



Anxiety in old age and dementia - implications for clinical and research practice

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ABSTRACT

While extensive research has been performed in relation to anxiety in general, there is a marked paucity of investigation on older adulthood, especially in relation to those individuals living with mild cognitive impairment (MCI) and dementia, with the majority of such studies clinically based and focusing upon 'formal' anxiety disorders. It is however becoming increasingly evident that the detrimental effects of anxiety are not limited to clinical anxiety disorders but can instead occur in response to anxiety per se, i.e., sub-syndromal anxiety including various levels of trait and state anxiety. Furthermore, it is increasingly apparent that even non-clinical anxiety can influence many more components of information processing than previously recognized.

Keywords

Anxiety, Ageing, Cognitive impairment, Dementia

Introduction

In ageing and dementia-related research, it is now common practice to determine the functional integrity of a much wider range and level of brain function rather than focusing predominantly on memory and cognition in order to improve disease characterization and understanding. Nevertheless, in many studies individuals with clinical anxiety disorders are excluded whereas those with lower levels of state or trait anxiety may be included. In the first scenario the results are applicable only to the population without an anxiety disorder and resultant failure to gain information about the effects of anxiety upon the function measured. In the second scenario we fail to take into account the potential effects of non-clinical anxiety upon brain function and thus study outcome, interpretation and general applicability and relevance.

In this review we explore evidence indicative of the potential influence anxiety per se may have upon tests of some aspects of brain function in

order to raise awareness, promote discussion and to possibly lead to a change in methodological practice in which anxiety-related factors are more appropriately considered. Anxiety in relation to MCI and dementia is given particular emphasis: a pertinent strategy when one considers the importance of dissociating the effects of potentially treatable anxiety from those of neurodegenerative disease, and the influence anxiety may have upon the outcome of research in this area.

Data bases searched

Medline, PubMed, Web of Science, PsycARTICLES, PsycINFO and searches of the References sections of published papers.

Principle Search terms

Anxiety, anxiety and ageing, cognitive impairment, dementia, information processing,

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vision, attention, inhibition, sleep, health and depression

Anxiety

Although definitions of anxiety vary it is generally recognized as an aversive feeling of unease, worry, nervousness or fear about something that is happening or might happen. State anxiety refers to temporarily experienced anxiety, related to a specific situation, with Trait anxiety describing a longer lasting response or a general disposition to anxiety. Psychiatric or clinical disorders such as general anxiety disorder (GAD), panic disorders and specific phobias are commonly described with respect to a wide range of assessment instruments [1-6]. Nevertheless, over the lifespan, irrespective of classification, anxiety tends to result in, or be associated with, a wide range of physical, affective and cognitive responses including palpitations, sleep problems, muscle tension, apprehension, poor concentration, restlessness and reassurance seeking behavior [7-13].

Anxiety aetiology and risk factors across the lifespan appear multidimensional and complex, and include personality traits (e.g. neuroticism and low self-efficacy) and environmental factors (e.g. trauma and stress) [3,6,9,14-17] and it is often associated, or coexistent, with health issues such as osteoarthritis, stroke, obesity; intellectual disability, cancer, cardiovascular disease, diabetes, Alzheimer's disease, pain, sleep issues, chronic physical illness, medical illness and increasing frailty (although ageing per se does not appear to be a risk factor), vision and hearing impairment [1,2,18-33] and depression [34-36]. Underpinning these anxiety-related associations are a variety of models, mechanisms and pathways [2,5,7,8,14,26,34-42]. Nevertheless, of particular relevance to this review, is that irrespective of its cause and associations, anxiety appears to affect a wide range of brain functions.

■ The potential impact of anxiety

The prevalence of anxiety disorders in older adults is high [12], with estimates up to 15.3% [10,11] with prevalence rates for anxiety sometimes equal to, or even exceeding, those for depressive disorders [2, 10,13,38,43-46]. Rather surprisingly, given the relative lack of research in this area [43,47], sub-syndromal anxiety symptoms appear more widespread than anxiety disorders [12], with prevalence ranging from 15% to 52.3% [10]. Furthermore, irrespective

of aetiology, type and theoretical approach, in practical, real life terms, a substantial body of research indicates that anxiety in older adults can be associated with considerable disease burden, poor outcome, detrimental impact upon daily living and quality of life, poor functional status and physical activity, poorer self-perceptions with regards to health, decreased life satisfaction, increased loneliness and service use, depression, urinary incontinence, sleep disturbance, unhealthy behaviors such as smoking, physical inactivity, poor diet and alcohol misuse [12,48,49], diabetes, stroke, cardiovascular disease, tachycardia, increased arousal and muscle tension, altered interoceptive prediction signals, enhanced sensitivity to new stimuli, impeded decision making skills, language and cognitive function, cognitive decline and dementia [2,9,24,26,38,41,42,45,47,50-62]. Less well known are the effects of anxiety upon some of the more fundamental levels of information processing, as described in the following sections. Despite such evidence, anxiety can reportedly be largely undetected and untreated in older adults, especially in medical settings [63-65]; a possible consequence of diagnostic difficulty in older adults with multiple psychiatric, medical conditions [2], the attribution of symptoms to other factors [12], issues related to clinical practice [43], limitations to classification systems and the definition of anxiety in diseases such as dementia and the properties of assessment instruments [65]. Arguably therefore, improvement in health and wellbeing in older adulthood may be attained by raising awareness of the potential detrimental effects of anxiety in this age group and of the benefits of diagnosis and treatment [66,67]. Lack of appreciation of the potential influence of anxiety is especially pertinent in relation to the clinical assessment, characterization, diagnosis and follow-up of mild cognitive impairment and dementia in older adults [2,45,68-72], especially when one considers that anxiety can be amenable to treatment [12] and that the physiological response to anxiety may also detrimentally influence cognitive function over time [42,51,73,74].

■ Anxiety, older adulthood, mild cognitive impairment and dementia

Anxiety in general is associated with decreased cognitive functioning in older adulthood and increased risk of cognitive decline [35,36,51,62,72-76]. Although there is some evidence of decreased performance in some components of cognition, including processing

speed, attention shifting and inhibition in sub-syndromal anxiety [72] in older adults, the majority of studies, especially those related to memory and executive function, have tended to include clinical samples, i.e., individuals meeting full diagnostic criteria for anxiety disorders or with comorbid anxiety and depressive disorders [12]. Arguably, this approach is at odds with the known high prevalence of sub-syndromal anxiety [12,76].

Anxiety is also increasingly recognized (independently from depression) as a common symptom in older adults individuals living with various aetiologies of dementia, including Alzheimer's disease, vascular dementia, fronto-temporal dementia, Lewy body disease, posterior cortical atrophy, dementia associated with Parkinson's disease, and in subjective and mild cognitive impairment, tending to result in poorer quality of life, problematic behaviours, limitations in activities of daily living, nighttime awakening and poorer neuropsychological performance [43,65,69,77-85]. The relationship between anxiety and dementia is however both complex and controversial with overlap between the symptoms of anxiety and dementia and other behavioral and psychological problems such as agitation and depression [10,12,43,62,65,71,73,77,82,86-88]. Although anxiety may increase the rate of conversion of MCI to Alzheimer's disease, be related to neuropathological status, associated with an increased risk of developing AD, and to influence cognitive impairment in MCI [19,47,62,68,73,74,87,89], directionality is complex [47,71,74,90]. For example, in some individuals, perceived change in cognition or a diagnosis of MCI or SCI, can promote anxiety, whereas others are more susceptible to both anxiety and cognitive impairment [12,65,68,70,79,82]. Nevertheless, one can argue that treating anxiety in cognitive impairment or dementia may both remove a potential detrimental contributor to cognitive function and also improve the health and wellbeing of the individual living with these conditions.

■ Anxiety and Clinical and Research Test Performance

While there is clearly a body of research examining the relationship between anxiety, cognitive decline and dementia, the potential for anxiety to influence the performance of tests used in the clinical assessment of cognitive function in older adults, especially in SCI, MCI and dementia, is

less well investigated, this is particularly the case with subclinical anxiety [91-93].

In addition to the traditional aspects of cognitive function explored in older adulthood, SCI, MCI and dementia, particularly in relation to diagnosis and progression, research has revealed that many other components and levels of information processing, particularly those related to attention [94-97], can also be abnormal in these conditions. However, the potential impact of anxiety upon such function remains a relative unknown and in the following section we highlight evidence related to the possibility that anxiety may directly or indirectly influence the results of both clinical and research tests of attention-related function.

■ Anxiety and Attention-related processing

The brain's functionally and structurally independent yet cooperative attention network [98], is a fundamental component of our ability to selectively direct the brain's limited processing resources to the information of most relevance within the environment, which in turn influences many other aspects and levels of processing including cognition and perception. Research evidence indicates that some aspects of attention-related function can be influenced and modulated by anxiety [12,47,99-101]. These include attentional narrowing [100], selective attention, attentional control [7,102], inhibition, alerting, orienting and attentional resource allocation [7,15,102-117], pre-attentive change detection, sensory processing, contrast sensitivity involved in low level visual processing, processing speed, increased processing of task-irrelevant information [106,118-123] and selective attention bias in relation to threat-relevant information [108-110,120,122,123], and which in some cases, is related to state or trait anxiety [114]. Furthermore, average pupil diameter can be greater in the presence of moderate to severe anxiety compared to mild or no anxiety symptoms [124] and thus may influence the pupillary light reflex [125-127] and possibly some aspects of attention-related function [128]. As pupillary function and the pupillary light reflex have been found to be significantly abnormal in AD [129] concomitant anxiety in AD may further exacerbate the effects of the disease and confound research results. Anxiety has also been reported to slow processing speeds in older adults with severe state anxiety [101,130,131].

As some of these functions or component processes have been found to be abnormal in AD and/or MCI [94-97], generally in studies in

which participants with anxiety disorders have been excluded, the detrimental effect may be exacerbated further in individuals with various forms of anxiety. It is possible that everyday environmental interpretation and response, highly dependent upon vision and attention-related function, may be significantly poorer in MCI and dementia compared to cognitively healthy ageing, as a result, at least in part, of concomitant anxiety in these disorders. Closely associated with attention-related processing is balance. The finding that state and trait anxiety can affect sensory inputs involved in balance [103,132-134] may have implications in relation to the already high risk of falls in MCI and dementia which may be further exacerbated by anxiety. Furthermore, expectations and beliefs may also modulate activity in the anxiety network [134], thus one must also consider the potential for 'testing' per se to induce anxiety which can adversely affect test performance in general [8,41,131,135,136], again potentially confounding study results.

Summary

In view of the research evidence highlighted above, one might argue that as anxiety is a potentially treatable condition [69,136-139], intervention may prove an important factor in the management of individuals living with cognitive impairment and dementia [2,62,75], with dissemination of information regarding late-life anxiety disorder vital as evidence-based treatments, pharmacological and psychotherapy, are available [43,131-141]. There are however important caveats to consider. For example,

the majority of anxiety-related research has been performed in younger adults and in the context of exploring theoretical approaches; there is a paucity of evidence relating to the potential effects of anxiety upon cognitive and other aspects of information processing in both cognitively healthy ageing and in cognitive impairment and dementia. Also apparent from this review process is the diversity in the types of anxiety investigated in previous studies and the instruments used to define and diagnose these events in both clinical and research domains. Many manuscripts failed to provide a definition or formal criteria for identifying the type of anxiety investigated, with many simply stating only the scale used in its measurement, rather than inclusion and exclusion criteria. Further study is also required in order to determine whether treatment of anxiety corresponds to improved functionality and changes in test scores in SCI, MCI and dementia [51].

Conclusion

We therefore call for debate of, and consensus in such matters as formally examining the anxiety status per se of both patients and controls taking part in dementia and cognitive impairment-related research studies, and determining and expressly stating the type of anxiety present (e.g., state, trait, general anxiety disorder, sub-syndromal anxiety) with respect to inclusion and exclusion criteria. Further improvement in this area could be made by explicitly stating the test(s) used to diagnose or exclude the presence of anxiety and by including anxiety as a factor in statistical analysis.

References

- Lindesay J, Stewart R, Bisla J. Anxiety disorders in older people. *Rev. Clin. Gerontol* 22(1), 204-217 (2012).
- Cassidy K, Rector N. The silent geriatric giant: anxiety disorders in late life. *Geriatrics. Aging* 11(3), 150-156 (2008).
- Katerndahl DA, Talamantes M. A comparison of persons with early-versus late-onset panic attacks. *J. Clin. Psychiatry* 61(6), 422-427 (2000).
- El-Gabalawy R, Mackenzie CS, Thibodeau MA, et al. Health anxiety disorders in older adults: Conceptualizing complex conditions in late life. *Clin. Psychol. Rev* 33(8), 1096-1105 (2013).
- Zwanger P, Eser D, Nothdurfter C, et al. Effects of the GABA-reuptake inhibitor tiagabine on panic and anxiety in patients with panic disorder. *Pharmacopsychiatry* 42(6), 266-269 (2009).
- Stein B, Stein J. Social anxiety disorder. *Lancet* 371(1), 1115-1125 (2008).
- Eysenck MW, Derakshan N. New perspectives in attentional control theory. *Pers. Individ. Dif* 50(7), 955-960 (2011).
- Guyer A, Lau J, McClure-Tone E, et al. Amygdala and ventrolateral prefrontal cortex function during anticipated peer evaluation in pediatric social anxiety. *Arch. Gen. Psychiatry* 65(11), 1303-1312 (2008).
- Paulus M, Stein M. An Insular View of Anxiety. *Biol. Psychiatry* 60(4), 383-387 (2006).
- Bryant C, Jackson H, Ames D. The prevalence of anxiety in older adults: methodological issues and a review of the literature. *J. Affect. Disord* 109(3), 233-250 (2008).
- Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. *Arch. Gen. Psychiatr* 62(6), 593-602 (2005).
- Yochim BP, Mueller A, Segal DL. Late life anxiety is associated with decreased memory and executive functioning in community dwelling older adults. *J. Anxiety. Disord* 27(6), 567-575 (2013).
- Samuelson G, McCamish-Svensson C, Hagberg B, et al. Incidence and risk factors for depression and anxiety disorders: results from a 34-year long Swedish cohort study. *Aging. Ment. Health* 9(6), 571-575 (2005).
- Tambis K, Czajkowski N, Roysamb E, et al. Structure of genetic and environmental risk

- factors for dimensional representations of DSM-IV anxiety disorders. *Br. J. Psychiatry* 195(4), 301-307 (2009).
15. D'Hondt F, Honoré J, Williot A, *et al.* State anxiety modulates emotional salience processing on peripheral vision. *Int. J. Psychophys* 85(1), 413-414 (2014).
 16. Mohlman J, Price RB, Vietri J. Attentional bias in older adults: Effects of generalized anxiety disorder and cognitive behavior therapy. *J. Anxiety. Disord* 27(6), 585-591 (2013).
 17. Price RB, Siegle G, Mohlman J. Emotional stroop performance in older adults: effects of habitual worry. *Am. J. Geriatr. Psychiatry* 20(9), 898-905 (2012).
 18. Bernabei V, Morini V, Moretti F, *et al.* Vision and hearing impairments are associated with depressive-anxiety syndrome in Italian elderly. *Aging. Ment. Health* 15(4), 467-474 (2011).
 19. Ramakers IH, Verhey FR, Scheltens P, *et al.* Anxiety is related to Alzheimer cerebrospinal fluid markers in subjects with mild cognitive impairment. *Psychol. Med* 43(5), 911-920 (2013).
 20. Hermands H, Evenhuis HM. Factors associated with depression and anxiety in older adults with intellectual disabilities: results of the healthy ageing and intellectual disabilities study. *Int. J. Geriatr. Psychiatry* 28(7), 691-699 (2013).
 21. Gariépy G, Porcelli P, Rafanelli C, *et al.* The spectrum of anxiety disorders in the medically ill. *J. Clin. Psychiatry* 71(7), 910-914 (2010).
 22. Stark DPH, House A. Anxiety in cancer patients. *Br. J. Cancer* 83(10), 1261-1267 (2000).
 23. Grenier S, Potvin O, Hudon C, *et al.* Twelve-month prevalence and correlates of subthreshold and threshold anxiety in community-dwelling older adults with cardiovascular diseases. *J. Affect. Disord* 136(3), 724-732 (2012).
 24. Smith KJ, Béland M, Clyde M, *et al.* Association of diabetes with anxiety: A systematic review and meta-analysis. *J. Psychosom. Res* 74(2), 89-99 (2013).
 25. Arola H-M, Nicholls E, Mallen C, *et al.* Self-reported pain interference and symptoms of anxiety and depression in community-dwelling older adults: Can a temporal relationship be determined? *Eur. J. Pain* 14(9), 966-971 (2010).
 26. Tampi R, Tampi D. Anxiety disorders in late life: A comprehensive review. *Healthy. Aging. Res* 3:14 (2014).
 27. Menlove L, Crayton E, Kneebone I, *et al.* Predictors of anxiety after stroke: A systematic review of observational studies. *J. Stroke. Cerebrovasc. Dis* 24(6), 1107-1117 (2015).
 28. Tan V, Jinks C, Chew-Graham C, *et al.* The triple whammy anxiety depression and osteoarthritis in long-term conditions. *BMC. Fam. Pract* 16: 163 (2015).
 29. Weber FD, Wang J, Born J, *et al.* Sleep benefits in parallel implicit and explicit measures of episodic memory. *Learn. Mem* 21(4), 190-198 (2014).
 30. Nere A, Hashmi A, Cirelli C, *et al.* Sleep-dependent synaptic down-selection (I): modeling the benefits of sleep on memory consolidation and integration. *Front. Neurol* 4: 143 (2013).
 31. Könen T, Dirk J, Schmiedek F. Cognitive benefits of last night's sleep: daily variations in children's sleep behavior are related to working memory fluctuations. *J. Child. Psychol. Psych. Allied. Discip* 56(2), 171-182 (2015).
 32. Saint Martin M, Sforza E, Barthélémy JC, *et al.* Does subjective sleep affect cognitive function in healthy elderly subjects? *Sleep. Med* 13(9), 1146-1152 (2012).
 33. Katan W. Epidemiology and treatment of depression in patients with chronic medical illness. *Dialogues. Clin. Neurosci* 13(1), 07-23 (2011).
 34. Magalhaes A, Holmes K, Dale L, *et al.* CRF receptor 1 regulates anxiety behavior via sensitization of 5-HT₂ receptor signaling. *Nat. Neurosci* 13(5), 622-629 (2010).
 35. Beaudreau SA, MacKay-Brandt A, Reynolds J. Application of a cognitive neuroscience perspective of cognitive control to late-life anxiety. *J. Anxiety. Disord* 27(6), 559-566 (2013).
 36. Hek K, Tiemeier H, Newson RS, *et al.* Anxiety disorders and comorbid depression in community dwelling older adults. *Int. J. Methods. Psychiatr. Res* 20(3), 157-168 (2011).
 37. Oathes DJ, Patenaute B, Schatzberg AF, *et al.* Neurobiological signatures of anxiety and depression in resting-state functional magnetic resonance imaging. *Biol. Psychiatry* 77(4), 385-393 (2015).
 38. Bassil N, Ghandour A, Grossberg G. How anxiety presents differently in older adults. *Curr. Psych* 10 (2011).
 39. Wilkes M, Wilson W, Woodard L, *et al.* Do negative affect characteristics and subjective memory concerns increase risk for late life anxiety? *J. Anxiety. Disord* 27(6), 606-618 (2013).
 40. Heisler K, Zhou L, Bajwa P, *et al.* Serotonin₅-HT_{2C} receptors regulate anxiety-like behavior. *Genes. Brain. Behav* 6(5), 491-496 (2007).
 41. Hoehn-Saric R, Kowalski P, McLeod D, *et al.* Somatic symptoms and physiologic response in generalized anxiety disorder and panic disorder. *Arch. Gen. Psychiatry* 61(9), 913-921 (2004).
 42. Burton C, Campbell P, Jordan K, *et al.* The association of anxiety and depression with future dementia diagnosis: a case-control study in primary care. *Fam. Pract* 30(1), 25-30 (2013).
 43. Schuurmans J, van Balkom A. Late-life anxiety disorders: A review. *Curr. Psychiatry. Rep* 13(4), 267-273 (2011).
 44. Beekman AT, Bremmer MA, Deeg DJ, *et al.* Anxiety disorders in later life: a report from the Longitudinal Aging Study Amsterdam. *Int. J. Geriatr. Psychiatry* 13(10), 717-726 (2000).
 45. Verhoeven JE, Révész D, van Oppen P, *et al.* Anxiety disorders and accelerated cellular ageing. *Br. J. Psychiatry* 206(5), 371-378 (2015).
 46. Wetherell JL, Thorp SR, Patterson TL, *et al.* Quality of life in geriatric generalized anxiety disorder: a preliminary investigation. *J. Psychiatr. Res* 38(3), 305-312 (2004).
 47. Rozzini L, Chilovi V, Peli M, *et al.* Anxiety symptoms in mild cognitive impairment. *Int. J. Geriatr. Psychiatry* 24(3), 300-305 (2009).
 48. Strine TW, Chapman DP, Kobau R, *et al.* Associations of self-reported anxiety symptoms with health-related quality of life and health behaviors. *Soc. Psychiatry. Psychiatr. Epidemiol* 40(6), 432-438 (2005).
 49. Van Hout HP, Beekman AT, de Beurs E, *et al.* Anxiety and the risk of death in older men and women. *Br. J. Psychiatry* 185(1), 399-404 (2004).
 50. Yang Y, Zhang X, Zhu Y, *et al.* Cognitive impairment in generalized anxiety disorder revealed by event-related potential N270. *Neuropsych. Dis. Treat* 11(1), 1405-1411 (2015).
 51. Alosco ML, Gunstad J, Beard C, *et al.* The synergistic effects of anxiety and cerebral hypoperfusion on cognitive dysfunction in older adults with cardiovascular disease. *J. Geriatr. Psychiatr. Neurol* 28(1), 57-66 (2015).
 52. Richardson TM, Simning A, He H, *et al.* Anxiety and its correlates among older adults accessing aging services. *Int. J. Geriatr. Psychiatry* 26(1), 31-38 (2011).
 53. Sherbourne CD, Sullivan G, Craske MG, *et al.* Functioning and disability levels in primary care outpatients with one or more anxiety disorders. *Psychol. Med* 40(12), 2059-2068 (2010).
 54. Olatunji BO, Cisler JM, Tolin DF. Quality of life in the anxiety disorders: A meta-analytic review. *Clin. Psychol. Rev* 27(5), 572-581 (2007).
 55. Lambiasi MJ, Kubzansky LD, Thurston RC. Prospective study of anxiety and incident stroke. *Stroke* 45(1), 438-443 (2014).
 56. Huffman JC, Smith FA, Blais MA, *et al.* Anxiety, independent of depressive symptoms is associated with in-hospital cardiac complications after acute myocardial infarction. *J Psychosom Res* 65(6), 557-563 (2008).
 57. Julian LJ. Measures of Anxiety. *Arthritis. Care. Res* 63(1), 0-11 (2011).
 58. Katz IR, Reynolds CF, Alexopoulos GS, *et al.* Venlafaxine ER as a treatment for generalized anxiety disorder in older adults: Pooled analysis of five randomized placebo controlled clinical

- trials. *J. Am. Geriatr. Soc* 50(1), 18-25.
59. Naragon-Gainey K, Gallagher MW, Brown TA. A longitudinal examination of psychosocial impairment across the anxiety disorders. *Psychol. Med* 44(8), 1691-1700 (2014).
60. Rodrigues P, Vendemia. Repressors vs. low-and high-anxious coping styles: EEG differences during a modified version of the emotional Stroop test. *Int. J. Psychophysiol* 78(3), 284-294 (2010).
61. Banich M, Curran T, Hutchinson N, et al. Neural inhibition enables selection during language processing. *Proc. Natl. Aca. Sci* 107(1), 16483-16488 (2010).
62. Gallagher J, Bayer A, Fish M, et al. Does anxiety affect risk of Dementia? Findings from the Caerphilly prospective study. *Psychosom. Med* 71(6), 659-666 (2009).
63. Calleo J, Stanley MA, Greisinger A, et al. Generalized anxiety disorder in older medical patients: Diagnostic recognition, mental health management, and service utilization. *J. Clin. Psychol. Med. Settings* 16(2), 178-185 (2009).
64. Kroenke K, Spitzer RL, Williams JB, et al. Anxiety disorders in primary care: Prevalence, impairment, comorbidity, and detection. *Ann. Intern. Med* 146(5), 317-325 (2007).
65. Seignourel P, Kunik M, Snow L, et al. Anxiety in dementia: A critical review. *Clin. Psychol. Rev* 28(7): 1071-1082 (2008).
66. Ayers CR, Sorrell JT, Thorp SR, et al. Evidence-based psychological treatments for late-life anxiety. *Psychol. Aging* 22(1), 8-17 (2009).
67. Loebach, Wetherell J, Maser JD, et al. Anxiety disorders in the elderly; outdated beliefs and a research agenda. *Acta Psychiatr Scand* 111(6), 401-402 (2005).
68. Palmer K, Berger AK, Montastero R, et al. Predictors of progression from mild cognitive impairment to Alzheimer disease. *Neurology* 68(19), 1596-1602 (2007).
69. Balasubramanyam V, Kunik M, Kraus C, et al. Cognitive-Behavioral Treatment for Anxiety in Patients with Dementia. *J. Psychiatr. Pract* 14(3), 186-192 (2008).
70. Amariaglio R, Breteler M, Ceccaldi M, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimers. Dement* 10(6), 844-852 (2014).
71. Arnaudova-Jekova M. Some Psychopathological Peculiarities at Early and Late Onset in Patients with Alzheimer's Disease. *J. IMAB* 16(1), 61-65 (2010).
72. Beaudreau SA, O'Hara R. The association of anxiety and depressive symptoms with cognitive performance in community-dwelling older adults. *Psychol. Aging* 24(2), 507-512 (2009).
73. Mah L, Szabuniewicz C, Fiocco A. Can anxiety damage the brain? *Curr. Opin. Psychiatry* 29(1), 56-63 (2016).
74. Mah L, Binnus M, Steffens D. Anxiety symptoms in amnesic mild cognitive impairment are associated with medial temporal atrophy and predict conversion to Alzheimer disease. *Am. J. Geriatric. Psychiatry* 23(5), 466-438 (2015).
75. Vytal K, Cornwell B, Arkin N, et al. Describing the interplay between anxiety and cognition: From impaired performance under low cognitive load to reduced anxiety under high load. *Psychophysiology* 49(6), 842-852 (2012).
76. Potvin O, Forget H, Grenier S, et al. Anxiety, depression, and 1-year incident cognitive impairment in community-dwelling older adults. *J. Am. Geriatr. Soc* 59(8), 1421-1428 (2011).
77. Porter V, Buxton W, Fairbanks L, et al. Frequency and characteristics of anxiety among patients with Alzheimers disease and related Dementias. *J. Neuropsychiatry. Clin. Neurosci* 15(2), 180-186 (2003).
78. Isella V, Villa G, Mapelli C, et al. The neuropsychiatric profile of posterior cortical atrophy. *J. Geriatr. Psychiatry. Neurol* 28(2), 136-144 (2015).
79. Reisberg B, Prichep L, Mosconi L, et al. The pre-mild cognitive impairment, subjective cognitive impairment stage of Alzheimer's disease. *Alzheimers. Dement* 4(1), S98-S108 (2008).
80. Hwang TJ, Masterman DL, Ortiz F, et al. Mild cognitive impairment is associated with characteristic neuropsychiatric symptoms. *Alzheimer. Dis. Assoc. Disord* 18(1), 17-21 (2004).
81. Gallagher D, Coen R, Kilroy D, et al. Anxiety and behavioural disturbance as markers of prodromal Alzheimer's disease in patients with mild cognitive impairment. *Int. J. Geriatr. Psychiatry* 26(2), 166-172 (2011).
82. Qazi A, Shankar K, Orrell M. Managing anxiety in people with dementia: A case series. *J. Affect. Disord* 76(1-3), 261-265 (2003).
83. Beaudreau S, Hara R. Late-life anxiety and cognitive impairment: A review. *Am J Geriatr Psychiatry* 16(10), 790-803 (2008).
84. Hynninen MJ, Breivte MH, Rongve A, et al. The frequency and correlates of anxiety in patients with first-time diagnosed mild dementia. *Int. Psychogeriatr* 24(11), 1771-1778 (2012).
85. Kobayashi K, Sumiya H, Nakano H, et al. Detection of Lewy body disease in patients with late-onset depression, anxiety and psychotic disorder with myocardial meta-iodobenzylguanidine scintigraphy. *Int J Geriatr Psychiatry* 25(1), 55-65 (2010).
86. Brujijn R, Direk N, Mira S, et al. Anxiety is not associated with the risk of Dementia or Cognitive Decline: The Rotterdam Study. *Am. J. Geriatr. Psychiatry* 22(12), 1382-1390 (2014).
87. Breivte M, Hynninen M, Bronnick K, et al. A longitudinal study of anxiety and cognitive decline in dementia with Lewy bodies and Alzheimer's disease. *Alzheimers. Res. Ther.* 8(1), 3 (2016).
88. Johansson L, Guo X, Hallstrom T, et al. Common psychosocial stressors in middle-aged women related to longstanding distress and increased risk of Alzheimer's disease: A 38-year longitudinal population study. *BMJ. Open* 3(9), e003142 (2013).
89. Pristera A, Saraulli D, Fariolo-Vecchioli S, et al. Impact of N-tau on adult hippocampal neurogenesis, anxiety, and memory. *Neurobiol. Aging* 34(11), 2551-2563 (2013).
90. Teri L, Ferretti L, Gibbons L, et al. Anxiety of Alzheimer's disease: prevalence, and comorbidity. *J. Gerontol. A. Biol. Sci. Med. Sci* 54(7), M348-M352 (1999).
91. Ortega V, Qazi A, Orrell M. Psychological treatments for depression and anxiety in dementia and mild cognitive impairment: systematic review and meta-analysis. *Br. J. Psychiatry* 207(4), 293-298 (2015).
92. Ninan P, Berger J. Symptomatic and syndromal anxiety and depression. *Depress. Anxiety* 14(2), 79-85 (2001).
93. Modi S, Trivedi R, Singh K, et al. Individual differences in trait anxiety are associated with white matter tract integrity in fornix and uncinate fasciculus: Preliminary evidence from a DTI based tractography study. *Behav. Brain. Res* 238(1), 188-192 (2013).
94. Amieva H, Phillips LH, Della Sala S, et al. Inhibitory functioning in Alzheimer's disease. *Brain* 127(5), 949-964 (2004).
95. Tse CS, Balota DA, Yap MJ, et al. Effects of healthy aging and early stage dementia of the Alzheimer's type on components of response time distributions in three attention tasks. *Neuropsychology* 24(3), 300-315 (2010).
96. Galletta EE, Lequerica AH, Pekrul SR, et al. Visual distraction: An altered aiming spatial response in dementia. *Demen. Geriatr. Cogn. Dis. Extra* 2(1), 229-237 (2012).
97. Bayer A, Phillips M, Porter G, et al. Abnormal inhibition of return in mild cognitive impairment: Is it specific to the presence of prodromal dementia? *J. Alzheimers. Dis* 40(1), 177-189 (2014).
98. Vossel S, Geng JJ, Fink GR. Dorsal and ventral attention systems. *Neuroscientist* 20(2), 150-159 (2014).
99. Bishop SJ, Jenkins R, Lawrence AD. Neural processing of fearful faces: Effects of anxiety are gated by perceptual capacity limitations. *Cerebral. Cortex* 17(7), 1595-1603 (2007).

100. Najmi S, Kuckertz JM, Amir N. Attentional impairment in anxiety: Inefficiency in expanding the scope of attention. *Depress. Anxiety* 29(3), 243-249 (2012).
101. Castaneda A, Tuulio-Henriksson A, Marttunen M, et al. A review on cognitive impairments in depressive and anxiety disorders with a focus on young adults. *J. Affect. Disord* 106(1-2):1-27 (2008).
102. Berggren N, Richards A, Taylor J, et al. Affective attention under cognitive load: reduced emotional biases but emergent anxiety-related costs to inhibitory control. *Front. Hum. Neurosci* 7(1), 188 (2013).
103. Hainaut JP, Caillet G, Lestienne FG, et al. The role of trait anxiety on static balance performance in control and anxiogenic situations. *Gait. Posture* 33(4), 604-608 (2011).
104. Moriya J, Sigiura Y. Impaired attentional disengagement from stimuli matching the contents of working memory in social anxiety. *PLoS. ONE* 7(10), e47221 (2012).
105. Dolcos F, Matveychuk D, O'Hare A, et al. Processing of emotional distraction is both automatic and modulated by attention: evidence from an event-related fMRI investigation. *J. Cog. Neurosci* 24(5), 1233-1252 (2012).
106. Sadeh N, Bredemeier K. Individual differences at high perceptual load: The relation between trait anxiety and selective attention. *Cogn. Emot* 25(4), 747-755 (2011).
107. Reinholdt-Dunne ML, Mogg K, Bradley BP. Attention control: Relationships between self-report and behavioural measures, and symptoms of anxiety and depression. *Cogn. Emot* 27(3), 430-440 (2013).
108. Poy R, del Carmen Eixarch, M, Ávila C. On the relationship between attention and personality; covert visual orienting of attention in anxiety and impulsivity. *Personality. Individ. Diff* 36(1), 1471-1481 (2004).
109. Bar-Haim Y, Lamy D, Pergamin L, et al. Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. *Psychol. Bull* 133(1), 1-24 (2007).
110. Derakshan N, Ansari TL, Hansard M, et al. Anxiety, inhibition, efficiency, and effectiveness. An investigation using antisaccade task. *Exp. Psychol* 56(1), 48-55 (2009).
111. Ansari TL, Derakshan N. The neural correlates of cognitive effort in anxiety: effects on processing efficiency. *Biol. Psychol* 86(3), 337-348 (2011).
112. Ansari TL, Derakshan N. The neural correlates of impaired inhibitory control in anxiety. *Neuropsychologia* 49(5), 1146-1153 (2011).
113. Bishop S. Trait anxiety and impoverished prefrontal control of attention. *Nature. Neuroscience* 12(1), 92-98 (2009).
114. Pacheco-Unguetti AP, Acosta A, Callejas A, et al. Attention and anxiety: Different attentional functioning under state and trait anxiety. *Psychol. Sci* 21(2), 298-304 (2010).
115. Eysenck MW, Derakshan N, Santos R, et al. Anxiety and cognitive performance: attentional control theory. *Emotion* 7(2), 336-353 (2007).
116. Ramirez E, Ortega AR, Reyes Del Pasa GA. Anxiety, attention, and decision making: The moderating role of heart rate variability. *Int. J. Psychophysiol* 490(3-1), 490-496 (2015).
117. Frick A, Engman J, Alaie I, et al. Enlargement of visual processing regions in social anxiety disorder is related to symptom severity. *Neurosci. Lett* 583(1), 114-119 (2014).
118. Ferneyhough E, Kim MK, Phelps EA, et al. Anxiety modulates the effects of emotion and attention on early vision. *Cogn. Emot* 27(1), 166-176 (2013).
119. Eramudugolla R, Wood J, Anstey KJ. Comorbidity of depression and anxiety in common age-related eye diseases: a population-based study of 662 adults. *Front. Aging. Neurosci* 5(1), 56 (2013).
120. Berggren N, Bloniewsky T, Derakshan N. Enhanced visual detection in trait anxiety. *Emotion* 15(4), 477-483 (2015).
121. Schirmer A, Escoffier N. Emotional MMN: Anxiety and heart rate correlate with the ERP signature for auditory change detection. *Clin. Neurophysiol* 121(1), 53-59 (2010).
122. Berggren N, Derakshan N. Attentional control deficits in trait anxiety: Why you see them and why you don't. *Biol. Psychol* 92(3), 440-446 (2013).
123. Moser JS, Becker MW, Moran TP. Enhanced attentional capture in trait anxiety. *Emotion* 12(2), 213-216 (2012).
124. Bertrand AL, Garcia JBS, Viera EB, et al. Pupillometry: The influence of Gender and Anxiety on the pain response. *Pain. Physician* 16(3), E257-E266 (2013).
125. Loewenfeld IE. The Pupil. Iowa State University Press/Amos Wayne State University Press, Detroit (1993).
126. Bitsios P, Szabadi E, Bradshaw CM. Relationship of the 'fear-inhibited light reflex' to the level of state/trait anxiety in healthy subjects. *Int. J. Psychophysiol* 43(2), 177-184 (2002).
127. Shiori T, Kuwabara H, Abe R, et al. Lack of a relationship between the pupillary light reflex response and state/trait anxiety in remitted patients with panic disorder. *J. Affect. Disord* 95(1-3), 159-164 (2006).
128. Mathöf S, van der Linden L, Grainger J, et al. The pupillary light response reveals the focus of covert visual attention. *PLoS. one* 8(10), e78168 (2013).
129. Tales A, Troscianko T, Lush D, et al. The pupillary light reflex in aging and Alzheimer's disease. *Aging. (Milano)* 13(6), 473-478 (2001).
130. Hainaut JP, Bolmont B. Moderate state-anxiety differentially modulates visual and auditory response times in normal- and very low trait-anxiety subjects. *Neurosci. Lett* 395(2), 129-132 (2006).
131. Coombes SA, Higgins T, Gamble M, et al. Attentional control theory; Anxiety, emotion and motor planning. *J. Anxiety. Disord* 23(8), 1072-1079 (2009).
132. Ohno H, Wada M, Saitoh J, et al. The effect of anxiety on postural control in humans depends on visual information processing. *Neurosci. Lett* 364(1), 37-39 (2004).
133. Ishida M, Saitoh J, Wada M, et al. Effects of anticipatory anxiety and visual input on postural sway in an aversive situation. *Neurosci. Lett* 474(1), 1-4 (2010).
134. Engel K, Bandelow B, Gruber O, et al. Neuroimaging in anxiety disorders. *J. Neural. Transm* 116(6), 703-716 (2009).
135. Chew SSL, Kerr M, Wong ABC, et al. Anxiety in visual field testing. *Br. J. Ophthalmol* 100:1-6 (2015).
136. Gonçalves DC, Byrn GJ. Interventions for generalized anxiety disorder in older adults: Systematic review and meta-analysis. *J. Anxiety. Disord* 26(1), 1-11 (2011).
137. Gould RL, Coulson MC, Howard RJ. Efficacy of cognitive behavioral therapy for anxiety disorders in older people: A meta-analysis and meta-regression of randomized controlled trials. *J. Am. Geriatr. Soc* 60(2), 218-229 (2012).
138. Keeton P, Kolos C, Walkup T. Pediatric generalized anxiety disorder: epidemiology, diagnosis, and management. *Paediatric. Drugs* 11(3), 171-183 (2009).
139. Akkerman R, Ostwald S. Reducing anxiety in Alzheimer's disease family caregivers: The effectiveness of a nine-week cognitive-behavioral intervention. *Am. J. Alzheimers. Dis. Other. Demen* 19(2), 117-124 (2004).
140. Orgeta V, Qazi A, Spector A, et al. Psychological treatments for depression and anxiety in dementia and mild cognitive impairment: systematic review and meta-analysis. *Br. J. Psych* 207(4), 293-298 (2015).
141. Wong WP, Hassed C, Chambers R, et al. The effects of mindfulness on persons with mild cognitive impairment: Protocol for a mixed-methods longitudinal study. *Front. Aging. Neurosci* 8(1), 156 (2016).