Psychiatria Danubina, 2024; Vol. 36, Suppl. 2, pp 376-38x
© Medicinska naklada - Zagreb, Croatia

Conference paper
Review

MIND LANGUAGE DISTURBANCES AND PET-SIGNS OF DEPRESSION VS ALZHEIMER'S DISEASE: ARE THERE ANY COMMON PATTERNS IDENTIFIED?

Daria Smirnova[1,2] & Paul Cumming[3,4]

[1]*Reaviz Medical University, Samara, Russia*
[2]*Psychiatric Studies Centre, Provaglio d'Iseo, Italy*
[3]*Department of Nuclear Medicine, Bern University Hospital, Bern, Switzerland*
[4]*School of Psychology and Counselling, Queensland University of Technology, Brisbane, Australia*

SUMMARY

Background: *There is a broad appreciation that a diagnosis of depression (D) in the elderly is a strong risk factor for incident dementia, particularly Alzheimer's disease (AD). Indeed, the two disorders might constitute a dyad, although their causal relationship is uncertain, given the likely bidirectional and compounding effects of social withdrawal and loss of previous activities, and the manifestation of language disturbances, cognitive dysfunction, and social disruption that are typical of both conditions. We argue that language declines in D and AD share common patterns and biological underpinnings, and that D/AD patients might benefit from intensive language remediation training aiming to improve the functioning of neural networks that are linked to similar cognitive impairments.*

Methods: *A literature search in PubMed database included topics of language disturbances, cognitive impairments, and molecular brain imaging by positron emission tomography (PET) to identify common patterns in D and AD regarding language decline and its neurobiological underpinnings.*

Results: *Language disturbances show a particular commonality in the two disorders, manifesting in simplified language and particular speech markers (e.g., lexical and semantic repetitions, arguably due to ruminations in D and memory deficits in AD). PET can reveal abnormal protein deposits that are practically diagnostic of AD, but cerebrometabolic deficits to PET with the glucose tracer FDG show a certain commonality in D and AD. Typical findings of hypometabolism in the frontal lobes doubtless underlie the executive function deficits, where frontal hypometabolism in prodromal D increases with AD progression. This may reflect overlapping changes in noradrenaline and other neurotransmitter (e.g. serotonin) changes. Cerebrometabolic deficits associated with language dysfunction may inform targeted language remediation treatments in the D/AD progression.*

Conclusions: *Language remediation techniques targeting specific language disturbances might present an important complimentary treatment strategy along with an adjusted pharmacotherapy approach and standard psychosocial rehabilitation interventions. We see a need for investigations of language remediation informed by the overlapping pathologies and language disturbances in D and AD.*

Key words: *action language treatment – Alzheimer's disease – aMCI – amnestic mild cognitive impairment – hypometabolism – cerebrometabolic profile – cognitive decline – depression – FDG PET – language disturbances – lexical repetitions – personal pronouns – prefrontal cortex – progressive aphasia – ruminations – simplified language – semantic memory loss – temporoparietal cortex – word finding difficulties*

Abbreviations: *AD – Alzheimer's disease; D – depression, i.e., major depressive disorder; aMCI – amnestic mild cognitive impairment; PET – positron emission tomography; FDG – [^{18}F]-fluorodeoxyglucose*

* * * * *

INRODUCTION

Clinical observations highlight the complex inter-relationship between depression (D) and Alzheimer's disease (AD), a devastating illness in which D is a common comorbidity and predisposing risk factor. Indeed, there is a clear association between D and risk of developing cognitive impairments and AD (2- to 5-fold increased risk in cases of late-life D), arguably in relation the shared pathophysiological pathways such as neuroinflammation, vascular disturbances, and neuro-degeneration processes (Andersen et al. 2005, Dafsari & Jessen 2020, Richard et al. 2013). Markers of key biogenic monoamine neurotransmitters, notably cortical noradrenaline loss due to degeneration of the locus coeruleus (LC), in conjunction with declining glucocorticoid production and increased levels of inflammatory cytokines in late life D likely affect healthy behavior patterns. Neurochemical and behavioral changes may together confer risk of developing cognitive decline and dementia (Butters et al. 2008, Elser et al. 2023, Porcelli et al. 2016, Sierksma et al. 2010, Steffens 2017, Smith et al. 2023). A landmark study of data collected from more than one million people in Denmark during 1977 to 2018 showed that D in middle age could more than double (OR 2.4) the risk of developing dementia later in life (Elser et al. 2023). Findings presented incident D as at once an early symptom of dementia and a risk factor; the depression-dementia link was significantly stronger in men than women across the entire population diagnosed with D in early adulthood and in mid-, and late-

life. Indeed, D emerged as the most consistent risk factor related to cognitive decline, behavioral symptoms, and psychological difficulties in AD patients (Hudon et al. 2020). The observation that pre-existing D can promote AD, here focusing on their common manifestations of thought, language and communication disturbances, finds support in longitudinal investigations highlighting the early and effective treatment of D through pharmacological or psychotherapeutic intervention might delay or reduce the risk of dementia onset (Sáiz-Vázquez et al. 2021).

Action language treatment is of proven efficacy for improving general cognitive functioning in patients with aphasia. Apart from restoration of communication abilities, language remediation techniques represent a resource for patient management systems that can include cognitive enhancement therapy, cognitive skills training, cognitive remediation, or other approaches targeting cognition in a variety of mental disorders, including D (Beck et al. 1988, Brady et al. 2016, Breitenstein et al. 2017, Volkmer et al. 2020). The key objective of the present narrative report is to focus the attention readers on overlapping and potentially modifiable aspects of the D-AD dyad. We see a need for broader study of common linguistic patterns in the D and AD through evidence-based prospective research, to elaborate target-related language interventions (e.g., the action-language treatment approach) for D/AD treatment. In our opinion, patients in the D/AD spectrum should benefit from language remediation exercises targeting specific language-patterns within the system of cognitive training within psychosocial interventions. We anticipate that such efforts might postponing dementia onset in elderly D patients.

We hypothesize that language decline in D and AD shares common patterns and biological underpinnings, and speculate that D/AD patients should similarly benefit from the intensive language remediation training aiming to improve the functioning of language-related neural networks. This model has pivotal implications for public health strategies aiming to moderate cognitive decline in the elderly (Ownby et al. 2006). In support of this model, we review findings on language disturbances patterns, neurochemical pathology, and PET that support a shared underlying neuropathology.

SUBJECTS AND METHODS

A literature search in PubMed database included topics of language disturbances (decline, impairments), cognitive impairments (decline, disturbances), and PET (FDG-PET) findings in D (major depressive disorder, depressive episode) and AD, to find common patterns specifying depression-dementia links in terms of language patterns and their biological underpinnings.

RESULTS

Clinical insights on D and AD via patterns of language decline

Exploring the connection between language patterns and brain health revealed specific insights into D and AD. Language patterns serve as diagnostic indicators for cognitive processes (e.g., mild cognitive impairments, verbal memory deficits), offering an approach to investigate brain function in D and AD. Patients with D tend to use negatively charged words like “sad”, “tears”, “cry”, "miserable", and past-focused words, reflecting their entrapped emotional state (Rude et al. 2010, Eichstaedt et al. 2018, Kim et al. 2021). Moreover, there is an increased usage of first-person pronouns such, indicating a self-focused attention, and past tense verbs, shifting into past life events, as well as polarized pronouns (e.g., “never”, “everyone”), demonstrating black and white thinking (Rude et al. 2010, Zimmermann et al. 2017, Smirnova et al. 2018). Syntactically, D patients often prefer simpler sentence structures (already in mild D state) and concrete language (especially in moderate and severe forms of D), making their communication less abstract and more tangible (Fineberg et al. 2016, Smirnova et al. 2019, Tackman et al. 2019). In terms of discourse, lexical and semantic repetitions are common, mirroring ruminative thinking (Nolen-Hoeksema et al. 2008, Smirnova et al. 2018).

AD patients frequently experience word-finding difficulties, semantic paraphasias, leading to pauses and substitutions, as well as repetitons to compensate lexical access problems (Garrard et al. 2005, Ahmed et al. 2013, Smirnova et al. 2021). With AD progression, syntax becomes simplified, and narratives often lack coherence, being characterized by fragmented and repetitive speech patterns related to the cognitive decline (Taler & Phillips 2008). D and AD exhibit shared linguistic features, such as simplified language and repetition, albeit arising for different reasons, namely rumination in D versus memory deficits in AD. The distinguishing features lie in emotional content and pronoun usage. Unlike AD, D is associated with negatively valenced language and increased first-person pronoun use. AD patients mostly struggle with word specificity, semantic issues, and lexical retrieval. The understanding of these language patterns has significant implications for both diagnosis and treatment. Clinical interviews focusing on language use provide further diagnostic insights, and, in terms of therapy, specific linguistic targets might be used for therapeutic interventions not only to improve communication and reduce social isolation, but also to train cognitive functions via language exercises. Thus, clarifying the distinct and overlapping language patterns in D and AD might enhance diagnostic and treatment strategies for both states.

Cognitive impairment, language disturbances and PET signs in D and AD: focusing on biological candidates explaining depression-dementia links

Clinical signs of typical AD have onset in late middle age, presenting first with subtle cognitive impairments and mood changes can precede overt memory loss by a decade or more. The cerebral pathologies of AD include a characteristic triad of atrophy of the hippocampus and neocortex in conjunction with aggregation of beta-amyloid and phosphorylated tau protein, which is moderated by gender and carriage of the APOE ε4 allele (Nemes et al. 2023). PET examinations with the glucose analogue [^{18}F]fluorodeoxyglucose (FDG) enables the mapping of cerebrometabolic deficits, whereas specific tracers depict the patterns of abnormal protein aggregates. There is an enormous literature attesting to the occurrence of amyloid-beta and tau deposits at a very early stage of AD, but less attestation of premorbid metabolic disturbances to FDG-PET.

The prodromal phase of AD, commonly designated as amnestic mild cognitive impairment (aMCI), manifests mainly in deficits in short term memory, but disturbances of spatial awareness are also present early in the disease process (Verghese et al. 2017). Depressive symptoms are a frequent finding in prodromal AD, but the causal nature of this association is uncertain; a depressive state in late middle may be an early indication of neuropathology, or might be a driver for AD disease, insofar as social withdrawal typical of D may reduce the individual's resilience in the face of an ongoing neurodegenerative disturbance. Thus, for example, failure or a marginal pass in a motor vehicle driving test was associated with biomarkers of AD pathology in a sample of non-demented elderly individuals, but the presence of D accelerated the onset of driving difficulties (Babulal et al. 2018). Furthermore, the presence of informant-reported increases in anxiety and depressed mood in non-demented elderly people shows an association with elevated levels of beta-amyloid to PET, suggesting that D may be an inherent aspect of early AD pathology (Gontrum et al. 2024). Self-reported subjective cognitive decline in the elderly was a risk factor for cognitive decline during subsequent years, which furthermore showed mediation by D and the presence of white matter hyperintensities (Liu et al. 2024). Such results might imply that an early cerebrovascular pathology manifesting in white matter changes may be a common substrate for geriatric D and AD.

As noted above, cerebral hypometabolism to FDG PET is characteristic finding in AD. However, the association with other hallmark pathologies is complex; in one study, a group of aMCI participants underwent FDG-PET as well as tau-PET and amyloid PET, with clinical follow-up during two years after scanning (Boccalini et al. 2024). Applying a data-driven algorithm indicated the presence distinct metabolic subtypes of aMCI in the study population, involving differing degrees of cortical versus hippocampal hypometabolism and differing associations with regional amyloid-beta and tau accumulation. Conceivably, such heterogeneous findings in mMCI may be indicative of a variety of pathophysiological pathways that converge on the more typical pattern of cerebrometabolic pathologies typical of AD. Stages of Objective Memory Impairment (SOMI) provides a standardized ranking of disease severity, which bears some relation to scores in the more widely used MMSE. In an FDG-PET study of aMCI patients, the SOMI-4 subgroup (mean MMSE = 27) showed hypometabolism mainly in posterior and temporal structures, with involvement extending into frontal structures in the SOMI-5 subgroup (mean MMSE = 25) (Brugnolo et al. 2024). This is in keeping with the well-known Braak staging of AD progression based upon the spreading of hyperphosphorylated tau protein aggregates, as first attested by histological examination of post-mortem tissue showing a predictable sequence of regional involvement (Braak et al. 2006).

FDG PET findings in D are considerably less distinct than in the progression from aMCI to manifest AD. An early study showed increased frontal to occipital FDG uptake ratios, and relatively decreased metabolism in the basal ganglia of a group of individuals with unipolar D (Buchsbaum et al. 1986), i.e., a partial match with the posterior-anterior progression of hypometabolism described in AD. In a study comparing small groups of AD patients with and without D, the former group showed a relatively greater frontal hypometabolism (Lee et al. 2006). Other FDG-PET studies linked reduced metabolism in (inter alia) frontal brain regions with a predilection for developing D in the context of pre-dialytic chronic kidney disease (Song et al. 2008), in oncology patients (Kumano et al. 2007), and in individuals with systemic lupus erythematosus (Saito et al. 2017). The common denominator of these various studies linked impaired metabolism in frontal brain structures with depressed mood, irrespective of the possibly precipitating medical illness.

A deficit in executive function, which is typically associated with the frontal lobes and anterior cingulate cortex, is an exacerbating factor in D, especially among the elderly (DeBattista 2005). In a meta-analysis of 37 studies assessing the Trail Making Test and the Stroop Color-Word Test in relation to D, gave strong evidence that psychomotor slowing and specific deficits in executive function are characteristic of depressive state per se (Nuño et al. 2021). In an FDG PET study of healthy young adults, depression inventory scores correlated inversely with a metabolic connectivity between the posterior cingulate cortex (PCC) and a network including the anterior cingulate, medial prefrontal cortex, inferior and middle frontal gyrus, as well as the insula (Wang et al. 2023). This raises the

possibility that metabolic network disturbances may be an early feature of mild, subclinical D. "Depressed", but "non-demented" elderly subjects showed significant hypometabolism to FDG-PET in the bilateral fronto-temporal cortex and posterior cingulate cortex (PCC) (Brendel et al. 2016). In an FDG-PET study of neural correlates of language disturbance in unmedicated D patients (who showed a distinct deficit in verbal learning), there was a positive correlation between verbal recall and FDG uptake in bilateral dorsomedial frontal cortex, dorsolateral prefrontal cortex (DLPFC), and dorsal anterior cingulate (Milak et al. 2019). Patients with diagnosis of D had reduced FDG uptake in the putamen, claustrum, insular, inferior frontal gyrus, and supramarginal gyrus (Su et al. 2018). These regions of reduced metabolic activity impaired functional connectivity to key network hubs, including the inferior frontal gyrus, middle frontal gyrus (MFG), angular gyrus, and calcarine sulcus, middle frontal gyrus (MFG), corresponding to regions of the salience network (SN), primary visual cortex (V1), and language network. Nonetheless, there was no correlation between perturbed metabolic connectivity and the severity of particular clinical symptoms.

In an FDG-PET study of patients with temporal lobe epilepsy, those with involvement of the (left) language dominant hemisphere had metabolic asymmetry in the frontal cortex, perhaps in relation to a history of secondarily generalized seizures (Jokeit et al. 1997). To multivariate analysis of variance, this prefrontal metabolic asymmetry had a main effect on neuropsychological 'frontal lobe measures', including verbal and performance intelligence measures.

Given certain commonalities in the cerebrometabolic profile and deficits in executive function reported in D and AD, it is unsurprising that the topic of antidepressant therapy in the elderly is a matter of concern. In particular, if geriatric depression is a "calling card" for incipient dementing illness, then prescription of antidepressants in later life might be predictor of onset of dementia. Furthermore, there is a paucity of evidence attesting to the efficacy of antidepressants in patients with established AD (Costello et al. 2023). The relative intransigence of D in association with dementia to pharmacotherapy suggests that it may be a distinct entity. Thus, D occurring in dementia might be a manifestation of a generally "sick brain", perhaps in relation to the considerable comorbidity of AD with vascular and white matter changes. A still more disturbing prospect arises in the context of antidepressant use as a precipitating factor in the advent of dementia in the elderly. A systematic literature review of such studies showed a very strong association (OR 2.2) between antidepressant use among the elderly, especially when initiated between the age of 65 years (Moraros et al. 2017). Naturally, observational and cross-sectional studies cannot attribute causality, i.e., distinguish between the two baleful possibilities: (1) depressive illness in the late life is a herald of pervasive neuropathology leading to dementia, or (2) antidepressant use contributes to or accelerates the onset of AD. This distinction would seem to be a matter calling for serious investigation, as it might prove to have fundamental bearing on the central question of this brief narrative.

Observations such as the association between social isolation and risks for late-life / geriatric depression and "dementing" illness draw further attention to this issue (Shafighi et al. 2023). Are social withdrawal and depression precipitating factors, prodromal symptoms, or non-specific signs of a greater frailty and debilitation that predisposes to physical illness? Missing in this debate is a clear pathophysiological pathway whereby D could be a factor in the development of AD.

PET findings highlight those reductions in the serotonin transporter were more robust than cerebral atrophy in patients with aMCI (Zacková et al. 2021). The noradrenergic neurons of LC present another possible central element in the D-AD link. The LC consists of small clusters of neurons in open medulla that provide the main innervation of noradrenergic fibres to the forebrain. The LC neurons contain the pigment neuromelanin, which is detectable by specific MR protocols. In a quantitative MRI study of groups of non-demented elderly individuals with or without late life D, there was no significant effect of diagnosis on the integrity of the LC (Calarco et al. 2022). However, a correlational analysis comprising the entire study population showed a significant correlation between LC integrity with cognition. This seems in keeping with well-established findings that noradrenergic signaling in brain is a key factor in cognitive flexibility and memory (Chamberlain & Robbins 2013), and other findings implicating impairment of noradrenergic signaling in association with major depressive disorder (Cottingham & Wang 2012). Furthermore, there are reports of degeneration of the LC in *post mortem* studies of patients dying with AD, and likewise in Parkinson's disease patients (Beardmore et al. 2021). Thus, we present as a conjecture that impairment of the LC and noradrenergic signaling may be a common factor linking depression, executive dysfunction, and the risk for dementia in the elderly.

While largely a matter of conjecture, we suppose that this model should motivate various studies that could better establish a link between brain noradrenaline, late-life D, and risk of dementia. Considering the potential of PET in this regard, radiopharmaceuticals that bind selectively to the noradrenaline transporter in brain are fit to detect degeneration of the LC innervations in cerebral cortex of rats (Sakai et al. 2023). However, there has still been no application of this technology to the study of aging and brain noradrenaline in humans. Similarly, PET studies with

the α_2 adrenergic receptor antagonist [^{11}C]-yohimbine reveal the distribution of binding sites in living brain, and serve for the indirect detection of central noradrenaline release upon stimulation of the vagus nerve (Landau et al. 2015). This may be particularly relevant, as vagal stimulation can be beneficial in treatment-resistant depression. Finally, a recent phase II trial of the noradrenergic drug atomoxetine showed in volunteers with aMCI positive benefits with respect to normalization of cerebral metabolism to FDG-PET, as well as decreasing levels of tau markers in cerebrospinal fluid (Levey et al. 2022). However, the brief trial with atomoxetine was not fit to test for an improvement in cognition. We anticipate that future explorations of noradrenergic mechanisms may cast new light on the pathology and therapeutics of late life depression in relation to dementia risk.

DISCUSSION

As attested by large-scale longitudinal studies, incident D, in mid-life age and late in life, is a risk factor for subsequent development of dementia, particularly AD (Elser et al. 2023). It is difficult to disentangle the multiple or reverse causality and clarify biological mechanisms underlying this relationship, given the likely bidirectional and compounding effects of social withdrawal and loss of previous social activities as occur in the D/AD dyad. However, common pathophysiological mechanisms (e.g., nerve growth factors, inflammatory response changes, dysregulation of lipoprotein, folate) were found in cohorts of D and AD patients, as well as similar genetic polymorphisms of the brain-derived neurotrophic factor, apolipoprotein E, and increased inflammatory cytokines have been registered in association with the elevated risk for late-life D and AD (Ye et al. 2016). This data points to potential role of the described molecular mechanisms acting as the triggers of D and AD progression with the age.

Language decline demonstrate a particular commonality in the two disorders, manifesting in simplified speech and particular linguistic markers, such as lexical and semantic repetitions. However, from the clinical point of view it happens due to rumination in depression vs. memory deficits in AD, but in both cases syntax decline and semantic deterioration, compared to other language disturbances, are more profound and increase with the severity of the disorders over their progression in time. This phenomenon of language decline still gives further credence to a model relating some common underlying biological underpinnings, such as disturbances at the level of neurotransmitters or other neuropathologies of D and AD.

PET studies observed the reduced glucose metabolism in the prefrontal cortex in D, in association with mild cognitive impairment, executive function, verbal memory deficit, impaired decision-making and emotional regulation, whereas mild cognitive impairment and verbal memory decline were related to dysregulation in the serotonin neurotransmission in D and AD (Smith et al. 2017, Zacková et al. 2021, Elser et al. 2023). PET studies in early AD show main hypometabolism in temporoparietal cortex, followed by progression to frontal lobe hypometabolism, doubtless underlying the deficits in executive functions and language abnormalities. Furthermore, common hub genes in frontal lobe are identified for different types of dementia (Tian et al. 2022). As a matter of speculation and based on our review, we draw attention to various preclinical and clinical findings implicating a failure of noradrenergic transmission (and deterioration in serotonin neuromediation) to aspects of cognitive dysfunction, including language impairments, in D and AD (Chamberlain & Robbins 2013, Cottingham & Wang 2012, Levey et al. 2022, Sakai et al. 2023).

CONCLUSIONS

There is a commonality in language disturbances between D and AD, characterized by simplified language use (simplified syntax) and specific speech markers, such as lexical and semantic repetitions. PET imaging in AD shows markers for amyloid and tau deposition, as well as metabolic deficits in temporoparietal areas and other brain zones. While protein deposits indicate AD, frontal hypometabolism is seen in both D and AD. Degeneration of serotonin and noradrenaline neurons may present a precise research focus in relation to the progression of cerebral hypometabolism and cognitive deficits. Language patterns common to D and AD present an additional target for evidence-based language remediation through intensive action language treatment, to complement pharmacotherapy and psychosocial rehabilitation in D and AD patients. Early interventions should proceed not only with the novel approaches to treatments (e.g., noradrenergic agents, serotoninergic agents, language remediation techniques), but also destigmatization and fostering supportive communities for individuals living with D and AD.

Acknowledgements:

We express our sincere gratitude to the Editorial Board members for managing the review of the article before its urgent submission to Psychiatria Danubina journal.

Conflict of interest: *None to declare.*

Contribution of individual authors:

Both authors elaborated the hypothesis and key message of the article, undertook a literature review, wrote the first draft of this manuscript and agreed on its final version for submission.

References

1. *Ahmed S, de Jager CA, Haigh AM, Garrard P: Semantic processing in connected speech at a uniformly early stage of autopsy-confirmed Alzheimer's disease. Neuropsychology 2013; 27:79-85. doi: 10.1037/a0031288*
2. *Andersen K, Lolk A, Kragh-Sørensen P, Petersen NE & Green A: Depression and the risk of Alzheimer disease. Epidemiology 2005; 16:233-238. https://doi.org/10.1097/01.ede.0000152116.32580.24*
3. *Babulal GM, Chen S, Williams MM, Trani JF, Bakhshi P, Chao GL, Stout SH, Fagan AM, Benzinger TLS, Holtzman DM, Morris JC & Roe CM: Depression and Alzheimer's Disease Biomarkers Predict Driving Decline. J Alzheimers Dis 2018; 66:1213-1221. https://doi.org/10.3233/jad-180564*
4. *Beardmore R, Hou R, Darekar A, Holmes C & Boche D: The Locus Coeruleus in Aging and Alzheimer's Disease: A Postmortem and Brain Imaging Review. J Alzheimers Dis 2021; 83:5-22. https://doi.org/10.3233/jad-210191*
5. *Beck C, Heacock P, Mercer S, Thatcher R & Sparkman C: The impact of cognitive skills remediation training on persons with Alzheimer's disease or mixed dementia. J Geriatr Psychiatry 1988; 21:73-88*
6. *Boccalini C, Caminiti SP, Chiti A, Frisoni GB, Garibotto V & Perani D: The diagnostic and prognostic value of tau-PET in amnestic MCI with different FDG-PET subtypes. Ann Clin Transl Neurol 2024; 11:1236-1249. https://doi.org/10.1002/acn3.52039*
7. *Braak H, Alafuzoff I, Arzberger T, Kretzschmar H & Del Tredici K: Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. Acta Neuropathol 2006; 112:389-404. https://doi.org/10.1007/s00401-006-0127-z*
8. *Brady MC, Kelly H, Godwin J, Enderby P & Campbell P: Speech and language therapy for aphasia following stroke. Cochrane Database Syst Rev 2016; 6:Cd000425. https://doi.org/10.1002/14651858.CD000425.pub4*
9. *Breitenstein C, Grewe T, Flöel A, Ziegler W, et al.: Intensive speech and language therapy in patients with chronic aphasia after stroke: a randomised, open-label, blinded-endpoint, controlled trial in a health-care setting. Lancet 2017; 389(10078), 1528-1538. https://doi.org/10.1016/s0140-6736(17)30067-3*
10. *Brendel M, Reinisch V, Kalinowski E, Levin J, Delker A, Därr S, Pogarell O, Förster S, Bartenstein P, Rominger A & Alzheimer's Disease Neuroimaging, I: Hypometabolism in Brain of Cognitively Normal Patients with Depressive Symptoms is Accompanied by Atrophy-Related Partial Volume Effects. Curr Alzheimer Res 2016; 13:475-486. https://doi.org/10.2174/1567205013666160314143922*
11. *Brugnolo A, Orso B, Girtler N, Ferraro PM, Arnaldi D, Mattioli P, Massa F, Famà F, Argenti L, Biffa G, Morganti W, Buonopane S, Uccelli A, Morbelli S & Pardini M: Tracking the progression of Alzheimer's disease: Insights from metabolic patterns of SOMI stages. Cortex 2024; 171:413-422. https://doi.org/10.1016/j.cortex.2023.11.011*
12. *Buchsbaum MS, Wu J, DeLisi LE, Holcomb H, Kessler R, Johnson J, King AC, Hazlett E, Langston K & Post RM: Frontal cortex and basal ganglia metabolic rates assessed by positron emission tomography with [18F]2-deoxyglucose in affective illness. J Affect Disord 1986; 10:137-152. https://doi.org/10.1016/0165-0327(86)90036-4*
13. *Butters MA, Young JB, Lopez O, Aizenstein HJ, Mulsant BH, Reynolds CF, 3rd, DeKosky ST & Becker JT: Pathways linking late-life depression to persistent cognitive impairment and dementia. Dialogues Clin Neurosci 2008; 10:345-357. https://doi.org/10.31887/DCNS.2008.10.3/mabutters*
14. *Calarco N, Cassidy CM, Selby B, Hawco C, Voineskos AN, Diniz BS & Nikolova YS: Associations between locus coeruleus integrity and diagnosis, age, and cognitive performance in older adults with and without late-life depression: An exploratory study. Neuroimage Clin 2022; 36:103182. https://doi.org/10.1016/j.nicl.2022.103182*
15. *Chamberlain SR & Robbins TW: Noradrenergic modulation of cognition: therapeutic implications. J Psychopharmacol 2013; 27:694-718. https://doi.org/10.1177/0269881113480988*
16. *Costello H, Roiser JP & Howard R: Antidepressant medications in dementia: evidence and potential mechanisms of treatment-resistance. Psychol Med 2023; 53:654-667. https://doi.org/10.1017/s003329172200397x*
17. *Cottingham C & Wang Q: α2 adrenergic receptor dysregulation in depressive disorders: implications for the neurobiology of depression and antidepressant therapy. Neurosci Biobehav Rev 2012; 36:2214-2225. https://doi.org/10.1016/j.neubiorev.2012.07.011*
18. *Dafsari FS & Jessen F: Depression-an underrecognized target for prevention of dementia in Alzheimer's disease. Transl Psychiatry 2020; 10:160. https://doi.org/10.1038/s41398-020-0839-1*
19. *DeBattista C: Executive dysfunction in major depressive disorder. Expert Rev Neurother 2005; 5:79-83. https://doi.org/10.1586/14737175.5.1.79*
20. *Elser H, Horváth-Puhó E, Gradus JL, Smith ML, Lash TL, Glymour MM, Sørensen HT & Henderson VW: Association of Early-, Middle-, and Late-Life Depression With Incident Dementia in a Danish Cohort. JAMA Neurol 2023; 80:949-958. https://doi.org/10.1001/jamaneurol.2023.2309*
21. *Eichstaedt JC, Smith RJ, Merchant RM, Ungar LH, Crutchley P, Preoţiuc-Pietro D, Asch DA, Schwartz HA: Facebook language predicts depression in medical records. Proc Natl Acad Sci U S A 201830; 115:11203-11208. doi:10.1073/pnas.1802331115*
22. *Fineberg SK, Leavitt J, Deutsch-Link S, Dealy S, Landry CD, Pirruccio K, Shea S, Trent S, Cecchi G, Corlett PR: Self-reference in psychosis and depression: a language marker of illness. Psychol Med 2016; 46:2605-15. doi:10.1017/S0033291716001215*
23. *Garrard P, Maloney LM, Hodges JR, Patterson K: The effects of very early Alzheimer's disease on the characteristics of writing by a renowned author. Brain 2005; 128(Pt 2):250-60. doi:10.1093/brain/awh341*
24. *Gontrum EQ, Paolillo EW, Lee S, Diaz V, Ehrenberg A, Saloner R, Mundada NS, La Joie R, Rabinovici G, Kramer JH & Casaletto KB: Neuropsychiatric Profiles and Cerebral Amyloid Burden in Adults without Dementia. Dement Geriatr Cogn Disord 2024; 53:119-127. https://doi.org/10.1159/000538376*
25. *Hudon C, Escudier F, De Roy J, Croteau J, et al.: Behavioral and Psychological Symptoms that Predict Cognitive Decline or Impairment in Cognitively Normal Middle-Aged or Older Adults: a Meta-Analysis. Neuropsychol Rev 2020; 30:558-579. https://doi.org/10.1007/s11065-020-09437-5*

26. *Jokeit H, Seitz RJ, Markowitsch HJ, Neumann N, Witte OW & Ebner A: Prefrontal asymmetric interictal glucose hypometabolism and cognitive impairment in patients with temporal lobe epilepsy. Brain 1997; 120(Pt 12):2283-2294. https://doi.org/10.1093/brain/120.12.2283*
27. *Kim J, Uddin ZA, Lee Y, Nasri F, Gill H, Subramanieapillai M, Lee R, Udovica A, Phan L, Lui L, Iacobucci M, Mansur RB, Rosenblat JD, McIntyre RS: A Systematic review of the validity of screening depression through Facebook, Twitter, Instagram, and Snapchat. J Affect Disord 2021; 286:360-369. doi:10.1016/j.jad.2020.08.091*
28. *Kumano H, Ida I, Oshima A, Takahashi K, Yuuki N, Amanuma M, Oriuchi N, Endo K, Matsuda H & Mikuni M: Brain metabolic changes associated with predispotion to onset of major depressive disorder and adjustment disorder in cancer patients - a preliminary PET study. J Psychiatr Res 2007; 41:591-599. https://doi.org/10.1016/j.jpsychires.2006.03.006*
29. *Landau AM, Dyve S, Jakobsen S, Alstrup AK, Gjedde A & Doudet DJ: Acute Vagal Nerve Stimulation Lowers α2 Adrenoceptor Availability: Possible Mechanism of Therapeutic Action. Brain Stimul 2015; 8:702-707. https://doi.org/10.1016/j.brs.2015.02.003*
30. *Lee DY, Choo IH, Jhoo JH, Kim KW, et al.: Frontal dysfunction underlies depressive syndrome in Alzheimer disease: a FDG-PET study. Am J Geriatr Psychiatry 2006; 14:625-628. https://doi.org/10.1097/01.JGP.0000214541.79965.2d*
31. *Levey AI, Qiu D, Zhao L, Hu WT, Duong DM, Higginbotham L, Dammer EB, Seyfried NT, Wingo TS, Hales CM, Gámez Tansey M, Goldstein DS, Abrol A, Calhoun VD, Goldstein FC, Hajjar I, Fagan AM, Galasko D, Edland SD, Weinshenker D: A phase II study repurposing atomoxetine for neuroprotection in mild cognitive impairment. Brain 2022; 145:1924-1938. https://doi.org/10.1093/brain/awab452*
32. *Liu S, Luo X, Chong JSX, Jiaerken Y, Youn SH, Zhang M, & Zhou JH: Brain structure, amyloid, and behavioral features for predicting clinical progression in subjective cognitive decline. Hum Brain Mapp 2024; 45:e26765. https://doi.org/10.1002/hbm.26765*
33. *Milak MS, Potter WA, Pantazatos SP, Keilp JG, Zanderigo F, Schain M, Sublette ME, Oquendo MA, Malone KM, Brandenburg H, Parsey RV & Mann JJ: Resting regional brain activity correlates of verbal learning deficit in major depressive disorder. Psychiatry Res Neuroimaging 2019; 283:96-103. https://doi.org/10.1016/j.pscychresns.2018.12.006*
34. *Moraros J, Nwankwo C, Patten SB & Mousseau DD: The association of antidepressant drug usage with cognitive impairment or dementia, including Alzheimer disease: A systematic review and meta-analysis. Depress Anxiety 2017; 34:217-226. https://doi.org/10.1002/da.22584*
35. *Nemes S, Logan PE, Manchella MK, Mundada NS, et al.: Sex and APOE ε4 carrier effects on atrophy, amyloid PET, and tau PET burden in early-onset Alzheimer's disease. Alzheimers Dement 2023; 19:(Suppl 9):S49-s63. https://doi.org/10.1002/alz.13403*
36. *Nolen-Hoeksema S, Wisco BE, Lyubomirsky S: Rethinking Rumination. Perspect Psychol Sci 2008; 3:400-24. doi:10.1111/j.1745-6924.2008.00088.x*
37. *Nuño L, Gómez-Benito J, Carmona VR & Pino O: A Systematic Review of Executive Function and Information Processing Speed in Major Depression Disorder. Brain Sci 2021; 11. https://doi.org/10.3390/brainsci11020147*
38. *Ownby RL, Crocco E, Acevedo A, John V & Loewenstein D: Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Arch Gen Psychiatry 2006; 63:530-538. https://doi.org/10.1001/archpsyc.63.5.530*
39. *Porcelli S, Crisafulli C, Donato L, Calabrò M, Politis A, Liappas I, Albani D, Atti AR, Salfi R, Raimondi I, Forloni G, Papadimitriou GN, De Ronchi D & Serretti A: Role of neurodevelopment involved genes in psychiatric comorbidities and modulation of inflammatory processes in Alzheimer's disease. J Neurol Sci 2016; 370:162-166. https://doi.org/10.1016/j.jns.2016.09.053*
40. *Richard E, Reitz C, Honig LH, Schupf N, Tang MX, Manly JJ, Mayeux R, Devanand D & Luchsinger JA: Late-life depression, mild cognitive impairment, and dementia. JAMA Neurol 2013; 70:374-382. https://doi.org/10.1001/jamaneurol.2013.603*
41. *Rude S, Gortner EM, & Pennebaker J: Language use of depressed and depression-vulnerable college students. Cognition and Emotion 2004; 18:1121–1133. doi:10.1080/02699930441000030*
42. *Saito T, Tamura M, Chiba Y, Katsuse O, Suda A, Kamada A, Ikura T, Abe K, Ogawa M, Minegishi K, Yoshimi R, Kirino Y, Ihata A & Hirayasu Y: Regional cerebral glucose metabolism in systemic lupus erythematosus patients with major depressive disorder. J Neurol Sci 2017; 379:127-130. https://doi.org/10.1016/j.jns.2017.05.059*
43. *Sáiz-Vázquez O, Gracia-García P, Ubillos-Landa S, Puente-Martínez A, Casado-Yusta S, Olaya B & Santabárbara J: Depression as a Risk Factor for Alzheimer's Disease: A Systematic Review of Longitudinal Meta-Analyses. J Clin Med 2021; 10. https://doi.org/10.3390/jcm10091809*
44. *Sakai T, Hattori S, Ogata A, Yamada T, Abe J, Ikenuma H, Ichise M, Suzuki M, Ito K, Kato T & Kimura Y: Noradrenaline transporter PET reflects neurotoxin-induced noradrenaline level decrease in the rat hippocampus. EJNMMI Res 2023; 13:82. https://doi.org/10.1186/s13550-023-01032-y*
45. *Shafighi K, Villeneuve S, Rosa Neto P, Badhwar A, Poirier J, Sharma V, Medina YI, Silveira PP, Dube L, Glahn D & Bzdok D: Social isolation is linked to classical risk factors of Alzheimer's disease-related dementias. PLoS One 2023; 18:e0280471. https://doi.org/10.1371/journal.pone.0280471*
46. *Sierksma AS, van den Hove DL, Steinbusch HW & Prickaerts J: Major depression, cognitive dysfunction and Alzheimer's disease: is there a link? Eur J Pharmacol 2010; 626:72-82. https://doi.org/10.1016/j.ejphar.2009.10.021*
47. *Smirnova D, Cumming P, Sloeva E, Kuvshinova N, Romanov D, Nosachev G: Language Patterns Discriminate Mild Depression From Normal Sadness and Euthymic State. Front Psychiatry 2018; 9:105. doi:10.3389/fpsyt.2018.00105*
48. *Smirnova D, Smirnova T, Cumming P: Language Impairments in Dementia: From Word-Finding Difficulties to Everyday Conversation in a Dementia-Friendly Community. In: Shankardass, M.K. (eds) Dementia Care. Springer, Singapor, 2021; 85-108. https://doi.org/10.1007/978-981-16-3864-0_6*
49. *Smirnova D, Romanov D, Sloeva E, Kuvshinova N, Cumming P, Nosachev G: Language in Mild Depression: How It Is Spoken, What It Is About, and Why It Is Important to Listen. Psychiatr Danub 2019; 31(Suppl 3):427-433. PMID: 31488766*

50. *Smith GS, Protas H, Kuwabara H, Savonenko A, Nassery N, Gould NF, Kraut M, Avramopoulos D, Holt D, Dannals RF, Nandi A, Su Y, Reiman EM, Chen K: Molecular imaging of the association between serotonin degeneration and beta-amyloid deposition in mild cognitive impairment. Neuroimage Clin. 2023;37:103322. doi:10.1016/j.nicl.2023.103322. Epub 2023 Jan 6. PMID: 36680976; PMCID: PMC9869478*
51. *Song SH, Kim IJ, Kim SJ, Kwak IS & Kim YK: Cerebral glucose metabolism abnormalities in patients with major depressive symptoms in pre-dialytic chronic kidney disease: statistical parametric mapping analysis of F-18-FDG PET, a preliminary study. Psychiatry Clin Neurosci 2008; 62:554-561. https://doi.org/10.1111/j.1440-1819.2008.01849.x*
52. *Steffens DC: Late-Life Depression and the Prodromes of Dementia. JAMA Psychiatry 2017; 74:673-674. https://doi.org/10.1001/jamapsychiatry.2017.0658*
53. *Su H, Zuo C, Zhang H, Jiao F, Zhang B, Tang W, Geng D, Guan Y & Shi S: Regional cerebral metabolism alterations affect resting-state functional connectivity in major depressive disorder. Quant Imaging Med Surg 2018; 8:910-924. https://doi.org/10.21037/qims.2018.10.05*
54. *Tackman AM, Sbarra DA, Carey AL, Donnellan MB, Horn AB, Holtzman NS, Edwards TS, Pennebaker JW, Mehl MR: Depression, negative emotionality, and self-referential language: A multi-lab, multi-measure, and multi-language-task research synthesis. J Pers Soc Psychol 2019; 116:817-834. doi:10.1037/pspp0000187*
55. *Taler V, Phillips NA: Language performance in Alzheimer's disease and mild cognitive impairment: a comparative review. J Clin Exp Neuropsychol 2008; 30:501-56. doi:10.1080/13803390701550128*
56. *Verghese J, Lipton R & Ayers E: Spatial navigation and risk of cognitive impairment: A prospective cohort study. Alzheimers Dement 2017; 13:985-992. https://doi.org/10.1016/j.jalz.2017.01.023*
57. *Volkmer A, Rogalski E, Henry M, Taylor-Rubin C, Ruggero L, Khayum R, Kindell J, Gorno-Tempini ML, Warren JD & Rohrer JD: Speech and language therapy approaches to managing primary progressive aphasia. Pract Neurol 2020; 20:154-161. https://doi.org/10.1136/practneurol-2018-001921*
58. *Wang Z, Baeken C & Wu GR: Metabolic Covariance Connectivity of Posterior Cingulate Cortex Associated with Depression Symptomatology Level in Healthy Young Adults. Metabolites 2023; 13. https://doi.org/10.3390/metabo13080920*
59. *Zacková L, Jáni M, Brázdil M, Nikolova YS, Marečková K: Cognitive impairment and depression: Meta-analysis of structural magnetic resonance imaging studies. Neuroimage Clin 2021; 32:102830. doi:10.1016/j.nicl.2021.102830. Epub 2021 Sep 16. PMID:34560530; PMCID:PMC8473769*
60. *Zimmermann J, Brockmeyer T, Hunn M, Schauenburg H, Wolf M: First-person Pronoun Use in Spoken Language as a Predictor of Future Depressive Symptoms: Preliminary Evidence from a Clinical Sample of Depressed Patients. Clin Psychol Psychother 2017; 24:384-391. doi:10.1002/cpp.2006*

Correspondence:
Daria Smirnova, MD, PhD
Reaviz Medical University
443016 Samara, Russia
E-mail: daria.smirnova.md.phd@gmail.com