Journal of
Alzheimer's Disease & Parkinsonism

Mini Review   **Open Access**

The Frontal-subcortical Syndrome

Rodrigo Tzovenos Starosta[1]*, Marcos Vinícius Vidor[1] and Matheus Roriz-Cruz[2]

[1]School of Medicine, Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil
[2]Department of Neurology, Hospital de Clínicas de Porto Alegre, Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil

Introduction

Frontal-subcortical syndrome (FSCS) is a broad-ranging disorder that primarily affects cognition, mood, and motor skills. This dysfunction is usually related to prevalent factors among the elderly population, such as strokes [1], small vessel lesions [2], and metabolic syndrome [3]. Its epidemiology is not precisely known. However, we do know that around 22% of the United States population older than 70 years old has some kind of mild cognitive impairment with no criteria for specific dementias [4]. Although far from proper prevalence data, this statistic gives us a picture of the natural functional decline at least partially linked to frontal-subcortical impairment. This is a particularly serious concern, since the mortality for FSCS patients seems to be higher than the mortality of other cognitive impaired patients, such as those with Alzheimer's disease, reaching 85% in a four-year follow-up [5].

Anatomy of Frontal-Subcortical Connections

The frontal lobe is a leading player for human superior functions. Restricted damage to certain parts of the frontal lobe, such as to prefrontal convexity, orbitofrontal, and medial frontal cortex, can cause specific and distinct syndromes. Nonetheless, the same pattern of syndromes can emerge from subcortical impairment, suggesting a well-defined circuitry connecting these otherwise autonomous portions of brain [6]. There are at least five of these circuits anatomically described: motor, oculomotor, dorsolateral prefrontal, orbital frontal and anterior cingulate circuits. They all originate in prefrontal cortex and form a loop, passing through striatum, globus pallidus and substantia nigra, and finally through thalamus [7].

Motor and oculomotor circuits are required for coordination and initiation of muscle movement by the frontal cortex. The former originates in the supplementary motor area, premotor cortex, motor cortex, and somatosensory cortex. The later in the frontal eye field and posterior parietal cortex. The dorsolateral prefrontal, orbitofrontal, and anterior cingulate circuits work on cognitive tasks and motivational states. The dorsolateral prefrontal circuit operates in a wide range of functions, including planning, learning new information, activating remote memories, and adjusting behavioral sets. The orbitofrontal circuit has a crucial role for behavioral inhibition and emotional liability. Finally, the anterior cingulate circuit has a special role in motivation parameters [7]. It's noteworthy that all the mentioned routes include the basal ganglia, which was once believed to be solely employed in motor coordination [8]. The actual knowledge of these anatomical features end up being of great value for a legitimate understanding of FSCS.

Frontal-Subcortical Syndrome and Metabolic Syndrome

One can define metabolic syndrome as the combinations of some or all of the following disturbances: obesity, high blood pressure, dyslipidemia, and insulin resistance; each of these is an independent risk factor for cardiovascular and endocrine disorders [9], and many, remarkably insulin resistance, are being discover to be associated also with neurological disease [10,11]. Roriz-Cruz et al. have shown, in 2007 [3], that metabolic syndrome predicts the development of FCSC in elderly subjects with an odds ratio of 5.9, being one of the main such predictors; therefore, we feel that understanding each of this syndrome's components' relation with FSCS is fundamental to build a solid approach to this disease.

Insulin resistance and frontal-subcortical syndrome

Insulin resistance is a bodily state in which higher levels of insulin are necessary to produce the same biological response that normal levels used to do [12]; it comprises both pre-diabetes and diabetes mellitus type 2. Although diabetes is known as a major cause of macro- and microvascular disease worldwide [13], we still understand little about how a hyperinsulinemic/hyperglycemic state causes vessel damage: whilst some research has implicated a role for excess glucose entry in endothelial mitochondria as a cause of oxidative stress and so endothelial damage [14], other groups have shown a role for advanced glycation end-products (AGEs) and eicosanoids [15-17]. It has been also demonstrated that diabetic patients can have superior cognitive function, including executive function, deficits [18,19], and elaborate neuroimaging studies in patients with this profile demonstrated that the deficit may be due to microvessel and axonal damage in the white matter connections between cortical and subcortical structures, as well as some cortical gray-matter areas [20,21]. Pugh and Lipsitz [2] have called, even before diffusion imaging had been made, this type of microvascular lesion against the white matter as "subcortical ischemic microangiopathy", and shown that it is a major component in the FSCS; Zunker et al. [22] had previously shown, in a clinical study, that patients with cerebral microangiopathy have higher insulin plasma levels than control patients. Taking together this body of evidence, it is reasonable to state that insulin resistance is a main risk factor for FSCS.

Obesity and FSCS

Obesity, commonly defined as a body mass index (BMI) equal or higher than 30, is an established cardiovascular risk factor; what is becoming increasingly discussed is its role as a risk factor for cognitive disorders: according to a very recent study by Lasselin et al. [23], obese individuals' performance in tests with power to assess frontal executive function is lower than that of non-obese controls, and the authors attribute this difference to the persistent, low-grade inflammatory state promoted by excessive adipose tissue. A plethora of studies have demonstrated that obesity is indeed capable of promoting such an inflammation [24-26], and in two recent studies in human subjects using brain magnetic resonance imaging (MRI), brain small-vessel disease [27,28]; moreover, obesity is straightforwardly linked to

*Corresponding author: Rodrigo Tzovenos Starosta, School of Medicine, Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil, Tel: +555181724749; E-mail: rodrigo.starosta@ufrgs.br

the development of insulin resistant through the same inflammatory pathways [24,26], which *per se* is a major risk factor for FSCS (see section 3.1).

Dyslipidemia and FSCS

There is controversial evidence that dyslipidemia (high blood LDL, high blood triglycerides, or low blood HDL) is linked to FSCS. Grotemeyer et al. have successfully demonstrated that, in humans, ischemic brain disease - comprising stroke, transient ischemic attack, and small-vessel disease – is associated with elevated plasma viscosity, which in turn is proportional to, amongst other factors, the concentration of plasma lipids [29]; however, leukoaraiosis, a surrogate measure of cerebral white matter small-vessel disease, is inversely associated with plasma lipid levels, which could indicate a protective role of these molecules against small-vessel disease [30]. In the study conducted by Roriz-Cruz et al. in 2007 on elderly people with metabolic syndrome and FSCS [3], total blood cholesterol was one of the few metabolic syndrome components that did not show a statistically significant association with the presence of FSCS, even though triglyceride levels did – this may suggest that the relationship between dyslipidemia and FSCS is more complex than it seems at first sight, and so that more studies must be made before we can draw any definitive conclusion about it.

Hypertension and FSCS

The relationship between hypertension and FSCS is thought to be due to the role of high blood pressure in promoting small-vessel disease: according to a recent review by Østergaard et al. [31], hypertension causes small-vessel disease by leading to pericyte degeneration, swelling of endothelium and surrounding astrocytic vascular feet, and thickening of the basement membrane; enlarged perivascular space has also been reported as a consequence of hypertension [32]. Although there is plenty of evidence that hypertension is a major risk factor for small-vessel disease [33], there is also a striking paucity of data from the medical literature on whether anti-hypertensive treatment provides any benefit for this condition.

Frontal Release Reflexes and FSCS

Frontal release reflexes (FRRs), sometimes also called "primitive reflexes", are a central part of FSCS: while small-vessel disease probably accounts for the major pathophysiologic component of the syndrome, FRRs form the cornerstone of its diagnosis: For a patient to be considered as having FSCS, a commonly adopted diagnostic criterion is the presence of at least one FRR plus three or more of the following: cognitive impairment; late-onset depression; lower-limbs neuromotor dysfunction; and urgency urinary incontinence [3]. FRRs consist in early-life reflexes that are normally suppressed along the maturation of the frontal lobe and its connections, being thus absent in a normal individual after its infancy [34]. Since the disappearance of these reflexes relies on frontal lobe activity, damage to this brain area or its connections may result in the reappearance of one or more of these signs, as shown by studies evaluating the features of bilateral anterior cerebral artery infarction [35] and subcortical infarction of frontal-subcortical pathways [36]. Age-induced hypometabolism of frontal cortex or putamen – structures involved in the corticostriatal motor circuit (see section 2) – as assessed by PET scanning was also associated with the presence of FRRs [37] confirms that such circuit function is necessary to suppress the primitive reflexes; as the pathophysiology of FSCS is determined by damage to these and other fibers, it makes sense that the syndrome should compromise the inhibition of primitive reflexes, leading to their release.

The palmomental reflex, which consists in an involuntary contraction of chin and eyelids in response to painful thenar stimulations, is a high-specific and low-sensitive test to detect for frontal lobe anatomical lesions [38]; however, still a significant share of health adult population can present this sign incidentally, and so usually more than just one positive FRR is necessary to indicate frontal damage without other signs [39]. There is currently not conclusive accuracy data for the other FRRs, but one can wonder that their sensitivity and specificity may behave as the ones of the palmomental reflex, since they are caused by the same kind of damage. Other common FRRs are the grasp reflex (hand and fingers contraction in response to palmar pressure stimulus), the sucking reflex (sucking movements with the lips when an object such as a spatula is inserted into the mouth), the snout reflex (plucking of the lips in response to nasal philtrum gentle pressure), glabellar reflex (bilateral eye blink in response to a tap in the glabella, which is the skin between the eyebrows), corneomandibular reflex (lateral movement of jaw in response to contralateral corneal stimulation), and the nuchocephalic reflex (holding of head position when the shoulders are vigorously turned to either side) [40]. The presence of any of such reflexes is enough to fulfill the FRR requirement for FSCS.

Frontal-Subcortical Syndrome and Cognition

Although cognitive impairment may refer to decline in any of higher cognitive functions, in FSCS it is related tightly only to executive control malfunctioning, since this is the cognitive domain originated by the frontal-subcortical networks. Executive function can be defined broadly as being able of planning and performing complex, self-interested activities [41], and may be measured with high sensitivity and low specificity by tests such as the Mini-Mental Status Examination (MMSE) [3]. The Montreal Cognitive Assessment (MoCA) has been suggested as equivalent to the MMSE regarding the sensitivity to cerebrovascular cognitive impairment [42], having the advantage of a greater specificity [43], but its use is not as widespread as MMSE's. Approximately 20% of patients with FSCS present executive cognitive impairment [3].

As studies with Parkinson's disease patients have told us, executive function impairment affects enormously quality of life [44]; nevertheless, and unfortunately, many researchers and doctors still regard it as "natural aging", when in fact it is a major symptom of an underlying disease. This makes it probably underreported, and so the diagnosis of FSCS becomes harder to be made, since it is partially dependent on executive function decline. Other issue that one faces when suspecting FSCS based on executive control impairment is the ubiquitous presence of Alzheimer's disease suspicion – having FSCS does not make a patient immune to having Alzheimer's (nor vice-versa), and the cognitive impairment caused by the latter can present in the same way as the one caused by the former: even a new subtype of Alzheimer's disease, the "dysexecutive", is now being discussed [45]. However, neuroimaging of the two conditions can be very different from each other, with a still predominant atrophy of temporal lobe in "dysexecutive Alzheimer's" [46] and a white-matter lesion pattern at the frontal lobe in FSCS [2]. The dysexecutive symptoms in FSCS are thought to be due to dorsolateral prefrontal circuit lesions [7].

Frontal-Subcortical Syndrome and Depression

The second component of the FSCS diagnosis is late-onset depression [3], and that is explained by the fact that frontal cortex and caudate nucleus hypoactivity is associated to depression, which is well demonstrated in patient with Alzheimer's disease, Parkinson's disease, Huntington's disease and epilepsy [7]. It is also known that strokes in

the dorsolateral prefrontal areas and basal ganglia might be implicated in depression pathogenesis [7,47]. In a Korean population, a study used suicide ideation scales and neuroimaging to show a reduced frontal-subcortical white matter connectivity in patients with stronger suicide risk [48], and there is evidence that this may be caused by decreased activity or connectivity in the circuit involving the anterior cingulate cortex and the nucleus accumbens [7,49]. In patients with FSCS, this decrease in connectivity would be caused by small-vessel ischemic damage [2].

Approximately 16% of FSCS present late-onset depression, as diagnosed by the DSM-IV [3]. There is no data in the literature regarding depression estimates in FSCS as diagnosed by DSM-V criteria.

Frontal-Subcortical Syndrome and "Neuromotor" Symptoms

Urinary urgency incontinence

Urinary urgency incontinence (UUI) is the involuntary loss of urine in urgency situations [50]. Although normally regarded as pelvic floor and detrusor muscle dysfunction, we now know that the anterior cingulate cortex plays a central role in the control of bladder filling and urine releasing [51], and, in patients with UUI, this brain region has an overt response to bladder filling interoceptive stimuli [52]. Therefore, it is no surprise that a significant share of patients with FSCS present UUI [3], since the pre-frontal cortex, with the help of the amygdala, functions as an inhibitor of anterior cingulate cortex activity [53], and patients with FSCS may have ischemic damage to the fibers responsible for this modulation [2].

Even though the evidence is robust for the association between ischemic white matter lesions leading to FSCS and UUI, we must acknowledge that a possible confounder in this relationship is that metabolic syndrome itself is strongly associated with the development of UUI, with an odds ratio of 4.8 [3], besides being associated with the development of FSCS; however, there is no reason to believe that metabolic syndrome accounts alone for the UUI cases in patients with FSC, being the answer to this question probably a composite of the metabolic factors, ischemic brain damage, and possibly other factors yet unknown.

Lower-limb neuromotor dysfunction

In FSCS, lower-limb neuromotor dysfunction (LLND) usually comes up as a "fear of falling" [3], being thus a factor that worsens quality of life: in a 1994 cohort study [54], 19% of community-dwelling elders reported avoiding daily life activities because of fear of falling. Nevertheless, fear of falling is also a potentially reversible symptom in FSCS, with treatment strategies ranging from the use of video-games [55,56] to exercise programs [57], and so detection of this symptom should always be actively sought, especially because it is common for elderly patients to not report it spontaneously due to embarrassment and feeling that "it is not important".

Although usually thought as a "peripheral issue", fear of falling is actually also related to damage to the superior frontal gyri and the supplementary motor area [58], that together form the frontal motor circuit (see section 2). We can also wonder if there is any influence from the anterior cingulate cortex, which is responsible, amongst other functions, for interoception, and this symptom, since Parkinson's disease patients treated with deep-brain stimulation bilaterally of the subthalamic nuclei have had this fear tackled [59] when their parkinsonian symptoms were lowered.

Final Comments

The frontal-subcortical syndrome is a long-debated, largely-ignored nosological entity, and we cannot help but to wonder if the explanation for this is that there is still much confusion about the concepts of "normal aging" and "healthy aging" or "successful aging". "Normal aging" reflects a type of aging associated with cognitive and bodily functions decay that renders the elder a fragile, frail individual; while this may be "normal" in numerical ways, it is by no means the sole way or the best way of aging. "Successful aging", at the other side, is achieved when the passage of time does not hamper independence for daily-life activities nor brings major debilitating diseases [60]; by definition, any FSCS symptom is not part of "successful aging", and should not, in any way, be seen as such, even if it is "normal" or "usual".

There is also a lot of ongoing debate on the diagnostic criteria for FSCS, such as the use of apathy and anhedonia as a criterion instead of late-onset depression [2]. This is both bad and good: because we lack still precise criteria for its diagnosis, FSCS is probably underreported and underestimated as a cause of low quality of life; the bright side is that the presence of this debate reflects the growing interest in this disorder, and that will probably result in more understanding of the disease and so treatment options for the patients.

References

1. Kandiah N, Wiryasaputra L, Narasimhalu K, Karandikar A, Marmin M, et al. (2011) Frontal subcortical ischemia is crucial for post stroke cognitive impairment. J Neurol Sci 309: 92-95.

2. Pugh KG, Lipsitz LA (2002) The microvascular frontal-subcortical syndrome of aging. Neurobiol Aging 23: 421-431.

3. Roriz-Cruz M, Rosset I, Wada T, Sakagami T, Ishine M, et al. (2007) Cognitive impairment and frontal-subcortical geriatric syndrome are associated with metabolic syndrome in a stroke-free population. Neurobiol Aging 28: 1723-1736.

4. Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, et al. (2008) Prevalence of cognitive impairment without dementia in the United States. Ann Intern Med 148: 427-434.

5. Pfitzenmeyer P, Mourey F, Manckoundia P, d'Athis P (2005) A 4 year follow-up of very old patients presenting with frontal-subcortical dysfunction compared with Alzheimer's disease patients. Gerontology 51: 62-65.

6. Cummings JL (1993) Frontal-subcortical circuits and human behavior. Arch Neurol 50: 873-880.

7. Tekin S, Cummings JL (2002) Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. J Psychosom Res 53: 647-654.

8. Middleton FA, Strick PL (2000) Basal ganglia and cerebellar loops: Motor and cognitive circuits. Brain Res Brain Res Rev 31: 236-250.

9. Kassi E, Pervanidou P, Kaltsas G, Chrousos G (2011) Metabolic syndrome: Definitions and controversies. BMC Med 9: 48.

10. Steculorum SM, Solas M, Brüning JC (2014) The paradox of neuronal insulin action and resistance in the development of aging-associated diseases. Alzheimers Dement 10: S3-11.

11. Mansur RB, Cha DS, Woldeyohannes HO, Soczynska JK, Zugman A, et al. (2014) Diabetes mellitus and disturbances in brain connectivity: A bidirectional relationship? Neuromolecular Med 16: 658-668.

12. Cefalu WT (2001) Insulin resistance: cellular and clinical concepts. Exp Biol Med (Maywood) 226: 13-26.

13. Szendroedi J, Saxena A, et al. (2016) Cohort profile: The German Diabetes Study (GDS). Cardiovasc Diabetol 15: 59.

14. Peiró C, Romacho T, Azcutia V (2016) Inflammation, glucose, and vascular cell damage: The role of the pentose phosphate pathway. Cardiovasc Diabetol 15: 82.

15. Giacco F, Brownlee M (2010) Oxidative stress and diabetic complications. Circ Res 107: 1058-1070.

16. Greifenhagen U, Frolov A, Blüher M, et al. (2016) Site-specific analysis of advanced glycation end products in plasma proteins of type 2 diabetes mellitus patients. Anal Bioanal Chem .

17. Hashimoto K, Kunikata H, Yasuda M, Ito A, Aizawa N, et al. (2016) The relationship between advanced glycation end products and ocular circulation in type 2 diabetes. J Diabetes Complications.

18. Northam EA, Anderson PJ, Jacobs R, Hughes M, Warne GL, et al. (2001) Neuropsychological profiles of children with type 1 diabetes 6 years after disease onset. Diabetes Care 24: 1541-1546.

19. Brands AM, Kessels RP, Hoogma RP, Henselmans JM, van der Beek Boter JW, et al. (2006) Cognitive performance, psychological well-being and brain magnetic resonance imaging in older patients with type 1 diabetes. Diabetes 55: 1800-1806.

20. Kodl CT, Franc DT, Rao JP, Anderson FS, Thomas W, et al. (2008) Diffusion tensor imaging identifies deficits in white matter microstructure in subjects with type 1 diabetes that correlate with reduced neurocognitive function. Diabetes 57: 3083-3089.

21. Hsu JL Chen YL, Leu JG, Jaw FS, Lee CH, et al. (2012) Microstructural white matter abnormalities in type 2 diabetes mellitus: A diffusion tensor imaging study. Neuroimage 59: 1098-1105.

22. Zunker P, Schick A, Buschmann HC, Georgiadis D, Nabavi DG, et al. (1996) Hyperinsulinism and cerebral microangiopathy. Stroke 27: 219-223.

23. Lasselin J, Magne E, Beau C, Aubert A, Dexpert S, et al. (2016) Low-grade inflammation is a major contributor of impaired attentional set shifting in obese subjects. Brain Behav Immun .

24. Hotamisligil GS (2008) Inflammation and endoplasmic reticulum stress in obesity and diabetes. Int J Obes (Lond) 32 Suppl 7: S52-54.

25. Wellen KE, Fucho R, Gregor MF, Furuhashi M, Morgan C, et al. (2007) Coordinated regulation of nutrient and inflammatory responses by STAMP2 is essential for metabolic homeostasis. Cell 129: 537-548.

26. Hirosumi J, Tuncman G, Chang L, Görgün CZ, Uysal KT, et al. (2002) A central role for JNK in obesity and insulin resistance. Nature 420: 333-336.

27. Dearborn JL, Schneider AL, Sharrett AR, Mosley TH, Bezerra DC, et al. (2015) Obesity, insulin resistance and incident small-vessel disease on magnetic resonance imaging: Atherosclerosis risk in communities study. Stroke 46: 3131-3136.

28. Kwon HM, Park JH, Park JH, Jeong HY, Lim JS, et al. (2016) Visceral fat is an independent predictor of cerebral microbleeds in neurologically healthy people. Cerebrovasc Dis 42: 90-96.

29. Grotemeyer KC, Kaiser R, Grotemeyer KH, Husstedt IW (2014) Association of elevated plasma viscosity with small vessel occlusion in ischemic cerebral disease. Thromb Res 133: 96-100.

30. Jimenez-Conde J, Biffi A, Rahman R, Kanakis A, Butler C, et al. (2010) Hyperlipidemia and reduced white matter hyperintensity volume in patients with ischemic stroke. Stroke 41: 437-442.

31. Østergaard L, Engedal TS, Moreton F, Hansen MB, Wardlaw JM, et al. (2016) Cerebral small vessel disease: Capillary pathways to stroke and cognitive decline. J Cereb Blood Flow Metab 36: 302-325.

32. Riba-Llena I, Nafría C, Mundet X, López-Rueda A, Fernández-Cortiñas I, et al. (2016) Assessment of enlarged perivascular spaces and their relation to target organ damage and mild cognitive impairment in patients with hypertension. Eur J Neurol 23: 1044-1050.

33. Pantoni L (2010) Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol 9: 689-701.

34. Nicolson SE, Chabon B, Larsen KA, Kelly SE, Potter AW, et al. (2011) Primitive reflexes associated with delirium: A prospective trial. Psychosomatics 52: 507-512.

35. Kobayashi S, Maki T, Kunimoto M (2011) Clinical symptoms of bilateral anterior cerebral artery territory infarction. J Clin Neurosci 18: 218-222.

36. Corbett AJ, Bennett H, Kos S (1992) Frontal signs following subcortical infarction. Clin Exp Neurol 29: 161-171.

37. Matias-Guiu JA, Cabrera-Martín MN, Fernández-Matarrubia M, Moreno-Ramos T, Valles-Salgado M, et al (2015) Topography of primitive reflexes in dementia: An F-18 fluorodeoxyglucose pósitron emission tomography study. Eur J Neurol 22: 1201-1217.

38. Ladino LD, Isaza S, Delgado J, Rascovsky S, Uribe C, et al. (2015) Diagnostic yield of the palmomental reflex in patients with suspected frontal lesion. J Neurol Sci 359: 156-160.

39. Isakov E, Sazbon L, Costeff H, Luz Y, Najenson T (1984) The diagnostic value of three common primitive reflexes. Eur Neurol 23: 17-21.

40. Schott JM, Rossor MN (2003) The grasp and other primitive reflexes. J Neurol Neurosurg Psychiatry 74: 558-560.

41. Abbatecola AM, Paolisso G, Lamponi M, Bandinelli S, Lauretani F, et al. (2004) Insulin resistance and executive dysfunction in older persons. J Am Geriatr Soc 52: 1713-1718.

42. Koski L (2013) Validity and applications of the Montreal cognitive assessment for the assessment of vascular cognitive impairment. Cerebrovasc Dis 36: 6-18.

43. Gil L, Ruiz de Sánchez C, Gil F, Romero SJ, Pretelt Burgos F (2015) Validation of the Montreal cognitive assessment (MoCA) in Spanish as a screening tool for mild cognitive impairment and mild dementia in patients over 65 years old in Bogotá, Colombia. Int J Geriatr Psychiatry 30: 655-662.

44. Lawson RA, Yarnall AJ, Duncan GW, Breen DP, Khoo TK, et al. (2016) Cognitive decline and quality of life in incident Parkinson's disease: The role of attention. Parkinsonism Relat Disord 27: 47-53.

45. Mez J, Mukherjee S, Thornton T, Fardo DW, Trittschuh E, et al. (2016) The executive prominent/memory prominent spectrum in Alzheimer's disease is highly heritable. Neurobiol Aging 41: 115-121.

46. Ossenkoppele R, Pijnenburg YA, Perry DC, Cohn-Sheehy BI, Scheltens NM, et al. (2015) The behavioural/dysexecutive variant of Alzheimer's disease: Clinical, neuroimaging and pathological features. Brain 138: 2732-2749.

47. Mayberg HS (1994) Frontal lobe dysfunction in secondary depression. J Neuropsychiatry Clin Neurosci 6: 428-442.

48. Myung W, Han CE, Fava M, Mischoulon D, Papakostas GI, et al. (2016) Reduced frontal-subcortical white matter connectivity in association with suicidal ideation in major depressive disorder. Transl Psychiatry 6: e835.

49. Craig AH, Cummings JL, Fairbanks L, Itti L, Miller BL, et al. (1996) Cerebral blood flow correlates of apathy in Alzheimer disease. Arch Neurol 53: 1116-1120.

50. Haylen BT, de Ridder D, Freeman RM, Swift SE, Berghmans B, Lee J et al. (2010) An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Int Urogynecol J 21: 5-26.

51. Griffiths D, Derbyshire S, Stenger A, Resnick N (2005) Brain control of normal and overactive bladder. J Urol 174: 1862-1867.

52. Ketai LH, Komesu YM, Dodd AB, Rogers RG, Ling JM, et al. (2016) Urgency urinary incontinence and the interoceptive network: A functional magnetic resonance imaging study. Am J Obstet Gynecol.

53. Drevets WC (1999) Prefrontal cortical-amygdalar metabolism in major depression. Ann N Y Acad Sci 877: 614-637.

54. Proteau L, Charest I, Chaput S (1994) Differential roles with aging of visual and proprioceptive afferent information for fine motor control. J Gerontol 49: P100-107.

55. Morone G, Paolucci T, Luziatelli S, Iosa M, Piermattei C, et al. (2016) Wii Fit is effective in women with bone loss condition associated with balance disorders: A randomized controlled trial. Aging Clin Exp Res .

56. Levy F, Leboucher P, Rautureau G, Komano O, Millet B, et al. (2016) Fear of falling: Efficacy of virtual reality associated with serious games in elderly people. Neuropsychiatr Dis Treat 12: 877-881.

57. Kumar A, Delbaere K, Zijlstra GA, Carpenter H, Iliffe S, et al. (2016) Exercise for reducing fear of falling in older people living in the community: Cochrane systematic review and meta-analysis. Age Ageing 45: 345-352.

58. Tuerk C, Zhang H, Sachdev P, Lord SR, Brodaty H, et al (2016) Regional gray matter volumes are related to concern about falling in older people: A voxel-based morphometric study. J Gerontol A Biol Sci Med Sci 71: 138-144.

59. Nilsson MH, Fransson PA, Jarnlo GB, Magnusson M, Rehncrona S (2009) The effects of high frequency subthalamic stimulation on balance performance and fear of falling in patients with Parkinson's disease. J Neuroeng Rehabil 6: 13.

60. Rowe JW, Kahn RL (1987) Human aging: Usual and successful. Science 237: 143-149.