hamilton's original version (Hamilton, 1960)) scores ≥20; comorbid psychiatric disorders (ICD axis 1) within the previous 6 months; history of psychotic symptoms; current/past substance abuse (e.g., drugs, alcohol); medication influencing CNS; brain damage or neurological diseases; dementia; intellectual disability; physical illnesses or therapeutic interventions with potential effects on cognition. Further exclusion criteria were: renal impairment, liver dysfunction, severe hyper/hypo-thyroidism or hyper/hypo-parathyroidism, vitamin D deficiency, current intake of Ca supplements and/or vitamin D supplements within the past month. The HC group was individually matched to the MDD group on age (within a ± 2-year range), sex, and education level. Inclusion/exclusion criteria for HCs were the same as for the MDD group, except none of the HCs had any history of psychiatric disorders (screened via M.I.N.I.). Only participants with serum Ca levels in the normal range (total: 1,85–2,6 mmol/l; ionized 1.12–1.32 mmol/l) (Central Laboratory, University Hospital Heidelberg; (Thomas, 2016)) entered the final sample. n = 39 patients and N = 12 HCs were excluded, while additional 8 HCs did not enter the sample because of missing matched pairs. Data from a total of N = 118 entered the final sample (n = 7 MDD patients with comorbidities 6 months previous to assessment, n = 11 MDD patients with comorbid personality disorders).