Pontifícia Universidade Católica
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Anna Fischer

Self-awareness and emotional processing in Alzheimer's disease

Tese de Doutorado

Thesis presented to the Programa de Pós-graduação em Psicologia of PUC-Rio in partial fulfillment of the requirements for the degree of Doutor em Psicologia.

Advisor: Prof. Daniel Correa Mograbi

Rio de Janeiro
April 2020

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Abstract

Fischer, Anna; Mograbi, Daniel Correa (Advisor). Self-awareness and emotional processing in Alzheimer's disease. Rio de Janeiro, 2020. 196p. Tese de Doutorado – Departamento de Psicologia, Pontifícia Universidade Católica do Rio de Janeiro.

Lack of awareness of condition, also termed anosognosia, is a common symptom in Alzheimer's disease (AD). However, its functional structure and underlying mechanisms are not fully understood. Level of awareness has great relevance for treatment success and caregiver burden. Another factor that has considerable impact on interpersonal relationships and thus on well-being of patients and caregivers is emotional processing. The current thesis explores these topics through four articles. In Article #1, structural equation modeling (SEM) was used in a large sample of people with AD (PwAD) to investigate the nature of the relationship between cognitive function, mood state, and functionality in predicting awareness. Results showed that lower cognitive function and higher level of depressive mood state negatively influenced PwAD's ability to perform daily living activities, which in turn were associated with better awareness. Article #2 investigated executive and mnemonic origins of anosognosia in AD, with a reaction time task being applied to examine awareness of task performance. The findings demonstrated that online monitoring was preserved, while medium- and long-term monitoring were impaired. This was supported by results from electrophysiological data. The results strengthen the evidence for a mnemonic rather than executive nature of anosognosia in PwAD in accordance with the Cognitive Awareness Model (CAM). Article #3 investigated emotional reactivity to negative, self-relevant, and neutral pictures using ratings of arousal and valence, facial expression recordings and electrophysiological data. Emotional reactivity of PwAD was similar to young adults, but electrophysiological responses were elevated compared to healthy older adults, which might be explained by a lack of cognitive control mechanisms. Apathy was associated with reduced

electrophysiological responses for negative pictures, and awareness of social impairments was linked to higher arousal ratings of self-relevant pictures. Article #4 discussed how higher emotional abilities are affected by AD, through a review of the literature on empathy in this clinical group. PwAD showed a pattern of relatively preserved affective aspects and impairments in cognitive components of empathy, whereby impairments in affective components can mainly be attributed to a general cognitive decline. Our findings highlight that different factors influence awareness in AD, emphasizing the role of neuropsychiatric symptoms (NPS), cognitive functioning and activities of daily living. Moreover, executive processes seem to be preserved, whereas impairments in updating and consolidation of this knowledge seem to be a possible cause for anosognosia in AD. Furthermore, we suggested that emotional abilities are largely preserved in PwAD. Our results have great significance for clinical practice. Translational research is needed to implement research findings into specific therapeutic approaches.

Key words

Dementia; anosognosia; performance monitoring; emotional reactivity; empathy; neuropsychiatric symptoms; electroencephalography

Resumo

Fischer, Anna; Mograbi, Daniel Correa. Autoconsciência e processamento emocional na Doença de Alzheimer. Rio de Janeiro, 2020. 196p. Tese de Doutorado – Departamento de Psicologia, Pontifícia Universidade Católica do Rio de Janeiro.

A falta de consciência da doença, também denominada anosognosia, é um sintoma comum da Doença de Alzheimer (DA). Sua estrutura funcional e seus mecanismos subjacentes, contudo, não são inteiramente compreendidos. O nível de consciência possui grande relevância para o sucesso do tratamento e para o fardo do cuidador. Outro fator de considerável impacto nas relações interpessoais e, portanto, no bem-estar dos pacientes e cuidadores, é o processamento emocional. A presente tese explora esses tópicos através de quatro artigos. No Artigo #1, utiliza-se a modelagem de equações estruturais (SEM, do inglês *structural equation modeling*) em uma grande amostra de pessoas com DA para investigar a natureza da relação entre função cognitiva, estado de humor e funcionalidade na previsão do nível de consciência da condição. Os resultados demonstraram que uma menor funcionalidade cognitiva e um maior nível de estado depressivo de humor influenciaram negativamente a capacidade dos pacientes de realizar atividades da vida cotidiana, o que, por sua vez, se mostrou associada a uma maior consciência da doença. O Artigo #2 investigou as origens executivas e mnemônicas da anosognosia na DA, utilizando uma tarefa de tempo de reação e medindo a consciência a respeito da performance na tarefa. Os dados demonstraram que o monitoramento 'online' dos pacientes estava preservado, enquanto o monitoramento a médio e longo prazo esteve comprometido. Tal achado foi corroborado por resultados de dados eletrofisiológicos. Dessa forma, os resultados fortalecem as evidências favoráveis a uma natureza mnemônica, e não executiva, da anosognosia na DA, o que se mostra de acordo com o *Cognitive Awareness Model* (CAM). O Artigo #3 investigou a reatividade emocional a imagens negativas, auto-relevantes e neutras utilizando medidas de excitação e valência,

gravações de expressões faciais e dados eletrofisiológicos. A reatividade emocional dos pacientes de DA foi similar à de jovens adultos, mas as respostas eletrofisiológicas foram elevadas quando comparadas às de idosos saudáveis, o que pode ser explicado por uma falta de mecanismos de controle cognitivo. A apatia esteve associada a menores respostas eletrofisiológicas a figuras negativas, e a consciência de prejuízos sociais se relacionou com maiores níveis de excitação em imagens auto-relevantes. Por sua vez, o Artigo #4 discutiu como a DA afeta as habilidades emocionais através de uma revisão de literatura sobre a empatia desses pacientes. Os aspectos afetivos da empatia deste grupo clínico estiveram relativamente preservados, enquanto foram apresentados déficits nos componentes cognitivos. Os prejuízos relacionados aos componentes afetivos foram principalmente atribuídos a um declínio cognitivo geral. Nossos achados ressaltam que diferentes fatores influenciam a consciência da doença na DA, enfatizando o papel de sintomas neuropsiquiátricos, do funcionamento cognitivo e das atividades da vida diária. Além disso, processos executivos pareceram estar preservados, ao passo que dificuldades em atualizar e consolidar esse conhecimento podem ser uma possível causa de anosognosia na DA. Ademais, sugerimos que as habilidades emocionais são amplamente preservadas em pacientes de DA. Tais resultados são de grande importância para a prática clínica. Pesquisas translacionais são necessárias para implementar os achados de pesquisas em abordagens terapêuticas específicas.

Palavras-chave

Demência; anosognosia; monitoramento de performance; reatividade emocional; empatia; sintomas neuropsiquiátricos; eletroencefalografia

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List of abbreviations

AD	Alzheimer's disease
ACC	Anterior Cingulate Cortex
ACE-r	Addenbrooke's Cognitive Examination revised
ADL	Activities of daily living
AES	Apathy Evaluation Scale
ANOVA	Analysis of variance
ASPIDD	Assessment Scale of Psychosocial Impact of the Diagnosis of Dementia
BDI-II	Beck's Depression Inventory II
BPSD	Behavioral and psychological symptoms of dementia
CAM	Cognitive Awareness Model
CCMs	Cognitive Comparator Mechanisms
CDA	Center for Alzheimer's disease and related disorders
CDR	Clinical Dementia Rating Scale
CFI	Comparative fit index
CI	Confidence interval
CSDD	Cornell Scale for Depression in Dementia
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders IV – Text Revision
EEG	Electroencephalogram
ERPs	Event-related potentials
FACS	Facial Action Coding System
FRN	Feedback-related negativity
FTD	Frontotemporal dementia
FTLD	Frontotemporal lobar degeneration
GDS	Geriatric Depression Scale
IAPS	International Affective Picture System
ICA	Independent Component Analysis
ICD-10	International Classification of Diseases, Tenth Revision

IPUB-UFRJ	Institute of Psychiatry of the Federal University of Rio de Janeiro
IRI	Interpersonal Reactivity Index
LPP	Late positive potential
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
NPS	Neuropsychiatric symptoms
PAM	Perception-Action Model
PDB	Personal Database
PFAQ	Pfeffer Functional Activities Questionnaire
PwAD	People with Alzheimer's disease
PwD	People with dementia
RMSEA	Root mean square error of approximation
RT	Reaction time
SAM	Self-Assessment Manikin
SD	Standard deviation
SEM	Structural equation modelling
SOME	Self to other model of empathy
SRMR	Standardized root mean square residual
ToM	Theory of Mind

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I. Theoretical background

1. Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia, with aging being the most significant risk factor (Piaceri, Nacmias, & Sorbi, 2013). An estimated 46.8 million people worldwide suffer from dementia, and this number is projected to nearly double every 20 years (Prince et al., 2015) in the presence of a worldwide population aging phenomenon (United Nations, Department of Economic and Social Affairs, 2015). Although research has shown that an accumulation of abnormally folded amyloid β and tau proteins in amyloid plaques and neuronal tangles is associated to cerebral neurodegeneration in AD, little is known about the cause of the disease (Scheltens et al., 2016).

AD is characterized by cognitive and non-cognitive symptoms that are related to cerebral atrophy (Nelson et al., 2012; Scheltens et al., 2016). Clinically, it presents with a progressive cognitive decline, frequently observed initially as memory dysfunction associated with atrophy in the hippocampal formation (Nobili et al., 2017). With progression of the disease people with AD (PwAD) suffer also from language, visuospatial, and executive dysfunctions, that are related to atrophy in temporal, parietal and frontal structures, typically sparing cortical motor regions until late stages of the disease (Pini et al., 2016). Recent research found that affective factors could be altered even before the appearance of cognitive symptoms (Fredericks et al., 2018).

Moreover, neuropsychiatric symptoms (NPS) are frequently observed in PwAD. NPS are related to caregiver burden and contribute to early institutionalization (Lanctôt et al., 2017). Hereby, apathy has the highest prevalence of approximately 49 %, followed by depression, aggression, anxiety, and sleep disorders, among others (Zhao et al., 2016). Apathy, as the most common NPS in AD, is characterized by emotional indifference, lack of motivation, decreased initiative, and akinesia (Lanctôt et al., 2017). NPS are best treated with nonpharmacological, individualized interventions,

such as structured social interaction or personalized music, and alternatively with antipsychotic medication (Corbett, Smith, Creese, & Ballard, 2012).

In the absence of a cure, pharmacological treatments of AD are principally delaying disease progression. Thus, supportive caregiving from family members and health care professionals contributes substantially to the quality of life of PwAD. Hereby it is crucial that caregivers receive education and training on how to deal with the progressive nature of the disease, and mobilize resources of patients, while taking care also of their own well-being (Scheltens et al., 2016).

2. Self-awareness in Alzheimer's disease

Self-awareness is a crucial component that allows us to optimally function in everyday life by recognizing our limits and thus choosing activities that are suited to our abilities (Rosen et al., 2010). In the context of neurological disease, the term anosognosia is used to describe a lack of awareness, that can range from complete unawareness of one's own condition, to milder forms of not recognizing deficits in specific areas, such as cognitive, motor, or behavioral changes, as well as impairments in social functioning or everyday life (Mograbi & Morris, 2018). Anosognosia is a common feature in AD (Morris & Hannesdottir, 2004) with a high prevalence ranging from above 30 % to above 50 % (Mograbi, Ferri, et al., 2012; Starkstein, Jorge, Mizrahi, Adrian, & Robinson, 2007).

Anosognosia has been shown to be linked to dementia severity, with declining cognitive functions being associated to worse awareness (Aalten et al., 2006; Mograbi, Ferri, et al., 2012; Starkstein, Jorge, Mizrahi, & Robinson, 2006). Moreover, higher levels of depression are related to better awareness in PwAD (Aalten et al., 2006; Mograbi & Morris, 2014), as are higher levels of daily living activities (Dourado, Laks, & Mograbi, 2016; Fischer et al., 2019; Starkstein et al., 2006). NPS have also been found to be related to awareness (Vogel, Waldorff, & Waldemar, 2015), especially apathy has been shown to be strongly related to level of awareness in PwAD (Derouesne et al., 1999; Spalletta, Girardi, Caltagirone, & Orfei,

2012; Starkstein, Petracca, Chemerinski, & Kremer, 2001). A possible explanation could be that in apathy, experiences are lacking emotional value, and thus errors and their consequences could be ignored. Emotional reactions mark instances of failed task performance with a level of personal significance, and the absence or diminution of error signals could thus be a leading cause of anosognosia in patients with neurodegenerative diseases, by preventing them to consider these events when evaluating their abilities (Rosen, 2011).

Higher levels of unawareness contribute to increased caregiver burden (Verhülsdonk, Quack, Höft, Lange-Asschenfeldt, & Supprian, 2013), enhance the risk of treatment refusal and engagement in high risk situations such as driving (Hurt et al., 2010; Patel & Prince, 2001; Starkstein et al., 2007), and moreover is associated with earlier institutionalization (Horning, Melrose, & Sultzer, 2014). Thus, it is essential to consider unawareness as a symptom in AD, since it can additionally complicate clinical management and the caregiving process.

Anosognosia is a complex, heterogeneous phenomenon, and the development in the course of the disease, as well as its neural correlates remain not fully resolved (Mondragón, Maurits, & De Deyn, 2019). However, several theoretical models have been suggested to explain its complexity, one of which is the Cognitive Awareness Model (CAM; Agnew & Morris, 1998; Morris & Hannesdottir, 2004; Morris & Mograbi, 2013). In the revised CAM (Morris & Mograbi, 2013), monitoring of performance takes place locally and centrally. Impairments in current ability are detected by Cognitive Comparator Mechanisms and compared with stored information. Information about changes in abilities is consolidated and updated throughout life in the Personal Data Base (PDB), which is supported by material from the Autobiographical Conceptual Memory System. If a mismatch between current performance and information stored in the PDB is detected, the Metacognitive Awareness System releases the information. According to the CAM, this process provides the basis for the conscious appraisal of our abilities, whereas failure in the control mechanisms gives rise to an executive form of anosognosia. On the other side, episodic memory impairments may cause failure in consolidating new

information about one self's abilities, leading to an outdated sense of self, and thus contributing to a mnemonic form of anosognosia (Morris & Mograbi, 2013).

3. Emotional processing in Alzheimer's disease

Recent decades have witnessed a growth in the scientific study of emotion. Affective processes are very complex and heterogeneous, and imply, among many others, basic emotions, such as fear, happiness, or sadness, but also higher order, social emotions, such as morality and empathy (Armony & Vuilleumier, 2013). How we react to emotional stimuli and situations, as well as how successful we regulate our emotions in such situations, has a very important influence on our daily life, interpersonal relationships, and overall well-being. Hereby, emotion and cognition cannot be considered as two separate systems; rather they are deeply interwoven (Okon-Singer, Hendler, Pessoa, & Shackman, 2015).

Experiencing positive emotions plays an important role in healthy, resilient aging. Research has shown that maintaining a high level of positive affect helps older adults to cope with age-related losses, and can also be beneficial for PwAD (Zhang, Ho, & Fung, 2015). On one side, studies found impairments in some aspects of emotional processing in PwAD, regarding expression of emotion (Henry, Rendell, Scicluna, Jackson, & Phillips, 2009) emotion decoding abilities (Klein-Koerkamp, Beaudoin, Baciu, & Hot, 2012), and recognition of facial expressions (McLellan, Johnston, Dalrymple-Alford, & Porter, 2008), as well as emotional memory enhancement (Kensinger, Anderson, Growdon, & Corkin, 2004). On the other side, it has been demonstrated that while patients did not remember the source of their emotions, their self-report was accurate and sustained over time (Guzmán-Vélez, Feinstein, & Tranel, 2014). Emotion perception deficits of PwAD could be secondary to their cognitive decline (Kemp, Després, Sellal, & Dufour, 2012). Consistent with this, recent reviews found that affective aspects of empathy are preserved, while PwAD are impaired in cognitive aspects of empathy, which is related to overall cognitive deterioration (Bartochowski, Gatla, Khoury, Al-Dahhak, & Grossberg, 2018; Christidi, Migliaccio, Santamaría-García, Santangelo, & Trojsi, 2018; Desmarais, Lanctôt, Masellis, Black,

& Herrmann, 2018). Numerous studies reported preserved emotional processing in PwAD. They seem to be able to regulate their emotions in a more automatic way, while more controlled, e.g. instructed regulation seems to be impaired (Amieva, Phillips, Della Sala, & Henry, 2004; Goodkind, Gyurak, McCarthy, Miller, & Levenson, 2010). Furthermore, PwAD did not differ in emotional reactivity from healthy older adults, indicated by similar affective ratings (Baran, Cangöz, & Ozel-Kizil, 2014; Goodkind et al., 2015; Henry et al., 2009) and physiologic responses (Chen et al., 2017; Mograbi, Brown, & Morris, 2012).

Emotional processing might also be associated with self-awareness in PwAD. Despite the established link with affective symptoms, such as apathy, and depression (see above), implicit awareness could be reflected in emotional reactions (Mograbi, Brown, Salas, & Morris, 2012). Emotional reactivity has great relevance for maintaining close interpersonal relationships and quality of life in PwAD, and also affects caregiver burden (Phillips, Scott, Henry, Mowat, & Bell, 2010; Shimokawa et al., 2001). It is typically measured as the subjective response to presented emotional stimuli. Hereby, self-report, such as ratings of emotional expressions, valence and arousal, as well as behavioral measures, such as facial expression recordings, are often used to evaluate this response. Additionally, emotional reactivity can be assessed by complementary physiologic methods, such as heart rate and skin conductance response, electromyography, or electroencephalography.

4. Electroencephalography

Electroencephalography is the most used method to study the temporal unfolding of mental operations. The electroencephalogram (EEG) is a direct measure of the electrical brain activity (Woodman, 2010), and its superior temporal resolution allows for the continuous investigation of the temporal course of mental processes in the millisecond range. Furthermore, it is a low cost, non-invasive and painless method (Luck, 2014). The electroencephalographic signal reflects the sum of synchronized post-synaptic activity from cortical pyramidal cells (Jackson & Bolger, 2014). The resulting dipoles can be measured at scalp electrodes as the subtraction of the

electrical potential at the data electrodes and the reference electrode. The signal constitutes of a mixture of frequencies that represent brain oscillations, as well as artifacts. After preprocessing the signal, a variety of aspects can be analyzed. In the present work, the interest was particularly in investigating event-related potentials (ERPs), which allow for the observation of mental processes related to an event, and how these unfold over time. ERPs are derived from the electrophysiological signal by averaging epochs in the time-domain that are time-locked to a specific event. They are characterized by their polarity, timing, scalp distribution, as well as their sensitivity to task manipulations (Woodman, 2010).

Apart from providing a continuous and immediate measure of mental processes, ERPs are also very useful to determine which processes, and which stages of these processes are influenced by an experimental task manipulation. Moreover, different components allow for a distinction between multiple related processes, while it is often not possible to discriminate between them by using only behavioral data. ERP research is also suited to study implicit processes, as well as mental processes in people whose behavioral responses are impaired because of sensory, motor or cognitive deficits (Luck, 2014). In this context, analyzing relevant ERPs in our studies can provide additional information on awareness and affective processes in PwAD.

II. Objectives

In line with the presented theoretical background, the thesis will be composed of two parts, whereof the first will focus on investigating different aspects of awareness, and the second on basic and higher order emotional abilities in AD.

The first part consists of two articles with the following objectives:

- To investigate the functional structure of awareness in AD using a statistical modeling approach;

- To examine executive and mnemonic origins of anosognosia in AD in an experimental study.

The second part includes two articles aiming at:

- Identifying impaired and preserved aspects of emotional reactivity in AD using a multi-method approach;

- Providing a review of the literature about the impact of AD on cognitive and affective components of empathy.

III. Articles section

Article 1

Fischer, A., Dourado, M. C. N., Laks, J., Landeira-Fernandez, J., Morris, R. G., & Mograbi, D. C. (2019). Modelling the impact of functionality, cognition, and mood state on awareness in people with Alzheimer's disease. *International Psychogeriatrics*, DOI: 10.1017/S1041610219001467.

Abstract

To investigate the nature of the relationship between cognitive function, mood state, and functionality in predicting awareness in a non-clinically depressed sample of participants with mild to moderate Alzheimer's disease (AD) in Brazil. People with AD (PwAD) aged 60 years or older were recruited from an outpatient unit at the Center of AD of the Federal University of Rio de Janeiro, Brazil. Measures of awareness of condition (Assessment Scale of the Psychosocial Impact of the Diagnosis of Dementia), cognitive function (Mini-Mental State Examination), mood state (Cornell Scale for Depression in Dementia), and functionality (Pfeffer Functional Activities Questionnaire) were applied to 264 people with mild to moderate AD and their caregivers. Hypotheses were tested statistically using SEM approach. Three competing models were compared. The first model, in which the influence of mood state and cognitive function on awareness was mediated by functionality, showed a very good fit to the data and a medium effect size. The competing models, in which the mediating variables were mood state and cognitive function, respectively, only showed poor model fit. Our model supports the notion that the relationship between different factors and awareness in AD is mediated by functionality and not by depressive mood state or cognitive level. The proposed direct and indirect effects on awareness are discussed, as well as the missing direct influence of mood state on awareness. The understanding of awareness in dementia is crucial and our model gives one possible explanation of its underlying structure in AD.

Key words

Awareness; anosognosia; dementia; functionality; depression

Introduction

Loss of awareness is a frequent symptom of Alzheimer's disease (AD), with patients not acknowledging reduced cognitive abilities, functional capacity, and consequences of their condition (Mograbi et al., 2012; Mograbi & Morris, 2018; Morris & Hannesdottir, 2004). This can complicate the caregiving process, with reduced awareness being associated with diminished treatment compliance (Patel & Prince, 2001), increased burden for caregivers (Verhülsdonk, Quack, Höft, Lange-Asschenfeldt, & Supprian, 2013), greater exposure to dangerous behaviors (by doing activities beyond current ability, such as driving) (Starkstein et al., 2007), and earlier institutionalization (Horning, Melrose, & Sultzer, 2014). Studies investigating loss of awareness in large samples, indicated a high prevalence, overall above 30%, and above 50% in moderate stages of the disease (Mograbi et al., 2012; Starkstein et al., 2007; Starkstein et al., 2006).

Although the contribution of specific cognitive abilities to awareness, such as memory and executive functions, has been highlighted in theoretical models (Morris & Mograbi, 2013; Rosen, 2011), the association with dementia severity and general cognitive level has been inconsistent (Ecklund-Johnson & Torres, 2005; Sunderaraman & Cosentino, 2017), with some studies finding a significant relationship (Lopez, Becker, Somsak, Dew, & DeKosky, 1994; Vasterling, Seltzer, Foss, & Vanderbrook, 1995; Wilson et al., 2015), but others not (Clare, Nelis, Martyr, Whitaker, et al., 2012; Michon, Deweer, Pillon, Agid, & Dubois, 1994; Reed, Jagust, & Coulter, 1993). This may be due to extraneous factors, such as psychosocial variables, exerting an important influence on the expression and therefore measurement of awareness (Clare, Nelis, Martyr, Roberts, et al., 2012). Nevertheless, more robust evidence from longitudinal studies or large scale studies (Aalten et al., 2006; Mograbi et al., 2012; Starkstein et al., 2006) have found a relationship with dementia severity, with more preserved cognitive functioning related to better awareness.

Another important aspect that can be strongly associated with awareness is mood state. Higher levels of depression are associated with higher levels of awareness in

people with dementia (PwD) (Aalten et al., 2006; Mograbi & Morris, 2014). This finding has been reported by many studies, although studies exist which have not found such a link (Arkin & Mahendra, 2001; Cummings, Ross, Absher, Gornbein, & Hadjiaghai, 1995). A review by Aalten et al. (2005) indicated that higher awareness in PwD may be only related to subsyndromal depression, rather than to severe depressive mood states. In summary, whilst mood state seems to be related to awareness in PwD, the characteristics of this relationship (Aalten et al., 2005), as well as the direction of causality, are yet unclear (Mograbi et al., 2012).

Activities of daily living (ADL) have also been shown to be correlated with unawareness in dementia. Dourado et al. (2016) found that functional level predicts unawareness in late onset AD but not in early onset AD. In line with the viewpoint of Starkstein et al. (2006), the authors conclude that people with early onset AD are more likely to become aware of their deficits, since their routines are still complex and they still have demanding activities, such as working or parenting. Another study investigating awareness across domains showed that unawareness of functional activity deficits was the domain with the biggest difference in discrepancy scores using the Assessment Scale of Psychosocial Impact of the Diagnosis of Dementia (ASPIDD; see method section) between people with AD (PwAD) and caregivers (Lacerda, Santos, Neto, & Dourado, 2017). It is possible that impairments in ADL prevent people from engaging in activities, which would prompt them about their deficits. Conversely, unawareness may lead to unrealistic expectations about functional ability. Accurate self-awareness is essential to choose activities according to our abilities and limitations and thus it plays a key role for optimal everyday functioning (Rosen et al., 2010).

Considering the above, although previous evidence has indicated that variables such as cognitive level, mood state and ADL may affect awareness in AD, it is still not clear how these factors interact and if their effects on awareness are direct or indirect. The study was carried out in Brazil, where the number of PwD is growing, but research in this field is still limited. The current paper explores the relationship between mood state, cognitive level, functional abilities and awareness using

structural equation modelling (SEM). A large sample of PwAD facilitated this multivariate approach in which key variables were considered together.

Methods

Sample

A consecutive series of 264 PwAD and their family caregivers were recruited from an outpatient unit at the Center of AD at the Institute of Psychiatry at the Federal University of Rio de Janeiro, Brazil. AD was diagnosed by a psychiatrist based on clinical presentation and cranial CT or MRI scans. Participants were diagnosed with probable AD according to DSM-IV-TR (APA, 2000). The study included people with mild to moderate AD, defined according to the Clinical Dementia Rating Scale (CDR; Maia et al., 2006) and the Mini-Mental State Examination (MMSE; Bertolucci et al., 1994; Folstein et al., 1975). Exclusion criteria were psychiatric or neurological disorders diagnosed according to the DSM IV-TR criteria, such as alcohol abuse, aphasia, head trauma, epilepsy, and depression. Nevertheless, subsyndromal depressive mood states were present in part of the sample and PwAD varied in mood state.

The primary family caregiver was defined as the individual who was most responsible for the care of the person with AD. Each caregiver resided in the same household as the person with AD and was able to provide detailed information about the person's life history, cognitive function and ADL. All caregivers had previously been informed about their relatives' diagnosis by a psychiatrist. The study was approved by the Ethics Committee of the Institute of Psychiatry at the Federal University of Rio de Janeiro. Informed consent was obtained directly from PwAD and their caregivers prior to the interviews.

Instruments

Awareness of Condition was assessed with the ASPIDD. The scale includes 30 items and is based on self- and caregiver reports. It was designed to evaluate awareness of

condition through the scoring of discrepant responses across different domains: awareness of cognitive functioning, health condition, instrumental and basic activities of daily living, emotional state, and social functioning and relationships. The caregiver answers the same questions as the person with AD. The score results from the discrepancy between the response of the person with AD and his or her caregiver, with one point being scored for each discrepant response (Dourado et al., 2014).

Cognitive function was tested using the MMSE as a screening tool for global cognition. It assesses orientation, registration, short-term memory, language use, comprehension, and basic motor skills. The total score ranges from 0 to 30, with lower scores indicating more impaired cognition (Bertolucci et al., 1994; Folstein et al., 1975).

The Pfeffer Functional Activities Questionnaire (PFAQ) is a caregiver-reported inventory that evaluates basic and instrumental ADL and was used to evaluate functionality in PwAD. The ratings for each item range from normal (0) to dependent (3), with a total score of 30. Higher scores indicate worse functional status (Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982).

To evaluate the mood state of PwAD, the Cornell Scale for Depression in Dementia (CSDD) was used. The scale is rated by a clinician and assesses mood symptoms, physical symptoms, circadian functions, and behavioral symptoms related to depression. Each item is rated for severity from absent (0) to severe (2). Scores above 13 indicate the presence of depression (Alexopoulos, Abrams, Young, & Shamoian, 1988; Portugal et al., 2012).

Each person in the patient-caregiver dyad was interviewed separately by a clinician, whereby PwAD completed ratings of awareness of disease (ASPIDD) and cognitive function (MMSE) and caregivers completed all demographic measurements, as well as informant ratings of functionality (PFAQ), mood state (CSDD), and awareness (ASPIDD). To interview the PwAD, the questionnaire materials were read aloud and shown simultaneously in large typeface.

SEM models and statistical analysis

Based on substantive theoretical considerations and the information from the correlation matrix of our data, we hypothesized three competing models. Our first model is based on the assumption that impairments in functionality could lead to higher unawareness by preventing PwAD from engaging in ADL (Dourado et al., 2016; Mograbi & Morris, 2014; Starkstein et al., 2006). Furthermore, there is evidence that ADL are affected negatively by depressed mood state in PwD (Baune et al., 2010; Mograbi & Morris, 2014) as well as by decreases in cognitive function (Mograbi et al., 2017). Accordingly, in the first model functionality would mediate the relationship between cognitive function, mood state and awareness of condition. Nevertheless, there is considerable evidence suggesting an association between mood state and unawareness (for a review, Mograbi & Morris, 2014) across different clinical populations (David, 2004), so it is possible that mood state has a direct relationship with unawareness and mediates the relationship of the latter with functionality and cognitive status (Model II). A final alternative hypothesis is that cognitive impairment is directly linked to unawareness (Mograbi et al., 2012; Starkstein et al., 2006), mediating the relationship between the latter, functionality and mood state (Model III). A graphic description of the three tested models can be seen in Figure 1.

PLEASE INSERT FIGURE 1 HERE.

To test our theoretical models and thus to understand better the relationships between the variables, SEM was used to explore possible causal relationships between observed independent (predictors) and dependent variables (outcomes) in our sample. Data preparation, data cleaning and descriptive statistics were conducted using IBM SPSS version 21. SEM was conducted using IBM AMOS version 24. The estimates were calculated using maximum likelihood estimation. The confidence intervals (CI) for the effects were calculated using bootstrapping. Considering our variables, models and type of analysis, the sample size was adequate for the intended analysis (SEM),

fulfilling the recommendations of MacCallum and Austin (2000) of N > 200, as well as the recommended sample-size-to-parameters ratio 20:1 (Jackson, 2003).

The goodness of fit indices were Chi-Square (χ^2), relative χ^2, standardized root mean square residual (SRMR), root mean square error of approximation (RMSEA), and the comparative fit index (CFI). The χ^2 value evaluates the magnitude of discrepancy between the sample and the fitted covariance matrices (Hu & Bentler, 1999). A good model fit would provide an insignificant result (Barrett, 2007). The relative χ^2 (χ^2/df; Wheaton et al., 1977) is not sensitive to sample size and therefore reported here. A good model fit is represented by a value smaller than 2.0 (Tabachnick & Fidell, 2007). The SRMR is the standardized square root of the difference between the residuals of the sample covariance matrix and the hypothesized covariance model. A value less than 0.05 indicates a well-fitting model (Byrne, 1998). The RMSEA is a measure of how well the model would fit the covariance matrix of the population (Byrne, 1998) and favors parsimony. A cut-off value close to 0.06 provides a very good fit (Hu & Bentler, 1999). The CFI belongs to the incremental fit indices, which compare the χ^2-value to a baseline model (McDonald & Ho, 2002). A value greater than 0.95 indicates a good fit (Hu & Bentler, 1999).

Results

Only data of participants who completed all the relevant questionnaires were included in the data set. Analyses for outliers were conducted based on the single variables involved and on the multivariate level. Cases, which differed three standard deviations (SD) or more from the mean were removed from the data set. Furthermore, multivariate outliers were analyzed using Mahalanobi's distance. Cases with a probability smaller than .001 were removed. The resulting data set contained 257 of the 264 original cases, with data of 257 PwAD (66% female) and 257 caregivers (72% female) included in the following analyses. Analyses for normality and multivariate normality showed no severe deviations, so that maximum likelihood method could be used to calculate the estimates. The data set was furthermore

checked for linearity of the relations between the variables and multicollinearity of the predicting variables, revealing linear relationships and no multicollinearity.

Sample characteristics

Table 1 shows the characteristics of PwAD and caregivers, as well as the descriptive statistics for all variables included in the models. The correlation matrix (Pearson correlations) is shown in Table 2.

PLEASE INSERT TABLE 1 HERE.

PLEASE INSERT TABLE 2 HERE.

Structural equation modelling

The analyses were based on four manifest variables, i.e. MMSE, PFAQ, CSDD, ASPIDD (see Table 1). Figure 2 shows the models with standardized coefficient estimates and p-values; goodness of fit statistics can be found in Table 3. The fit indices for the first model (Figure 2a) provided a very good fit to the data [$\chi^2 = 2.0$, $p = .368$; $\chi^2/df = 1.0$; SRMR = 0.02; RMSEA < 0.01; CFI = 1.00], whereas the fit indices for the second model (Figure 2b; [$\chi^2 = 43.53$, $p < .001$; $\chi^2/df = 21.77$; SRMR = 0.14; RMSEA = 0.29; CFI = 0.62]) and the third model (Figure 2c; [$\chi^2 = 30.69$, $p < .001$; $\chi^2/df = 15.35$; SRMR = 0.09; RMSEA = 0.24; CFI = 0.74]) suggested a poor model fit (see Table 3).

As shown in Table 3, the fit for the first model was very good and both the direct path coefficient from PFAQ to ASPIDD [$\beta = 0.39$, $p < .001$] as well as the mediated coefficients from CSDD to PFAQ [$\beta = 0.19$, $p < .001$] and from MMSE to PFAQ [$\beta = -0.41$, $p < .001$] were significant, as well as the correlation between MMSE and CSDD [$r = -0.14$, $p < .05$; Figure 2a]. Thus, total effects on awareness of condition were $\beta = 0.39$ [95% CI = 0.29 – 0.48] for functionality, $\beta = 0.08$ [95% CI = 0.03 –

0.12] for mood state, and β = -0.16 [95% CI = -0.22 – -0.10] for cognitive function. Cohen's f^2 was 0.19 for the first model and thus constitutes a medium effect (Cohen, 1988). In the second and third model, respectively, the measures for mood state (CSDD) and functionality (PFAQ), as well as for cognitive function (MMSE) and functionality (PFAQ) were exchanged to test which variable is best suited to mediate the relationship (Figure 2b and c). The better fit statistics gave support for the first model.

PLEASE INSERT FIGURE 2 HERE.

PLEASE INSERT TABLE 3 HERE.

Secondary analyses

Relationship between awareness and functionality

To test further our hypotheses, additional analyses were conducted. This included exchanging the position of PFAQ and ASPIDD in model one. In the resulting fourth path model, the ASPIDD mediated the relationship between CSDD and MMSE with the PFAQ. This model did not fit the data [$\chi^2 = 53.16$, $p < .001$; $\chi^2/df = 26.58$; SRMR = 0.13; RMSEA = 0.32; CFI = 0.53]. Path coefficients were β = 0.39 [$p < .001$] for ASPIDD to PFAQ, β = 0.2 [$p = .743$] for CSDD to ASPIDD, β = -0.22 [$p < .001$] for MMSE to ASPIDD, and r = -0.14 [$p < .05$] for the correlation between CSDD and MMSE.

Dementia Severity

To investigate the influence of dementia severity in the relationship between variables, the sample was split into mild and moderate AD using the CDR score (mild AD CDR = 1, N = 136; moderate AD CDR = 2, N = 121). Each model was then tested in both subsamples. For mild AD, the first model (see Figure 1) still had a very

good model fit [χ^2 = 0.54, p = .762; χ^2/df = 0.27; SRMR = 0.02; RMSEA < 0.01 with 90% CI = 0.00 – 0.12; CFI = 1.00] and a medium effect size [Cohen's f^2 = 0.31]. Path coefficients were β = 0.48 [p < .001] for PFAQ to ASPIDD, β = 0.15 [p = .079] for CSDD to PFAQ, β = -0.27 [p < .001] for MMSE to PFAQ, and r = -0.23 [p < .01] for the correlation between CSDD and MMSE. Total effects on awareness of condition were β = 0.48 [95% CI = 0.33 – 0.61] for functionality, β = 0.07 [95% CI = -0.003 – 0.17] for mood state, and β = -0.13 [95% CI = -0.23 – -0.05] for cognitive function. Consistent with results for the whole sample, the second [χ^2 = 33.36, p < .001; χ^2/df = 16.68; SRMR = 0.15; RMSEA = 0.34; CFI = 0.41], third [χ^2 = 34.18, p < .001; χ^2/df = 17.09; SRMR = 0.15; RMSEA = 0.35; CFI = 0.40] (see Figure 1), and fourth model [χ^2 = 12.73, p < .01; χ^2/df = 6.37; SRMR = 0.09; RMSEA < 0.20; CFI = 0.80] presented a poor model fit for the mild AD group.

Regarding the moderate AD group, the first model fit the data [χ^2 = 1.68, p = .432; χ^2/df = 0.84; SRMR = 0.03; RMSEA < 0.01 with 90% CI = 0.00 – 0.17; CFI = 1.00], whereas all but one path coefficient did not reach significance [β = 0.14, p = .122 for PFAQ to ASPIDD; β = 0.31, p < .001 for CSDD to PFAQ; β = -0.02, p = .845 for MMSE to PFAQ; r = -0.09, p = .320 for MMSE-CSDD]. Model two [χ^2 = 3.54, p = .171; χ^2/df = 1.77; SRMR = 0.05; RMSEA = 0.08; CFI = 0.87] and three [χ^2 = 4.01, p = .134; χ^2/df = 2.01; SRMR = 0.05; RMSEA = 0.09; CFI = 0.82] showed an acceptable fit to the data, but again only the relationship between CSDD and PFAQ was significant in both models [Model two: β = 0.31, p < .001 for PFAQ to CSDD; Model three: r = 0.31, p < .001 for PFAQ-CSDD]. Reflecting the preceding results, model four showed a poor model fit [χ^2 = 13.4, p < .001; χ^2/df = 6.7; SRMR = 0.10; RMSEA = 0.20; CFI = 0.00].

Discussion

The present study investigated the underlying structure of the relationship between cognitive level, mood state, ADL and awareness of condition in a sample of PwAD in a developing country using SEM. We tested three competing models in 257 PwAD. Results indicated the best fit for the first model, in which ADL have a direct, positive

effect on awareness, and mediate the relationship between cognitive level and mood state with awareness, both of which having only indirect effects on awareness of disease (see Figure 2a). A second step in the analysis revealed that the goodness of model fit, path coefficients, as well as effect size increased when the model was applied only to the mild AD group. On the contrary, for the moderate AD subsample results were less promising. This pattern suggests that the underlying structure of awareness in AD varies with progression of the disease.

To describe the relationship between ADL and awareness there are two possible hypotheses. First, impairments in ADL could prevent PwAD from engaging in activities, and thus they do not become aware of the dementia-introduced changes of functional level (Mograbi & Morris, 2014). Second, unawareness may lead to unrealistic expectations about functional ability and would prevent PwAD from the integration of the "new" functional level (Mograbi, Brown, & Morris, 2009). Our model supports the first hypothesis, in which a reduced level of ADL leads to reduced awareness. Moreover, exchanging the position of awareness and functionality in an additional model led to a poor model fit, which suggests that the level of awareness is influenced by the level of functionality, and not the contrary. This is in line with the findings of Dourado et al. (2016) as well as Starkstein et al. (2006) who also assume that a loss of functional ability leads to reduced awareness. However, awareness is a complex and multifactorial construct and most likely the underlying structure of the relationship between awareness and ADL cannot be described simply as a unidirectional influence. It is likely that other variables also affect the relationship. Apathy, for instance, leads to a loss of goal directed activity and thus reduces the activity level, which in turn may lead to unawareness (Mograbi & Morris, 2014). Moreover, it has been linked to awareness in AD (Derouesne et al., 1999; Spalletta, Girardi, Caltagirone, & Orfei, 2012; Starkstein, Petracca, Chemerinski, & Kremer, 2001). The engagement in activities exposes PwAD to their limits and deficits. If apathy prevents people from engaging in activities, then it would be difficult to know their actual abilities and limits. Future studies exploring specifically the role of apathy are needed to test this hypothesis.

General cognition or dementia severity level is typically poorly linked to awareness, with PwAD at the same severity level showing wide variations in the expression of awareness (Reed et al., 1993). Our model suggests an indirect influence of cognitive level on awareness. Preserved cognition is associated with better daily life functioning, which in turn is related to better awareness. Early studies that found an influence from general cognition or dementia severity to awareness investigated specifically loss of awareness for cognitive deficits (Lopez et al., 1994) or found that the relationship follows a trilinear instead of a linear pattern (Zanetti et al., 1999). Considering that there is no consensus in the literature about the nature of a possible relationship between awareness and general cognitive function or dementia severity in PwAD, our model proposes a compromise in which that influence is mediated by ADL. This is in line with Mograbi et al. (2017), who state that in ADLs with a higher cognitive demand even subtle changes in cognitive performance can lead to impairments. Whereas the PFAQ measures basic and instrumental ADL, the MMSE evaluates basic cognitive performance. In our sample the highest correlation was found between cognitive function (MMSE scores) and functionality (PFAQ scores). Therefore, MMSE and PFAQ share variance related to basic ADL. Based on our results, it can be suggested that instrumental ADL, measured with the PFAQ, have a direct influence on awareness, while basic cognitive functions, measured with the MMSE, only have an indirect influence on awareness via functionality. Future studies should take into account the difference of basic, instrumental and advanced ADLs in predicting awareness in dementia.

Another factor that influences levels of awareness in PwAD is mood disorder (Aalten et al., 2005; Bertrand et al., 2016; Mograbi & Morris, 2014; Starkstein, 2014). Although many studies confirmed this relationship, some studies did not find a relationship between awareness and mood or depression (Arkin & Mahendra, 2001; Cummings et al., 1995; Derouesne et al., 1999; Dourado et al., 2016; Lopez et al., 1994; Michon et al., 1994; Ott et al., 1996; Reed et al., 1993; Starkstein, 1995; Verhey et al., 1993; Zanetti et al., 1999). Our model does not support a direct relationship between mood state and awareness. One explanation could be that the majority of the PwAD in our sample showed no depressive mood states, with a

diagnosis of depression being an exclusion criterion, and a relatively low mean score of 5.4 (SD = 4.0) points on the CSDD. On the other hand, our model does suggest an indirect influence of mood state on awareness which is mediated by ADL. More specifically, higher levels of depressed mood state led to decreased functionality, which was associated with lower levels of awareness. Mograbi et al. (2017) also found depression associated with decreased ADL, although this influence was smaller compared to the influence of dementia on ADL and restricted to advanced ADL. Interestingly, the study by Dourado et al. (2016) did find that functional status predicts awareness in late onset AD, but also failed to show a direct relationship between depression and awareness, which is in line with our findings. Although the authors did not explicitly exclude PwAD with a depression diagnosis, the level of depression for late onset AD, measured also with the CSDD, was lower than in our sample (M = 4.0, SD = 3.2). Depressed mood state is typically associated with changes in behavioral activities, which affect daily cognitive functioning additionally to the effects of dementia (Mograbi & Morris, 2014).

Furthermore, mood state is a multidimensional phenomenon, comprising psychological as well as somatic and behavioral symptoms. Thus, the relationship with awareness could be mediated by the specific factors involved (Mograbi & Morris, 2014). Troisi et al. (1996) suggested that only the psychological symptoms of depression, like mood or anxiety, are related to awareness in PwAD, whereas somatic symptoms, for instance fatigue or slowness, are not related to awareness. This is in agreement with Cines et al. (2015), who suggest that studies which found a positive relationship between depressive mood state and awareness focused on the psychological and affective factors of depression, instead of somatic symptoms such as changes in sleep or appetite. The measure used to evaluate depressive mood state in this study was the total score of the CSDD, including not only mood symptoms, but also physical and behavioral symptoms of depression. Thus, a different measure, which focuses more on the psychological and affective symptoms of depression, may yield a direct influence on awareness, in addition to the indirect influence that is mediated by ADL. Similarly, the results of a study by Starkstein et al. (1996) indicated that only awareness of cognitive impairments is associated with depression,

whereas awareness of behavioral difficulties was not related to depression, which illustrates that awareness also is a multidimensional construct, that can be assessed for different domains (e.g. awareness of cognitive deficits, behavioral problems, functionality level; Aalten et al., 2005). Each domain may have unique and shared relationships with other constructs like mood state, functionality or cognitive level.

Lack of awareness in different types of dementia has been explored in the last decades, with increasing evidence for this phenomenon. Nevertheless, changes in awareness in the course of dementia, as well as its neural correlates, remain not fully resolved (Mondragón, Maurits, & De Deyn, 2019). Furthermore, large scale or longitudinal studies are still scarce in the field. Recent studies, using a large sample of PwD, only included a few PwAD, and focused on awareness of memory deficits, and how it varies between dementia forms (Lehrner et al., 2015). A longitudinal study investigating awareness in mild AD over the course of 36 months found no consistent association between cognitive decline and awareness, but showed a relationship between increasing neuropsychiatric symptoms, like for example depression and apathy, and reduced awareness over time (Vogel, Waldorff, & Waldemar, 2015). The authors also conclude that awareness is a complex construct, and that its longitudinal course is only little explored. Thus, it is crucial to define influencing and mediating variables using statistical approaches that consider the interconnectedness between involved variables to predict individual trajectories of awareness in PwAD, adjusting home care and interventions accordingly. To the best of our knowledge, our study is the first using a modeling approach in a large sample of PwAD and their caregivers to consider the influence of key variables on awareness together. This way it is an advance in providing deeper insight into the functional structure of awareness in AD, and thus aiming at a better understanding of how awareness can be influenced in PwAD. Current findings on the relationship between awareness, functionality, cognitive level and mood state may ultimately contribute to improve clinical care and quality of life for PwAD and their caregivers.

Some limitations of the study must be considered. We did not assess mood constructs other than depression, like apathy or anxiety. Especially apathy could be interesting to include in the model, since it has been shown to be strongly related to level of

awareness in PwAD (Derouesne et al., 1999; Spalletta et al., 2012; Starkstein et al., 2001). Another point is that we only included global measures of awareness without considering awareness in different domains, such as awareness of memory performance or awareness of functionality. In future studies it could be interesting to model the influence of cognitive level, ADLs, and mood state on different domains or objects of awareness. Indeed, a more complex model, including different domains of awareness, as well as of ADLs, and further variables, such as apathy and anxiety, would be desirable to obtain a better understanding of the structure underlying awareness in dementia. Another point to mention is the influence of self- vs. caregiver reports. Our study assessed mood state and functionality of PwAD through caregiver reports. This could have an influence on the relationship of the variables in the models, with caregiver burden, as well as their mood state, potentially influencing the perception of mood state and functionality of the person with AD. The influence of caregiver variables should therefore be controlled in future studies. Finally, the study was conducted in an outpatient unit from a university hospital, which may have introduced sampling biases. For instance, participants that did not complete the session typically preferred to withdraw/not take part in the study due to personal constraints, such as limited time or difficulties making travel arrangements. Although there are no data available for them, it is possible these were patients who had slightly less structured social support or lived further away from the hospital. Future studies would benefit from community based samples to explore unawareness in dementia.

Our study showed that the relationship between different factors and awareness is mediated by functionality and not by depressive mood state or cognitive level. In a population of functionally and cognitively impaired PwAD without a diagnosis of depression, the model that best fit the data supported an indirect effect of both, cognitive function and mood state on awareness of condition, mediated by functionality, which itself showed a moderate relationship with awareness. Awareness is linked to treatment compliance, caregiver burden, dangerous behaviors and earlier institutionalization. On the other side, preserved awareness can lead to depressive mood states. Hence, it is important to know the factors that influence awareness of changes and difficulties in PwD, so that they can be considered for

diagnosis and for the development of person-centered interventions that improve awareness without putting patients at higher risk for mood disorders. The proposed model brings us one step further towards an understanding of the underlying structure of awareness in PwD. Thus, it can also serve the development of more detailed models, including for example other mood constructs like apathy and different domains of awareness, to explain the structure and causality of awareness in PwD.

References

Aalten, P., Van Valen, E., Clare, L., Kenny, G., & Verhey, F. (2005). Awareness in dementia: A review of clinical correlates. *Aging & Mental Health*, *9*(5), 414–422. https://doi.org/10.1080/13607860500143075

Aalten, P., Van Valen, E., De Vugt, M. E., Lousberg, R., Jolles, J., & Verhey, F. R. J. (2006). Awareness and behavioral problems in dementia patients: A prospective study. *International Psychogeriatrics*, *18*(1), 3–17. https://doi.org/10.1017/S1041610205002772

Alexopoulos, G. S., Abrams, R. C., Young, R. C., & Shamoian, C. A. (1988). Cornell Scale for Depression in Dementia. *Biological Psychiatry*, *23*(3), 271–284. https://doi.org/10.1016/0006-3223(88)90038-8

Arkin, S., & Mahendra, N. (2001). Insight in Alzheimer's patients: Results of a longitudinal study using three assessment methods. *American Journal of Alzheimer's Disease and Other Dementias*, *16*(4), 211–224. https://doi.org/10.1177/153331750101600401

Barrett, P. (2007). Structural equation modelling: Adjudging model fit. *Personality and Individual Differences*, *42*(5), 815–824. https://doi.org/10.1016/j.paid.2006.09.018

Baune, B. T., Miller, R., McAfoose, J., Johnson, M., Quirk, F., & Mitchell, D. (2010). The role of cognitive impairment in general functioning in major depression. *Psychiatry Research*, *176*(2–3), 183–189. https://doi.org/10.1016/j.psychres.2008.12.001

Bertolucci, P. H. F., Brucki, S. M. D., Campacci, S. R., & Juliano, Y. (1994). O Mini-Exame do Estado Mental em uma população geral: impacto da escolaridade. *Arquivos de Neuro-Psiquiatria*, *52*(1), 01–07. https://doi.org/10.1590/s0004-282x1994000100001

Bertrand, E., Dourado, M. C. N., Laks, J., Morris, R. G., Landeira-fernandez, J., & Mograbi, D. C. (2016). Mood-congruent recollection and anosognosia in Alzheimer ' s disease. *Cortex*, *84*, 55–62.

https://doi.org/10.1016/j.cortex.2016.09.001

Byrne, B. M. (1998). *Structural equation modeling with LISREL, PRELIS, and SIMPLIS : basic concepts, applications, and programming*. *Multivariate applications book series* (2nd ed.). Mahwah: Routledge.

Cines, S., Farrell, M., Steffener, J., Sullo, L., Huey, E., Karlawish, J., & Cosentino, S. (2015). Examining the Pathways between Self-Awareness and Well-Being in Mild to Moderate Alzheimer Disease. *American Journal of Geriatric Psychiatry*, *23*(12), 1297–1306. https://doi.org/10.1016/j.jagp.2015.05.005

Clare, L., Nelis, S. M., Martyr, A., Roberts, J., Whitaker, C. J., Markova, I. S., … Morris, R. G. (2012). The influence of psychological, social and contextual factors on the expression and measurement of awareness in early-stage dementia: Testing a biopsychosocial model. *International Journal of Geriatric Psychiatry*, *27*(2), 167–177. https://doi.org/10.1002/gps.2705

Clare, L., Nelis, S. M., Martyr, A., Whitaker, C. J., Marková, I. S., Roth, I., … Morris, R. G. (2012). Longitudinal trajectories of awareness in early-stage dementia. *Alzheimer Disease and Associated Disorders*, *26*(2), 140–147. https://doi.org/10.1097/WAD.0b013e31822c55c4

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum Associates.

Cummings, J. L., Ross, W., Absher, J., Gornbein, J., & Hadjiaghai, L. (1995). Depressive symptoms in Alzheimer disease: Assessment and determinants. *Alzheimer Disease and Associated Disorders*, *9*(2), 87–93. https://doi.org/10.1097/00002093-199509020-00005

David, A. S. (2004). The clinical importance of insight: an overview. In X. F. E. Amador & A. S. E. David (Eds.), *Insight and Psychosis: Awareness of Illness in Schizophrenia and Related Disorders* (pp. 359–392). New York: Oxford University Press.

Derouesne, C., Thibault, S., Lagha-Pierucci, S., Baudouin-Madec, V., Ancri, D., & Lacomblez, L. (1999). Decreased awareness of cognitive deficits in patients with

mild dementia of the Alzheimer type. *International Journal of Geriatric Psychiatry*, *14*(12), 1019–1030. https://doi.org/10.1002/(SICI)1099-1166(199912)14:12<1019::AID-GPS61>3.0.CO;2-F

Dourado, M. C. N., Laks, J., & Mograbi, D. (2016). Functional Status Predicts Awareness in Late-Onset but not in Early-Onset Alzheimer Disease. *Journal of Geriatric Psychiatry and Neurology*, *29*(6), 313–319. https://doi.org/10.1177/0891988716640372

Dourado, M. C. N., Mograbi, D. C., Santos, R. L., Fernanda, M., Sousa, B., Sousa, M. F. B., … Laks, J. (2014). Awareness of disease in dementia: factor structure of the assessment scale of psychosocial impact of the diagnosis of dementia. *Journal of Alzheimer's Disease*, *41*, 947–956. https://doi.org/10.3233/JAD-140183

Ecklund-Johnson, E., & Torres, I. (2005). Unawareness of deficits in Alzheimer's disease and other dementias: Operational definitions and empirical findings. *Neuropsychology Review*, *15*(3), 147–166. https://doi.org/10.1007/s11065-005-9026-7

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189–198.

Horning, S. M., Melrose, R., & Sultzer, D. (2014). Insight in Alzheimer's disease and its relation to psychiatric and behavioral disturbances. *International Journal of Geriatric Psychiatry*, *29*(1), 77–84. https://doi.org/10.1002/gps.3972

Hu, L. T., & Bentler, P. M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling*, *6*(1), 1–55. https://doi.org/10.1080/10705519909540118

Jackson, D. L. (2003). Revisiting sample size and number of parameter estimates: Some support for the N:q hypothesis. *Structural Equation Modeling*, *10*(1), 128–141. https://doi.org/10.1207/S15328007SEM1001_6

Lacerda, I. B., Santos, R. L., Neto, J. P. S., & Dourado, M. C. N. (2017). Factors

Related to Different Objects of Awareness in Alzheimer Disease. *Alzheimer Disease and Associated Disorders*, *31*(4), 335–342. https://doi.org/10.1097/WAD.0000000000000210

Lehrner, J., Kogler, S., Lamm, C., Moser, D., Klug, S., Pusswald, G., … Auff, E. (2015). Awareness of memory deficits in subjective cognitive decline, mild cognitive impairment, Alzheimer's disease and Parkinson's disease. *International Psychogeriatrics*, *27*(3), 357–366. https://doi.org/10.1017/S1041610214002245

Lopez, O. L., Becker, J. T., Somsak, D., Dew, M. A., & DeKosky, S. T. (1994). Awareness of cognitive deficits and anosognosia in probable alzheimer's disease. *European Neurology*, *34*(5), 277–282. https://doi.org/10.1159/000117056

MacCallum, R. C., & Austin, J. T. (2000). Applications of Structural Equation Modeling in Psychological Research. *Annual Review of Psychology*, *51*(1), 201–226. https://doi.org/10.1146/annurev.psych.51.1.201

Maia, A. L. G., Godinho, C., Ferreira, E. D., Almeida, V., Schuh, A., Kaye, J., & Chaves, M. L. F. (2006). Application of the Brazilian version of the CDR scale in samples of dementia patients. *Arquivos de Neuropsiquiatria*, *64*, 485–489. https://doi.org/10.1590/S0004-282X2006000300025

McDonald, R. P., & Ho, M. H. R. (2002). Principles and practice in reporting structural equation analyses. *Psychological Methods*, *7*(1), 64–82. https://doi.org/10.1037//1082-989X.7.1.64

Michon, A., Deweer, B., Pillon, B., Agid, Y., & Dubois, B. (1994). Relation of anosognosia to frontal lobe dysfunction in Alzheimer's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *57*, 805–809. https://doi.org/10.1136/jnnp.57.7.805

Mograbi, D. C., Brown, R. G., & Morris, R. G. (2009). Anosognosia in Alzheimer's disease - The petrified self. *Consciousness and Cognition*, *18*(4), 989–1003. https://doi.org/10.1016/j.concog.2009.07.005

Mograbi, D. C., Ferri, C. P., Sosa, A. L., Stewart, R., Laks, J., Brown, R., & Morris, R. G. (2012). Unawareness of memory impairment in dementia: A population-based study. *International Psychogeriatrics*, *24*(6), 931–939. https://doi.org/10.1017/S1041610211002730

Mograbi, D. C., & Morris, R. G. (2014). On the relation among mood, apathy, and anosognosia in Alzheimer's disease. *Journal of the International Neuropsychological Society*, *20*(1), 2–7. https://doi.org/10.1017/S1355617713001276

Mograbi, D. C., & Morris, R. G. (2018). Anosognosia. *Cortex*, *103*, 385–386. https://doi.org/10.1016/j.cortex.2018.04.001

Mograbi, D. C., Morris, R. G., Fichman, H. C., Faria, C. A., Sanchez, M. A., Ribeiro, P. C. C. C., & Lourenço, R. A. (2017). The impact of dementia, depression and awareness on activities of daily living in a sample from a middle-income country. *International Journal of Geriatric Psychiatry*, *33*(6), 807–813. https://doi.org/10.1002/gps.4765

Mondragón, J. D., Maurits, N. M., & De Deyn, P. P. (2019). Functional Neural Correlates of Anosognosia in Mild Cognitive Impairment and Alzheimer's Disease: a Systematic Review. *Neuropsychology Review*, 139–165. https://doi.org/10.1007/s11065-019-09410-x

Morris, R. G., & Hannesdottir, K. (2004). Loss of "awareness" in Alzheimer's Disease. In R. G. Morris & J. T. Becker (Eds.), *The Cognitive Neuropsychology of Alzheimer's Disease* (pp. 275–296). Oxford: Oxford University Press.

Morris, R. G., & Mograbi, D. C. (2013). Anosognosia, autobiographical memory and self knowledge in Alzheimer's disease. *Cortex*, *49*(6), 1553–1565. https://doi.org/10.1016/j.cortex.2012.09.006

Ott, B. R., Lafleche, G., Whelihan, W. M., Buongiorno, G. W., Albert, M. S., & Fogel, B. S. (1996). Impaired awareness of deficits in Alzheimer disease. *Alzheimer Disease and Associated Disorders*, *10*(2), 68–76. https://doi.org/10.1097/00002093-199601020-00003

Patel, V., & Prince, M. (2001). Ageing and mental health in a developing country: who cares? Qualitative studies from Goa, India. *Psychological Medicine*, *31*(1), 29–38. https://doi.org/10.1017/S0033291799003098

Pfeffer, R. I., Kurosaki, T. T., Harrah, C. H., Chance, J. M., & Filos, S. (1982). Measurement of functional activities in older adults in the community. *Journal of Gerontology*, *37*(3), 323–329. https://doi.org/10.1093/geronj/ 37.3.323

Portugal, M. G., Coutinho, E. S. F., Almeida, C., Barca, M. L., Knapskog, A. B., Engedal, K., & Laks, J. (2012). Validation of montgomery-Åsberg rating scale and cornell scale for depression in dementia in Brazilian elderly patients. *International Psychogeriatrics*, *24*(8), 1291–1298. https://doi.org/10.1017/S1041610211002250

Reed, B. R., Jagust, W. J., & Coulter, L. (1993). Anosognosia in Alzheimer's disease: Relationships to depression, cognitive function, and cerebral perfusion. *Journal of Clinical and Experimental Neuropsychology*, *15*, 231–244. https://doi.org/10.1080/01688639308402560

Rosen, H. J. (2011). Anosognosia in neurodegenerative disease. *Neurocase*, *17*(173), 231–241. https://doi.org/10.1080/13554794.2010.522588

Rosen, H. J., Alcantar, O., Rothlind, J., Sturm, V., Kramer, J. H., Weiner, M., & Miller, B. L. (2010). Neuroanatomical correlates of cognitive self-appraisal in neurodegenerative disease. *NeuroImage*, *49*(4), 3358–3364. https://doi.org/10.1016/j.neuroimage.2009.11.041

Spalletta, G., Girardi, P., Caltagirone, C., & Orfei, M. D. (2012). Anosognosia and neuropsychiatric symptoms and disorders in mild Alzheimer disease and mild cognitive impairment. *Journal of Alzheimer's Disease*, *29*(4), 761–772. https://doi.org/10.3233/JAD-2012-111886

Starkstein, S. E. (2014). Anosognosia in Alzheimer's disease: Diagnosis, frequency, mechanism and clinical correlates. *Cortex*, *61*, 64–73. https://doi.org/10.1016/j.cortex.2014.07.019

Starkstein, S. E., Jorge, R., Mizrahi, R., Adrian, J., & Robinson, R. G. (2007). Insight

and danger in Alzheimer's disease. *European Journal of Neurology*, *14*(4), 455–460. https://doi.org/10.1111/j.1468-1331.2007.01745.x

Starkstein, S. E., Jorge, R., Mizrahi, R., & Robinson, R. G. (2006). A diagnostic formulation for anosognosia in Alzheimer's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *77*(6), 719–725. https://doi.org/10.1136/jnnp.2005.085373

Starkstein, S. E., Petracca, G., Chemerinski, E., & Kremer, J. (2001). Syndromic validity of apathy in Alzheimer's disease. *American Journal of Psychiatry*, *158*(6), 872–877. https://doi.org/10.1176/appi.ajp.158.6.872

Starkstein, S. E., Sabe, L., Chemerinski, E., Jason, L., & Leiguarda, R. (1996). Two domains of anosognosia in Alzheimer's disease. *Journal of Neurology Neurosurgery and Psychiatry*, *61*(5), 485–490. https://doi.org/10.1136/jnnp.61.5.485

Starkstein, S. E., Vázquez, S., Migliorelli, R., Tesón, A., Sabe, L., & Leiguarda, R. (1995). A single-photon emission computed tomographic study of anosognosia in Alzheimer's disease. *Archives of Neurology*, *52*, 415–420. https://doi.org/10.1001/archneur.1995.00540280105024

Sunderaraman, P., & Cosentino, S. (2017). Integrating the Constructs of Anosognosia and Metacognition: a Review of Recent Findings in Dementia. *Current Neurology and Neuroscience Reports*, *17*(3). https://doi.org/10.1007/s11910-017-0734-1

Tabachnick, B. G., Fidell, L. S., G. Tabachnick, B., & S. Fidell, L. (2007). *Using Multivariate Statistics* (5th ed.). New Jersey: Pearson Education.

Troisi, A., Pasini, A., Gori, G., Sorbi, T., Baroni, A., & Ciani, N. (1996). Clinical predictors of somatic and psychological symptoms of depression in Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *11*, 23–27. https://doi.org/10.1002/(SICI)1099-1166(199601)11:1<23::AID-GPS264>3.0.CO;2-4

Vasterling, J. J., Seltzer, B., Foss, J. W., & Vanderbrook, V. (1995). Unawareness of

deficit in alzheimer's disease: Domain-specific differences and disease correlates. *Neuropsychiatry, Neuropsychology and Behavioral Neurology*, *8*(1), 26–32.

Verhey, F. R. J., Rozendaal, N., Ponds, R. W. H. M., & Jolles, J. (1993). Dementia, awareness and depression. *International Journal of Geriatric Psychiatry*, *8*, 851–856. https://doi.org/10.1002/gps.930081008

Verhülsdonk, S., Quack, R., Höft, B., Lange-Asschenfeldt, C., & Supprian, T. (2013). Anosognosia and depression in patients with Alzheimer's dementia. *Archives of Gerontology and Geriatrics*, *57*(3), 282–287. https://doi.org/10.1016/j.archger.2013.03.012

Vogel, A., Waldorff, F. B., & Waldemar, G. (2015). Longitudinal changes in awareness over 36 months in patients with mild Alzheimer's disease. *International Psychogeriatrics*, *27*(1), 95–102. https://doi.org/10.1017/S1041610214001562

Wheaton, B., Muthen, B., Alwin, D. F., & Summers, G. (1977). Assessing Reliability and Stability in Panel Models. *Sociological Methodology*, *8*(1), 84–136. https://doi.org/10.2307/270754

Wilson, R. S., Boyle, P. A., Yu, L., Barnes, L. L., Sytsma, J., Buchman, A. S., … Schneider, J. A. (2015). Temporal course and pathologic basis of unawareness of memory loss in dementia. *Neurology*, *85*(11), 984–991. https://doi.org/10.1212/WNL.0000000000001935

Zanetti, O., Vallotti, B., Frisoni, G. B., Geroldi, C., Bianchetti, a, Pasqualetti, P., & Trabucchi, M. (1999). Insight in dementia: when does it occur? Evidence for a nonlinear relationship between insight and cognitive status. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *54*(2), P100–P106. https://doi.org/10.1093/geronb/54B.2.P100

Tables

Table 1 – Clinical and demographical characteristics of PwAD and their caregivers (n = 257).

	Mean (SD) / Min - Max
PwAD	
Age‡	76.5 (7.2) / 60 - 93
Gender†	169 (66%) / 88 (34%)
Time since onset‡	4.3 (2.4) / 1 - 14
Education‡	7.7 (3.6) / 0 - 15
PFAQ	17.0 (8.6) / 0 - 30
CSDD	5.4 (4.0) / 0 - 18
ASPIDD	7.8 (5.5) / 0 - 24
MMSE	19.7 (3.9) / 13 - 26
Caregivers	
Age‡	58.8 (14.3) / 18 - 93
Gender†	184 (72%) / 73 (28%)
Education‡	11.0 (3.3) / 0 - 15

† Female/male; ‡numbers in years. M = mean; SD = standard deviation; AD = Alzheimer's disease; PFAQ = Pfeffer Functional Activities Questionnaire; CSDD = Cornell Scale for Depression in Dementia; ASPIDD = Assessment Scale of the Psychosocial Impact of the Diagnosis of Dementia; MMSE = Mini-Mental State Examination.

Table 2 – Correlation matrix.

	MMSE	PFAQ	CSDD	ASPIDD
MMSE		-.43**	-.14*	-.23**
PFAQ			.25**	.39**
CSDD				.05

PFAQ = Pfeffer Functional Activities Questionnaire; CSDD = Cornell Scale for Depression in Dementia; ASPIDD = Assessment Scale of the Psychosocial Impact of the Diagnosis of Dementia; MMSE = Mini-Mental State Examination. * p < .05, **p < .01.

Table 3 – Goodness of fit and χ^2 differences between models.

Model	χ^2 (p)	χ^2/df	SRMR	RMSEA (90% CI)	CFI
Model I	2.0 (.368)	1.0	0.02	0.00 (0.00 – 0.12)	1.00
Model II	43.53 (< .001)	21.77	0.14	0.29 (0.22 – 0.36)	0.62
Model III	30.69 (< .001)	15.35	0.09	0.24 (0.17 – 0.31)	0.74

SRMR = standardized root mean square residual; RMSEA = root mean square error of approximation; CFI = comparative fit index.

Figures

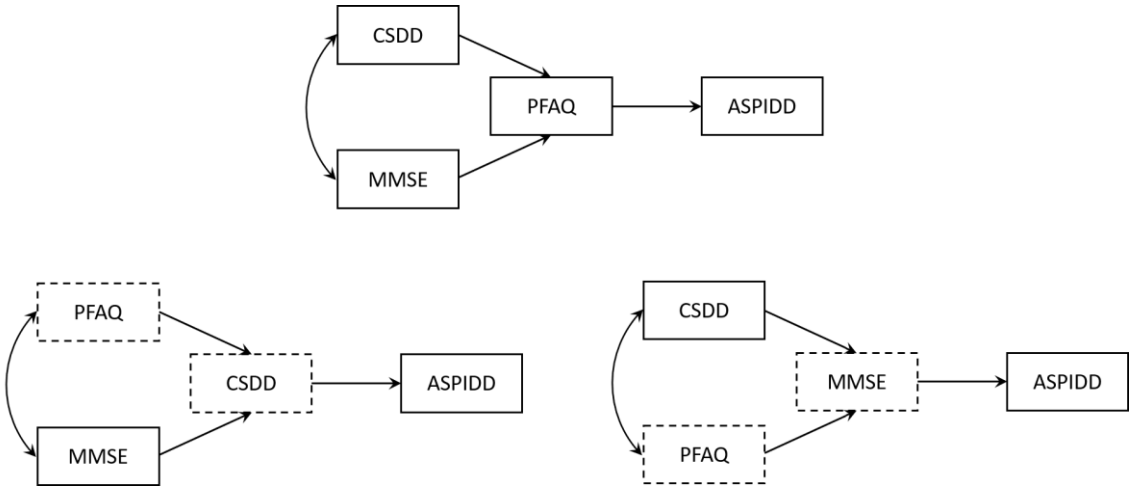

Figure 1 – Schematic representation of Models I, II and III. *Top*: Model I. The influence of mood state (CSDD) and cognitive function (MMSE) on awareness of disease (ASPIDD) is mediated by functionality (PFAQ). *Bottom left*: Model II. The variables PFAQ and CSDD are switched (indicated by the dashed boxes). Here, mood state is the mediating variable. *Bottom right*: Model III. The variables PFAQ and MMSE are switched (indicated by the dashed boxes). Here, cognitive function is the mediating variable. CSDD = Cornell Scale for Depression in Dementia; ASPIDD = Assessment Scale of the Psychosocial Impact of the Diagnosis of Dementia; MMSE = Mini-Mental State Examination; PFAQ = Pfeffer Functional Activities Questionnaire.

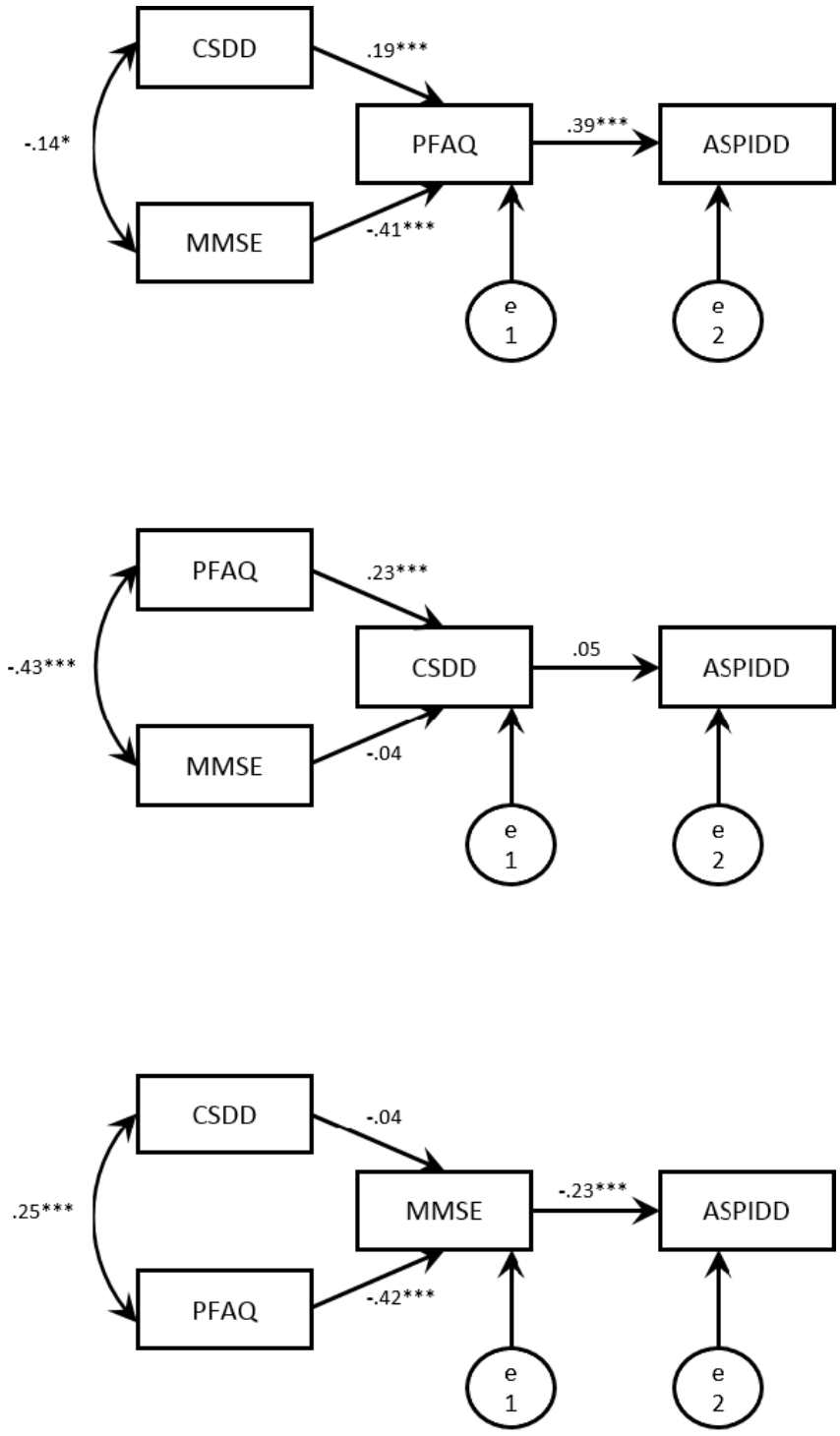

Figure 2 – Model I, II and III with standardized coefficient estimates. *Top*: Model I, the influence of mood state and cognitive function on awareness is mediated by functionality. *Middle*: Model II, the influence of functionality and cognitive function on awareness is mediated by mood state. *Bottom*: Model III, the influence of functionality and mood state on awareness is mediated by cognitive function. CSDD = Cornell Scale for Depression in Dementia; ASPIDD = Assessment Scale of the Psychosocial Impact of the Diagnosis of Dementia; MMSE = Mini-Mental State Examination; PFAQ = Pfeffer Functional Activities Questionnaire. *p < .05, ***p < .001.

Article 2

Fischer, A., Pariz, C., Lobo, I., Deslandes, A. C., Landeira-Fernandez, J., & Mograbi, D. C. Preserved online response to feedback but impaired consolidation of information about performance in Alzheimer's Disease. (In preparation)

Abstract

Anosognosia is a frequent symptom in Alzheimer's disease (AD). It is a heterogeneous phenomenon, and its causes are not yet fully understood. We aimed at investigating mnemonic and executive origins of anosognosia in AD, as proposed by the Cognitive Awareness Model. A reaction time task was used to examine awareness of task performance in people with AD (PwAD; n = 12), healthy older (n = 16) and young adults (n = 17). Self-evaluation of task performance after ten, 100, and 500 trials served as measures of online, medium-, and long-term performance monitoring, respectively. Furthermore, neurophysiological responses to positive and negative performance feedback were recorded, and two components related to feedback processing were analyzed: the feedback-related negativity (FRN), and the P300. Our findings demonstrated that PwAD were impaired in medium- and long-term performance monitoring, whereas online monitoring was intact. This was supported by ERP results. The FRN amplitude was sensitive to feedback valence, showing enhanced amplitudes after negative feedback in all groups. PwAD and healthy older adults had strongly decreased P300 amplitudes compared to young adults, which could indicate impairments in attentional and memory processes related to performance monitoring. Our study points to a critical role of mnemonic rather than executive factors in the generation of anosognosia in PwAD. Consolidation of information seems to be a key factor in the generation of anosognosia and should thus be strengthened in neuropsychological therapy.

Key words

Anosognosia; EEG; FRN; dementia, metacognition

Introduction

Anosognosia is a term used in the context of neurological disease describing lack of awareness of having a condition (Mograbi & Morris, 2018). It can range from total lack of awareness of having a disease to limited knowledge of specific cognitive, motor or behavioral alterations, as well as impairments in activities of daily living or interpersonal relationships (Mograbi & Morris, 2018). In dementia it has a high prevalence (Mograbi, Ferri, et al., 2012; Starkstein, Jorge, Mizrahi, Adrian, & Robinson, 2007; Starkstein, Jorge, Mizrahi, & Robinson, 2006) and has been associated with diminished treatment compliance (Patel & Prince, 2001), increased burden for caregivers (Verhülsdonk, Quack, Höft, Lange-Asschenfeldt, & Supprian, 2013), greater exposure to dangerous behaviors (Starkstein et al., 2007), and earlier institutionalization (Horning, Melrose, & Sultzer, 2014). Thus, anosognosia is an important factor that can additionally complicate clinical management and caregiving.

To account for the complexity of anosognosia, several theoretical models have been proposed. The Cognitive Awareness Model (CAM; Agnew & Morris, 1998; Morris & Hannesdottir, 2004; Morris & Mograbi, 2013) attempts to explain its heterogeneity based on multi-level cognitive abilities, including monitoring and comparator mechanisms. The revised CAM (Morris & Mograbi, 2013) suggests that sensory and motor information about performance is monitored both, locally and centrally. Central Cognitive Comparator Mechanisms (CCMs) detect alterations in current abilities and compare these with stored information. The Personal Data Base (PDB) contains information about the self, which develops and updates throughout life, being supported by material from the Autobiographical Conceptual Memory System. If the comparator mechanisms detect a mismatch between information stored in the PDB and current performance, this information is released via the Metacognitive Awareness System, thus providing the basis for conscious appraisal of ability (for a more detailed explanation of the model see (Morris & Mograbi, 2013).

According to the CAM, anosognosia in dementia can be executive or mnemonic in nature, which relates, respectively, to a principal failure in central CCMs or to a

primary deficit in updating personal knowledge in the PDB. Regarding the latter, in people with Alzheimer's disease (PwAD) this could be due to the characteristic memory impairments (Mograbi, Brown, & Morris, 2009). Existing evidence supports this notion. For example, some studies could show that online monitoring of PwAD's own performance was largely intact, while they did not succeed in maintaining this realistic evaluation of task performance when asked after a one-hour delay (Stewart, McGeown, Shanks, & Venneri, 2010), and even after an extended memory training (Silva, Pinho, Macedo, Souchay, & Moulin, 2017).

Event-related potentials (ERPs) associated to performance monitoring provide a possibility to investigate underlying alterations in the neurophysiological processes on a trial by trial basis and could help to better understand mnemonic and executive anosognosia in Alzheimer's disease (AD). The feedback related negativity (FRN; Miltner, Braun, & Coles, 1997) is a negative component that occurs approximately 200 - 300 ms after a feedback stimulus. It is part of a performance monitoring system and is involved in external feedback processing. Thus, the FRN provides a measure to investigate performance monitoring using externally provided feedback information, whereby it can be elicited by purely perceptional tasks (Potts, Martin, Kamp, & Donchin, 2011). This way it is possible to examine whether PwAD are able to monitor their performance in a continuous fashion by processing externally provided information on their performance.

Another component that has been used to study feedback is the P300, which can be observed following the FRN (Di Gregorio, Ernst, & Steinhauser, 2019; Johnson & Donchin, 1978; Ludowicy, Czernochowski, Weis, Haese, & Lachmann, 2019; Qiu, Casey, & Diamond, 2019). It peaks approximately 300 - 600 ms after stimulus onset in predominantly parietal areas (Sutton, Braren, Zubin, & John, 1965), and could represent a more controlled, top-down evaluation of the outcome (Nitta et al., 2017). It is thought to reflect information processing associated with attention and memory operations, that can be used to modify future behavior (Polich, 2007, 2012). Very few studies so far investigated components in PwAD that are related to performance monitoring. One study investigating feedback-related ERPs found enhanced

amplitudes after negative and positive feedback in PwAD in comparison to healthy age-matched controls, but no difference to young controls (Nitta et al., 2017).

In addition to valence of feedback, other affective factors may play a crucial role in executive anosognosia. This idea is consistent with findings indicating a relationship between anosognosia and apathy in neurodegenerative disease (Mograbi & Morris, 2014), with higher levels of apathy being related to poorer awareness in PwAD and mild cognitive impairment (MCI; Jacus, 2017). In apathy, experiences lack emotional value, and thus errors and their consequences could be ignored. Emotional reactions mark instances of failed task performance with a level of personal significance, and the absence or diminution of error signals could thus be a leading cause of anosognosia in patients with neurodegenerative diseases, by preventing them to consider these events when evaluating their abilities (Rosen, 2011).

Considering the above, in the current study a multi-method approach was used to test assumptions of the CAM about mnemonic and executive anosognosia, as well as the influence of apathy on performance monitoring. To be able to distinguish between effects caused by age and AD, performance monitoring was investigated in PwAD, as well as in healthy older and young participants, hereby combining self-reports, ERPs, and questionnaire measures. We hypothesized that PwAD over-estimate their performance after longer time intervals, with reduced group differences when evaluating their performance after a short time interval, indicating anosognosia for task performance. Moreover, we aimed to investigate feedback-related ERPs as a possibility to better explain changes in performance monitoring in PwAD. Executive impairments that lead to anosognosia of task performance in PwAD should be related to differences in the FRN, whereby differences in the P300 component between groups could indicate deficits in attentional and memory processes related to performance monitoring. If affective factors play a key role in the generation of anosognosia in AD, we expect an association between a measure of apathy, performance monitoring indices and ERPs. To the best of our knowledge, these questions have not been addressed so far in a single study.

Methods

Participants

A total of 51 participants were recruited and screened for the study. 14 PwAD were recruited from an outpatient unit at the Alzheimer's Disease Centre at the Institute of Psychiatry at the Federal University of Rio de Janeiro (CDA-IPUB-UFRJ). PwAD were asked to participate with a caregiver who could act as informant. AD was diagnosed by a psychiatrist according to the DSM-IV-TR (American Psychiatric Association, 2000). Therapy and medication of PwAD was done at the outpatient unit. A total of 18 healthy older adults were recruited in the vicinity of the universities and the clinic. A total of 19 young participants were recruited amongst college students from the Federal University and the Pontifical Catholic University of Rio de Janeiro.

Exclusion criteria were psychiatric or neurological diseases diagnosed according to the ICD-10 (World Health Organization, 2004) criteria, e.g. major depressive disorder and anxiety disorders, excluding also cases with mixed or vascular dementia in the PwAD group; head trauma with loss of consciousness for more than one hour, as well as abuse of alcohol or other drugs, except tobacco. Moreover, participants with uncorrected hearing loss or visual impairment were not included in the study. All participants must have had a minimum of four years of formal education. The age range for healthy young volunteers was 18 to 30 years, and a minimum of 60 years for older adults and PwAD. All participants underwent neuropsychological assessment, which was carried out by a psychologist (see below).

A screening for depression was conducted to exclude participants exceeding a cut-off score. Level of depression was measured with the Beck's Depression Inventory II (BDI II; Beck, Steer, & Brown, 1996; Gomes-Oliveira, Gorenstein, Neto, Andrade, & Wang, 2012) for young adults. According to the authors, a cut-off score of more than 14 points is indicative of mild depression and was thus used as exclusion criterion. The Geriatric Depression Scale (GDS; Almeida & Almeida, 1999a; Sheikh & Yesavage, 1986) was used to screen PwAD and healthy older participants for depression. A cut-off score above seven points was used as exclusion criterion

(Almeida & Almeida, 1999b). Two participants in each group were excluded. The final sample consisted of 17 young adults, 16 older adults, and twelve PwAD. Characteristics of participants can be seen in Table 1. All participants provided written informed consent before the experiment, with caregivers validating consent in the case of patients. The study was conducted under ethical approval of the ethics committee of the IPUB-UFRJ (CAAE: 63181816.8.0000.5263).

PLEASE INSERT TABLE 1 HERE.

Instruments

Cognition

The Addenbrooke's Cognitive Examination Revised (ACE-r; Carvalho & Caramelli, 2007; Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006) was used to assess cognitive impairment in PwAD, whereas the Mini-Mental State Examination (MMSE; Bertolucci, Brucki, Campacci, & Juliano, 1994; Folstein, Folstein, & McHugh, 1975) was used as a control measure for healthy participants. Since the MMSE is part of the ACE-r, it was possible to compare the groups on the MMSE score. The ACE-r measures orientation, attention, memory, verbal fluency, language, and visuospatial abilities with a maximum score of 100 and a cut-off score of 83 points for the presence of dementia. The MMSE is a screening tool for global cognition assessing orientation, registration, short-term memory, language use, comprehension, and basic motor skills. The total score ranges from zero to 30 points, with lower scores indicating more impaired cognition. We applied education-adjusted cut-off scores (Bertolucci et al., 1994). Scores below 24 were used as exclusion criterion for healthy participants.

Awareness of disease

Awareness of condition was assessed for PwAD using a short version of the Assessment Scale of Psychosocial Impact of the Diagnosis of Dementia (ASPIDD; Dourado, Laks, & Mograbi, 2019). The scale includes twelve items to evaluate awareness in four domains: cognitive functioning and health condition, instrumental and basic ADLs, affective state, as well as social functioning and relationships. The scoring is based on discrepant responses of self- and caregiver reports, whereby both answer the same questions with frequently (four points), sometimes (three points), rarely (two points), or never (one point). The score is calculated as the sum of discrepant answers (caregiver minus patient rating), thus positive values indicate over-estimation.

Apathy

The degree of apathy was evaluated only in PwAD and healthy older adults, using the Apathy Evaluation Scale (AES; Caeiro, Silva, Ferro, Ribeiro, & Figueira, 2012; Marin, Biedrzycki, & Firinciogullari, 1991). It has 18 items with answers ranging from “not at all true” (four points) to “very true” (one point) resulting in a score between 18 and 72 points. Higher scores indicate higher levels of apathy. Apathy was evaluated as self-report for older adults, and as caregiver report for PwAD.

Procedures

Participants were received in a room at the CDA-IPUB-UFRJ by two experimenters. Before starting the experimental task (below), all participants signed the informed consent and answered the demographic questionnaire. After that, participants were prepared for recording of the electroencephalogram (EEG). In the case of PwAD, caregivers answered questionnaires during this period (see below). Once the experimental task was over, the electrodes were removed. Following a short break, participants answered the questionnaires, as well as the MMSE or ACE-r, respectively. All participants received R$ 30 as reimbursement for participation.

Healthy participants completed all questionnaires by themselves, except the MMSE, which was carried out by a psychologist. PwAD completed ratings of awareness (ASPIDD), level of depression (GDS), and were tested for cognitive functioning (ACE-r) by a psychologist. Caregivers completed all demographic information, as well as informant ratings of awareness (ASPIDD), and apathy (AES). If needed, the experimenter helped PwAD completing the questionnaires by reading the questions aloud and explaining them.

Performance monitoring task

E-prime 3 professional (Psychology Software Tools) was used to program the task. Participants were seated approximately 70 cm in front of a 22-inch computer screen and asked to fixate the middle of the screen. They were instructed to press a button as soon as they see a moving object appearing from the left side of the screen. The objects were little cars that moved with a certain velocity. This velocity determined the difficulty of the trial, the faster the car the more difficult to press the button in time (see Figure 1).

The task was designed in a way that the difficulty could be manipulated by the experimenter. The average reaction time (RT) of the participant was evaluated at the beginning of the task following a practice phase. Thus, during the following test phase 10 % of the trials were presented with a velocity that was faster than the average RT of the participant in order to provoke errors. Performance was continuously monitored, and the RT threshold adjusted if participants performed above or below expected in three or more out of five trials. If they managed to react quickly enough, before the car disappeared on the right side of the screen, a positive feedback followed their response, and in case of failure, negative feedback was provided. A high-pitched tone was used as positive feedback, whereas a deep tone was used as a negative feedback sound.

The task was divided in five blocks with 100 trials each, and took 20 to 25 minutes to complete, allowing time for participants to rest in between blocks. Participants were asked to evaluate their performance three times during the task by rating in how many

trials they pressed the button fast enough after the first 100 trials, after the first ten trials of the forth block, and after 500 trials at the end of the task. The time point for the estimation of the ten-trial interval was chosen to prevent people from expecting these questions, and thus from counting their errors.

The EEG of the participants was recorded during the task (see below). After the experiment was finished, participants were informed about the purpose of the experiment and offered feedback on the results of their neuropsychological assessment and questionnaires via e-mail.

PLEASE INSERT FIGURE 1 HERE.

Awareness of performance

Awareness of performance was measured using the self-rated and the actual task performance in corresponding intervals. The ten-trial estimation served as online monitoring measure, whereas performance after 100 and 500 trials was interpreted as medium- and long-term monitoring. Finally, a discrepancy score was calculated using a quotient to account for the different scales. Hereby, estimated correct trials were divided by actual correct trials. Thus, a value bigger than one indicates over-estimation, while a value smaller than one represents under-estimation of performance.

EEG recording and preprocessing

EEG was recorded with an EMSA BrainNet BNT 36 amplifier from 20 AgCl electrodes (Fp2, Fp1, F8, F4, Fz, F3, F7, C4, Cz, C3, T8, T7, P8, P4, Pz, P3, P7, O2, Oz, O1) with electrode Cz as online reference and a sampling rate of 600 Hz. A chin support was used to limit head movements. The electrodes were attached to a cap according to the 10/20 system. The signal was filtered online with a low-pass filter of

70 Hz, a high-pass filter of 0.1 Hz, and a notch filter to remove 60 Hz electrical noise. All impedances were kept below 5 kΩ.

The software EEGLAB (Delorme & Makeig, 2004) and ERPLAB (Lopez-Calderon & Luck, 2014) were used for preprocessing. The signal was re-referenced to the average of the left and right mastoids and filtered offline with a low-pass filter. A period of 200 ms before feedback onset was used for baseline correction. Filters and baseline corrections were necessary because of a lower signal-to-noise ratio in older adults and especially in PwAD. Signal distortions caused by filters are a serious issue in ERP research (Widmann, Schröger, & Maess, 2015). A zero-phase (non-causal), one-pass FIR filter with a cut-off frequency of 50.625 Hz (-6 dB), a filter order of 176, and a transition band width of 11.25 Hz was used to low-pass filter the signal offline as implemented in the firfilt EEGLAB function. Afterwards, the signal was cut into segments of interest, 200 ms before stimulus onset until 600 ms post-stimulus. Epochs that exceeded +/- 100 μV were rejected. ICA was applied to correct for blinks and horizontal eye movements. Feedback-synchronized averages were computed separately for negative and positive feedback trials.

Statistical analyses

Descriptive statistics were used to illustrate sample characteristics. Differences in age and apathy between PwAD and older adults were tested with t-tests for independent samples. MMSE scores were analyzed using a one-way analysis of variance (ANOVA) followed by post-hoc t-tests. To test differences in gender and education levels between groups, χ^2 tests were used. Because of a small sample size and imbalanced cell distributions, p-values of χ^2 tests were corrected using Fisher's exact test to compare gender and education between groups. Due to Bonferroni correction the alpha level is set to $p = .017$ for these post-hoc tests.

Before analyzing outcomes of the study, the data was screened for outliers. Cases, which differed three standard deviations (SD) or more from the mean were excluded from the data analyses which included the variable in question. For all group

comparisons, mixed-design ANOVAs were computed to analyze key outcomes of the study with group (PwAD, older adults, young adults) as the between subject factor. To evaluate task performance, a 5x3 mixed-design ANOVA included block (one to five) as a within-subject factor and number of correct trials as dependent variable was computed. To test behavioral results, a 3x3 mixed-design ANOVA with number of trials (ten-, 100-, and 500-trial intervals) as a within-subject factor was computed with discrepancy scores of awareness of performance as the dependent variable.

Based on the literature, measurements for the FRN were calculated at electrode Fz, and at electrodes Fz, Cz, and Pz for the P300 (Polich, 2012). The FRN was analyzed in the time window 150 - 400 ms after feedback onset, and peak amplitude and 50 % fractional peak latency were computed. Regarding the P300, a time window of 250 - 600 ms after feedback onset was chosen. As the P300 is a large component, positive area amplitude and 50 % fractional area latency were computed (Kiesel, Miller, Jolicœur, & Brisson, 2008). Mixed-design ANOVAs with feedback valence (positive, negative) as within-subject factor were computed to investigate amplitude and latency of the FRN. To evaluate amplitudes and latencies of the P300, feedback valence, as well as electrode position (Fz, Cz, Pz) were used as within-subject factors.

Effects are reported including partial η^2 (η_p^2) as a measure of effect size. According to Cohen (1988), $\eta_p^2 \geq .06$ corresponds with a medium effect size (.25), and $\eta_p^2 \geq .14$ with a large effect size (.40). Greenhouse-Geisser correction procedure was used when sphericity assumptions were violated. Post hoc comparisons were corrected using the Bonferroni procedure.

Finally, bivariate Pearson correlations were computed between ERP amplitude measures, awareness of performance (discrepancy scores), as well as for ASPIDD and AES scores for PwAD. Statistical analyses were carried out with SPSS version 21. For all analyses α was set at .05, two-tailed.

Results

Sociodemographic and clinical variables

A significant age difference between older adults and PwAD was found ($t(25) = -3.1$, $p = .005$). Regarding gender, a significant effect was found ($\chi^2(2) = 9.6$, Fisher's exact $p = .007$). Post-hoc comparisons showed that only young and older adults differed significantly ($\chi^2(1) = 9.6$, Fisher's exact $p = .003$). Educational levels also differed significantly between groups ($\chi^2(1) = 19.1$, Fisher's exact $p < .001$). Post-hoc comparisons showed that young adults differed from PwAD ($\chi^2(2) = 15.7$ Fisher's exact $p < .001$). Moreover, a significant difference between groups was observed for the MMSE ($F(2, 41) = 90.7$, $p < .001$), with PwAD having significantly smaller scores than young adults and older adults (both $p < .001$). Finally, older adults and PwAD differed on the AES ($t(14.8) = -6.5$, $p < .001$). Mean and SD of sociodemographic and clinical variables can be seen in Table 1. Follow-up correlation analyses were carried out to examine whether age was associated to key variables in the healthy older adult group and PwAD. Results are reported in the corresponding sections below.

Behavioral results

Task performance

Two participants in the PwAD group completed only three blocks of the task because of tiredness and were thus excluded from behavioral analyses. The interaction term was not significant ($F (6.4, 128.2) = 1.4$, $p = .231$, $\eta p2 = .06$), but significant effects of block ($F (3.2, 128.2) = 6.1$, $p < .001$, $\eta_p^2 = .13$), and group ($F(2, 40) = 12.1$, $p < .001$, $\eta_p^2 = .38$) were observed. Post-hoc comparisons showed that more errors were committed in the first compared to all other blocks (all $p < .050$), and that PwAD committed more errors than healthy older, and young adults (both $p < .001$). Numbers of correct trials are shown in Table 2. Age was negatively correlated to the number of correct trials in the third ($r = -.534$, $p = .005$) and fifth block ($r = -.540$, $p = .005$) in the older adult groups (healthy and PwAD).

PLEASE INSERT TABLE 2 HERE.

Awareness of performance

A significant interaction (F (4, 80) = 2.8, p = .032, η_p^2 = .12) was found, whereby PwAD underestimated their performance significantly more than young adults in the 100-trial-ratio (p = .023), and the 500-trial-ratio (p = .006). Furthermore, results showed a trend for a significant difference of the discrepancy score (F (2, 80) = 3.1, p = .051, η_p^2 = .07). Groups differed significantly (F (2, 40) = 3.8, p = .030, η_p^2 = .16), with post-hoc tests revealing higher discrepancy (i.e. lower quotient) scores for PwAD compared to young adults (p = .043). Mean and SD for estimated and actual performance can be seen in Table 3, and discrepancy scores are graphically shown in Figure 2. Performance of awareness was not correlated with age in the older adult groups (healthy and PwAD).

PLEASE INSERT TABLE 3 HERE.

PLEASE INSERT FIGURE 2 HERE.

ERPs

Participants with fewer than ten negative feedback trials after preprocessing were omitted from the analysis (one young adult, one older adult, two PwAD). Moreover, one outlier was detected in the young adult group and excluded from the ERP analyses. The resulting sample for the EEG analyses included 15 young adults, 15 older adults, and ten PwAD. There were more positive (PwAD: Mean = 161.6, SD = 80.1; older: Mean = 242.8, SD = 56.4; young: Mean = 197.7, SD = 65.7) than

negative feedback trials (PwAD: M = 37.3, SD = 15.8; older: M = 40.1, SD = 13.8; young: M = 36.7, SD = 11.3) included in the analyses.

FRN

The interaction term did not reach significance for the FRN amplitude ($F(2,37) = 2.5$, $p < .098$, $\eta_p^2 = .12$). However, the FRN was significantly increased (more negative) ($F(1,37) = 25.7$, $p < .001$, $\eta_p^2 = .41$) after negative feedback, and the group effect was significant ($F(2,37) = 4.2$, $p = .022$, $\eta_p^2 = .19$). Post-hoc comparisons showed significantly smaller (less negative) amplitudes in PwAD than older controls ($p = .018$). Regarding latency, the interaction term ($F(2,36) = 0.13$, $p = .875$, $\eta_p^2 = .01$), as well as feedback valence ($F(2,36) = 0.13$, $p = .722$, $\eta_p^2 = .00$) did not reach significance, but there was a significant group effect ($F(2,36) = 6.6$, $p = .004$, $\eta_p^2 = .27$), whereby latencies were prolonged in PwAD compared to older ($p = .009$), and young adults ($p = .006$). Age in the older adult groups (healthy and PwAD) was correlated with FRN amplitude after positive feedback ($r = .508$, $p = .011$), as well as after negative feedback ($r = .518$, $p = .009$), meaning reduced amplitudes (more positive) with older age. Age was also correlated with latency after positive ($r = .678$, $p < .001$) and negative feedback ($r = .419$, $p = .041$).

P300

For P300 amplitudes, the interaction feedback*group was significant ($F(2,37) = 6.8$, $p = .003$, $\eta_p^2 = .27$). Post-hoc comparisons showed larger amplitudes for young compared to older adults after positive feedback ($p = .010$), and larger amplitudes for young adults after negative feedback in comparison to older adults and PwAD (both $p < .001$). Amplitude size differed between positive and negative feedback only in the young adult group. A significant effect of factor feedback was also observed ($F(1,37) = 6.1$, $p = .019$, $\eta_p^2 = .14$), with larger amplitudes following negative feedback. Moreover, groups differed significantly ($F(2,37) = 14.8$, $p < .001$, $\eta_p^2 = .44$). Young adults had larger amplitudes than older adults ($p < .001$) and PwAD ($p = .001$). The

interactions electrode*group (F(3.8,69.4) = 0.9, p = .488, η_p^2 = .04), electrode*feedback (F(1.5,54.7) = 2.0, p = .151, η_p^2 = .05), and feedback*electrode*group (F(3.0,54.7) = 0.7, p = .542, η_p^2 = .04), as well as factor electrode (F(1.9,69.4) = 1.0, p = .366, η_p^2 = .03) did not reach significance. Regarding latency, the interaction feedback*electrode*group was significant (F(3.1,43.5) = 3.4, p = .024, η_p^2 = .20). Post-hoc tests found that older controls had prolonged latencies for positive feedback at all electrode sites compared to young adults and PwAD (all p < .050). Regarding negative feedback, latencies were prolonged for older adults compared to young adults at all electrode sites (all p < .050), as well as compared to PwAD at electrode Pz (p = .001). Significant effects of factor feedback (F (1,28) = 68.3, p < .001, η_p^2 = .71) and group (F(2,28) = 14.8, p < .001, η_p^2 = .51) were also observed. Post-hoc comparisons showed prolonged latencies for negative feedback (p < .001), as well as in older adults compared to young adults (p < .001) and PwAD (p = .001). The interactions feedback*group (F (2,28) = 0.1, p = .910, η_p^2 = .00), electrode*group (F (3.9,54.2) = 1.6, p = .192, η_p^2 = .10), and feedback*electrode (F (1.6,43.5) = 2.2, p = .137, η_p^2 = .07), as well as factor electrode (F (1.9,54.2) = 2.1, p = .134, η_p^2 = .07) were not significant. Age was not correlated with P300 characteristics. Amplitude and latencies can be seen in Table 4. Feedback-locked waveforms are represented in Figure 3.

PLEASE INSERT TABLE 4 HERE.

PLEASE INSERT FIGURE 3 HERE.

Correlation analyses

Awareness of disease (ASPIDD scores) and awareness of performance (discrepancy scores) were significantly correlated. The ASPIDD total score correlated with medium-term monitoring (r = -.636, p = 026), as did the social sub-score (r = -.717, p = .009). Moreover, medium- and long-term performance monitoring were correlated

(r = .416, p = .006). Furthermore, awareness of performance correlated with neurophysiologic measures. FRN amplitude was correlated with online monitoring after positive (r = .368, p = .019) and negative feedback (r = .329, p = .038). FRN amplitude after positive feedback was also correlated with medium-term performance monitoring (r = -.323, p = .042). However, long-term performance monitoring was correlated with P300 amplitudes after negative feedback at electrodes Fz (r = .356, r = .026) and Cz (r = .345, p = .032). Medium-term performance monitoring also correlated with P300 amplitudes after negative feedback at electrode Cz (r = .330, p = .037). Apathy was not correlated to awareness of performance, awareness of disease, and neurophysiologic measures.

Discussion

In the present study, we aimed at investigating awareness of task performance in PwAD. We applied a RT task with an adaptive algorithm to compensate for differences caused by age or AD between groups, and combined data from self-report measures, EEG recordings, and questionnaires. PwAD, healthy older and young adults did not differ regarding online monitoring, but PwAD were impaired in medium- and long-term monitoring of performance. In relation to the ERP analyses, all groups showed a sensitivity to feedback valence indicated by increased FRN amplitudes after negative feedback. However, sensitivity to feedback valence was only reflected in young adults in the P300 component, having larger amplitudes after negative feedback. Moreover, young adults had larger P300 amplitudes than older adults and PwAD. In line with the CAM, our results support a mnemonic, rather than an executive origin of anosognosia for performance in PwAD.

Manipulation of task difficulty in our paradigm worked well within groups, as well as for healthy participants. Decreased numbers of errors after the first block represented very likely a practice effect. However, PwAD committed more errors than older and young adults. Although the task had very low cognitive demands, we conclude that execution was still more challenging for PwAD. Since our task was a pure reaction time and not a learning task, we think it is unlikely that these differences in task

performance have biased our results, in particular because the focus was on awareness rather than on actual performance per se. Furthermore, age was negatively correlated to the number of correct trials in some blocks, thus the higher age of PwAD in comparison to healthy older adults might have contributed to their elevated numbers of errors. Nevertheless, creating a task that meets the same requirements for healthy older and young adults, and at the same time for PwAD, remains a challenge for future research.

Regarding awareness of performance, results show that PwAD are not impaired in online-performance monitoring, indicated by similar performance in the groups regarding the ten-trial interval evaluations. This is in line with previous research (Silva et al., 2017; Stewart et al., 2010) that also supported the idea of preserved online performance monitoring in PwAD. Interestingly, online-monitoring performance was also not related to medium- or long-term performance monitoring indices, while the latter were correlated. This could suggest that online monitoring reflects a different process than medium- and long-term performance monitoring. In contrast to online-monitoring performance, PwAD were less exact than young adults in self-evaluating performance after medium- and long-term intervals, and worse awareness of disease was associated to lower ratings of medium-term performance. This is consistent with studies also showing that PwAD were not able to transfer online monitoring to long-term predictions (Silva et al., 2017; Stewart et al., 2010). According to the CAM, online monitoring is related to executive control mechanisms (CCMs), whereas deficits in the integration of this information lead to a principal failure in updating personal knowledge in the PDB, resulting in mnemonic anosognosia. The fact that older adults did not differ from young adults or PwAD could be evidence for an accumulation of age and AD related effects in medium- and long-term performance monitoring impairment in PwAD. In agreement with other studies that used tasks that led to high success rates in PwAD (Mograbi, Brown, Salas, & Morris, 2012), patients exhibited a pattern of underestimation of performance, which highlights that unawareness of performance in AD does not have a positive bias. Instead, PwAD anchored their estimation of performance very close to the midpoint, a phenomenon that has been discussed before (Ernst, Moulin,

Souchay, & Mograbi, 2015). Thus, alternatively to PwAD underestimating their performance, we could speculate that they rather use a general guess to compensate for monitoring impairments.

Regarding the FRN, amplitudes were bigger after negative feedback compared to positive feedback for all groups. This is in line with previous studies showing that the FRN is usually larger after negative feedback (e.g., Hajcak, Moser, Holroyd, & Simons, 2006; Holroyd & Coles, 2002; Ludowicy et al., 2019). Although showing prolonged latencies, PwAD did not differ from young adults regarding FRN amplitudes. Moreover, age was associated with amplitude and latency, which suggests that the higher age of PwAD might have contributed to smaller amplitudes and prolonged latencies in this group. Hence, older adults, as well as PwAD were able to process external feedback and to differentiate between good and bad outcomes on a neurophysiological level. Additionally, FRN amplitudes were associated with online monitoring performance. Therefore, we assume that at least regarding the processing of environmental feedback, neither age, nor AD caused a deficit.

According to the CAM, this is additional evidence for relatively preserved executive performance monitoring processes in PwAD. However, previous studies investigating performance monitoring components in aging and AD typically found differences between groups. Regarding feedback processing, various studies found decreased FRN amplitudes in older compared to younger adults (Hämmerer, Li, Müller, & Lindenberger, 2011; Mathewson, Dywan, Snyder, Tays, & Segalowitz, 2008; Pietschmann, Endrass, Czerwon, & Kathmann, 2011; West & Huet, 2020; Wild-Wall, Willemssen, & Falkenstein, 2009). Using a gambling task, Nitta and colleagues (Nitta et al., 2017) reported delayed latencies in PwAD compared to young adults, and larger FRN amplitudes for PwAD compared to healthy age-matched adults. Although our results are in line with previous research showing overall that older adults as well as PwAD have neurophysiological components that indicate preserved performance monitoring, the type of the task seemed to have influenced results. Whereas most studies used learning or gambling paradigms and found age or AD related differences between groups, the present study tried to investigate performance monitoring in a

pure RT task to avoid as much as possible the influence of cognitive factors, such as learning or decision making, that are well known to be impaired in PwAD.

A P300 was observed following the FRN, that was most pronounced for young adults, whereas older adults and PwAD only showed subtle manifestations. In contrast to the FRN, P300 amplitudes were not sensitive to feedback valence in PwAD and older adults, showing increased amplitudes after negative feedback only in young adults. These findings are in line with previous research showing decreased amplitudes and longer latencies related to aging and AD (Bennys, Portet, Touchon, & Rondouin, 2007; Lai, Lin, Liou, & Liu, 2010; Nitta et al., 2017; Parra, Ascencio, Urquina, Manes, & Ibáñez, 2012; Polich & Corey-Bloom, 2005). Since the P300 is involved in various cognitive processes reflecting top-down processing of stimuli (Polich, 2012), like for example context updating (Donchin, 1981; Polich, 2007), memory encoding (e.g., Guo, Duan, Li, & Paller, 2006; Polich, 2007), and attention and stimulus evaluation (e.g., Duncan-Johnson & Donchin, 1982; Katada, Sato, Ojika, & Ueda, 2004), it is difficult to determine the cause of alterations in P300 characteristics in aging and AD. One speculation is that the P300 could arise from neural inhibitory activity that facilitates attentional focus to promote memory storage (Polich, 2012). Bennys and colleagues (Bennys et al., 2007), as well as Lai and colleagues (Lai et al., 2010) interpret decreased P300 amplitudes as indices of attentional and memory deficits in PwAD. Although PwAD and healthy older adults did not differ regarding P300 amplitude in our sample, more exact medium- and long-term performance evaluations were associated with elevated P300 amplitudes after negative feedback. This supports the idea of an impairment in attentional processes related to feedback processing, which could contribute to deficits in subsequent memory updating of unpleasant events. Nevertheless, more studies are needed to draw reliable conclusions about the relationship between the P300 and awareness of performance in aging and AD.

Apathy was not related to task performance, measures of awareness, and ERP characteristics. We expected apathy to be associated to awareness of performance if affective factors would play a role in this process. The link between affective

processing, apathy and performance monitoring is based on a lack of emotional significance of failed task performance in apathy, by which those events could be ignored when patients evaluate their abilities (Rosen, 2011). However, a high success rate was used in this paradigm and errors were rare and more salient events. Therefore, the effect of negative valence of errors that could have been associated to apathy, might have been confounded with effects of salience. On top of that, our sample of PwAD could be restricted in variance because depression, which is highly associated with apathy, was an exclusion criterion (Wei, Irish, Hodges, Piguet, & Kumfor, 2019).

Limitations

Some limitations of the present study must be mentioned. Our task design was rather explorative, in the sense that we did not use a classic error monitoring, learning, or gambling task to investigate performance monitoring. It was our goal to create a paradigm that can be used to explore performance monitoring with low cognitive effort and increased ecological validity. Moreover, we aimed at developing a task that leads to similar levels of difficulty for PwAD, as well as for healthy older and young adults. Therefore, the paradigm used in the present study differs from the tasks used in the literature, and future studies using similar designs are needed to validate our findings. Furthermore, we recommend implementing a classic control task in future studies to compare results directly. Another point is the significant age difference between older adults and PwAD. We could show that higher age was related to elevated numbers of errors, as well as to reduced FRN amplitudes and prolonged latencies, which is in line with our interpretation of intact executive performance monitoring abilities in healthy older adults and PwAD. Moreover, age was not associated to awareness of performance and P300 characteristics. Older adults and PwAD did not differ regarding gender and educational level, but younger adults differed from PwAD regarding educational level, and from older adults regarding gender. Because of the age difference and related differences in various characteristics, it was not possible to clearly investigate the influence of education

and gender between these groups. Thus, we cannot rule out that gender and education influenced the differences found between older (healthy and PwAD) and young participants.

Conclusion

In the present study, we used positive and negative feedback in a RT performance-monitoring task to study different aspects of awareness of performance in PwAD, healthy older and young adults. According to the CAM, anosognosia can be caused by mnemonic and executive deficits. We found that neither aging, nor AD caused deficits in online performance monitoring, whereas medium- and long-term performance monitoring were impaired in PwAD. These findings support a mnemonic nature of anosognosia in AD, which is further supported by findings of related ERP components. The FRN amplitude was sensitive to feedback valence, showing enhanced amplitudes after negative feedback in all groups. Thus, PwAD were able to differentiate between positive and negative outcomes on a neurophysiological level. In contrast, PwAD and healthy older adults had strongly decreased P300 amplitudes in comparison to young adults, indicating deficits in attentional and memory processes that could be related to performance monitoring. Studies investigating performance monitoring in PwAD are still scarce and more research is needed to draw reliable conclusions. Nevertheless, consolidation of information about performance seems to be a key factor in the generation of anosognosia in PwAD. Neuropsychological therapy approaches could try to implement methods to strengthen consolidation processes, which could lead to improved awareness.

References

Agnew, S. K., & Morris, R. G. (1998). The heterogeneity of anosognosia for memory impairment in Alzheimer's disease: A review of the literature and a proposed model. *Aging & Mental Health*, *2*, 7–19. https://doi.org/10.1080/13607869856876

Almeida, O. P., & Almeida, S. A. (1999a). Confiabilidade da versão brasileira da Escala de Depressão em Geriatria (GDS) versão reduzida. *Arquivos de Neuro-Psiquiatria*, *57*(2B), 421–426. https://doi.org/10.1590/S0004-282X1999000300013

Almeida, O. P., & Almeida, S. A. (1999b). Short versions of the Geriatric Depression Scale: A study of their validity for the diagnosis of a major depressive episode according to ICD-10 and DSM-IV. *International Journal of Geriatric Psychiatry*, *14*(10), 858–865. https://doi.org/10.1002/(SICI)1099-1166(199910)14:10<858::AID-GPS35>3.0.CO;2-8

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., T). Washington, DC: American Psychiatric Association.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). Manual for the Beck depression inventory-II. *San Antonio, TX: Psychological Corporation*.

Bennys, K., Portet, F., Touchon, J., & Rondouin, G. (2007). Diagnostic value of event-related evoked potentials N200 and P300 subcomponents in early diagnosis of Alzheimer's disease and mild cognitive impairment. *Journal of Clinical Neurophysiology*. https://doi.org/10.1097/WNP.0b013e31815068d5

Bertolucci, P. H. F., Brucki, S. M. D., Campacci, S. R., & Juliano, Y. (1994). O Mini-Exame do Estado Mental em uma população geral: impacto da escolaridade. *Arquivos de Neuro-Psiquiatria*, *52*(1), 01–07. https://doi.org/10.1590/s0004-282x1994000100001

Caeiro, L., Silva, T., Ferro, J. M., Ribeiro, J. L. P., & Figueira, M. L. (2012). Metric

properties of the portuguese version of the apathy evaluation scale. *Psicologia, Saúde & Doenças*, *13*(2), 266–282.

Carvalho, V. A., & Caramelli, P. (2007). Adaptação brasileira do Exame Cognitivo de Addenbrooke-Revisado. *Dementia & Neuropsychologia*, *1*(2), 212–216. https://doi.org/10.1590/s1980-57642008dn10200015

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum Associates.

Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*. https://doi.org/10.1016/j.jneumeth.2003.10.009

Di Gregorio, F., Ernst, B., & Steinhauser, M. (2019). Differential effects of instructed and objective feedback reliability on feedback-related brain activity. *Psychophysiology*, *56*(9), 1–10. https://doi.org/10.1111/psyp.13399

Donchin, E. (1981). Surprise!… Surprise? *Psychophysiology*, *18*, 493–513. https://doi.org/10.1111/j.1469-8986.1981.tb01815.x

Dourado, M. C. N., Laks, J., & Mograbi, D. C. (2019). Awareness in Dementia: Development and Evaluation of a Short Version of the Assessment Scale of Psychosocial Impact of the Diagnosis of Dementia (ASPIDD-s) in Brazil. *Alzheimer Disease and Associated Disorders*, *33*(3), 220–225. https://doi.org/10.1097/WAD.0000000000000306

Duncan-Johnson, C. C., & Donchin, E. (1982). The P300 component of the event-related brain potential as an index of information processing. *Biological Psychology*. https://doi.org/10.1016/0301-0511(82)90016-3

Ernst, A., Moulin, C. J. A., Souchay, C., & Mograbi, D. C. (2015). Anosognosia and Metacognition in Alzheimer's Disease. *The Oxford Handbook of Metamemory*, (June 2016), 1–41. https://doi.org/10.1093/oxfordhb/9780199336746.013.12

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician.

Journal of Psychiatric Research, *12*(3), 189–198.

Gomes-Oliveira, M. H., Gorenstein, C., Neto, F. L., Andrade, L. H., & Wang, Y. P. (2012). Validation of the Brazilian Portuguese Version of the Beck Depression Inventory-II in a community sample. *Revista Brasileira de Psiquiatria*. https://doi.org/10.1016/j.rbp.2012.03.005

Guo, C., Duan, L., Li, W., & Paller, K. A. (2006). Distinguishing source memory and item memory: Brain potentials at encoding and retrieval. *Brain Research*. https://doi.org/10.1016/j.brainres.2006.08.034

Hajcak, G., Moser, J. S., Holroyd, C. B., & Simons, R. F. (2006). The feedback-related negativity reflects the binary evaluation of good versus bad outcomes. *Biological Psychology*, *71*(2), 148–154. https://doi.org/10.1016/j.biopsycho.2005.04.001

Hämmerer, D., Li, S. C., Müller, V., & Lindenberger, U. (2011). Life span differences in electrophysiological correlates of monitoring gains and losses during probabilistic reinforcement learning. *Journal of Cognitive Neuroscience*. https://doi.org/10.1162/jocn.2010.21475

Holroyd, C. B., & Coles, M. G. H. (2002). The neural basis of human error processing: Reinforcement learning, dopamine, and the error-related negativity. *Psychological Review*, *109*(4), 679–709. https://doi.org/10.1037//0033-295X.109.4.679

Horning, S. M., Melrose, R., & Sultzer, D. (2014). Insight in Alzheimer's disease and its relation to psychiatric and behavioral disturbances. *International Journal of Geriatric Psychiatry*, *29*(1), 77–84. https://doi.org/10.1002/gps.3972

Jacus, J. P. (2017). Awareness, apathy, and depression in Alzheimer's disease and mild cognitive impairment. *Brain and Behavior*, *7*(4), 1–8. https://doi.org/10.1002/brb3.661

Johnson, R. J., & Donchin, E. (1978). On how the P300 amplitude varies with the utility of the eliciting stimuli. *Electroencephalography and Clinical*

Neurophysiology, *44*, 424–437.

Katada, E., Sato, K., Ojika, K., & Ueda, R. (2004). Cognitive Event-Related Potentials: Useful Clinical Information in Alzheimers Disease. *Current Alzheimer Research*, *1*(1), 63–69. https://doi.org/10.2174/1567205043480609

Kiesel, A., Miller, J., Jolicœur, P., & Brisson, B. (2008). Measurement of ERP latency differences: A comparison of single-participant and jackknife-based scoring methods. *Psychophysiology*, *45*(2), 250–274. https://doi.org/10.1111/j.1469-8986.2007.00618.x

Lai, C.-L., Lin, R.-T., Liou, L.-M., & Liu, C.-K. (2010). The role of event-related potentials in cognitive decline in Alzheimer's disease. *Clinical Neurophysiology*, *121*, 194–199. https://doi.org/10.1016/j.clinph.2009.11.001

Lopez-Calderon, J., & Luck, S. J. (2014). ERPLAB: An open-source toolbox for the analysis of event-related potentials. *Frontiers in Human Neuroscience*, *8*, 1–14. https://doi.org/10.3389/fnhum.2014.00213

Ludowicy, P., Czernochowski, D., Weis, T., Haese, A., & Lachmann, T. (2019). Neural correlates of feedback processing during a sensory uncertain speech - nonspeech discrimination task. *Biological Psychology*, *144*, 103–114. https://doi.org/10.1016/j.biopsycho.2019.03.017

Marin, R. S., Biedrzycki, R. C., & Firinciogullari, S. (1991). Reliability and validity of the apathy evaluation scale. *Psychiatry Research*, *38*(2), 143–162. https://doi.org/10.1016/0165-1781(91)90040-V

Mathewson, K. J., Dywan, J., Snyder, P. J., Tays, W. J., & Segalowitz, S. J. (2008). Aging and electrocortical response to error feedback during a spatial learning task. *Psychophysiology*, *45*(6), 936–948. https://doi.org/10.1111/j.1469-8986.2008.00699.x

Miltner, W. H. R., Braun, C. H., & Coles, M. G. H. (1997). Event-related brain potentials following incorrect feedback in a time-estimation task: Evidence for a "generic" neural system for error detection. *Journal of Cognitive Neuroscience*,

9(6), 788–798. https://doi.org/10.1162/jocn.1997.9.6.788

Mioshi, E., Dawson, K., Mitchell, J., Arnold, R., & Hodges, J. R. (2006). The Addenbrooke's Cognitive Examination revised (ACE-R): A brief cognitive test battery for dementia screening. *International Journal of Geriatric Psychiatry*, *21*(11), 1078–1085. https://doi.org/10.1002/gps.1610

Mograbi, D. C., Brown, R. G., & Morris, R. G. (2009). Anosognosia in Alzheimer's disease - The petrified self. *Consciousness and Cognition*, *18*(4), 989–1003. https://doi.org/10.1016/j.concog.2009.07.005

Mograbi, D. C., Brown, R. G., Salas, C., & Morris, R. G. (2012). Emotional reactivity and awareness of task performance in Alzheimer's disease. *Neuropsychologia*, *50*(8), 2075–2084. https://doi.org/10.1016/j.neuropsychologia.2012.05.008

Mograbi, D. C., Ferri, C. P., Sosa, A. L., Stewart, R., Laks, J., Brown, R., & Morris, R. G. (2012). Unawareness of memory impairment in dementia: A population-based study. *International Psychogeriatrics*, *24*(6), 931–939. https://doi.org/10.1017/S1041610211002730

Mograbi, D. C., & Morris, R. G. (2014). On the relation among mood, apathy, and anosognosia in Alzheimer's disease. *Journal of the International Neuropsychological Society*, *20*(1), 2–7. https://doi.org/10.1017/S1355617713001276

Mograbi, D. C., & Morris, R. G. (2018). Anosognosia. *Cortex*, *103*, 385–386. https://doi.org/10.1016/j.cortex.2018.04.001

Morris, R. G., & Hannesdottir, K. (2004). Loss of "awareness" in Alzheimer's Disease. In R. G. Morris & J. T. Becker (Eds.), *The Cognitive Neuropsychology of Alzheimer's Disease* (pp. 275–296). Oxford: Oxford University Press.

Morris, R. G., & Mograbi, D. C. (2013). Anosognosia, autobiographical memory and self knowledge in Alzheimer's disease. *Cortex*, *49*(6), 1553–1565. https://doi.org/10.1016/j.cortex.2012.09.006

Nitta, E., Onoda, K., Ishitobi, F., Okazaki, R., Mishima, S., Nagai, A., & Yamaguchi, S. (2017). Enhanced feedback-related negativity in Alzheimer's disease. *Frontiers in Human Neuroscience*, *11*, 1–12. https://doi.org/10.3389/fnhum.2017.00179

Parra, M. A., Ascencio, L. L., Urquina, H. F., Manes, F., & Ibáñez, A. M. (2012). P300 and neuropsychological assessment in mild cognitive impairment and Alzheimer dementia. *Frontiers in Neurology*, *3*, 1–10. https://doi.org/10.3389/fneur.2012.00172

Patel, V., & Prince, M. (2001). Ageing and mental health in a developing country: who cares? Qualitative studies from Goa, India. *Psychological Medicine*, *31*(1), 29–38. https://doi.org/10.1017/S0033291799003098

Pietschmann, M., Endrass, T., Czerwon, B., & Kathmann, N. (2011). Aging, probabilistic learning and performance monitoring. *Biological Psychology*, *86*(1), 74–82. https://doi.org/10.1016/j.biopsycho.2010.10.009

Polich, J. (2007). Updating P300: An Integrative Theory of P3a and P3b. *Clinical Neurophysiology*, *118*(10), 2128–2148. https://doi.org/10.1016/j.clinph.2007.04.019

Polich, J. (2012). Neuropsychology of P300. In E. S. Kappenman & S. J. Luck (Eds.), *The Oxford Handbook of Event-Related Potential Components*. New York: Oxford University Press.

Polich, J., & Corey-Bloom, J. (2005). Alzheimers Disease and P300: Review and Evaluation of Task and Modality. *Current Alzheimer Research*, *2*(5), 515–525. https://doi.org/10.2174/156720505774932214

Potts, G. F., Martin, L. E., Kamp, S.-M., & Donchin, E. (2011). Neural Response to Action and Reward Prediction Errors: Comparing the Error Related Negativity to Behavioral Errors and the Feedback Related Negativity to Reward Prediction Violations. *Psychophysiology*, *48*(2), 218–228. https://doi.org/10.1111/j.1469-8986.2010.01049.x.Neural

Qiu, J. M., Casey, M. A., & Diamond, S. G. (2019). Assessing Feedback Response With a Wearable Electroencephalography System. *Frontiers in Human Neuroscience*, *13*, 1–14. https://doi.org/10.3389/fnhum.2019.00258

Rosen, H. J. (2011). Anosognosia in neurodegenerative disease. *Neurocase*, *17*(173), 231–241. https://doi.org/10.1080/13554794.2010.522588

Sheikh, J. I., & Yesavage, J. A. (1986). Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. *Clinical Gerontologist: The Journal of Aging and Mental Health*, *5*(1–2), 165–173. https://doi.org/10.1300/J018v05n01_09

Silva, A. R., Pinho, M. S., Macedo, L., Souchay, C., & Moulin, C. (2017). Mnemonic anosognosia in Alzheimer's disease is caused by a failure to transfer online evaluations of performance: Evidence from memory training programs. *Journal of Clinical and Experimental Neuropsychology*, *39*(5), 419–433. https://doi.org/10.1080/13803395.2016.1231799

Starkstein, S. E., Jorge, R., Mizrahi, R., Adrian, J., & Robinson, R. G. (2007). Insight and danger in Alzheimer's disease. *European Journal of Neurology*, *14*(4), 455–460. https://doi.org/10.1111/j.1468-1331.2007.01745.x

Starkstein, S. E., Jorge, R., Mizrahi, R., & Robinson, R. G. (2006). A diagnostic formulation for anosognosia in Alzheimer's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *77*(6), 719–725. https://doi.org/10.1136/jnnp.2005.085373

Stewart, G., McGeown, W. J., Shanks, M. F., & Venneri, A. (2010). Anosognosia for memory impairment in Alzheimer's disease. *Acta Neuropsychiatrica*, *22*(4), 180–187. https://doi.org/10.1111/j.1601-5215.2010.00463.x

Sutton, S., Braren, M., Zubin, J., & John, E. R. (1965). Evoked-potential correlates of stimulus uncertainty. *Science*, *150*(3700), 1187–1188. https://doi.org/10.1126/science.150.3700.1187

Verhülsdonk, S., Quack, R., Höft, B., Lange-Asschenfeldt, C., & Supprian, T. (2013).

Anosognosia and depression in patients with Alzheimer's dementia. *Archives of Gerontology and Geriatrics*, *57*(3), 282–287. https://doi.org/10.1016/j.archger.2013.03.012

Wei, G., Irish, M., Hodges, J. R., Piguet, O., & Kumfor, F. (2019). Disease-specific profiles of apathy in Alzheimer's disease and behavioural-variant frontotemporal dementia differ across the disease course. *Journal of Neurology*. https://doi.org/10.1007/s00415-019-09679-1

West, & Huet. (2020). The Effect of Aging on the ERP Correlates of Feedback Processing in the Probabilistic Selection Task. *Brain Sciences*, *10*(1), 40. https://doi.org/10.3390/brainsci10010040

Widmann, A., Schröger, E., & Maess, B. (2015). Digital filter design for electrophysiological data - a practical approach. *Journal of Neuroscience Methods*, *250*, 34–46. https://doi.org/10.1016/j.jneumeth.2014.08.002

Wild-Wall, N., Willemssen, R., & Falkenstein, M. (2009). Feedback-related processes during a time-production task in young and older adults. *Clinical Neurophysiology*, *120*(2), 407–413. https://doi.org/10.1016/j.clinph.2008.11.007

World Health Organization. (2004). *ICD-10 : international statistical classification of diseases and related health problems* (2nd ed., 1). World Health Organization. Retrieved from https://apps.who.int/iris/handle/10665/42980

Tables

Table 1 – Sociodemographic and clinical characteristics of participants.

Variable	PwAD (n = 12) Mean (SD) / Range	Older adults (n = 15^) Mean (SD) / Range	Young adults (n = 17) Mean (SD) / Range
Age	77.9 (8.3) / 62-88	69.7 (5.5) / 61-82	21.5 (2.6) / 18-29
Sex*	7/5	14/1	7/10
Primary education~	6 (50)	1 (6.7)	0
High school education~	2 (16.7)	2 (13.3)	0
University degree~	4 (33.3)	12 (80)	17 (100)
ACE-R	47.1 (11.8) / 23-64	–	–
MMSE	15.8 (4.8) / 8-23	27.7 (2.0) / 24-30	29.1 (0.7) / 28-30
AES	47.8 (11.2) / 29-63	25.0 (5.3) / 18-40	–
ASPIDD total score	12.1 (6.0) / 3/24	–	–
Cognition	3.9 (2.0) / 0/8	–	–
ADL	4.5 (2.5) / -1/8	–	–
Affective	2.3 (2.5) / -2/7	–	–
Social	1.3 (2.0) / -1/5	–	–

^ for one participant in the older adult group demographic data was not available; * #female/male; ~ absolute number (%); SD – standard deviation; ACE-R – Addenbrooke's Cognitive Examination – Revised, < 83 points = cut-off score for presence of dementia (maximum score = 100); MMSE – Mini Mental State Examination, < 24 points = cut-off score for presence of cognitive impairment (maximum score = 30); AES – Apathy Evaluation Scale, higher scores indicate higher levels of apathy (total range 18 - 72 points), apathy was measured as caregiver report for PwAD and as self-report for healthy older adults; ASPIDD – Assessment Scale of Psychosocial Impact of the Diagnosis of Dementia (total score and sub-scales); ADL – activities of daily living.

Table 2 – Number of correct trials.

Block	PwAD Mean (SD)	Older adults Mean (SD)	Young adults Mean (SD)
1	70.9 (14.0)	80.9 (7.1)	82.5 (4.7)
2	74.6 (15.2)	84.4 (6.6)	86.6 (3.8)
3	76.6 (10.8)	85.4 (5.5)	85.9 (3.6)
4	79.1 (9.6)	85.4 (5.9)	87.4 (4.5)
5	72.8 (14.6)	88.3 (3.6)	87.1 (4.7)

Number of correct trials for all five blocks for PwAD (n = 10), older (n = 16), and young adults (n = 17). SD – standard deviation.

Table 3 – Estimated and actual performance for ten-, 100-, and 500-trial intervals.

Group Performance	10-trial interval Mean (SD)	100-trial interval Mean (SD)	500-trial interval Mean (SD)
PwAD			
Estimated	8.0 (1.8)	55.9 (30.9)	261.4 (169.4)
Actual	8.0 (1.5)	70.9 (14.0)	375.9 (52.4)
Older adults			
Estimated	7.4 (2.2)	66.0 (25.2)	362.2 (92.9)
Actual	8.6 (1.3)	80.9 (7.1)	424.3 (19.9)
Young adults			
Estimated	7.8 (1.7)	77.4 (7.7)	412.0 (38.7)
Actual	8.6 (1.0)	82.5 (4.7)	429.5 (13.4)

Estimated, self-evaluated performance (correct trials) after ten, 100, and 500 trials, and correct, actual performance (correct trials) in the corresponding interval for PwAD (n = 10), older (n = 16), and young adults (n = 17). SD – standard deviation.

Table 4 – Amplitude and latency values for FRN and P300 at relevant electrode sites.

	PwAD		Older adults		Younger adults	
ERP at electrode	**Amplitude**	**Latency**	**Amplitude**	**Latency**	**Amplitude**	**Latency**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
FRN at Fz						
positive	-2.2 (4.6)	226.7 (58.6)	-4.3 (2.8)	193.6 (39.1)	-4.8 (2.1)	195.7 (11.9)
negative	-5.2 (2.5)	226.8 (47.8)	-9.3 (3.3)	193.3 (35.3)	-6.5 (3.9)	186.9 (20.7)
P300 at Fz						
positive	0.5 (0.9)	325.8 (48.2)	0.3 (0.2)	372.0 (47.3)*	0.7 (0.4)	328.1 (32.2)
negative	0.4 (0.3)	401.7 (80.4)	0.5 (0.6)	437.2 (70.6)^	1.8 (1.1)	390.7 (43.5)
P300 at Cz						
›sitive	0.5 (0.5)	333.8 (67.7)	0.3 (0.3)	381.1 (87.7)*	0.7 (0.5)	321.5 (23.5)
‹gative	0.2 (0.1)°	444.8 (78.7)	0.5 (0.8)	465.2 (80.1)^	1.7 (1.1)	401.1 (47.4)
P) at Pz						
›sitive	0.5 (0.6)	378.5 (94.6)	0.2 (0.3)	371.9 (87.2)#	0.6 (0.4)	325.1 (28.4)
‹gative	0.4 (0.7)º	379.2 (102.6)	0.3 (0.6)	467.3 (90.4)^	1.3 (1.1)	392.6 (50.6)

M and standard deviation (SD) for feedback-locked ERPs at electrode sites Fz, Cz, and Pz for PwAD (n = 10), older (n = 15), and yo g adults (n = 15). For the FRN, the peak amplitude (in μV) was computed relative to baseline in a time window 150 - 400 ms after fe ack onset. The latency values were calculated as 50 % fractional peak latency. For the P300, the positive area amplitude was cc uted (in μVs), and 50 % fractional area latencies in the time window 250 - 600 ms after feedback onset. * n = 12; # n = 11; ^ n = 1 n = 9.

Figures

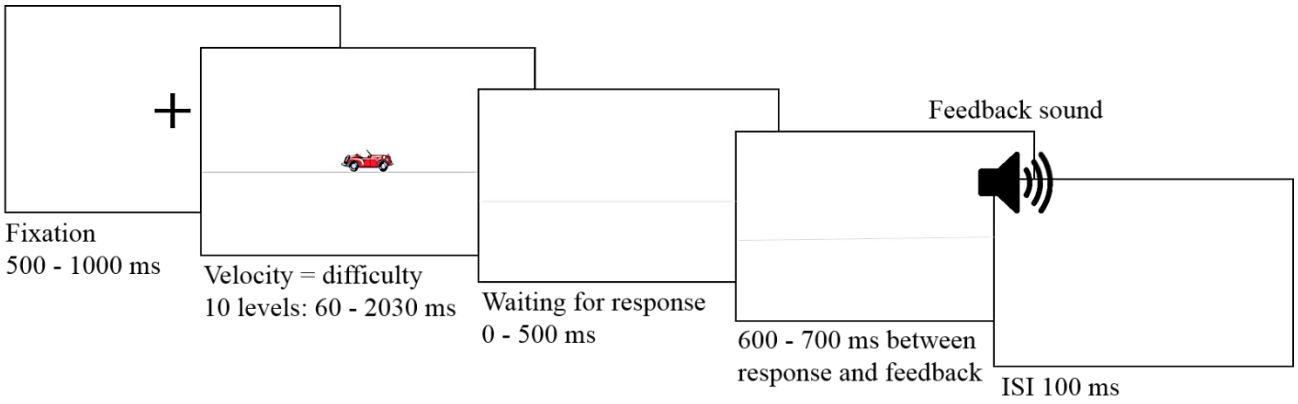

Figure 1 – Schematic representation of one trial in the performance monitoring task. After a fixation cross, a little car appeared on the left side of the screen, moving from left to right with a velocity varying on ten levels, from 60 ms (fastest level) to 2030 ms (slowest level). Participants were instructed to press a button as soon as they see a car appearing on the screen. After the car disappeared, responses were still recorded in a short time interval. After each response, participants received auditory feedback that indicated if they answered correct (fast enough) or not. ISI – inter stimulus interval.

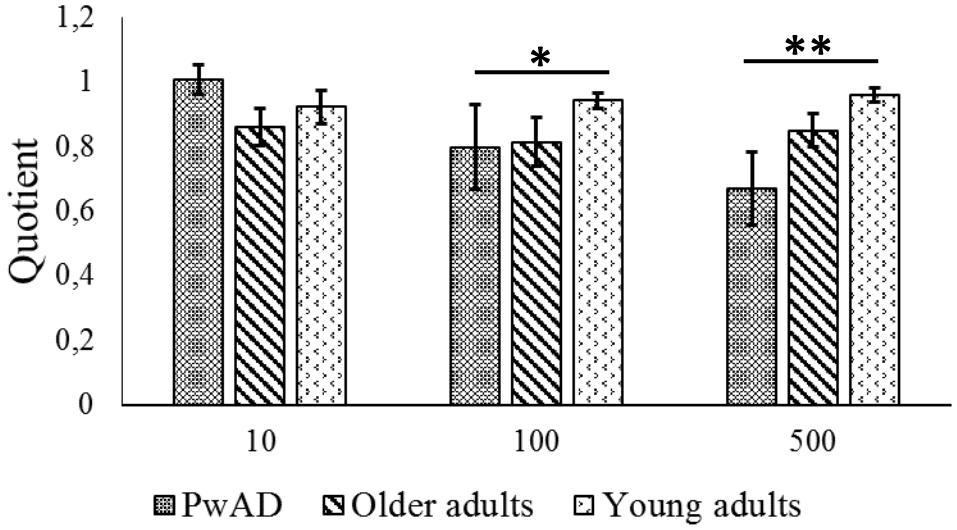

Figure 2 – Representation of means of the quotient as estimation of awareness of task performance (estimated correct trials / actual correct trials; values smaller than one represents under-estimation) for the 10-trial, 100-trial, and 500-trial intervals for PwAD (n = 10), older (n = 16), and young adults (n = 17). Error bars indicate +/- one standard error (SE). * $p < .050$; ** $p < .001$.

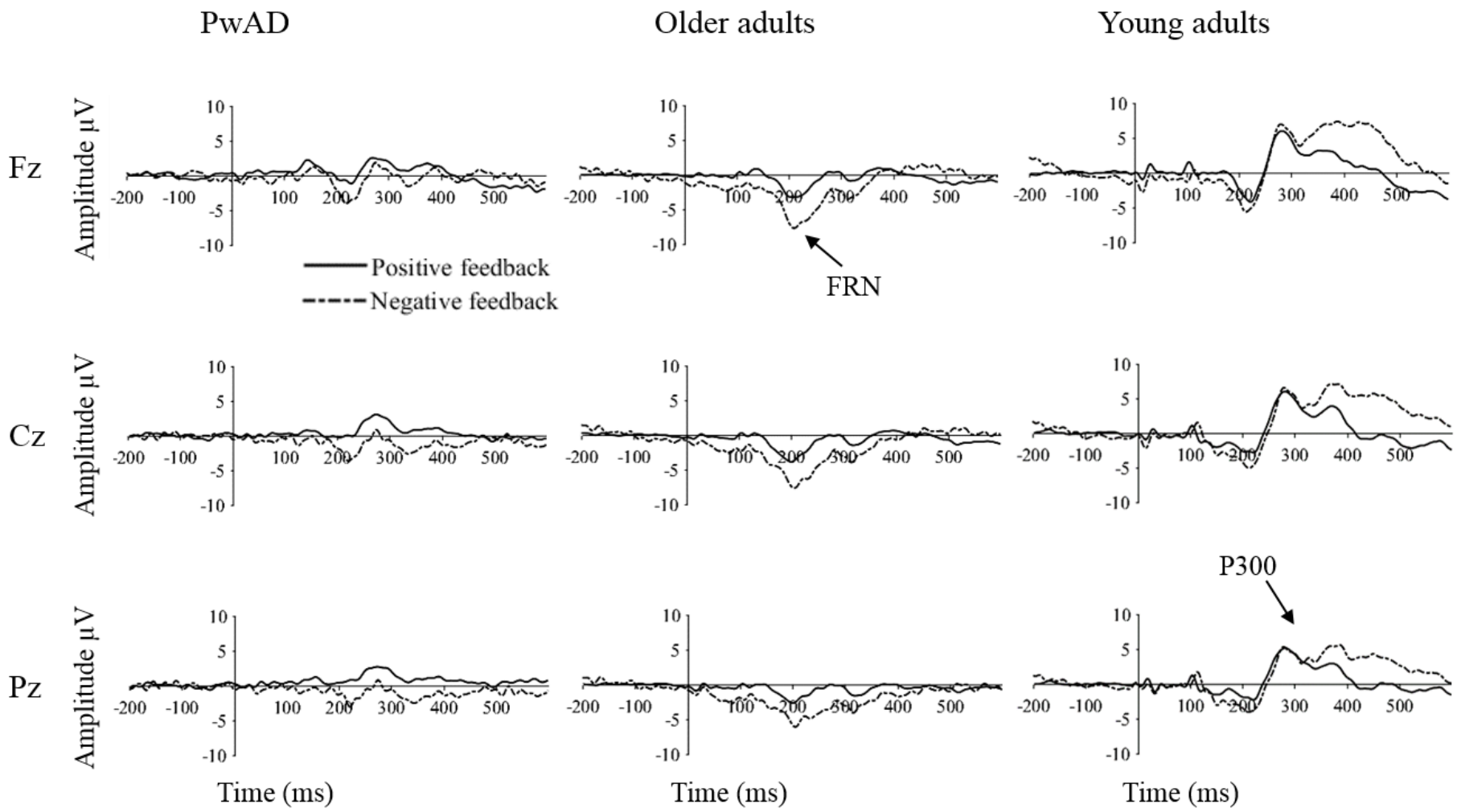

Figure 3 – Feedback-locked ERP waveforms at Fz, Cz, and Pz, for PwAD (n = 10), older (n = 15) and young adults (n = 15) following positive (solid line) and negative (dotted line) feedback in the time window -200 - 600 ms (positive voltage is plotted up). A period of 200 ms before feedback onset was used as baseline.

Article 3

Fischer, A., Lobo, I., Salles, B., Laks, J., Landeira-Fernandez, J., & Mograbi, D. C. Emotional reactivity in Alzheimer's disease and healthy aging. (In preparation)

Abstract

In the presence of substantial cognitive decline caused by Alzheimer's Disease (AD), it is crucial to focus on preserved abilities to improve quality of life for patients and caregivers. Affective processing abilities have been increasingly investigated in AD in recent decades. The present study examined emotional reactivity to negative, self-relevant, and neutral pictures in people with AD (PwAD; n = 15), healthy older (n = 18), and young adults (n = 24), combining data from affective ratings, event-related potentials (the late positive potential; LPP), and facial expression recordings. Results showed that emotional reactivity of PwAD was similar to young adults, whereas older adults showed elevated subjective ratings and diminished neurophysiologic responses. The enhanced neurophysiologic responses to emotional stimuli of PwAD compared to healthy older adults could be related to a lack of cognitive control mechanisms. Moreover, LPP amplitudes were elevated for self-relevant stimuli in PwAD, although those were not subjectively perceived as more salient than negative pictures. Our results give further evidence for relatively preserved emotional capacities in PwAD, further suggesting we should maximize our efforts in developing approaches that use these preserved abilities to improve clinical and home care.

Key words

Awareness; apathy; EEG; LPP; self-relevant stimuli

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that was classically characterized by principal cognitive impairments. In recent decades, the field has seen growing interest in exploring gains and losses in affective processing in AD (for reviews see Klein-Koerkamp, Beaudoin, Baciu, & Hot, 2012; Zhang, Ho, & Fung, 2015), as well as its relation to awareness (e.g., Mograbi, Brown, Salas, & Morris, 2012). Emotional processing may have a deeper impact than cognition in the prognosis of dementia, since it has been shown that emotion perception is related to well-being (Phillips, Scott, Henry, Mowat, & Bell, 2010), and that affective alterations already occur before a cognitive decline in AD (Fredericks et al., 2018). Furthermore, affective processing seems to be less impaired than cognition in people with AD (PwAD), and thus could represent a chance for compensation and innovative therapy concepts.

Whereas impairments exist regarding identification of facial emotions (for reviews see Klein-Koerkamp et al., 2012; McLellan, Johnston, Dalrymple-Alford, & Porter, 2008), emotional reactivity to affective stimuli seems to be largely preserved when using film clips (Goodkind et al., 2015; Henry, Rendell, Scicluna, Jackson, & Phillips, 2009; Mograbi & Morris, 2013; Smith, 1995). Some studies used pictures from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2008), and findings support preserved emotional reactivity in PwAD to emotional pictures, indicated by similar arousal (Burton & Kaszniak, 2006; Hamann, Monarch, & Goldstein, 2000) and valence ratings (Baran, Cangöz, & Ozel-Kizil, 2014; Burton & Kaszniak, 2006; Schultz, De Castro, & Bertolucci, 2009), as well as no differences in physiologic measures, like skin conductance response (Hamann et al., 2000) compared to healthy older controls. In addition to physiological data, behavioral data, such as facial expressions, has also been explored in response to emotional stimuli. Again, studies found relatively preserved facial expressions in PwAD in response to affective stimuli (Chen et al., 2017; Goodkind et al., 2015; Mograbi, Brown, & Morris, 2012).

One important factor mediating reactivity is self-relevance of stimuli. Initial research comparing younger and older adults suggested alterations in reactivity in the latter group, with no differences in subjective experience, but diminished autonomic responses (Labouvie-Vief, Lumley, Jain, & Heinze, 2003; Tsai, Levenson, & Carstensen, 2000). However, more recent findings contradicted this notion, suggesting that previous studies did not use stimuli appropriate for this age group. Using material related to health issues and personal losses (e.g. cancer films) Kunzmann and Grühn (2005) identified personal relevance as a key factor driving emotional reactivity in older adults. In their study, healthy older adults showed greater subjective and similar physiological reactions to negative film clips that were relevant to their age, in comparison to young participants.

For PwAD self-relevance could be an important factor as well, also linking emotional reactivity to awareness. Reduced awareness about the condition itself or related deficits, also called anosognosia, is a common feature in AD (Morris & Hannesdottir, 2004). It has important implications regarding treatment compliance (Patel & Prince, 2001), caregiver burden (Verhülsdonk, Quack, Höft, Lange-Asschenfeldt, & Supprian, 2013), exposure to dangerous behaviors (Starkstein, Jorge, Mizrahi, Adrian, & Robinson, 2007), and earlier institutionalization (Horning, Melrose, & Sultzer, 2014). Mograbi and colleagues (Mograbi, Brown, & Morris, 2012) suggested that self-relevant stimuli would produce greater emotional reactivity only in aware PwAD who identify with the content of the stimulus material, and that awareness could mediate reactions to self-relevant stimuli. In line with this, Clare and colleagues (Clare et al., 2012) reported that PwAD are more likely to provide appropriate advice for people with dementia presented in vignettes, when they had higher levels of awareness of their own condition. Personal relevance seems to be important for affective processes, but illness related material has not often been used in investigating this relationship in AD. Moreover, it has been suggested that also apathy influences emotional reactivity (Eling, Maes, & Van Haaf, 2006; Mograbi & Morris, 2014) and awareness in PwAD by depriving experiences of their emotional depth, which then fail to receive attention (Mograbi & Morris, 2014).

Because of their excellent temporal resolution, event-related potentials (ERPs) could represent a great opportunity to gain deeper insight in the time course of affective processes (Hajcak, Weinberg, MacNamara, & Foti, 2012). The late positive potential (LPP) is a marker of emotional reactivity, since it has been shown that its amplitude is elevated for emotional compared to neutral stimuli (Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Hajcak & Olvet, 2008; Schupp et al., 2000). Whereas valence seems to influence relatively early components in the 100 to 250 ms range, arousal appears to influence later components around 200 to 1000 ms after stimulus onset (Olofsson, Nordin, Sequeira, & Polich, 2008; Olofsson & Polich, 2007). To the best of our knowledge, the LPP has not yet been investigated in relation to emotional reactivity in PwAD. Studies investigating the effect of aging on emotional reactivity, frequently found no differences in subjective ratings of emotional stimuli between young and older adults, but a decline of physiologic responses to unpleasant stimuli related to aging (Kisley, Wood, & Burrows, 2007; Kunzmann & Grühn, 2005; Mathieu et al., 2014). Some studies also reported elevated emotional reactivity for positive stimuli reflected in subjective and behavioral data, as well as in increased LPP amplitudes for older adults (Langeslag & Van Strien, 2009; Meng et al., 2015).

The present study aims to investigate reactivity to emotional and self-relevant stimuli in PwAD, healthy older and young adults, using ERPs, facial expression recordings, and ratings of emotional stimuli. We aim to gain a deeper understanding of the time course of emotional processing in PwAD by investigating the LPP. According to the literature, we hypothesize an aging effect in emotional reactivity reflected by diminished neurophysiologic responses to negative stimuli in healthy older adults. Due to higher levels of apathy, we expect a decrease in the neurophysiologic responses to negative stimuli in PwAD compared to older and young adults. Additionally, we explore the idea of heightened significance of self-relevant stimuli in PwAD, which should be reflected in increased LPP amplitudes compared to controls. Although we expect PwAD to have fairly preserved subjective emotional reactivity, reflected by similar ratings and facial expressions as healthy older controls, it is our goal to investigate if potential alterations in emotional reactivity behavior are related to neurophysiological changes.

Methods

Participants

67 participants were recruited. 16 PwAD were recruited from an outpatient unit at the Alzheimer's Disease Centre at the Institute of Psychiatry at the Federal University of Rio de Janeiro (CDA-IPUB-UFRJ). PwAD were asked to participate with a caregiver who could act as informant. AD was diagnosed by a psychiatrist according to the DSM-IV-TR (American Psychiatric Association, 2000). Therapy and medication of PwAD was done at the outpatient unit. A total of 21 healthy older adults were recruited in the vicinity of the universities and the clinic. A total of 30 young adults were recruited amongst college students from the Federal University and the Pontifical Catholic University of Rio de Janeiro. Characteristics of participants can be seen in Table 1.

Exclusion criteria were psychiatric or neurological diseases (other than AD, in the PwAD group) diagnosed according to the ICD-10 (World Health Organization, 2004) criteria, e.g. major depressive disorder and anxiety disorders, excluding also cases with mixed or vascular dementia in the PwAD group; head trauma with loss of consciousness for more than one hour, as well as abuse of alcohol or other drugs, except tobacco. Moreover, participants with uncorrected hearing loss or visual impairment were not included in the study. All participants had a minimum of four years of formal education. The age range for healthy young volunteers was 18 to 30 years, and a minimum of 60 years for older adults and PwAD. All participants underwent a brief neuropsychological assessment, which was carried out by a psychologist. All participants provided written informed consent before the experiment, with caregivers validating consent in the case of patients. The study was conducted under ethical approval of the ethics committee of the IPUB-UFRJ (CAAE: 63181816.8.0000.5263).

In addition to the above, a depression screening was conducted to exclude participants with undiagnosed depressive symptoms. Level of depression was measured with the Beck's Depression Inventory II (BDI II; Beck, Steer, & Brown, 1996; Gomes-Oliveira, Gorenstein, Neto, Andrade, & Wang, 2012) for young adults.

According to the authors, a cut-off score of more than 14 points is indicative of mild depression and was thus used as exclusion criterion. The Geriatric Depression Scale (GDS; Almeida & Almeida, 1999a; Sheikh & Yesavage, 1986) was used to screen PwAD and healthy older adults for depression. A cut-off score above seven points was used as exclusion criterion (Almeida & Almeida, 1999b). One participant in the AD group, three in the healthy older adult group, and six in the young adult group were excluded. The final sample consisted of 15 PwAD, 18 healthy older, and 24 healthy young adults.

PLEASE INSERT TABLE 1 HERE.

Instruments

Cognition

The Addenbrooke's Cognitive Examination Revised (ACE-r; Carvalho & Caramelli, 2007; Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006) was used to assess cognitive impairment in PwAD, whereas the Mini-Mental State Examination (MMSE; Bertolucci, Brucki, Campacci, & Juliano, 1994; Folstein, Folstein, & McHugh, 1975) was used as a control measure for healthy participants. Since the MMSE is part of the ACE-r, it was possible to compare the groups on the MMSE score. The ACR-r measures orientation, attention, memory, verbal fluency, language, and visuospatial abilities with a maximum score of 100 and a cut-off score of 83 points for the presence of dementia. The MMSE is a screening tool for global cognition assessing orientation, registration, short-term memory, language use, comprehension, and basic motor skills. The total score ranges from zero to 30 points, with lower scores indicating more impaired cognition. We applied education-adjusted cut-off scores (Bertolucci et al., 1994), and scores below 24 were used as exclusion criterion for healthy participants.

Awareness of disease

Awareness of condition was assessed for PwAD using a short version of the Assessment Scale of Psychosocial Impact of the Diagnosis of Dementia (ASPIDD; Dourado, Laks, & Mograbi, 2019). The scale includes twelve items to evaluate awareness in four domains: cognitive functioning and health condition, instrumental and basic activities of daily living (ADL), emotional state, as well as social functioning and relationships. The scoring is based on discrepant responses of self- and caregiver reports, whereby both answer the same questions with frequently (four points), sometimes (three points), rarely (two points), or never (one point). The score is calculated as the sum of discrepant answers (caregiver minus patient rating), thus positive values indicate over-estimation.

Apathy

The degree of apathy was evaluated only in PwAD and healthy older adults, using the Apathy Evaluation Scale (AES; Caeiro, Silva, Ferro, Pais-Ribeiro, & Figueira, 2012; Marin, Biedrzycki, & Firinciogullari, 1991). It has 18 items with answers ranging from “not at all true” (four points) to “very true” (one point) resulting in a score between 18 and 72 points. Higher scores indicate higher levels of apathy. Apathy was evaluated as self-report for older adults and as caregiver report for PwAD.

Procedure

Participants were received in a room at the CDA-IPUB-UFRJ by two experimenters. Before starting the experimental task (described below), all participants signed the informed consent and answered the demographic questionnaire. After that, participants were prepared for the recording of the electroencephalogram (EEG). In the case of PwAD, the caregiver answered questionnaires during this period (see below). Once the experimental task was finished, the electrodes were removed. Following a short break, participants answered the questionnaires, as well as the MMSE or ACE-r. Healthy participants completed all questionnaires by themselves,

except the MMSE, which was carried out by a psychologist. PwAD completed ratings of awareness (ASPIDD), level of depression (GDS), and were tested for cognitive functioning (ACE-r) by a psychologist. Caregivers completed all demographic information, as well as informant ratings of awareness (ASPIDD) and apathy (AES). If needed, the experimenter helped PwAD completing the questionnaires by reading the questions aloud and explaining them.

Emotional reactivity task

E-prime 3 professional (Psychology Software Tools) was used to create the task. Participants were seated approximately 70 cm in front of a computer screen and asked to fixate the middle of the screen. Each trial started with the presentation of a fixation cross for 500 ms, followed by an instruction slide "view" for a variable interval between 1700 and 2000 ms. Participants were instructed to passively view the image following this instruction and to react naturally without trying to regulate their emotions. Instructions were emphasized again in between the blocks for PwAD. The images were presented for 4000 ms and could be negative, neutral or dementia-related (see below). After viewing the pictures, participants rated their emotions on a computerized version of the arousal and valence scales of the Self-Assessment Manikin (SAM; Bradley & Lang, 1994). Both rating scales use pictures of manikins that range from no arousal (1) to high arousal (9), and from high negative valence (1) to high positive valence (9), respectively (see Figure 1). At the beginning of the task, participants completed twelve practice trails (four in each condition) to familiarize with the task and the rating scales. After the practice phase, participants were asked to explain what they have to do during the task to ensure that the concept of passively viewing the pictures and of the SAM was well understood. The training phase was repeated if necessary. The task was divided into three blocks with a total duration of approximately 30 minutes, whereas 27 images were presented randomly in each block. In between the blocks, participants could take breaks. EEG and facial expressions of the participants were recorded during the task. After the experiment

was finished, participants were informed about the experiment, and offered to obtain the results of their neuropsychological assessment and questionnaires via e-mail.

PLEASE INSERT FIGURE 1 HERE.

Stimuli

Negative, neutral, and dementia-related pictures were presented to the participants. Each category consisted of 27 pictures, which were shown randomly in three blocks, whereby always nine pictures of each category were included in each block. Pictures were presented full screen on a 22 inch monitor. Negative and neutral images were taken from the IAPS (Lang et al., 2008), whereby negative images had low valence (M = 2.39, SD = 0.64) and high arousal (M = 5.92, SD = 0.76), and neutral images had medium valence (M = 5.25, SD = 0.58) and low arousal (M = 3.43, SD = 0.5). Negative pictures depicted mutilations or people in dangerous or tragic situations, including fearful, angry or sad face expressions. Neutral images depicted people in daily life situations that were apparently healthy, or portraits with a neutral face expression. The dementia related pictures were taken from the internet. In total 50 pictures were chosen and evaluated by five raters. The 27 images rated to be most related to dementia were selected and included in the task. The images depicted older adults with difficulty performing daily household tasks such as eating or dressing, as well as older adults in need of help and with facial expressions that indicate doubt or forgetfulness. Those stimuli are exploratory and were included because they were thought to represent self-relevant stimuli for PwAD. All pictures showed humans or human body parts, and physical characteristics of all images were matched on spatial frequency, contrast, and brightness.

EEG recording and preprocessing

EEG was recorded with an EMSA BrainNet BNT 36 amplifier from 20 AgCl electrodes (Fp2, Fp1, F8, F4, Fz, F3, F7, C4, Cz, C3, T8, T7, P8, P4, Pz, P3, P7, O2, Oz, O1) with electrode Cz as online reference, and a sampling rate of 600 Hz. A chin support was used to limit head movements. The electrodes were attached to a cap according to the 10/20 system. The signal was filtered online with a low-pass filter of 70 Hz, a high-pass filter of 0.1 Hz, and a notch filter to remove 60 Hz electrical noise. All impedances were kept below 5 kΩ. The software EEGLAB (Delorme & Makeig, 2004) and ERPLAB (Lopez-Calderon & Luck, 2014) were used for preprocessing. The signal was re-referenced to the average of the left and right mastoids and filtered offline with a low-pass filter. Filters and baseline corrections were necessary because of a lower signal-to-noise ratio in older adults, especially in PwAD. Signal distortions caused by filters are a serious issue in ERP research (Widmann, Schröger, & Maess, 2015). The offline filter was carefully designed; a zero-phase (non-causal), one-pass FIR filter with a cut-off frequency of 50.625 Hz (-6 dB), a filter order of 176, and a transition band width of 11.25 Hz was used to low-pass filter the signal, as implemented in the firfilt EEGLAB function. Afterwards, the signal was cut into segments of interest, 200 ms before stimulus onset (baseline) until 2000 ms post-stimulus. ICA was applied to remove blinks and horizontal eye movements. Epochs in which the signal exceeded +/- 100 μV were excluded from statistical analyses. Participants with a minimum of eight trials in each condition after the preprocessing were included in the analyses (Moran, Jendrusina, & Moser, 2013). Because of technical problems, three PwAD had to be excluded, as well as four more because of too little trials after preprocessing. In the older adult group, two participants had to be excluded because of technical problems, and five because of less than eight trials per condition. For young adults, four were excluded because of technical problems, and two more because of an insufficient number of trials. Thus, the final sample for EEG analyses consisted of eight PwAD, eleven older, and 18 young adults.

Facial expression recording and preprocessing

Facial expressions of participants were recorded during the task using a Logitech C920 Pro full HD webcam. From those recordings, two trials per block per condition (negative, neutral, dementia-related) were selected randomly and analyzed using the Facial Action Coding System (FACS; Ekman, Friesen, & Hager, 2002), by a coder blind to the study design and group membership. Facial expressions were categorized for all conditions in specific emotional labels as anger, contempt, disgust, fear, happiness, interest, sadness, surprise, and pain (single emotions). In addition, intensity of the emotional expressions was evaluated on a scale from one to five, according to the FACS methodology (Ekman et al., 2002), with five representing the highest intensity. Repertoire, the number of different action units (facial behavior assessed by the FACS), was also registered. Finally, facial expressions were characterized more generally according to their valence as positive (happiness, interest) or negative (anger, contempt, disgust, fear, pain).

Statistical analyses

Descriptive statistics were used to illustrate sample characteristics. Differences in age and apathy between PwAD and older adults were tested with t-tests for independent samples. MMSE scores were analyzed using a one-way analysis of variance (ANOVA) followed by post-hoc t-tests. To test differences in gender and education levels between groups, χ^2 tests were used. Because of a small sample size and imbalanced cell distributions, p-values of χ^2 tests were corrected using Fisher's exact test to compare gender and education between groups. Due to Bonferroni correction the alpha level is set to $p = .017$ for these post-hoc tests. Follow-up analyses were performed to evaluate whether gender or educational level of the participants influenced emotional reactivity. For each planned ANOVA (see below), a second ANOVA was computed, with gender and educational level (primary, high school, university) instead of group as between-subject factors.

The data was screened for outliers. Cases, which differed three standard deviations (SD) or more from the mean were excluded from the data analyses which included the variable in question. Mixed-design ANOVAs were computed to analyze key outcomes of the study with group (PwAD, older adults, young adults) as between subject factor. To analyze valence and arousal ratings of the SAM, two mixed-design ANOVAs with category (negative, dementia-related, neutral) as within-subject factors were computed. Regarding facial expressions, we computed mixed-design ANOVAs for positive and negative valence, intensity, repertoire, and single emotions, with category as within-subject factor. To analyze statistical differences in the LPP, positive area amplitudes were computed. Based on the literature and grand average waveforms, three time windows were chosen: 200 - 800 ms (early), 800 - 1400 ms (middle), and 1400 - 2000 ms (late) after stimulus onset. Time windows were chosen to investigate effects on the LPP over time (Hajcak, Macnamara, & Olvet, 2010). Since the LPP has a centro-parietal scalp distribution (Hajcak et al., 2010), ANOVAs were calculated separately for electrodes Cz and Pz. Thus, two 3x3x3 mixed-design ANOVAs with category (negative, dementia-related, neutral), and time (early, middle, late) as within- and, as for the other analyses, group as between-subject factor were computed. Moreover, 50 % fractional area latencies were computed and compared for the early time window to investigate if the timing of the LPP differed between electrodes, categories or groups. A 2x3x3 mixed design ANOVA was computed, with electrode (Cz, Pz), and category (negative, dementia-related, neutral) as within-subject factors.

Effects are reported including partial η^2 (η_p^2) as a measure of effect size. According to Cohen (1988), $\eta_p^2 \geq .06$ corresponds with a medium effect size (.25), and $\eta_p^2 \geq .14$ with a large effect size (.40). Greenhouse-Geisser correction procedure was used when sphericity assumptions were violated. Post hoc comparisons were corrected using the Bonferroni procedure.

Finally, bivariate Pearson correlations were computed between key outcomes, as well as for ASPIDD and AES scores for PwAD. ASPIDD scores were correlated with neurophysiologic responses, facial expression, and ratings for dementia-related and

negative pictures to explore the relationship between awareness and self-relevant, as well as negative stimuli. The AES scores were correlated with the LPP amplitudes, facial expressions, and ratings for negative pictures to investigate if a higher level of apathy leads to diminished responses to emotional stimuli. Statistical analyses were carried out with SPSS version 21. For all analyses α was set at .05, two-tailed.

Results

Sociodemographic and clinical variables

PwAD and healthy older adults differed regarding age ($t(22.7) = -3.6$, $p = .001$). Furthermore, groups differed significantly for gender ($\chi^2(2) = 14.2$, Fisher's exact $p < .001$), and educational level ($\chi^2(4) = 29.5$, Fisher's exact $p < .001$). Post-hoc comparisons showed that PwAD and healthy older adults differed in relation to gender ($\chi^2(1) = 7.5$, Fisher's exact $p = .012$), and education ($\chi^2(2) = 12.8$, Fisher's exact $p = .001$). Young adults differed regarding education from PwAD ($\chi^2(2) = 21.5$, Fisher's exact $p < .001$), as well as from older adults for gender ($\chi^2(1) = 14.1$, Fisher's exact $p < .001$). As expected, MMSE scores ($F(2, 56) = 97.8$, $p < .001$) were lower for PwAD than for the other groups (both $p < .001$), and PwAD had higher levels of apathy than healthy older adults ($t(16.0) = -8.9$, $p < .001$).

Self-report measures – SAM

For valence ratings, one outlier in the older adult group was identified and excluded from this analysis. For valence ratings, the interaction term was significant ($F(4, 106) = 5.5$, $p < .001$, $\eta_p^2 = .17$). Post-hoc tests showed that older adults rated negative pictures more negative than young adults and PwAD (both $p = .005$). A main effect of category was also found ($F(2, 106) = 237.2$, $p < .001$, $\eta_p^2 = .82$), whereas groups did not differ significantly ($F(2, 53) = 1.2$, $p = .317$, $\eta_p^2 = .04$). Post-hoc comparisons showed significant differences between all conditions (Figure 2; all $p < .001$, except for neutral and dementia pictures in PwAD $p = .021$). Regarding arousal, the

interaction was not significant ($F(2.6, 71.1) = 2.1$, $p = .117$, $\eta_p^2 = .07$), but category (Figure 3; $F(1.3, 71.1) = 136.1$, $p < .001$, $\eta_p^2 = .72$) and group ($F(2, 54) = 6.1$, $p = .004$, $\eta_p^2 = .18$) differed significantly. Post-hoc comparisons showed p-values < .001 between all categories. Furthermore, older adults rated pictures of all categories significantly more arousing than PwAD ($p = .005$) and young adults ($p = .033$).

PLEASE INSERT FIGURE 2 HERE.

PLEASE INSERT FIGURE 3 HERE.

Facial expressions

Due to failure with recordings, some participants had to be excluded for these analyses (final sample sizes were n = 16 for young adults, n = 12 for older adults, and n = 12 for PwAD). Regarding intensity of facial expressions, the interaction category*group was significant ($F(4.0, 73.5) = 4.5$, $p = .003$, $\eta_p^2 = .20$). Facial expressions of young adults were less intense than those of older adults for all categories ($p_{neutral} = .001$, $p_{dementia} = .037$, $p_{negative} = .003$) and than those of PwAD in negative picture trials ($p = .001$). A main effect of category was found ($F(2.0, 73.5) = 3.1$, $p = .050$, $\eta_p^2 = .08$), with post-hoc tests showing more intense facial expressions for negative compared to dementia trials ($p = .045$). Moreover, the group effect was significant ($F(2, 37) = 6.6$, $p = .003$, $\eta_p^2 = .26$). Post-hoc comparisons showed less intense expressions for young compared to older adults ($p = .005$), and to PwAD ($p = .042$).

For the variable repertoire, the interaction was not significant ($F(4, 74) = 1.2$, $p = .323$, $\eta_p^2 = .06$), but a significant effect for category was found ($F(2, 74) = 3.9$, $p = .025$, $\eta_p^2 = .10$), with negative picture trials evoking more action units than dementia trials ($p = .030$). Factor group was also significant ($F(2, 37) = 4.1$, $p = .025$, $\eta_p^2 = .18$). Post-hoc tests showed less action units of young adults than of PwAD ($p = .039$).

Regarding single emotions, a main effect of category was found for anger ($F(1.3, 47.8) = 4.2$, $p = .037$, $\eta_p^2 = .10$), with more angry face expressions being evoked for negative compared to dementia-related images ($p = .021$). The interaction was not significant ($F(2.6, 47.8) = 1.1$, $p = .363$, $\eta_p^2 = .06$), as well as the group effect ($F(2, 37) = 2.3$, $p = .113$, $\eta_p^2 = .11$). For disgust, a main effect of category was also found ($F(1.2, 44.0) = 3.9$, $p = .047$, $\eta_p^2 = .10$), with negative pictures evoking more disgust expressions than neutral ($p = .009$) and dementia-related pictures ($p = .037$). Again, the interaction ($F(2.4, 44.0) = 0.5$, $p = .621$, $\eta_p^2 = .03$) and the group factor ($F(2, 37) = 0.9$, $p = .427$, $\eta_p^2 = .05$) were not significant.

One outlier in each group was identified for positive valence and excluded from this analysis. The main effect of category was significant ($F(1.4, 46.2) = 5.8$, $p = .013$, $\eta_p^2 = .15$). Negative pictures evoked significantly fewer positive expressions than dementia-related pictures ($p = .028$). The interaction ($F(2.7, 46.2) = 0.5$, $p = .650$, $\eta_p^2 = .03$), as well as factor group ($F(2, 34) = 0.5$, $p = .601$, $\eta_p^2 = .03$) were not significant. No effects were found for negative valence (interaction ($F(4, 74) = 1.6$, $p = .187$, $\eta_p^2 = .08$); category ($F(2, 74) = 2.2$, $p = .117$, $\eta_p^2 = .06$); group ($F(2, 37) = 2.1$, $p = .139$, $\eta_p^2 = .10$)).

LPP

Two outliers were detected in the young adult group and excluded from these analyses. No effects were found regarding latencies (see Table 2). For electrode Cz, a significant time*group interaction was found ($F(2.6, 41.5) = 3.5$, $p = .012$, $\eta_p^2 = .18$). Post-hoc comparisons revealed that young adults had larger amplitudes than older adults in the early time window ($p = .012$). Moreover, older controls differed from PwAD in middle ($p = .005$) and late ($p = .013$) time windows, with PwAD having larger amplitudes. Furthermore, there was a significant effect of time ($F(1.3, 41.5) = 68.5$, $p < .001$, $\eta_p^2 = .68$), with post-hoc tests showing that amplitudes were larger in the early than in the middle and late time windows (both $p < .001$). Finally, a significant group effect was found ($F(2, 32) = 4.1$, $p = .026$, $\eta_p^2 = .21$). Post-hoc comparisons showed smaller amplitudes for older adults compared to young adults (p

= .035). The interactions category*group (F(3.5, 56.1) = 0.4, p = .814, η_p^2 = .02), time*category*group (F(5.0, 79.8) = 1.2, p = .324, η_p^2 = .07), as well as factor category (F(1.8, 56.1) = 1.7, p = .197, η_p^2 = .05) were not significant.

At electrode Pz, a significant main effect of time was found (F(1.3, 42.5) = 52.7, p < .001, η_p^2 = .62). Post-hoc comparisons revealed larger amplitudes in the early than in the middle and late time windows (both p < .001). There was also a significant group effect (F(2, 32) = 5.1, p = .012, η_p^2 = .24), with PwAD having larger amplitudes than older adults (p = .011). A trend with a large effect size was found for the time*group interaction (F(2.7, 42.5) = 2.7, p = .067, η_p^2 = .14), and a trend with a medium effect size for the interaction time*category*group was also observed (F(4.6, 73.9) = 2.3, p = .059, η_p^2 = .13). Amplitude values of the LPP are reported in Table 3. Figure 4 represents stimulus-locked LPP waveforms at electrodes Fz, Cz, Pz and Oz for all groups and categories. The interactions category*group (F(3.0, 48.8) = 0.6, p = .593, η_p^2 = .04), and category*time (F(2.3, 73.9) = 1.5, p = .224, η_p^2 = .05), as well as factor category (F(1.5, 48.8) = 0.1, p = .871, η_p^2 = .00) were not significant.

PLEASE INSERT TABLE 2 HERE.

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PLEASE INSERT FIGURE 4 HERE.

Correlation analyses

SAM valence and arousal ratings were not correlated with LPP characteristics. However, intensity of facial expressions was correlated with SAM valence ratings in neutral picture trials (r = .337, p = .033). Moreover, intensity of facial expression was correlated with amplitudes at electrode Pz in the middle time window for dementia-

related pictures (r = -.435, p = .030). AES scores were only related to amplitudes at electrode Cz in the early time window for PwAD after negative pictures (r = -.758, p = .029). The ASPIDD total score was not correlated with LPP amplitudes, facial expression indices, and SAM ratings, but the social sub-score was correlated to arousal ratings of dementia pictures (r = -.622, p = .013). Moreover, the cognition sub-score was correlated with amplitude at electrode Pz in the early (r = -.831, p = .011) and middle time window (r = -.729, p = .040) after negative pictures.

Follow-up analyses

Regarding the follow-up analyses to examine effects of gender and education level on emotional reactivity, no significant main effect or any interaction with other factors was found for gender or education regarding SAM valence and arousal ratings. For facial expressions, a significant main effect of factor education ($F(2, 34) = 4.2$, $p = .024$, $\eta_p^2 = .20$), as well as a significant interaction gender*education ($F(2, 34) = 6.5$, $p = .004$, $\eta_p^2 = .28$) were found for the variable repertoire. The interaction term gender*education was also significant for the variable intensity ($F(3.9, 60.8) = 3.8$, $p = .032$, $\eta_p^2 = .18$). Regarding LPP amplitude, no main effects of gender, educational level, or any interactions were observed at electrode Cz. At electrode Pz, also no main effects were found, but the interaction category*education ($F(3.9, 60.8) = 2.6$, $p = .048$, $\eta_p^2 = .14$), as well as category*education*gender ($F(3.9, 60.8) = 4.0$, $p = .006$, $\eta_p^2 = .21$) were significant.

Discussion

The present study investigated emotional reactivity to negative, dementia-related, and neutral pictures in PwAD, healthy older and young adults, as well as its relationship with apathy and awareness. PwAD and young adults did not differ regarding subjective emotional reactivity, whereas healthy older adults showed more extreme ratings of valence and arousal. Negative pictures evoked more intense facial expressions than dementia-related pictures, with young adults showing the least

intensity. Moreover, negative pictures evoked more anger related expressions than dementia-related pictures, and more disgust related expressions than neutral and dementia-related pictures. The effects of valence and arousal of the pictures that were reflected in subjective ratings and facial expressions, was surprisingly absent in the ERP data. Older adults had smaller amplitudes than young adults and PwAD.

The pattern of our results supports relatively preserved emotional reactivity in PwAD. Although some studies reported slightly decreased emotional reactivity in PwAD (Drago et al., 2010; Eling et al., 2006; Mograbi, Brown, & Morris, 2012), our findings are consistent with previous research showing that physiologic responses (Chen et al., 2017; Hamann et al., 2000; Mograbi & Morris, 2013), as well as subjective ratings (Baran et al., 2014; Burton & Kaszniak, 2006; Goodkind et al., 2015; Hamann et al., 2000; Henry et al., 2009; Schultz et al., 2009) are preserved in PwAD.

Healthy older adults showed heightened arousal ratings across all categories but diminished neurophysiological responses. This is consistent with previous research reporting smaller LPP amplitudes for negative and neutral stimuli (Mathieu et al., 2014), as well as elevated arousal ratings for negative pictures (Grühn & Scheibe, 2008) in older compared to young adults. Also, when using age-relevant negative film clips, older adults reported greater sadness than young adults in response to the films (Kunzmann & Grühn, 2005; Kunzmann & Richter, 2009). Because physiological activity in older adults was comparable to young adults, the authors speculated that physiological and subjective reactions to emotional stimuli become more disconnected with age, which could be accompanied by an increasing cognitive influence on affective processes (Kunzmann & Richter, 2009). Olofsson and colleagues (2008) argue that waveforms of affective ERPs could reflect coping abilities for unpleasant situations, and therefore the emotional ERP reactivity could depend on executive control capacities. PwAD in our study did not show such an age-related decrease of neurophysiological responses, but rather indicated an elevation in comparison to older adults. Therefore, our results could be in line with the ideas of Kunzmann and Richter (2009) and Olofsson and colleagues (2008). A lack of

cognitive control could make PwAD more prone to affective stimuli in their environment, as also suggested by Sturm and colleagues (2013), and thus lead to enhanced neurophysiological responses to emotional stimuli. Although speculation, it would be interesting to further investigate the role of cognitive control mechanisms in emotional reactivity for PwAD in future studies.

Furthermore, it has been proposed that stimuli which are personally relevant, could drive emotional reactivity (Kunzmann & Grühn, 2005; Kunzmann & Richter, 2009). Valence and arousal ratings of the included explorative dementia-related images were different than for negative and neutral stimuli, but neither PwAD nor older adults rated those pictures different than young adults. Our results show that potentially self-relevant pictures are not subjectively perceived as more salient or affect-laden than negative pictures by PwAD. This is in line with previous research (Mograbi, Brown, & Morris, 2012), also suggesting that personal experience with dementia does not lead to PwAD being more emotionally responsive to this topic. Nevertheless, we found indications for elevated LPP amplitudes in PwAD compared to older and young adults for dementia-related pictures in middle and late latency ranges, which could indicate that these stimuli possess higher motivational significance for PwAD becoming relevant in later processing stages. However, the quality of the dementia-related pictures has not been validated with a bigger sample, or with older adults. Even though we intended to present situations that indicate dementia related situations, such as difficulty performing daily household tasks, i.e. eating or dressing, or interactions with medical doctors, it is possible that participants perceived those pictures merely as depicting older adults interacting with family members or in daily life situations.

We also investigated associations between awareness, apathy, and emotional reactivity. Higher levels of apathy were associated with smaller LPP amplitudes in the early time window at electrode Cz for negative pictures in PwAD. Thus, apathy led to a reduction of neurophysiologic responses to unpleasant pictures but did not influence subjective ratings. A cognitive and an affective component of apathy could be linked to different processes of emotional reactivity, and these aspects of apathy

can be differently affected in dementia patients (Eling et al., 2006; Wei, Irish, Hodges, Piguet, & Kumfor, 2019). Indeed, the AES includes questions about goal oriented behaviors. A measure that focuses more on the affective component of apathy could be more appropriate to investigate the relationship with emotional reactivity on a subjective behavioral level.

Awareness scores were not correlated with subjective ratings, facial expressions, and LPP characteristics. However, awareness of social impairments was related to subjective arousal of dementia-related pictures. This is consistent with the content of those pictures being highly social, showing older people interacting with other persons in medical and caregiving settings. Furthermore, awareness of cognitive deficits was correlated with LPP amplitudes for negative pictures. Awareness is a multidimensional construct, that can be assessed for different domains (e.g. awareness of cognitive deficits, behavioral problems, functionality level; Aalten, Van Valen, Clare, Kenny, & Verhey, 2005), and each domain may influences different constructs. Thus, awareness of disease as an overall score could be too broad to investigate the relationship with affective reactions to emotional stimuli. On top of that, higher levels of depression are typically associated with higher levels of awareness (Aalten et al., 2006; Mograbi & Morris, 2014). Therefore, a possible effect might not have been shown because of restricted variance in our sample due to the exclusion of participants with clinical depression and with a high score on a depression rating scale.

Unexpectedly, the differences that were evident between negative, neutral, and dementia-related pictures in ratings of valence and arousal and in facial expressions, were not reflected in the characteristics of the LPP. Although unusual, there are several possible explanations. Whereas valence is thought to influence early components, arousal level appears to influence relatively late components (Olofsson et al., 2008; Olofsson & Polich, 2007). Thus, higher arousal leads to an increase in attentional resources for affective picture processing related to motivational significance of the stimulus (Olofsson et al., 2008; Weinberg & Hajcak, 2010). Indeed, studies show increased LPP amplitudes for high- compared to low-arousal

stimuli (Feng et al., 2014; Mathieu et al., 2014). The mean arousal values of neutral pictures derived from the IAPS that were used in other studies, which found a difference between negative and neutral stimuli, were much smaller than those used in our study (3.43 in our study compared to < 3.0 in e.g., Chen et al., 2018; Mathieu et al., 2014; Weinberg & Hajcak, 2010). This is also true for the dementia-related pictures that had slightly higher arousal ratings than neutral stimuli. In relation with this point, all images, including the neutral ones, depicted people or human body parts, whereas other studies typically used a mixture of landscape, object and animal pictures in the neutral category (Weinberg & Hajcak, 2010). It has been shown that neutral images that depict people attract more attention and elicit larger LPPs than pictures without people (Ito & Cacioppo, 2000; Weinberg & Hajcak, 2010). Finally, all pictures were presented randomly in the present study. To our knowledge, the effect of block- versus randomized designs on the LPP has not yet been tested, but several interferences like surprise and local probability effects (Weinberg & Hajcak, 2010), as well as carry-over effects from negative to neutral stimuli could influence the amplitude of the LPP. These would have to be tested in future studies to gain a clearer understanding of additional factors that might influence the LPP. Nevertheless, it seems likely that a combination of these factors could have contributed to elevated LPP amplitudes in neutral and dementia-related pictures in the present study, so that differences between the emotional categories are not evident in our study.

Limitations

Some limitations of the present study must be mentioned. Even though the effects found in this study had medium and large effect sizes, the sample sizes, especially for PwAD, were quite small. This could have led to power issues leading to effects not reaching significance despite reasonable effect sizes. Moreover, significant differences in age between PwAD and older adults, as well as regarding gender and education between groups were found. For ratings, no influences of gender or education were significant, whereas both variables had a limited influence on

neurophysiological responses. The biggest influence was found for intensity and repertoire of facial expressions. Kunzmann and Richter (2009) systematically tested the effects of gender and education on emotional reactivity. The authors found only little evidence that gender and education level make a difference in subjective and autonomic emotional reactivity. However, age is known as a variable that influences emotional reactivity, with many studies having shown an association between aging and alterations in processing of emotional stimuli, including decreased physiologic responses (Hajcak et al., 2012; Mathieu et al., 2014). PwAD in our sample did not differ from young adults, but only from older adults regarding subjective ratings, and furthermore showed elevated neurophysiologic responses compared to older adults. Therefore, it is unlikely that the higher age of PwAD is the factor causing these differences in emotional reactivity. Another factor that might have influenced our results could be cultural differences in emotional reactivity (Olofsson et al., 2008). Since our study was conducted in Brazil, cultural differences could complicate comparisons with results from studies that were conducted for example in North America or Europe. Research on emotional reactivity in PwAD is still scarce, and basic processes of emotional reactivity have yet to be investigated in this population. Therefore, we recommend to also include positive stimuli in future studies to explore PwAD's reactions to a broader emotional spectrum, as well as to maximize the difference between physiological responses to affective stimuli as discussed above. An alternative possibility could be the use of GIFs or film clips instead of pictures, which possess higher ecological validity (Goodkind et al., 2015).

Conclusion

We investigated emotional reactivity to negative, neutral and possible self-relevant stimuli in PwAD, healthy older, and healthy young adults. Emotional reactivity in this sample of PwAD was similar to young adults, whereas older adults showed elevated subjective ratings and diminished physiological responses. In line with previous research, physiological and subjective reactions to emotional stimuli might become more disconnected with age which could be due to an increasing cognitive

influence on affective processing (Kunzmann & Richter, 2009). We suggest that a lack of cognitive control mechanisms could be the reason why PwAD showed heightened neurophysiologic responses compared to older controls. It is important to further investigate PwAD's emotional processing capacities. In the presence of cognitive decline, preserved emotional abilities are not only an important point to consider for therapies, but also for the management of patients, for example by integrating emotional cues in PwAD's daily life. Focusing on, and thus using capacities that are still preserved, will benefit the quality of life of patients and caregivers much more than focusing on lost abilities.

References

Aalten, P., Van Valen, E., Clare, L., Kenny, G., & Verhey, F. (2005). Awareness in dementia: A review of clinical correlates. *Aging & Mental Health*, *9*(5), 414–422. https://doi.org/10.1080/13607860500143075

Aalten, P., Van Valen, E., De Vugt, M. E., Lousberg, R., Jolles, J., & Verhey, F. R. J. (2006). Awareness and behavioral problems in dementia patients: A prospective study. *International Psychogeriatrics*, *18*(1), 3–17. https://doi.org/10.1017/S1041610205002772

Almeida, O. P., & Almeida, S. A. (1999a). Confiabilidade da versão brasileira da Escala de Depressão em Geriatria (GDS) versão reduzida. *Arquivos de Neuro-Psiquiatria*, *57*(2B), 421–426. https://doi.org/10.1590/S0004-282X1999000300013

Almeida, O. P., & Almeida, S. A. (1999b). Short versions of the Geriatric Depression Scale: A study of their validity for the diagnosis of a major depressive episode according to ICD-10 and DSM-IV. *International Journal of Geriatric Psychiatry*, *14*(10), 858–865. https://doi.org/10.1002/(SICI)1099-1166(199910)14:10<858::AID-GPS35>3.0.CO;2-8

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., T). Washington, DC: American Psychiatric Association.

Baran, Z., Cangöz, B., & Ozel-Kizil, E. T. (2014). The impact of aging and Alzheimer's disease on emotional enhancement of memory. *European Neurology*, *72*(1–2), 30–37. https://doi.org/10.1159/000359924

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). Manual for the Beck depression inventory-II. *San Antonio, TX: Psychological Corporation*.

Bertolucci, P. H. F., Brucki, S. M. D., Campacci, S. R., & Juliano, Y. (1994). O Mini-Exame do Estado Mental em uma população geral: impacto da escolaridade. *Arquivos de Neuro-Psiquiatria*, *52*(1), 01–07. https://doi.org/10.1590/s0004-

282x1994000100001

Bradley, M., & Lang, P. J. (1994). Measuring Emotion: The Self-Assessment Semantic Differential Manikin and the. *Journal of Behavior Therapy and Experimental Psychiatry*, *25*(I), 49–59. https://doi.org/10.1016/0005-7916(94)90063-9

Burton, K., & Kaszniak, A. (2006). Emotional experience and facial expression in Alzheimer's disease. *Aging, Neuropsychology, and Cognition*. https://doi.org/10.1080/13825580600735085

Caeiro, L., Silva, T., Ferro, J. M., Pais-Ribeiro, J., & Figueira, M. L. (2012). Propriedades métricas da versão portuguesa da escala de avaliação de apatia. *Psicologia, Saúde & Doenças*, *13*(2), 266–282. https://doi.org/10.15309/12psd130209

Carvalho, V. A., & Caramelli, P. (2007). Adaptação brasileira do Exame Cognitivo de Addenbrooke-Revisado. *Dementia & Neuropsychologia*, *1*(2), 212–216. https://doi.org/10.1590/s1980-57642008dn10200015

Chen, D., Wu, J., Yao, Z., Lei, K., Luo, Y., & Li, Z. (2018). Negative association between resilience and event-related potentials evoked by negative emotion. *Scientific Reports*, *8*(1), 1–6. https://doi.org/10.1038/s41598-018-25555-w

Chen, K. H., Lwi, S. J., Hua, A. Y., Haase, C. M., Miller, B. L., & Levenson, R. W. (2017). Increased subjective experience of non-target emotions in patients with frontotemporal dementia and Alzheimer's disease. *Current Opinion in Behavioral Sciences*, *15*, 77–84. https://doi.org/10.1016/j.cobeha.2017.05.017

Clare, L., Nelis, S. M., Martyr, A., Whitaker, C. J., Marková, I. S., Roth, I., … Morris, R. G. (2012). "She might have what I have got": the potential utility of vignettes as an indirect measure of awareness in early-stage dementia. *Aging & Mental Health*, *16*(5), 566–575. https://doi.org/10.1080/13607863.2011.652594

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum Associates.

Cuthbert, B. N., Schupp, H. T., Bradley, M. M., Birbaumer, N., & Lang, P. J. (2000). Brain potentials in affective picture processing: Covariation with autonomic arousal and affective report. *Biological Psychology*, *52*(2), 95–111. https://doi.org/10.1016/S0301-0511(99)00044-7

Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*. https://doi.org/10.1016/j.jneumeth.2003.10.009

Dourado, M. C. N., Laks, J., & Mograbi, D. C. (2019). Awareness in Dementia: Development and Evaluation of a Short Version of the Assessment Scale of Psychosocial Impact of the Diagnosis of Dementia (ASPIDD-s) in Brazil. *Alzheimer Disease and Associated Disorders*, *33*(3), 220–225. https://doi.org/10.1097/WAD.0000000000000306

Drago, V., Foster, P. S., Chanei, L., Rembisz, J., Meador, K., Finney, G., & Heilman, K. M. (2010). Emotional indifference in Alzheimer's disease. *Journal of Neuropsychiatry and Clinical Neurosciences*, *22*(2), 236–242. https://doi.org/10.1176/jnp.2010.22.2.236

Ekman, P., Friesen, W. V., & Hager, J. C. (2002). *Facial Action Coding System - Investigator's Guide*. *FACS*.

Eling, P. A. T. M., Maes, J. H. R., & Van Haaf, M. (2006). Processing of emotionally toned pictures in dementia. *International Journal of Geriatric Psychiatry*. https://doi.org/10.1002/gps.1568

Feng, C., Li, W., Tian, T., Luo, Y., Gu, R., & Zhou, C. (2014). Arousal modulates valence effects on both early and late stages of affective picture processing in a passive viewing task Arousal modulates valence effects on both early and late stages of affective picture processing in a passive viewing task, (September), 37–41. https://doi.org/10.1080/17470919.2014.896827

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189–198.

Fredericks, C. A., Sturm, V. E., Brown, J. A., Hua, A. Y., Bilgel, M., Wong, D. F., … Seeley, W. W. (2018). Early affective changes and increased connectivity in preclinical Alzheimer's disease. *Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring*, *10*, 471–479. https://doi.org/10.1016/j.dadm.2018.06.002

Gomes-Oliveira, M. H., Gorenstein, C., Neto, F. L., Andrade, L. H., & Wang, Y. P. (2012). Validation of the Brazilian Portuguese Version of the Beck Depression Inventory-II in a community sample. *Revista Brasileira de Psiquiatria*. https://doi.org/10.1016/j.rbp.2012.03.005

Goodkind, M. S., Sturm, V. E., Ascher, E. A., Shdo, S. M., Miller, B. L., Rankin, K. P., & Levenson, R. W. (2015). Emotion recognition in frontotemporal dementia and alzheimer's disease: A new film-based assessment. *Emotion*, *15*(4), 416–427. https://doi.org/10.1037/a0039261

Grühn, D., & Scheibe, S. (2008). Age-related differences in valence and arousal ratings of pictures from the International Affective Picture System (IAPS): Do ratings become more extreme with age ? *Behavior Research Methods*, *40*(2), 512–521. https://doi.org/10.3758/BRM.40.2.512

Hajcak, G., Macnamara, A., & Olvet, D. M. (2010). Event-related potentials, emotion, and emotion regulation: An integrative review. *Developmental Neuropsychology*, *35*(2), 129–155. https://doi.org/10.1080/87565640903526504

Hajcak, G., & Olvet, D. M. (2008). The Persistence of Attention to Emotion: Brain Potentials During and After Picture Presentation. *Emotion*, *8*(2), 250–255. https://doi.org/10.1037/1528-3542.8.2.250

Hajcak, G., Weinberg, A., MacNamara, A., & Foti, D. (2012). ERPs and the Study of Emotion. In E. S. Kappenman & S. J. Luck (Eds.), *The Oxford Handbook of Event-Related Potential Components*. New York: Oxford University Press. https://doi.org/10.1093/oxfordhb/9780195374148.013.0222

Hamann, S. B., Monarch, E. S., & Goldstein, F. C. (2000). Memory enhancement for emotional stimuli is impaired in early Alzheimer's disease. *Neuropsychology*,

14(1), 82–92. https://doi.org/10.1037/0894-4105.14.1.82

Henry, J. D., Rendell, P. G., Scicluna, A., Jackson, M., & Phillips, L. H. (2009). Emotion experience, expression, and regulation in Alzheimer's disease. *Psychology and Aging*, *24*(1), 252–257. https://doi.org/10.1037/a0014001

Horning, S. M., Melrose, R., & Sultzer, D. (2014). Insight in Alzheimer's disease and its relation to psychiatric and behavioral disturbances. *International Journal of Geriatric Psychiatry*, *29*(1), 77–84. https://doi.org/10.1002/gps.3972

Ito, T. A., & Cacioppo, J. T. (2000). Electrophysiological Evidence of Implicit and Explicit Categorization Processes. *Journal of Experimental Social Psychology*. https://doi.org/10.1006/jesp.2000.1430

Kisley, M. A., Wood, S., & Burrows, C. L. (2007). Looking at the Sunny Side of Life - Age-Related Change in an Event-Related Potential Measure of the Negativity Bias. *Psychological Science*, *18*(9), 838–843. https://doi.org/10.1111/j.1467-9280.2007.01988.x

Klein-Koerkamp, Y., Beaudoin, M., Baciu, M., & Hot, P. (2012). Emotional decoding abilities in Alzheimer's disease: A meta-analysis. *Journal of Alzheimer's Disease*, *32*(1), 109–125. https://doi.org/10.3233/JAD-2012-120553

Kunzmann, U., & Grühn, D. (2005). Age differences in emotional reactivity: The sample case of sadness. *Psychology and Aging*, *20*(1), 47–59. https://doi.org/10.1037/0882-7974.20.1.47

Kunzmann, U., & Richter, D. (2009). Emotional Reactivity Across the Adult Life Span: The Cognitive Pragmatics Make a Difference. *Psychology and Aging*, *24*(4), 879–889. https://doi.org/10.1037/a0017347

Labouvie-Vief, G., Lumley, M. A., Jain, E., & Heinze, H. (2003). Age and gender differences in cardiac reactivity and subjective emotion responses to emotional autobiographical memories. *Emotion, 3*, 115–126.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (2008). *International affective picture system (IAPS): Affective ratings of pictures and instruction manual. Technical*

Report A-8. Gainesville, FL.

Langeslag, S. J. E., & Van Strien, J. W. (2009). Aging and Emotional Memory : The Co-Occurrence of Neurophysiological and Behavioral Positivity Effects. *Emotion*, *9*(3), 369–377. https://doi.org/10.1037/a0015356

Lopez-Calderon, J., & Luck, S. J. (2014). ERPLAB: An open-source toolbox for the analysis of event-related potentials. *Frontiers in Human Neuroscience*, *8*(1 APR), 1–14. https://doi.org/10.3389/fnhum.2014.00213

Marin, R. S., Biedrzycki, R. C., & Firinciogullari, S. (1991). Reliability and validity of the apathy evaluation scale. *Psychiatry Research*. https://doi.org/10.1016/0165-1781(91)90040-V

Mathieu, N. G., Gentaz, E., Harquel, S., Vercueil, L., Chauvin, A., Bonnet, S., & Campagne, A. (2014). Brain processing of emotional scenes in aging: Effect of arousal and affective context. *PLoS ONE*, *9*(6). https://doi.org/10.1371/journal.pone.0099523

McLellan, T., Johnston, L., Dalrymple-Alford, J., & Porter, R. (2008). The recognition of facial expressions of emotion in Alzheimer's disease: A review of findings. *Acta Neuropsychiatrica*, *20*(5), 236–250. https://doi.org/10.1111/j.1601-5215.2008.00315.x

Meng, X., Yang, J., Cai, A., Ding, X., Liu, W., Li, H., & Yuan, J. (2015). The neural mechanisms underlying th e aging-related enhancement of positive affects: Electrophysiological evidences. *Frontiers in Aging Neuroscience*, *7*(JUL), 1–15. https://doi.org/10.3389/fnagi.2015.00143

Mioshi, E., Dawson, K., Mitchell, J., Arnold, R., & Hodges, J. R. (2006). The Addenbrooke's Cognitive Examination revised (ACE-R): A brief cognitive test battery for dementia screening. *International Journal of Geriatric Psychiatry*. https://doi.org/10.1002/gps.1610

Mograbi, D. C., Brown, R. G., & Morris, R. G. (2012). Emotional reactivity to film material in alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*,

34(5–6), 351–359. https://doi.org/10.1159/000343930

Mograbi, D. C., Brown, R. G., Salas, C., & Morris, R. G. (2012). Emotional reactivity and awareness of task performance in Alzheimer's disease. *Neuropsychologia*, *50*(8), 2075–2084. https://doi.org/10.1016/j.neuropsychologia.2012.05.008

Mograbi, D. C., & Morris, R. G. (2013). Implicit awareness in anosognosia: Clinical observations, experimental evidence, and theoretical implications. *Cognitive Neuroscience*, *4*(3–4), 181–197. https://doi.org/10.1080/17588928.2013.833899

Mograbi, D. C., & Morris, R. G. (2014). On the relation among mood, apathy, and anosognosia in Alzheimer's disease. *Journal of the International Neuropsychological Society*, *20*(1), 2–7. https://doi.org/10.1017/S1355617713001276

Moran, T. P., Jendrusina, A. A., & Moser, J. S. (2013). The psychometric properties of the late positive potential during emotion processing and regulation. *Brain Research*, *1516*, 66–75. https://doi.org/10.1016/j.brainres.2013.04.018

Morris, R. G., & Hannesdottir, K. (2004). Loss of "awareness" in Alzheimer's Disease. In R. G. Morris & J. T. Becker (Eds.), *The Cognitive Neuropsychology of Alzheimer's Disease* (pp. 275–296). Oxford: Oxford University Press.

Olofsson, J. K., Nordin, S., Sequeira, H., & Polich, J. (2008). Affective picture processing: An integrative review of ERP findings. *Biological Psychology*. https://doi.org/10.1016/j.biopsycho.2007.11.006

Olofsson, J. K., & Polich, J. (2007). Affective visual event-related potentials: Arousal, repetition, and time-on-task. *Biological Psychology*. https://doi.org/10.1016/j.biopsycho.2006.12.006

Patel, V., & Prince, M. (2001). Ageing and mental health in a developing country: who cares? Qualitative studies from Goa, India. *Psychological Medicine*, *31*(1), 29–38. https://doi.org/10.1017/S0033291799003098

Phillips, L. H., Scott, C., Henry, J. D., Mowat, D., & Bell, J. S. (2010). Emotion

perception in Alzheimer's disease and mood disorder in old age. *Psychology and Aging*, *25*(1), 38–47. https://doi.org/10.1037/a0017369

Schultz, R. R., De Castro, C. C., & Bertolucci, P. H. F. (2009). Memory with emotional content, brain amygdala and Alzheimer's disease. *Acta Neurologica Scandinavica*, *120*(2), 101–110. https://doi.org/10.1111/j.1600-0404.2008.01132.x

Schupp, H. T., Cuthbert, B. N., Bradley, M. M., Cacioppo, J. T., Ito, T., & Lang, P. J. (2000). Affective picture processing: the late positive potential is modulated by motivational relevance. *Psychophysiology*, *37*(2), 257–261. https://doi.org/10.1111/1469-8986.3720257

Sheikh, J. I., & Yesavage, J. A. (1986). Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. *Clinical Gerontologist: The Journal of Aging and Mental Health*, *5*(1–2), 165–173. https://doi.org/10.1300/J018v05n01_09

Smith, M. C. (1995). Facial expression in mild dementia of the Alzheimer type. *Behavioural Neurology*, *8*(3–4), 149–156.

Starkstein, S. E., Jorge, R., Mizrahi, R., Adrian, J., & Robinson, R. G. (2007). Insight and danger in Alzheimer's disease. *European Journal of Neurology*, *14*(4), 455–460. https://doi.org/10.1111/j.1468-1331.2007.01745.x

Sturm, V. E. V., Yokoyama, J. S., Seeley, W. W., Kramer, J. H., Miller, B. L., & Rankin, K. P. (2013). Heightened emotional contagion in mild cognitive impairment and Alzheimer's disease is associated with temporal lobe degeneration. *Proceedings of the National Academy of Sciences*, *110*(24), 9944–9949. https://doi.org/10.1073/pnas.1301119110

Tsai, J. L., Levenson, R. W., & Carstensen, L. L. (2000). Autonomic, subjective, and expressive responses to emotional films in older and younger Chinese Americans and European Americans. *Psychology and Aging*, *15*, 684–693.

Verhülsdonk, S., Quack, R., Höft, B., Lange-Asschenfeldt, C., & Supprian, T. (2013).

Anosognosia and depression in patients with Alzheimer's dementia. *Archives of Gerontology and Geriatrics*, *57*(3), 282–287. https://doi.org/10.1016/j.archger.2013.03.012

Wei, G., Irish, M., Hodges, J. R., Piguet, O., & Kumfor, F. (2019). Disease-specific profiles of apathy in Alzheimer's disease and behavioural-variant frontotemporal dementia differ across the disease course. *Journal of Neurology*, (0123456789). https://doi.org/10.1007/s00415-019-09679-1

Weinberg, A., & Hajcak, G. (2010). Beyond Good and Evil: The Time-Course of Neural Activity Elicited by Specific Picture Content. *Emotion*, *10*(6), 767–782. https://doi.org/10.1037/a0020242

Widmann, A., Schröger, E., & Maess, B. (2015). Digital filter design for electrophysiological data - a practical approach. *Journal of Neuroscience Methods*, *250*, 34–46. https://doi.org/10.1016/j.jneumeth.2014.08.002

World Health Organization. (2004). *ICD-10 : international statistical classification of diseases and related health problems* (2nd ed., 1). World Health Organization. Retrieved from https://apps.who.int/iris/handle/10665/42980

Zhang, F., Ho, Y. W., & Fung, H. H. (2015). Learning from Normal Aging: Preserved Emotional Functioning Facilitates Adaptation among Early Alzheimer's Disease Patients. *Aging and Disease*. https://doi.org/10.14336/AD.2014.0620

Tables

Table 1 – Sociodemographic and clinical characteristics of participants.

Variable	PwAD (n = 15) Mean (SD) / Range	Older adults (n = 18) Mean (SD) / Range	Young adults (n = 24) Mean (SD) / Range
Age	78.0 (8.8) / 62-91	68.5 (5.6) / 61-82	22.5 (3.4) / 18-29
Sex*	8/7	17/1	9/15
Primary education^	7 (46.7)	–	–
High school education^	3 (20.0)	2 (11.1)	–
University degree^	5 (33.4)	16 (88.9)	24 (100.0)
ACE-R	47.8 (13.3) / 23-70	–	–
MMSE	16.1 (5.4) / 8-25	27.7 (1.8) / 24-30	29.1 (0.7) / 28-30
AES	49.6 (10.7) / 29-63	24.2 (3.1) / 18-29	–
ASPIDD total score	13.3 (6.7) / 3-26	–	–
Cognition	4.0 (2.1) / 0-8	–	–
ADL	4.9 (2.5) / -1-9	–	–
Affective	2.9 (2.9) / -2-9	–	–
Social	1.5 (1.9) / -1-5	–	–

* absolute numbers female/male; ^ absolute numbers (%); SD – standard deviation; ACE-R – Addenbrooke's Cognitive Examination – Revised, < 83 points = cut-off score for presence of dementia (maximum score = 100); MMSE – Mini Mental State Examination, < 24 points = cut-off score for presence of cognitive impairment (maximum score = 30); AES – Apathy Evaluation Scale, higher scores indicate higher levels of apathy (total range 18 – 72 points), apathy was measured as caregiver report for PwAD and as self-report for healthy older adults; ASPIDD – Assessment Scale of Psychosocial Impact of the Diagnosis of Dementia (total score and sub-scales); ADL – activities of daily living.

Table 2 – Latency values for the LPP in the early time window at electrodes Cz and Pz.

Electrode Category	PwAD Mean (SD)	Older adults Mean (SD)	Young adults Mean (SD)
Cz			
negative	449.1 (76.5)	403.3 (83.1)	429.9 (56.5)
neutral	418.4 (71.2)	414.2 (69.6)	418.5 (66.5)
dementia	436.3 (101.1)	425.2 (74.1)	398.8 (42.2)
Pz			
negative	480.6 (79.6)	360.8 (101.6)	414.4 (62.9)
neutral	383.1 (85.2)	422.4 (75.8)	404.8 (64.2)
dementia	454.6 (141.1)	389.1 (80.1)	396.1 (47.3)

Mean and standard deviation (SD) for LPP latencies at electrodes Cz and Pz for PwAD (n = 7), older (n = 10), and young adults (n = 16). 50 % fractional area latencies (in ms) were computed in the early time window 200 - 800 ms after stimulus onset.

Table 3 – Amplitude values for the LPP at electrodes Cz and Pz in the early, middle, and late time windows after negative, neutral, and dementia-related pictures.

Electrode Category	PwAD Mean (SD)	Older adults Mean (SD)	Young adults Mean (SD)
Cz early			
negative	3.8 (2.1)	3.0 (2.4)	4.7 (2.1)
neutral	2.9 (2.0)	3.2 (1.7)	4.8 (2.3)
dementia	3.6 (3.1)	2.4 (1.9)	4.5 (1.8)
Cz middle			
negative	2.0 (2.0)	0.5 (0.6)	1.2 (1.4)
neutral	1.8 (2.0)	0.7 (0.9)	1.5 (1.2)
dementia	1.4 (1.6)	0.3 (0.4)	0.7 (0.6)
Cz late			
negative	2.0 (2.0)	0.3 (0.4)	0.9 (1.0)
neutral	2.2 (2.4)	0.6 (1.3)	1.3 (1.4)
dementia	1.1 (1.8)	0.2 (0.3)	1.3 (1.6)
Pz early			
negative	4.1 (2.4)	2.0 (2.0)	3.3 (2.2)
neutral	2.3 (1.9)	2.6 (1.6)	3.9 (2.0)
dementia	3.4 (3.1)	1.9 (1.7)	3.6 (1.5)
Pz middle			
negative	2.2 (2.1)	0.3 (0.5)	0.6 (0.8)
neutral	1.4 (2.3)	0.4 (0.6)	1.2 (1.2)
dementia	2.0 (1.8)	0.4 (0.7)	0.7 (0.6)
Pz late			
negative	1.4 (1.8)	0.1 (0.2)	0.6 (0.8)
neutral	2.5 (3.7)	0.4 (1.1)	1.0 (1.1)
dementia	2.1 (2.9)	0.4 (0.7)	1.1 (1.4)

Mean and standard deviation (SD) for LPP amplitudes at electrodes Cz and Pz for PwAD (n = 8), older (n = 11), and young adults (n = 16). Positive area amplitudes (in µVs) were computed in the early (200 -

800 ms), middle (800 - 1400 ms) and late time windows (1400 - 2000 ms) after stimulus onset relative to baseline (200 ms prior stimulus onset).

Figures

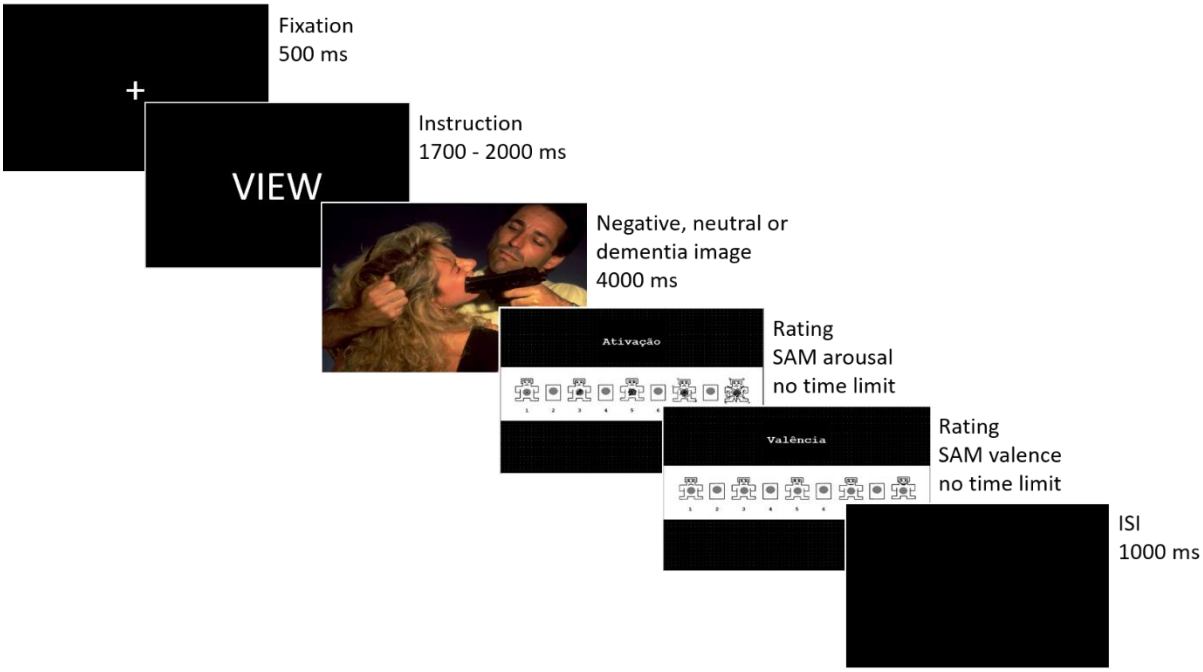

Figure 1 – Schematic representation of a trial in the emotional reactivity task. After passively viewing a negative, neutral, or dementia-related picture, participants rated how they felt after viewing the image on two scales (arousal and valence) of the Self-Assessment Manikin (SAM). ISI – inter stimulus interval.

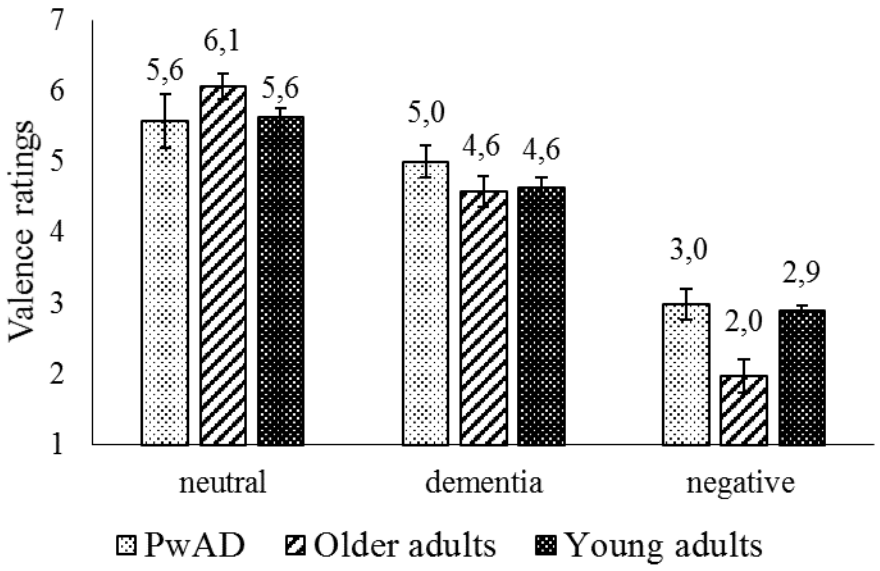

Figure 2 – Representation of means of valence ratings over all trials for the three picture categories negative, dementia-related, and neutral for PwAD (n = 15), older adults (n = 17), as well as young adults (n = 24). Error bars indicate +/- one standard error.

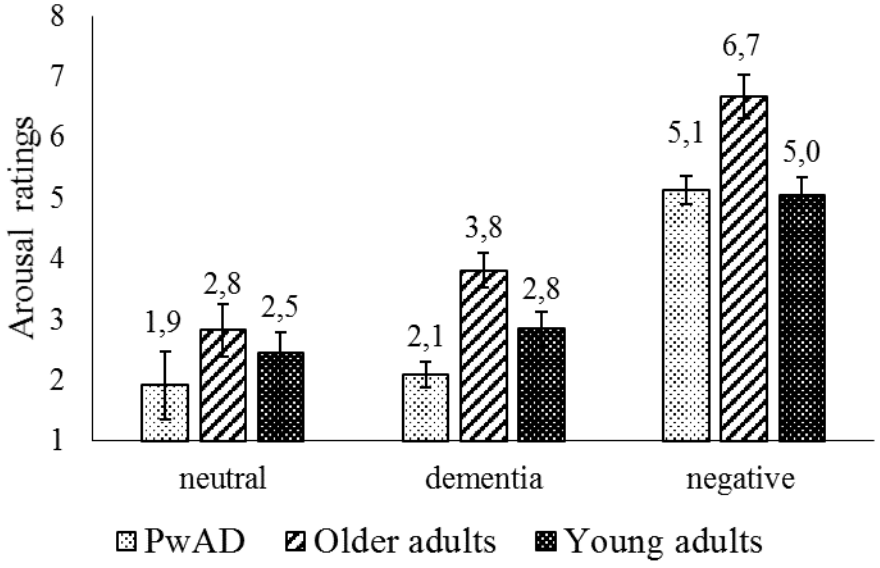

Figure 3 – Representation of means of arousal ratings over all trials for the three picture categories negative, dementia, and neutral for PwAD (n = 15), older adults (n = 18), as well as young adults (n = 24). Error bars indicate +/- one standard error.

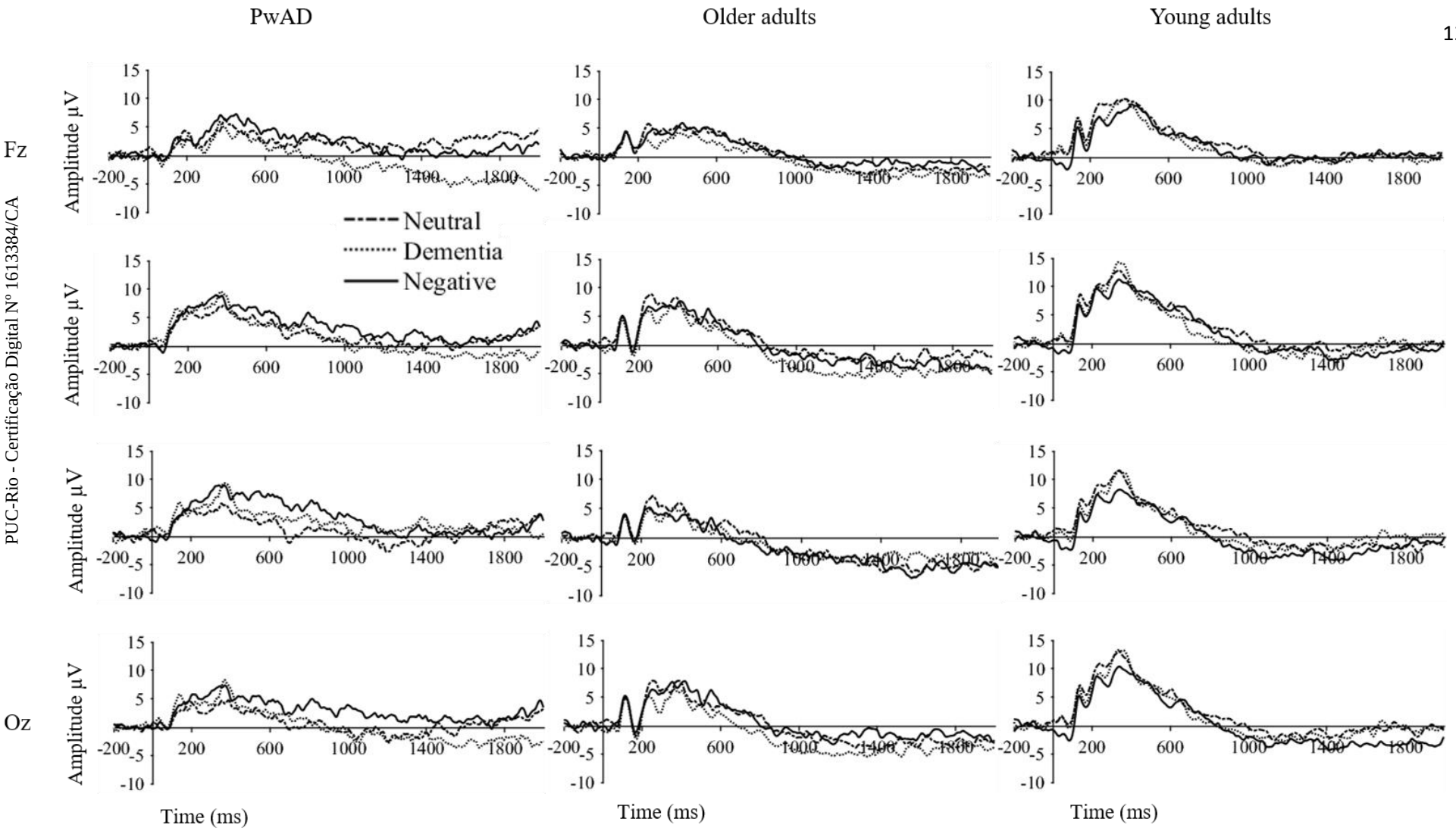

Figure 4 – Stimulus-locked LPP waveforms at electrodes Fz, Cz, Pz, and Oz from PwAD (n = 8), older (n = 11) and young adults (n = 16) for negative (solid line), neutral (dash-dotted line), and dementia-related (dotted line) images in the time window -200 - 2000 ms after stimulus onset (positive voltage is plotted up). The period of 200 ms before stimulus onset was used as baseline. A 20 Hz low-pass filter was applied to grand-average waveforms for better visualization.

Article 4

Fischer, A., Landeira-Fernandez, J., Sollero de Campus, F., & Mograbi, D. C. (2019). Empathy in Alzheimer's Disease: Review of Findings and Proposed Model. *Journal of Alzheimer's Disease*, 69(4), 921-933. DOI: 10.3233/JAD-180730.

Abstract

Empathy is essential for social interaction and a crucial trait to understand the intentions and behaviors of others and to react accordingly. Alzheimer's disease (AD) affects both cognitive and emotional processes and can lead to social dysfunction. Empathy results from the interaction of four components: shared neural representation, self-awareness, mental flexibility, and emotion regulation. This review discusses the abilities and deficits of patients with AD from the perspective of subcomponents of empathy and integrates these facets into a model of human empathy. The aim was to investigate the components that are affected by AD and the ways in which patients are still able to empathize with others in their social environment. It concludes that AD patients show a pattern of relatively preserved affective aspects and impairments in cognitive components of empathy and points out specific areas with the need for further research.

Key words

Dementia; affective sharing; awareness; mental flexibility; emotion regulation

Introduction

Humans are social beings, and our repertoire for understanding others is manifold. For example, we are able to cognitively understand the thoughts, beliefs, and intentions of others, an ability referred to as "mentalizing" or "Theory of Mind" (ToM). The discovery of mirror neurons (Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996) provided evidence of humans' ability to understand the motor intentions of others, based on shared neural representations. Additionally, there is an "emotional route" for the understanding of others, called emotional contagion. Cognitive and emotional abilities to share and understand thoughts, beliefs, and intentions of others have often been called cognitive empathy and emotional empathy. Decety and colleagues (Decety, 2011; Decety & Jackson, 2004; Decety & Meyer, 2008; Decety & Moriguchi, 2007; Decety & Svetlova, 2012) integrated the concept of shared representations with cognitive and affective aspects in a model of human empathy.

Empathy is a crucial ability for comprehending the intentions and behaviors of others and adapting our own behavior to achieve successful interpersonal social functioning (Leiberg & Anders, 2006). Cognitive and emotional components appear to be closely intertwined to create successful social functioning through our ability to empathize. Hence, investigating empathy in patients who suffer from cognitive and emotional deficits is a promising line of research to shed light on social dysfunction in these patients.

An estimated 46.8 million people worldwide suffer from dementia, and this number is projected to nearly double every 20 years (Prince et al., 2015). Alzheimer's disease (AD) is the leading cause of dementia worldwide. It is characterized as a progressive neurodegenerative disorder, whereby patients are often considered to have primarily cognitive impairments. However, dementia also clearly involves deficits in emotional processing that lead to behavioral dysregulation (Wright, 2011). Two factors that may decisively affect the treatment of people with dementia (PwD) are changes in social cognitive aspects and emotional processing, and both have great relevance to everyday life and social relationships.

Of the diverse changes that accompany dementia, progressive deficits in social functioning that can cause problems with daily life, social difficulties, and social isolation are likely to be more stressful for patients and their caregivers than cognitive symptoms. Coen et al. (1997) emphasized that behavioral and psychological symptoms of dementia (BPSD) are often more demanding for nursing staff and patients' relatives than cognitive symptoms. BPSD range from aggression, anxiety, and depression to apathy and agitation (Hughes, 2011). In the case of AD, such symptoms as anosognosia and low functionality in daily life can lead to substantial caregiver burden, which is potentially linked to interpersonal stress (Clare, Nelis, Martyr, Roberts, et al., 2012; Starkstein, 2014). Although the changes may be subtle, there seems to be some preservation of emotional competencies (Blessing, Forstmeier, & Eschen, 2014) and interpersonal functioning in AD patients compared with other dementias (Dermody et al., 2016; Fernandez-Duque, Hodges, Baird, & Black, 2010).

Initial research focused on cognitive impairments in AD patients, with less attention devoted to emotional deficits and competencies. In recent decades, however, the integration of emotional aspects in studies of AD has increased. Nevertheless, more research is needed in this field to explore emotional processing abilities in AD patients. Empathy plays an important role in successful socioemotional functioning. The present review discusses the extent to which AD leads to difficulties in the ability to empathize. Better insights into the empathic abilities of AD patients could help elucidate social dysfunction and promote interventions that seek to improve the quality of life of AD patients. We review current findings on empathy in AD and integrate these findings with the model of human empathy that was proposed by Decety and colleagues (Decety, 2011; Decety & Jackson, 2004; Decety & Meyer, 2008; Decety & Moriguchi, 2007; Decety & Svetlova, 2012).

A model of human empathy

The model of empathy that was proposed by Decety and colleagues includes affective bottom-up and cognitive top-down processes that regulate the empathic response. The articles by Decety and colleagues (Decety, 2011; Decety & Jackson, 2004; Decety & Meyer, 2008; Decety & Moriguchi, 2007; Decety & Svetlova, 2012)

provide a detailed overview of the development of empathy and its subcomponents and different and overlapping neural correlates that underlie these components. The present review focuses on components of empathy and the ways in which they are affected by AD.

Decety and Jackson (2004) defined empathy according to Ickes (1997) as a complex form of psychological inference, in which observation, memory, knowledge, and reasoning are combined to yield insights into the thoughts and feelings of others. Despite the fact that empathy is considered a necessary precursor for prosocial behavior, it also helps us predict the behaviors of others and react accordingly (Klimecki & Singer, 2013).

Evolved biological predispositions build the bases for the development of empathic feelings and behavior through emotional bonds and social interaction (Decety & Moriguchi, 2007). Self-other-awareness and the self-regulation of emotions are important conditions for human empathy. Furthermore, empathy involves the affective experience of the others' actual or inferred emotional state and understanding their emotional experience. The former is defined as the ability to share the emotional experience of another person and constitutes the affective component of empathy, which does not require conscious awareness. The latter can be viewed as its cognitive component and implies some minimal mentalizing ability and mental flexibility to adopt the subjective viewpoint of the other person (Decety & Jackson, 2004).

According to Decety and colleagues, there are four macrocomponents of empathy that are underpinned by specific neural systems: shared neural representation, self-awareness, mental flexibility, and emotion regulation. These components are combined to create their model of empathy (Figure 1), which is composed of three major functional components that dynamically interact to produce the experience of empathy in humans: affective sharing between the self and others (based on shared neural representations), self-other-awareness (self-awareness without confusion between the self and others), and mental flexibility (to adopt the subjective perspective of others and includes also regulation processes). Brain areas associated with affective sharing include the inferior parietal lobule, posterior superior temporal sulcus, anterior insula, premotor cortex, and the anterior cingulate cortex. The

temporoparietal junction, temporal pole, posterior cingulate cortex, and medial prefrontal cortex are related to mentalizing (Zaki & Ochsner, 2012). The medial prefrontal cortex has been shown to be also involved in self-other differentiation (Kalenzaga & Clarys, 2013).

PLEASE INSERT FIGURE 1 HERE.

Decety and colleagues emphasized that both affective and cognitive components are crucial for creating the phenomenological experience of empathy through a dynamic interaction. For example, affective sharing without self-other-awareness results in emotional contagion. De Vignemont and Singer (2006) also stated that empathy must be distinguished from related concepts, such as mentalizing, emotional contagion, sympathy, and empathic concern. Although the components of the model of empathy interact to create empathy, one must keep in mind that they are still distinct processes.

Alternative models of empathy include the Perception-Action Model (PAM) by Preston and de Waal (2002). At the core of the PAM is a mechanism that leads to a similar emotional state in the empathizer through motor mimicry and emotional contagion (De Waal & Preston, 2017), but it also addresses more complex forms of empathy like for example emotion regulation and experience. Even though the authors acknowledge that mirror neurons cannot produce empathy only by themselves, the PAM emphasizes the role of mirror neurons located in the inferior frontal gyrus and parietal cortices as a neural basis of shared representations of perception and action (Preston & de Waal, 2002). The basis of the PAM is in accordance with the perception-action coupling suggested in the model by Decety and colleagues that lead to shared representations.

Another alternative is the self to other model of empathy (SOME) by Bird and Viding (2014), which suggests five systems and a self/other switch to create empathy in the observer. It includes two input and appraisal systems that rely on deductive reasoning or associations with relevant stimuli, as well as on person-level cues like tone of voice or facial expression to signal another person's affective state. This model also includes a mirror-neuron system that can lead to emotional contagion but

is, according to the authors, not necessary for empathy to occur. The last two systems are the theory of mind system, which represents the mental state of the self and the other, and a system including the current affective state of the self simulating the other's emotional state if affective sharing took place. We decided for the model by Decety and colleagues as the basis for investigating empathy in AD because it is a well-established and clearly structured model that allows for the investigation of its sub-components. Furthermore, the models have some overlap, with all of them assuming an affective empathy component as a bottom-up affective sharing mechanism, which keeps the distinction between the self and the other, as well as top-down cognitive control mechanisms like regulation and perspective taking.

Search strategy and selection criteria

A comprehensive review of the literature was performed using electronic databases (PubMed, Google scholar) for papers published in English including keywords and synonyms associated with "empathy," "affective sharing," "contagion," "self-other-awareness," "self-other distinction," "mental flexibility," "regulation," "perspective taking," and "theory of mind (ToM)" paired with the keyword "Alzheimer" and "AD". We manually searched the reference lists of identified articles for additional papers to supplement the electronic search, which was conducted until September 2018, without restrictions for time. We included reviews and meta-analyses that investigated relevant constructs (empathy and/or subcomponents) in neurodegenerative diseases only if they included AD patients. Studies were included when they compared AD patients to a healthy control group and/or pre-illness state. An exception is the study by Ramanan et al. (2017), which does not include a healthy control group, but was considered relevant because of its data-mining and statistical modeling approach.

The section "self-other-awareness" focused on the distinction between the self and the other, but the amount of studies here is scarce. Nevertheless, we also included a few studies on self-awareness in AD. The literature on self-awareness and anosognosia in AD is vast and since this was not a focus of our review, we just intended to give a broad overview over this topic here. Information about authors and article type, as well as descriptions of used methods and relevant results of included studies can be found in the supplementary material (Supplementary Table 1).

Empathy in Alzheimer's disease

Unfortunately, studies that have investigated empathy in dementia, especially AD, are still relatively scarce. Moreover, the majority of studies used the Interpersonal Reactivity Index (IRI), a questionnaire to assess empathy. It consists of four subscales, perspective taking and fantasy to measure cognitive empathy, and empathic concern and personal distress to assess affective empathy. One study was recently conducted by Dermody and colleagues (2016). They investigated cognitive and affective aspects of empathy in dementia patients using caregiver ratings on the IRI. The results showed that AD patients were only impaired in cognitive aspects of empathy compared with healthy age- and education-matched controls, whereas affective components were preserved. These deficits were related to predominantly left-sided temporoparietal atrophy. Statistically controlling for overall cognitive dysfunction ameliorated the empathy-related cognitive deficits in AD patients, and the authors concluded that socioemotional deficits mainly arise because of global cognitive dysfunction rather than a loss of empathy itself in AD patients. These findings are in line with the results from a study by Narme and colleagues (2013). The authors found that the AD group differed from healthy controls only on the perspective taking subscale of the IRI after statistically controlling for age and gender. The study by Rankin and colleagues (2006) also supports these results, and furthermore, did not find direct anatomic evidence of empathy loss in AD patients. Synn and colleagues (2018) reported lower scores for affective and cognitive empathy in AD patients relative to healthy controls by using caregiver ratings of the empathic concern and perspective taking subscale of the IRI. Moreover, the authors did not find differences to patients with frontotemporal dementia (FTD).

In contrast, Alladi et al. (2011) did not find impairments in affective or cognitive aspects of empathy in AD patients, based on caregiver ratings on the IRI comparing scores before and after disease onset. Another study using caregiver informed IRI ratings supports these results by also not finding significant differences on any of the four subscales between AD and healthy controls (Rankin, Kramer, & Miller, 2005). Moreover, a study by Hsieh and colleagues (2013) did not find significant associations between loss of empathy in AD patients, measured with the IRI, and carer variables like burden and relationship quality. Fernandez-Duque and colleagues (2010) used more naturalistic stimuli to examine empathy in dementia. Three people

had given an interview about emotionally relevant events in their lives. The participants in the study watched a video of these interviews and were asked to answer questions about the feelings of these three people. AD patients exhibited no impairment in inferring the people's emotions in the first two videos, which showed clear positive and negative emotions. The emotions that were displayed in the third interview were more ambiguous and variable. The video presented a mother who had more ambiguous feelings about her recent motherhood. In this case, the AD patients' performance became impaired relative to healthy older adults. The AD patients presented an overoptimistic bias, meaning they endorsed a more positive description of the third interviewee compared with the healthy controls. The authors (Fernandez-Duque et al., 2010) explained this result from the perspective of a global discrimination hypothesis. They concluded that AD patients might have relied on a global judgment about the interviewee's overall feelings and situation rather than trying to decode each particular thought or emotion. They also stated that the exact mechanism of this bias was unclear. In accordance with their conclusion, one could infer that these results reflect cognitive impairment in perspective taking or a simpler and less nuanced understanding of more subtle emotional contents (i.e., motherhood in general is considered a happy event).

These studies reported different results with regard to empathy in AD, ranging from no difficulties at all to exclusively cognitive empathy impairments to problems only in inferring more complex and sophisticated emotions. Nevertheless, most studies reported AD patients to be able to experience empathy despite their deficiency in certain cognitive and affective domains. Furthermore, recent reviews also point to a relative preservation of affective empathy and a loss in cognitive empathy, which is related to the overall cognitive decline including ToM and perspective taking abilities (Bartochowski, Gatla, Khoury, Al-Dahhak, & Grossberg, 2018; Christidi, Migliaccio, Santamaría-García, Santangelo, & Trojsi, 2018; Desmarais, Lanctôt, Masellis, Black, & Herrmann, 2018). The following sections take a closer look at the components of empathy to address the issue of which of them may be more compromised in AD.

Affective sharing

This process is based on the fact that perception and action are functionally intertwined in the human nervous system, and this perception-action coupling leads to shared representations (Decety, 2011; Decety & Jackson, 2004; Decety & Meyer, 2008; Decety & Moriguchi, 2007). Shared representations between the self and others mean that the perception of a given behavior in others automatically activates the representation of that behavior in the self (Preston & de Waal, 2002), thus leading to the process of affective sharing.

Before considering affective sharing from the perspective of AD, a fundamental issue is whether AD diminishes such basic skills as facial expression recognition because the most accessible information that specifies an individual's affective state is information that is conveyed through the face (McLellan, Johnston, Dalrymple-Alford, & Porter, 2008). Klein-Koerkamp and colleagues (2012) found in a meta-analysis that AD patients were significantly impaired in their emotion decoding abilities. These difficulties were found in various emotional tasks, for various stimuli, for different types of emotion, and for different degrees of disease severity. After the authors controlled for the cognitive deficits, the patients' emotional abilities were still worse than those of healthy controls. The authors (Klein-Koerkamp et al., 2012) concluded that the impairments in emotion decoding abilities in AD patients cannot be solely explained by cognitive deficits. McLellan et al. (2008) reported similar results in their literature review. However, these authors emphasized that because of the very different results that have been reported in the literature, the issue of whether AD patients are generally impaired in their ability to accurately decode emotional facial expressions remains unresolved. Furthermore, unclear is whether these deficits are caused by a general cognitive decline or verbal or spatial deficits or whether it reflects an impairment in specific emotion-processing mechanisms, although they could not find clear evidence of the latter (McLellan et al., 2008).

Other studies found different results. For example, Bucks and Radford (2004) reported a relatively preserved ability to recognize and identify non-verbal affective cues in emotional facial expressions and emotional prosody in AD patients, but they did observe a decline in general cognitive ability. Moreover, the authors could also not confirm differences in the recognition of different emotions (i.e., happiness,

sadness, anger, fear, and neutral) among AD patients. Studies by Torres and colleagues (2015) and Phillips et al. (2010) provided evidence that AD patients present emotion decoding impairments, especially when facial expressions become subtler (Phillips et al., 2010) or when complex emotional situations are involved (Torres et al., 2015). Kemp and colleagues (2012) suggest that emotion perception deficits in AD could be secondary to their cognitive deficits, rather than a primary impairment in the perception of emotion.

Similar to the aforementioned studies that investigated empathy in AD, a cognitive component seems to contribute to the emotional decoding deficits that are found in some studies. Additionally, two of the aforementioned studies also point to difficulties in the perception of more complex emotions. Although there is no systematic pattern of a deficit with regard to basic emotional processing, current evidence suggests that AD leads to some type of impairment in emotional decoding abilities.

Another important point is the mirror neuron network that plays a key role in affective sharing (Bird & Viding, 2014; Decety & Jackson, 2004; Preston & de Waal, 2002). Disruptions of the mirror neuron network in the inferior parietal cortex have been associated to prodromal AD (Moretti, 2016; Poletti & Bonuccelli, 2013; Rapoport, 1989). A recent study supports this hypothesis and found a gradual posterior-anterior decline of the mirror neuron network related to the AD pathology (Farina et al., 2017).

Nevertheless, Sturm and colleagues (2013) found a linear increase in emotional contagion in mild cognitive impairment (MCI) and AD patients. To our knowledge, this is the only study to date that explicitly investigated emotional contagion in AD. According to these results, AD appears to increase the affective aspect of empathy, meaning that AD patients may be more sensitive to affective sharing than healthy controls. This result needs to be confirmed in future studies. Moreover, the authors used caregivers' ratings on the IRI as a measure of emotional contagion instead of using a naturalistic experimental setting. Nonetheless, they confirmed their results on the neuronal level. Using structural magnetic resonance imaging (voxel-based morphometry), they found an association between the degradation of temporal lobe structures (i.e., smaller volume in the right inferior, middle, and superior temporal

gyri, right temporal pole, anterior hippocampus, parahippocampal gyrus, and left middle temporal gyrus) and an up-regulation of emotional contagion. These temporal lobe structures play an important role in affective signal detection and emotion inhibition. One explanation could be that less efficient emotion inhibition leads to a change in interpersonal emotional reactivity and thus to a dysregulation of emotional contagion in the sense of an intensification of automatic affective sharing (Sturm et al., 2013).

This greater ability for affective sharing can be viewed as an advantage that perhaps partly compensates for cognitive deficits in AD with regard to empathy. In contrast, the disinhibition of emotional contagion may make AD patients more vulnerable to negative emotions that are expressed by people in their social environment, which could lead to greater anxiety (Sturm et al., 2013).

Shared representations between the self and others provide a neurophysiological basis for social cognition through the automatic activation of motor representations or emotions (Decety & Jackson, 2004). According to the model of human empathy, the mechanism of affective sharing is necessary but not sufficient for empathic understanding. Two other important aspects are self-other-awareness and mental flexibility, which are discussed in the following sections.

Self-other-awareness

Knowledge of the mental states of others is based on knowledge of the self. A reasonable assumption is that other-awareness implies consideration of the perspective of another person. However, self-awareness (i.e., to see the self as an object of knowledge) also requires a capacity for secondary representation (Decety & Jackson, 2004). Although some conditions can lead to impairments in the sense of self, such as somatoparaphrenia and psychosis, we usually do not confuse the self and others. To maintain a distinction between these two and to determine the source of feelings, empathy is crucial (Decety, 2011; Decety & Jackson, 2004; Decety & Meyer, 2008; Decety & Moriguchi, 2007; Decety & Svetlova, 2012).

Unfortunately, studies that investigate self-other-awareness and the distinction between self and other in AD patients are scarce. Studies in the field of self-awareness indicate a decline in AD patients with regard to the self-appraisal of

cognitive, behavioral, and physical traits (Zamboni et al., 2013), memories of words that were previously recorded in the patient's own voice (Bond et al., 2016), ratings of the patient's own task performance (Mograbi, Brown, Salas, & Morris, 2012) and cognitive and emotional functioning (Shany-Ur et al., 2014) among others. Shany-Ur and colleagues (2014) state that self-awareness involves modality-independent as well as modality-specific anatomical regions. The authors found that overestimation of functioning in PwD is related to atrophy in dorsal frontal, orbitofrontal and subcortical regions, like the anterior insula, thalamus, putamen and caudate.

Moreover, Mograbi, Ferri et al. (2012) found that between 63% and 81% of PwD, including AD patients, suffer from self-awareness impairments, especially regarding their own cognitive abilities.

In contrast, the results of other-awareness in AD are more ambiguous. A study by Zamboni and colleagues (Zamboni et al., 2013) did not find significant discrepancies between AD patients' ratings of cognitive, behavioral, and physical traits of another person and the other persons' ratings himself, while being less able to rate themselves on a list of traits. These higher discrepancies for questions regarding themselves were related to decreased activation in medial prefrontal and anterior temporal regions, whereas there were no differences in MCI or control groups for neither self- nor other-condition.

Furthermore, Bond et al. (Bond et al., 2016) found that AD patients' memories of words that were presented in the voices of others were less consistently affected than when it was the patient's own voice. By contrast, Mograbi and colleagues (Mograbi, Brown, Landeira-Fernandez, & Morris, 2014) found that AD patients differed from healthy older adults in terms of ratings of the performance of an imagined other. Patients suggested that others of similar age would do as well as they themselves would do in memory and reaction time tasks, despite their cognitive impairments. This is consistent with their lack of self-performance awareness, but it also demonstrates their difficulties in assuming the perspective of others. A study by Ruby et al. (Ruby et al., 2009) investigated AD patients' awareness of personality traits of the self and another person from both first- and third-person perspectives. The results indicated a decline of accuracy in self-awareness in AD patients and impairments in the judgment of personality traits of another person. The authors

concluded that to appropriately attribute social emotions (e.g., selfishness, boringness, and politeness) to oneself or another person, a third-person perspective is needed, which is perhaps a notable impairment in AD patients. During the self-personality assessment, AD patients showed stronger recruitment of the intraparietal sulcus than control participants. When assessing their personality from a third-person view, the posterior dorsomedial prefrontal and orbitofrontal cortex were more activated than in elderly controls, but similar to young controls. While the authors interpret the first result as a familiarity-based reliance on non-updated personal semantic information to assess the self, they suggest that AD patients, due to their memory deficits, rely more on inferring and monitoring when evaluating the self from a third-person perspective (Ruby et al., 2009).

Self-awareness in AD is likely affected by cognitive impairments, more specifically episodic memory impairments that lead to difficulties in updating representations of the self (Mograbi, Brown, & Morris, 2009). Such episodic memory impairments are referred to as mnemonic anosognosia (Morris & Mograbi, 2013). It has also been suggested anosognosia may be executive in nature, with difficulties in error monitoring and metacognition that underpin unawareness of the disease. The neural networks that mediate executive functions show some overlap with those that support perspective taking (Hynes, Baird, & Grafton, 2006; Saxe & Powell, 2006; Shamay-Tsoory, Tibi-Elhanany, & Aharon-Peretz, 2006), so neurodegeneration at these sites may lead to both self- and other-unawareness. Moreover, it has been shown that the medial prefrontal cortex, that is involved in differentiating between the self and others, is impaired in AD patients (Rosen et al., 2010; Salmon et al., 2006; Wang et al., 2006). Nevertheless, AD patients more accurately identify dementia in others than in themselves (Clare, Nelis, Martyr, Whitaker, et al., 2012). This was investigated using a vignette method, whereby PwD could frequently correctly identify the problems of the depicted persons with dementia or healthy aging, although they scored lower than controls. Evidence of greater awareness of others in unaware patients has also been suggested in other conditions (Bertrand, Landeira-Fernandez, & Mograbi, 2016). Considering these studies, Morris and Mograbi (Morris & Mograbi, 2013) proposed a revised cognitive awareness model (CAM), in which different modules store self and non-self information, thus including the possibility of impairments in self-awareness with preserved other-awareness.

Self-other-awareness develops in early childhood (Asendorpf & Baudonnière, 1993), based on knowledge about the self and dynamic interrelations with others (Decety & Jackson, 2004). A reasonable assumption is that AD patients are able to maintain the distinction between the self and others. Bond et al. (Bond et al., 2016) reported that AD patients could successfully attribute tactile events to the self *vs*. external agents, indicating that AD patients retain intact tactile body schema processing and are able to distinguish between the self and others. This may suggest that problems in self-awareness in AD are more pronounced for knowledge about the "AD-self" rather than reflecting a general disability of self-other-awareness.

Mental Flexibility and Self-Regulation

As mentioned above, empathy can be felt in a variety of situations which requires us to adopt more or less consciously the subjective perspective of another person, which is also called mentalizing or ToM (Klimecki & Singer, 2013). For this purpose, some form of active inhibitory mechanism is necessary to regulate the own perspective to allow cognitive and affective flexibility in evaluating the perspective of another person. Moreover, top-down information processing and control, such as self-regulation, are also needed to modulate one's own emotions in order to not be overwhelmed by them and to not experience them as aversive (Decety, 2011; Decety & Jackson, 2004; Decety & Moriguchi, 2007). Thus, appropriate emotion regulation strategies play an important role in managing and optimizing intersubjective transactions between the self and others; in doing so, such strategies allow for empathic experiences (Decety & Jackson, 2004).

Goodkind and colleagues (2010) examined instructed and spontaneous emotion regulation in dementia patients and age-matched healthy controls. They presented an aversive acoustic startle stimulus to the participants under three conditions: (*i*) unwarned without instructions to downregulate their emotions, (*ii*) warned without instructions to downregulate, and (*iii*) warned with instructions to downregulate. The investigators measured overall somatic activity and emotional facial expressions. The downregulation of emotions in terms of somatic activity did not differ between groups. With regard to emotional facial expressions as a marker of downregulation, AD patients only presented moderate impairment in the "warned with instruction"

condition, in which they were less able to downregulate their emotions compared with controls. The authors concluded that this deficit in AD was caused by greater cognitive demands (e.g., remembering a countdown until the startle stimulus appeared, tracking its progress, and remembering the instructions) that were inherent to the instructed downregulation. However, because of their relatively good performance in the "warned without instruction" condition, the authors conclude that AD patients were able to naturally downregulate their emotional response to an aversive stimulus. Thus, AD patients appear to be able to regulate their emotions successfully in situations that do not overtax memory and other cognitive resources (Goodkind et al., 2010). Another group of dementia patients that was investigated suffered from frontotemporal lobar degeneration (FTLD). In contrast to AD patients, this group was unable to spontaneously downregulate their emotions. The authors concluded that this pattern is consistent with the lack of social concern and social inappropriateness, which are important symptoms of FTLD (Levenson & Miller, 2007).

In AD patients, Nash et al. (Nash et al., 2007) did not find differences in perceived emotion regulation capacity that was measured by the Difficulties in Emotion Regulation Scale and affective empathy that was measured with the IRI between AD patients and controls. However, AD patients had more inhibitory failures in the Hayling Sentence Completion Test and lower self-reported cognitive empathy. Nevertheless, refuting their hypothesis, the authors did not find a relationship between emotion regulation and inhibitory control or between cognitive empathy and inhibitory control. With regard to the reported cognitive empathy deficits, the authors speculated about the existence of a different underlying mechanism apart from cognitive disinhibition that contributes to these deficits in AD. Concerning the lack of a hypothesized relationship between emotion regulation and cognitive inhibition, the results of a study by Henry and colleagues (2009) are also somewhat surprising. AD patients and controls watched amusement film clips coupled with three different instructions (i.e., spontaneous expression, suppression, or amplification of emotion). The results indicated that the intentional use of suppression was intact in AD patients, whereas both groups had difficulties with the amplification of emotions. Their results are also in agreement with Nash et al. (Nash et al., 2007), who did not find a relationship between cognitive disinhibition and emotion regulation in AD.

Hence, neither of these studies related cognitive disinhibition in AD patients to emotion regulation deficits. Although deficits in cognitive inhibitory control are prominent features in AD, Amieva et al. (Amieva, Phillips, Della Sala, & Henry, 2004) concluded that this is not a consequence of the breakdown of general inhibitory processes, and an inhibitory mechanism may indeed be preserved in AD. Thus, AD appears to have a strong impact on tasks that require controlled inhibition but a considerably smaller impact on tasks that require more automatic inhibition (Henry et al., 2009). Moreover, Henry et al. (Henry et al., 2009) discussed their results from the perspective of models of aging that consider that some emotion control processes are relatively more automatic in older age. They suggested that emotion regulation strategies, such as the effective behavioral suppression of emotions, may depend on well-practiced, automatic processes by the time one reaches older adulthood. This is consistent with a range of studies that reported that emotional experiences change with age (Lawton, Kleban, Rajagopal, & Dean, 1992; Levenson, Carstensen, & Gottman, 1994; Mroczek & Kolarz, 1998; Zhang, Ho, & Fung, 2015). Leclerc and Kensinger (Leclerc & Kensinger, 2011) found that older adults exhibited greater activity in areas that are associated with emotion regulation, namely the prefrontal cortex, compared with younger adults, and less activity in the amygdala, an area that is responsible for processing emotionally arousing stimuli, when viewing negative images compared with neutral images.

Additional evidence that AD patients possess relatively intact emotional regulation abilities, at least for some of its forms despite their cognitive deficits (e.g., disinhibition), derives from the phenomenon of habitual emotion regulation. Gyurak and colleagues (Gyurak, Gross, & Etkin, 2011) reasoned that the frequent use of a given explicit strategy can quickly render the initiation of the strategy more implicit during regulation, thus making it more implicit over time. Hence, a reasonable speculation is that AD patients are able to conduct at least more automatic, spontaneous emotion regulation processes successfully.

The last component of empathy that is considered here is the ability of adopting the perspective of another person. The number of studies investigating cognitive ToM, measured for example using first and second order false belief tasks, and affective ToM, which can be assessed using the Faux-Pas or the Reading the Mind in the Eyes Test, in PwD increased in the last decade. Using different perspective taking tasks,

Marková et al. (Marková, Laczó, Andel, Hort, & Vlcek, 2015) reported diminished overhead and first-person view perspective taking abilities in AD patients, while people with MCI were only impaired in the first-person view task. Studies showed that AD patients perform relatively normal in first order false belief tasks (Castelli et al., 2011; Cuerva et al., 2001; Fernandez-Duque, Baird, & Black, 2009; Gregory et al., 2002; Zaitchik, Koff, Brownell, Winner, & Albert, 2004; Zaitchik et al., 2006), and are impaired in higher order false belief tasks (Cuerva et al., 2001; Fernandez-Duque et al., 2009; Freedman, Binns, Black, Murphy, & Stuss, 2013; Gregory et al., 2002; Zaitchik et al., 2004, 2006), which could be secondary to their cognitive impairments (especially executive functions) (Cuerva et al., 2001; Fliss et al., 2016; Kemp et al., 2012; Poletti, Enrici, & Adenzato, 2012; Zaitchik et al., 2004, 2006) or episodic memory deficits (Synn et al., 2018) rather than reflecting a primary impairment in ToM. Moreover, Fliss et al. (Fliss et al., 2016) found that, while patients in moderate stages of the disease were impaired in first and second order false belief tasks, patients in early phases showed only deficits in second order false belief tasks. This suggests a decrease of ToM abilities with the progression of the disease (Fliss et al., 2016; Laisney et al., 2013).

A data mining study by Ramanan and colleagues (Ramanan et al., 2017) also found that difficulties of AD patients in cognitive ToM tasks do indeed not reflect a genuine ToM deficit but are rather mediated by a particularly executive cognitive decline. This is consistent with the results of a systematic review by Sandoz et al. (Sandoz, Démonet, & Fossard, 2014) and a meta-analysis by Bora and colleagues (Bora, Walterfang, & Velakoulis, 2015). Bora et al. (Bora et al., 2015) found that AD patients' ToM deficits are only modest relative to their general cognitive dysfunction and compared with patients with FTD. Furthermore, the authors found that a longer disease duration and the degree of general cognitive deterioration lead to more severe ToM deficits in both types of dementia. Sandoz and colleagues (Sandoz et al., 2014) stated that the deficits in ToM task performance that are caused by AD are mainly attributable to a decline in cognitive and executive abilities and do not reflect a specific ToM impairment. Other studies interpreted their results as a genuine ToM impairment in AD patients (Freedman et al., 2013; Laisney et al., 2013; Moreau, Rauzy, Viallet, & Champagne-Lavau, 2016), whereas Laisney and colleagues (Laisney et al., 2013) found that impairments in working memory and executive

functions were associated only to more complex cognitive ToM abilities. The different results are maybe due to the inclusion of AD patients at different stages of disease severity (Fortier, Besnard, & Allain, 2018; Laisney et al., 2013). Concerning affective ToM, although not central to this article but reported for completeness, the results are more ambiguous. Some studies did not find an impairment in affective ToM (Fliss et al., 2016; Freedman et al., 2013; Gregory et al., 2002), while others did (Castelli et al., 2011; Laisney et al., 2013). Fliss et al. (2016) suggested that affective ToM abilities could be affected by decreasing decoding abilities of facial emotions.

The ToM network includes at least the posterior superior temporal sulci, the adjacent temporoparietal junction, the precuneus, and the medial prefrontal cortex (Kemp et al., 2012; Poletti et al., 2012). According to Fortier et al. (Fortier et al., 2018), a deficit in the temporoparietal junction, which is frequently reported in AD patients (Villain et al., 2010), may be central to understanding ToM impairments in this patient population. Le Bouc and colleagues (Le Bouc et al., 2012) reported a correlation between the severity of the deficit in inferring someone else's beliefs and a hypometabolism in the left temporoparietal junction. This kind of deficit was predominant in the AD group. The FTD, group on the other hand, was particularly impaired in inhibiting their own mental perspective, which was associated with hypometabolism in the right lateral prefrontal cortex.

In summary, emotion regulation and perspective taking abilities appear to be relatively preserved in early stages of the disease, as long as the situation does not overwhelm the cognitive capacities of patients. Most studies show a decline in perspective taking abilities with decreasing cognitive abilities and thus, with the progression of the disease. Moreover, emotion regulation and perspective taking to some extent involve inhibitory mechanisms. At least concerning emotion regulation, AD patients may rely more on automatic inhibitory mechanisms than on controlled ones, which may help them satisfactorily cope with task demands.

Limitations and future directions

The conclusions drawn from this review must be considered keeping some limitations in mind. The number of studies investigating empathy and its subcomponents in AD is still relatively small, especially regarding emotional

contagion and self-other distinction. Moreover, most studies used small samples and different methods, as well as included patients in different stages of the disease. Therefore, it is not surprising that sometimes results differ or are even controversial. On top of that, a lack of experimental and more naturalistic studies raises questions about the ecological validity of results and their generalization into daily life. Furthermore, the subcomponents themselves are complex psychological processes, each underpinned by its own neural network. Thus, it represents a huge challenge to summarize them in a single model. Here, we just tried to give an overview about how these processes could be affected by the disease and how that diminishes the empathic abilities of AD patients. To the best of our knowledge, this is the first review exploring empathic abilities and its subcomponents in depth in AD. Exploration and investigation of emotional abilities in AD has just begun and with more research being done in the field, the present conclusions can be modified and extended.

Nevertheless, we believe that some conclusions can be drawn from the presented studies. Figure 2 shows a revised version of the model of human empathy for AD, depicting the influence of cognitive changes on components of the model. The effect of general cognitive impairments on emotion regulation abilities can be viewed in accordance with Henry et al. (Henry et al., 2009). AD patients are able to conduct more automatic, spontaneous emotion regulation and present difficulties in tasks that require the controlled inhibition of emotional responses. With regard to their ToM abilities, evidence indicates that AD patients have more pronounced deficits in more complex tasks, which can be attributed to a decline in cognitive and executive abilities (Sandoz et al., 2014). Memory deficits may also influence performance in ToM tasks (Synn et al., 2018), in which AD patients may be unable to keep all details in mind that are required to infer the beliefs of others (Zaitchik et al., 2004).

PLEASE INSERT FIGURE 2 HERE.

More research is needed on the influence of different aspects of cognitive impairment on the different components of the model of empathy. Unclear are the effects of controlled cognitive inhibition *vs.* automatic cognitive inhibition on

emotion regulation abilities in AD patients and the influence of memory and executive function deficits on self-other-awareness. Although some studies have investigated self-awareness and other-awareness in AD, a dearth of studies have explored the borders between self- and other-awareness in AD patients (e.g., tracking the origin of feelings [self *vs*. other]). In the context of empathy, unknown is whether the deficits of AD patients in more complex emotional situations are caused by impairments in perspective taking or whether such difficulties reflect a deficit in emotional abilities.

The combination of preserved skills and deficits in AD patients with regard to empathy is in accordance with Decety and Jackson (Decety & Jackson, 2004), who did not assume a single source of empathy deficit in different conditions because of its multidimensional nature. The ability to experience empathy depends on various processes. Some components may compensate for other components, and the overall ability to empathize may be viewed as a continuum. Interactions with the social environment are essential for human beings. Declines in social relationships and interactions, combined with social isolation, substantially affect AD patients' quality of life. Even if AD patients exhibit impairments in cognitive abilities to share and understand the thoughts, beliefs, and intentions of others, they may be able to utilize more emotional processes to fulfill these tasks. Furthermore, preserved competencies in the emotional domain can be used as a resource in AD patients (Blessing et al., 2014). A deeper understanding of emotional processing in PwD could lead to the greater participation of these patients in social life, thus improving the quality of life of both patients and their caregivers. A future goal is to incorporate current knowledge about AD in the domain of empathy and social functioning and thus promote further research in this field. By extending our understanding of the ways in which AD affects emotional abilities, we may be able to adapt clinical and home care to the individual needs of patients and caregivers.

Conclusion

The goal of this review was to explore empathy in AD and investigate the subcomponents of empathy that are affected by the disease according to the model of human empathy. Emotional processing/decoding, affective sharing, self-other-

awareness, mental flexibility, and self-regulation abilities in AD patients were briefly reviewed. Although the performance of AD patients differed from healthy controls in all aspects that were reviewed herein, AD patients were still able to perform basic emotional processes that contribute to empathy, whereby their difficulties can largely be attributed to their cognitive impairments. Furthermore, AD patients do not exhibit impairments in all domains of cognitive processes that are related to empathy. Emotion self-regulation and perspective taking are partly based on the ability of cognitive inhibition to regulate one's own emotions or perspective. Both aspects have been shown to be preserved to a certain degree in AD patients, and they may rely more on automatic inhibitory mechanisms that are considered to be less affected by the disease (Amieva et al., 2004; Henry et al., 2009).

By contrast, the majority of studies reviewed here, reported intact affective empathy in AD (Alladi et al., 2011; Bartochowski et al., 2018; Christidi et al., 2018; Dermody et al., 2016; Narme et al., 2013; Rankin et al., 2006, 2005). Furthermore, AD patients seem to have a greater ability of affective sharing, reflected by greater emotional contagion (Sturm et al., 2013). Shared representations between the self and others are at the core of the proposed model of human empathy and provide a neurophysiological basis for social cognition. Although this enhanced ability could make AD patients more prone to negative emotions that are expressed by other people in their social environment, it may also be used to compensate for cognitive deficits in AD with regard to empathy. The pattern of relatively preserved aspects of affective empathy and impairments in components of cognitive empathy in AD also indicates the importance and intertwined nature of interactions between cognition and emotion in producing a holistic experience and the ability of socioemotional functioning.

References

Alladi, S., Ch, S., Shailaja, M., Santhoshi, C., Nigam, R., & Kaul, S. (2011). Empathy and frontal behavioral patterns discriminate between vascular dementia, Alzheimer's disease and frontotemporal dementia. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *7*(4), 43–44. https://doi.org/https://doi.org/10.1016/j.jalz.2011.09.185

Amieva, H., Phillips, L. H., Della Sala, S., & Henry, J. D. (2004). Inhibitory functioning in Alzheimer's disease. *Brain*, *127*, 949–964. https://doi.org/10.1093/brain/awh045

Asendorpf, J. B., & Baudonnière, P. M. (1993). Self-Awareness and Other-Awareness: Mirror Self-Recognition and Synchronic Imitation Among Unfamiliar Peers. *Developmental Psychology*, *29*, 88–95. https://doi.org/10.1037/0012-1649.29.1.88

Bartochowski, Z., Gatla, S., Khoury, R., Al-Dahhak, R., & Grossberg, G. T. (2018). Empathy changes in neurocognitive disorders: A review. *Annals of Clinical Psychiatry*, *30*(3), 220–232.

Bertrand, E., Landeira-Fernandez, J., & Mograbi, D. C. (2016). Metacognition and perspective-taking in Alzheimer's disease: A mini-review. *Frontiers in Psychology*, *7*, 1–7. https://doi.org/10.3389/fpsyg.2016.01812

Bird, G., & Viding, E. (2014). The self to other model of empathy: Providing a new framework for understanding empathy impairments in psychopathy, autism, and alexithymia. *Neuroscience and Biobehavioral Reviews*, *47*, 520–532. https://doi.org/10.1016/j.neubiorev.2014.09.021

Blessing, A., Forstmeier, S., & Eschen, A. (2014). Emotionen als wirkfaktoren psychosozialer interventionen bei Alzheimer-demenz. *Zeitschrift Fur Psychiatrie, Psychologie Und Psychotherapie*, *62*(3), 191–199. https://doi.org/10.1024/1661-4747/a000195

Bond, R. L., Downey, L. E., Weston, P. S. J., Slattery, C. F., Clark, C. N., Macpherson, K., … Warren, J. D. (2016). Processing of Self versus Non-Self in Alzheimer's Disease. *Frontiers in Human Neuroscience*, *10*, 1–10. https://doi.org/10.3389/fnhum.2016.00097

Bora, E., Walterfang, M., & Velakoulis, D. (2015). Theory of mind in behavioural-variant frontotemporal dementia and Alzheimer's disease: a meta-analysis. *Journal of Neurology, Neurosurgery & Psychiatry*, *86*, 714–719. https://doi.org/10.1136/jnnp-2014-309445

Bucks, R. S., & Radford, S. A. (2004). Emotion processing in Alzheimer's disease. *Aging and Mental Health*, *8*(3), 222–232. https://doi.org/10.1080/13607860410001669750

Castelli, I., Pini, A., Alberoni, M., Liverta-Sempio, O., Baglio, F., Massaro, D., … Nemni, R. (2011). Mapping levels of theory of mind in Alzheimer ' s disease : A preliminary study. *Aging & Mental Health*, *15*(2), 157–168. https://doi.org/10.1080/13607863.2010.513038

Christidi, F., Migliaccio, R., Santamaría-García, H., Santangelo, G., & Trojsi, F. (2018). Social cognition dysfunctions in neurodegenerative diseases: Neuroanatomical correlates and clinical implications. *Behavioural Neurology*. https://doi.org/10.1155/2018/1849794

Clare, L., Nelis, S. M., Martyr, A., Roberts, J., Whitaker, C. J., Markova, I. S., … Morris, R. G. (2012). The influence of psychological, social and contextual factors on the expression and measurement of awareness in early-stage dementia: Testing a biopsychosocial model. *International Journal of Geriatric Psychiatry*, *27*(2), 167–177. https://doi.org/10.1002/gps.2705

Clare, L., Nelis, S. M., Martyr, A., Whitaker, C. J., Marková, I. S., Roth, I., … Morris, R. G. (2012). "She might have what I have got": the potential utility of vignettes as an indirect measure of awareness in early-stage dementia. *Aging & Mental Health*, *16*(5), 566–575. https://doi.org/10.1080/13607863.2011.652594

Coen, R. F., Swanwick, G. R. J., O'Boyle, C. A., & Coakley, D. (1997). Behaviour disturbance and other predictors of carer burden in Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *12*, 331–336. https://doi.org/10.1002/(SICI)1099-1166(199703)12:3<331::AID-GPS495>3.0.CO;2-J

Cuerva, A. G., Sabe, L., Kuzis, G., Tiberti, C., Dorrego, F., & Starkstein, S. E. (2001). Theory of Mind and Pragmatic Abilities in Dementia. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology*, *14*(3), 153–158.

de Vignemont, F., & Singer, T. (2006). The empathic brain: how, when and why? *Trends in Cognitive Sciences*, *10*(10), 435–441. https://doi.org/10.1016/j.tics.2006.08.008

De Waal, F. B. M., & Preston, S. D. (2017). Mammalian empathy: Behavioural manifestations and neural basis. *Nature Reviews Neuroscience*, *18*(8), 498–509. https://doi.org/10.1038/nrn.2017.72

Decety, J. (2011). Dissecting the neural mechanisms mediating empathy. *Emotion Review*, *3*(1), 92–108. https://doi.org/10.1177/1754073910374662

Decety, J., & Jackson, P. L. (2004). The Functional Architecture of Human Empathy. *Behavioral and Cognitive Neuroscience Reviews*, *3*(2), 71–100. https://doi.org/10.1177/1534582304267187

Decety, J., & Meyer, M. (2008). From emotion resonance to empathic understanding: A social developmental neuroscience account. *Development and Psychopathology*, *20*, 1053–1080. https://doi.org/10.1017/S0954579408000503

Decety, J., & Moriguchi, Y. . Y. (2007). The empathic brain and its dysfunction in psychiatric populations: Implications for intervention across different clinical conditions. *BioPsychoSocial Medicine*, *1*, 22–65. https://doi.org/10.1186/1751-0759-1-22

Decety, J., & Svetlova, M. (2012). Putting together phylogenetic and ontogenetic perspectives on empathy. *Developmental Cognitive Neuroscience*, *2*, 1–24. https://doi.org/10.1016/j.dcn.2011.05.003

Dermody, N., Wong, S., Ahmed, R., Piguet, O., Hodges, J. R., & Irish, M. (2016). Uncovering the Neural Bases of Cognitive and Affective Empathy Deficits in Alzheimer's Disease and the Behavioral-Variant of Frontotemporal Dementia. *Journal of Alzheimer's Disease*, *53*(3), 801–816. https://doi.org/https://doi.org/10.3233/JAD-160175

Desmarais, P., Lanctôt, K. L., Masellis, M., Black, S. E., & Herrmann, N. (2018). Social inappropriateness in neurodegenerative disorders. *International Psychogeriatrics*, *30*(2), 197–207. https://doi.org/10.1017/S1041610217001260

Farina, E., Baglio, F., Pomati, S., D'Amico, A., Campini, I. C., Tella, S. Di, … Pozzo, T. (2017). The mirror neurons network in aging, mild cognitive

impairment, and Alzheimer disease: A functional mri study. *Frontiers in Aging Neuroscience*, *9*, 1–13. https://doi.org/10.3389/fnagi.2017.00371

Fernandez-Duque, D., Baird, J. A., & Black, S. E. (2009). False-belief understanding in frontotemporal dementia and Alzheimer ' s disease. *Journal of Clinical and Experimental Neuropsychology*, *31*(4), 489–497. https://doi.org/10.1080/13803390802282688

Fernandez-Duque, D., Hodges, S. D., Baird, J. A., & Black, S. E. (2010). Empathy in frontotemporal dementia and Alzheimer's disease. *Journal of Clinical and Experimental Neuropsychology*, *32*(3), 289–298. https://doi.org/http://dx.doi.org/10.1080/13803390903002191

Fliss, R., Le Gall, D., Etcharry-Bouyx, F., Chauviré, V., Desgranges, B., & Allain, P. (2016). Theory of Mind and social reserve: Alternative hypothesis of progressive Theory of Mind decay during different stages of Alzheimer's disease. *Social Neuroscience*, *11*(4), 409–423. https://doi.org/10.1080/17470919.2015.1101014

Fortier, J., Besnard, J., & Allain, P. (2018). Theory of mind, empathy and emotion perception in cortical and subcortical neurodegenerative diseases. *Revue Neurologique*, *174*(4), 237–246. https://doi.org/10.1016/j.neurol.2017.07.013

Freedman, M., Binns, M. A., Black, S. E., Murphy, C., & Stuss, D. T. (2013). Theory of Mind and Recognition of Facial Emotion in Dementia. *Alzheimer Disease & Associated Disorders*, *27*(1), 56–61. https://doi.org/10.1097/WAD.0b013e31824ea5db

Gallese, V., Fadiga, L., Fogassi, L., & Rizzolatti, G. (1996). Action recognition in the premotor cortex. *Brain*, *119*, 593–609. https://doi.org/10.1093/brain/119.2.593

Goodkind, M. S., Gyurak, A., McCarthy, M., Miller, B. L., & Levenson, R. W. (2010). Emotion Regulation Deficits in Frontotemporal Lobar Degeneration and Alzheimer's Disease. *Psychology and Aging*, *25*(1), 30–37. https://doi.org/10.1037/a0018519

Gregory, C., Lough, S., Stone, V., Erzinclioglu, S., Martin, L., Baron-Cohen, S., & Hodges, J. R. (2002). Theory of mind in patients with frontal variant frontotemporal dementia and Alzheimer's disease: theoretical and practical

implications. *Brain*, *125*(4), 752–764. https://doi.org/10.1093/brain/awf079

Gyurak, A., Gross, J., & Etkin, A. (2011). Explicit and implicit emotion regulation: A dual process framework. *Cognition & Emotion*, *25*(3), 400–412. https://doi.org/10.1080/02699931.2010.544160

Henry, J. D., Rendell, P. G., Scicluna, A., Jackson, M., & Phillips, L. H. (2009). Emotion experience, expression, and regulation in Alzheimer's disease. *Psychology and Aging*, *24*(1), 252–257. https://doi.org/10.1037/a0014001

Hsieh, S., Irish, M., Daveson, N., Hodges, J. R., & Piguet, O. (2013). When One Loses Empathy. *Journal of Geriatric Psychiatry and Neurology*, *26*(3), 174–184. https://doi.org/10.1177/0891988713495448

Hughes, J. (2011). *Alzheimer's and other dementias*. New York: Oxford University.

Hynes, C. A., Baird, A. A., & Grafton, S. T. (2006). Differential role of the orbital frontal lobe in emotional versus cognitive perspective-taking. *Neuropsychologia*, *44*(3), 374–383. https://doi.org/10.1016/j.neuropsychologia.2005.06.011

Ickes, W. (1997). *Empathic Accuracy*. New York: Guilford.

Kalenzaga, S., & Clarys, D. (2013). Self-referential processing in Alzheimer's disease: Two different ways of processing self-knowledge? *Journal of Clinical and Experimental Neuropsychology*, *35*(5), 455–471. https://doi.org/10.1080/13803395.2013.789485

Kemp, J., Després, O., Sellal, F., & Dufour, A. (2012). Theory of Mind in normal ageing and neurodegenerative pathologies. *Ageing Research Reviews*, *11*(2), 199–219. https://doi.org/10.1016/j.arr.2011.12.001

Klein-Koerkamp, Y., Beaudoin, M., Baciu, M., & Hot, P. (2012). Emotional decoding abilities in Alzheimer's disease: A meta-analysis. *Journal of Alzheimer's Disease*, *32*(1), 109–125. https://doi.org/10.3233/JAD-2012-120553

Klimecki, O., & Singer, T. (2013). Empathy from the Perspective of Social Neuroscience. In J. Armony & P. Vuilleumier (Eds.), *The Cambridge Handbook of Human Affective Neuroscience* (pp. 533–551). New York: Cambridge University.

Laisney, M., Bon, L., Guiziou, C., Daluzeau, N., Eustache, F., & Desgranges, B.

(2013). Cognitive and affective Theory of Mind in mild to moderate Alzheimer's disease. *Journal of Neuropsychology*, *7*(1), 107–120. https://doi.org/10.1111/j.1748-6653.2012.02038.x

Lawton, M. P., Kleban, M. H., Rajagopal, D., & Dean, J. (1992). Dimensions of affective experience in three age groups. *Psychology and Aging*, *7*(2), 171–184. https://doi.org/10.1037//0882-7974.7.2.171

Le Bouc, R., Lenfant, P., Delbeuck, X., Ravasi, L., Lebert, F., Semah, F., & Pasquier, F. (2012). My belief or yours? Differential theory of mind deficits in frontotemporal dementia and Alzheimer's disease. *Brain*, *135*(10), 3026–3038. https://doi.org/10.1093/brain/aws237

Leclerc, C. M., & Kensinger, E. A. (2011). Neural processing of emotional pictures and words: A comparison of young and older adults. *Developmental Neuropsychology*, *26*, 519–538. https://doi.org/10.1080/87565641.2010.549864

Leiberg, S., & Anders, S. (2006). The multiple facets of empathy: a survey of theory and evidence. *Progress in Brain Research*, *156*, 419–440. https://doi.org/10.1016/S0079-6123(06)56023-6

Levenson, R. W., Carstensen, L. L., & Gottman, J. M. (1994). The Influence of Age and Gender on Affect, Physiology, and Their Interrelations: A Study of Long-Term Marriages. *Journal of Personality and Social Psychology*, *67*(1), 56–68. https://doi.org/10.1037/0022-3514.67.1.56

Levenson, R. W., & Miller, B. L. (2007). Loss of cells - Loss of self: Frontotemporal lobar degeneration and human emotion. *Current Directions in Psychological Science*, *15*, 289–294. https://doi.org/10.1111/j.1467-8721.2007.00523.x

Marková, H., Laczó, J., Andel, R., Hort, J., & Vlcek, K. (2015). Perspective taking abilities in amnestic mild cognitive impairment and Alzheimer's disease. *Behavioral Brain Research*, *281*, 229–238. https://doi.org/10.1016/j.bbr.2014.12.033

McLellan, T., Johnston, L., Dalrymple-Alford, J., & Porter, R. (2008). The recognition of facial expressions of emotion in Alzheimer's disease: A review of findings. *Acta Neuropsychiatrica*, *20*(5), 236–250. https://doi.org/10.1111/j.1601-5215.2008.00315.x

Mograbi, D. C., Brown, R. G., Landeira-Fernandez, J., & Morris, R. G. (2014). Metacognition and attribution of diffculty for self and others in alzheimer's disease. *Psychology and Neuroscience*, *7*(3), 417–424. https://doi.org/10.3922/j.psns.2014.036

Mograbi, D. C., Brown, R. G., & Morris, R. G. (2009). Anosognosia in Alzheimer's disease - The petrified self. *Consciousness and Cognition*, *18*(4), 989–1003. https://doi.org/10.1016/j.concog.2009.07.005

Mograbi, D. C., Brown, R. G., Salas, C., & Morris, R. G. (2012). Emotional reactivity and awareness of task performance in Alzheimer's disease. *Neuropsychologia*, *50*(8), 2075–2084. https://doi.org/10.1016/j.neuropsychologia.2012.05.008

Mograbi, D. C., Ferri, C. P., Sosa, A. L., Stewart, R., Laks, J., Brown, R., & Morris, R. G. (2012). Unawareness of memory impairment in dementia: A population-based study. *International Psychogeriatrics*, *24*(6), 931–939. https://doi.org/10.1017/S1041610211002730

Moreau, N., Rauzy, S., Viallet, F., & Champagne-Lavau, M. (2016). Theory of Mind in Alzheimer Disease: Evidence of Authentic Impairment During Social Interaction. *Neuropsychology*, *30*(3), 312–321. https://doi.org/10.1037/neu0000220

Moretti, D. V. (2016). Involvement of mirror neuron system in prodromal Alzheimer's disease. *BBA Clinical*, *5*, 46–53. https://doi.org/10.1016/j.bbacli.2015.12.001

Morris, R. G., & Mograbi, D. C. (2013). Anosognosia, autobiographical memory and self knowledge in Alzheimer's disease. *Cortex*, *49*(6), 1553–1565. https://doi.org/10.1016/j.cortex.2012.09.006

Mroczek, D. K., & Kolarz, C. M. (1998). The effect of age on positive and negative affect: a developmental perspective on happiness. *Journal of Personality and Social Psychology*, *75*(5), 1333–1349. https://doi.org/10.1037/0022-3514.75.5.1333

Narme, P., Mouras, H., Roussel, M., Devendeville, A., & Godefroy, O. (2013). Assessment of socioemotional processes facilitates the distinction between

frontotemporal lobar degeneration and Alzheimers disease. *Journal of Clinical and Experimental Neuropsychology*, *35*(7), 728–744. https://doi.org/10.1080/13803395.2013.823911

Nash, S., Henry, J. D., McDonald, S., Martin, I. I., Brodaty, H., Peek-O'Leary, M.-A. A., … Peek-O'Leary, M.-A. A. (2007). Cognitive disinhibition and socioemotional functioning in Alzheimer's disease. *Journal of the International Neuropsychological Society*, *13*(6), 1060–1064. https://doi.org/10.1017/S1355617707071184

Phillips, L. H., Scott, C., Henry, J. D., Mowat, D., & Bell, J. S. (2010). Emotion perception in Alzheimer's disease and mood disorder in old age. *Psychology and Aging*, *25*(1), 38–47. https://doi.org/10.1037/a0017369

Poletti, M., & Bonuccelli, U. (2013). Alteration of affective Theory of Mind in amnestic mild cognitive impairment. *Journal of Neuropsychology*, *7*(1), 121–131. https://doi.org/10.1111/j.1748-6653.2012.02040.x

Poletti, M., Enrici, I., & Adenzato, M. (2012). Cognitive and affective Theory of Mind in neurodegenerative diseases: Neuropsychological, neuroanatomical and neurochemical levels. *Neuroscience and Biobehavioral Reviews*, *36*(9), 2147–2164. https://doi.org/10.1016/j.neubiorev.2012.07.004

Preston, S. D., & de Waal, F. B. M. (2002). Empathy: Its ultimate and proximate bases. *Behavioral and Brain Sciences*, *25*, 1–20. https://doi.org/10.1017/S0140525X02000018

Prince, M., Wimo, A., Guerchet, M., Ali, G.-C., Wu, Y.-T., & Prina, M. (2015). *World Alzheimer Report 2015: The Global Impact of Dementia - An Analysis of Prevalence, Incidence, Cost and Trends*. *Alzheimer's Disease International*. London.

Ramanan, S., Souza, L. C. De, Moreau, N., Sarazin, M., Teixeira, A. L., Allen, Z., … Ad, T. (2017). Determinants of Theory of Mind performance in Alzheimer's disease: A data-mining study. *Cortex*, *88*, 8–18. https://doi.org/10.1016/j.cortex.2016.11.014

Rankin, K. P., Gorno-Tempini, M. L., Allison, S. C., Stanley, C. M., Glenn, S., Weiner, M. W., & Miller, B. L. (2006). Structural anatomy of empathy in

neurodegenerative disease. *Brain*, *129*(11), 2945–2956. https://doi.org/10.1093/brain/awl254

Rankin, K. P., Kramer, J. H., & Miller, B. L. (2005). Patterns of cognitive and emotional empathy in frontotemporal lobar degeneration. *Cognitive and Behavioral Neurology*, *18*(1), 28–36. https://doi.org/10.1097/01.wnn.0000152225.05377.ab

Rapoport, S. I. (1989). Hypothesis: Alzheimer's disease is a phylogenetic disease. *Medical Hypotheses*, *29*(3), 147–150. https://doi.org/10.1016/0306-9877(89)90185-0

Rizzolatti, G., Fadiga, L., Gallese, V., & Fogassi, L. (1996). Premotor cortex and the recognition of motor actions. *Cognitive Brain Research*, *3*, 131–141. https://doi.org/10.1016/0926-6410(95)00038-0

Rosen, H. J., Alcantar, O., Rothlind, J., Sturm, V., Kramer, J. H., Weiner, M., & Miller, B. L. (2010). Neuroanatomical correlates of cognitive self-appraisal in neurodegenerative disease. *NeuroImage*, *49*(4), 3358–3364. https://doi.org/10.1016/j.neuroimage.2009.11.041

Ruby, P., Collette, F., D'Argembeau, A., Péters, F., Degueldre, C., Balteau, E., … Salmon, E. (2009). Perspective taking to assess self-personality: What's modified in Alzheimer's disease? *Neurobiology of Aging*, *30*, 1637–1651. https://doi.org/10.1016/j.neurobiolaging.2007.12.014

Salmon, E., Perani, D., Herholz, K., Marique, P., Kalbe, E., Holthoff, V., … Garraux, G. (2006). Neural correlates of anosognosia for cognitive impairment in Alzheimer's disease. *Human Brain Mapping*, *27*(7), 588–597. https://doi.org/10.1002/hbm.20203

Sandoz, M., Démonet, J.-F., & Fossard, M. (2014). Theory of mind and cognitive processes in aging and Alzheimer type dementia: a systematic review. *Aging & Mental Health*, *18*(7), 815–827. https://doi.org/10.1080/13607863.2014.899974

Saxe, R., & Powell, L. J. (2006). It's the thought that counts: Specific brain regions for one component of theory of mind. *Psychological Science*, *17*(8), 692–699. https://doi.org/10.1111/j.1467-9280.2006.01768.x

Shamay-Tsoory, S. G., Tibi-Elhanany, Y., & Aharon-Peretz, J. (2006). The

ventromedial prefrontal cortex is involved in understanding affective but not cognitive theory of mind stories. *Social Neuroscience*, *1*(3–4), 149–166. https://doi.org/10.1080/17470910600985589

Shany-Ur, T., Lin, N., Rosen, H. J., Sollberger, M., Miller, B. L., & Rankin, K. P. (2014). Self-awareness in neurodegenerative disease relies on neural structures mediating reward-driven attention. *Brain*, *137*(8), 2368–2381. https://doi.org/10.1093/brain/awu161

Starkstein, S. E. (2014). Anosognosia in Alzheimer's disease: Diagnosis, frequency, mechanism and clinical correlates. *Cortex*, *61*, 64–73. https://doi.org/10.1016/j.cortex.2014.07.019

Sturm, V. E. V., Yokoyama, J. S., Seeley, W. W., Kramer, J. H., Miller, B. L., & Rankin, K. P. (2013). Heightened emotional contagion in mild cognitive impairment and Alzheimer's disease is associated with temporal lobe degeneration. *Proceedings of the National Academy of Sciences*, *110*(24), 9944–9949. https://doi.org/10.1073/pnas.1301119110

Synn, A., Mothakunnel, A., Kumfor, F., Chen, Y., Piguet, O., Hodges, J. R., & Irish, M. (2018). Mental States in Moving Shapes: Distinct Cortical and Subcortical Contributions to Theory of Mind Impairments in Dementia. *Journal of Alzheimer's Disease*, *61*, 521–535. https://doi.org/10.3233/JAD-170809

Torres, B., Santos, R. L., Sousa, M. F. B. de, Simões Neto, J. P., Nogueira, M. M. L., Belfort, T. T., … Dourado, M. C. N. (2015). Facial expression recognition in Alzheimer's disease: a longitudinal study. *Arquivos de Neuro-Psiquiatria*, *73*(5), 383–389. https://doi.org/10.1590/0004-282X20150009

Villain, N., Fouquet, M., Baron, J. C., Mézenge, F., Landeau, B., De La Sayette, V., … Chételat, G. (2010). Sequential relationships between grey matter and white matter atrophy and brain metabolic abnormalities in early Alzheimer's disease. *Brain*, *133*(11), 3301–3314. https://doi.org/10.1093/brain/awq203

Wang, L., Zang, Y., He, Y., Liang, M., Zhang, X., Tian, L., … Li, K. (2006). Changes in hippocampal connectivity in the early stages of Alzheimer's disease: Evidence from resting state fMRI. *NeuroImage*, *31*(2), 496–504. https://doi.org/10.1016/j.neuroimage.2005.12.033

Wright, C. I. (2011). Emotion and Behavior in Alzheimer's Disease and Other Dementias. In A. E. Budson & N. W. Kowall (Eds.), *The Handbook of Alzheimer's Disease and Other Dementias* (pp. 416–456). Oxford: Blackwell.

Zaitchik, D., Koff, E., Brownell, H., Winner, E., & Albert, M. (2004). Inference of mental states in patients with Alzheimer's disease. *Cognitive Neuropsychiatry*, *9*(4), 301–313. https://doi.org/10.1080/13546800344000246

Zaitchik, D., Koff, E., Brownell, H., Winner, E., Albert, M., Koff, E., & Albert, M. (2006). Inference of beliefs and emotions in patients with Alzheimer's disease. *Neuropsychology*, *20*(1), 11–20. https://doi.org/10.1037/0894-4105.20.1.11

Zaki, J., & Ochsner, K. (2012). The neuroscience of empathy: Progress, pitfalls and promise. *Nature Neuroscience*, *15*(5), 675–680. https://doi.org/10.1038/nn.3085

Zamboni, G., Drazich, E., McCulloch, E., Filippini, N., Mackay, C. E., Jenkinson, M., … Wilcock, G. K. (2013). Neuroanatomy of impaired self-awareness in Alzheimer's disease and mild cognitive impairment. *Cortex*, *49*, 668–678. https://doi.org/10.1016/j.cortex.2012.04.011

Zhang, F., Ho, Y. W., & Fung, H. H. (2015). Learning from Normal Aging: Preserved Emotional Functioning Facilitates Adaptation among Early Alzheimer's Disease Patients. *Aging and Disease*, *6*(3), 208–215. https://doi.org/10.14336/AD.2014.0620

Figures

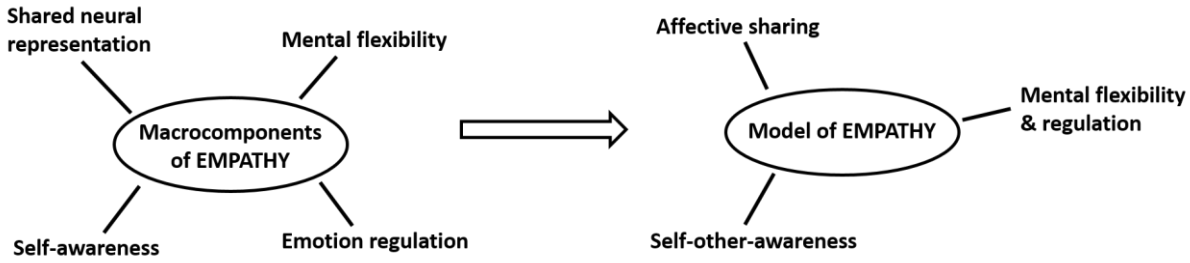

Figure 1 – Components of empathy according to Decety and colleagues. *Left:* The four macrocomponents of empathy. *Right:* The components of empathy in the model of Decety and colleagues. The mechanism of affective sharing is based on shared neural representations. Self-other-awareness is related to the ability to maintain a distinction between the self and others. Mental flexibility refers to perspective taking and regulation processes.

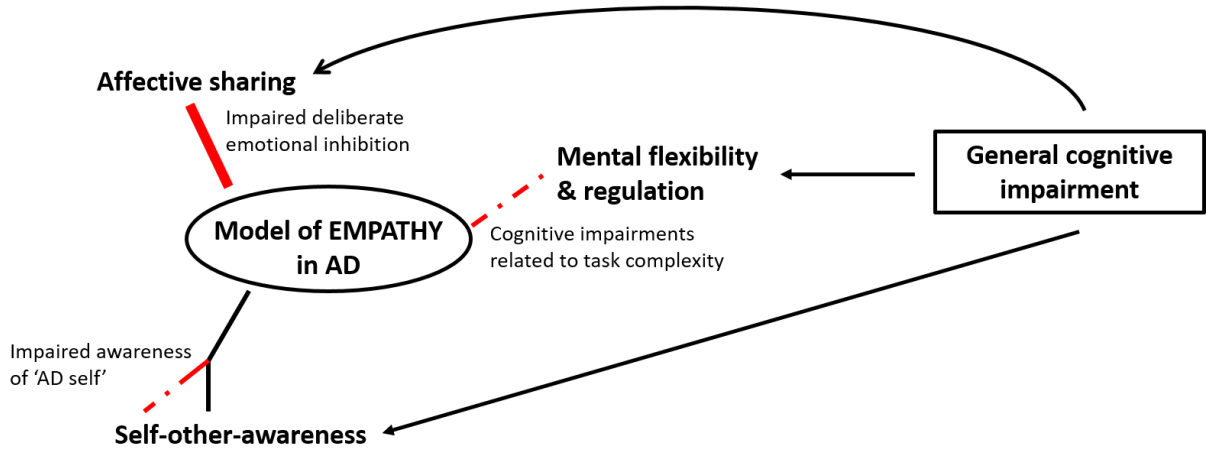

Figure 2 – A revised model of empathy in AD. A draft of the empathy model in AD. The figure highlights the processes that are most likely affected by the AD pathology. Deficits in empathy can mainly be attributed to their general cognitive impairment, particularly in executive functioning and memory. AD patients appear to be able to regulate their emotions and conduct ToM tasks to a certain degree, at least in earlier stages of the disease. But they can present difficulties when task demands become more complex. Thus, mental flexibility and regulation, which comprise the cognitive aspect of empathy, are somewhat impaired in AD (indicated by the dashed line). Moreover, general cognitive impairments also influence the affective aspect of empathy. Less emotion inhibition could lead to greater emotional contagion and thus lead to the intensification of automatic affect sharing (indicated by the thicker line). Furthermore, cognitive impairment leads to problems of awareness that are related to the "AD-self," whereas other awareness appears to remain mostly intact. However, there is no evidence of confusion of the self and others in AD. In contrast to AD, patients with FTD seem to present a primary impairment in empathy related abilities. Thus, their deficits cannot be mainly explained by other cognitive impairments.

IV. General discussion

The general objective of the present work was to investigate different aspects of awareness, as well as basic and higher emotional abilities in AD. Furthermore, we explored the influence of affective factors, such as self-relevance and apathy, on awareness processes. Our work aimed at contributing to a better understanding of factors that influence awareness, as well as to explore preserved abilities of PwAD, which both are directly relevant for clinical practice and caregiving. Hereby, we employed a variety of methods, such as statistical and theoretical modeling, as well as a combination of behavioral, self-report, and electrophysiological data in the experimental studies. The first part of the thesis explored the underlying structure and mechanisms of awareness processes in AD, whereas the second part focused on affective processing and emotional abilities of PwAD.

The first study used a statistical modeling approach to investigate the functional structure of awareness in AD. The findings suggested that mood state and cognitive level affect the ability to engage in ADL, which in turn are related to awareness. Higher levels of depressive mood state and lower cognitive functioning complicate the participation on and performance of ADL, and lower levels of ADL lead to lower overall levels of awareness. In other words, PwAD need to engage in activities to be aware of their limits and abilities, and among the factors that decisively impact the ability to engage in ADL are mood state and cognitive level. Interestingly, our model was more consistent for mild AD, which suggests that other aspects become more relevant for awareness with the progression of the disease.

The role of specific cognitive factors on awareness are discussed in the CAM (Agnew & Morris, 1998; Morris & Hannesdottir, 2004; Morris & Mograbi, 2013). According to this model, each individual constantly evaluates his or her own performance on everyday tasks by comparing it to expected performance on domain-specific and central levels. This expected performance is based on the individual's self-knowledge stored in the PDB. A failure in comparator mechanisms would lead to executive forms of unawareness, whereas a failure in updating and consolidating the PDB would result in mnemonic unawareness. The findings of our second study support a mnemonic, rather than an executive origin of unawareness in AD. We applied a reaction time task to examine awareness of task performance online, as

well as after longer time intervals. Whereas online monitoring was preserved in PwAD and healthy older adults, PwAD had more difficulties to transfer online monitoring to long-term predictions. This was reflected, for example, in the ERP results. The FRN, a component associated with the processing of external feedback, was related to online monitoring, and was sensitive to feedback valence in all groups, thus indicating preserved executive performance monitoring processes in PwAD and aging. On the other hand, the P300 was associated with medium- and long-term performance monitoring indices and was strongly reduced in PwAD and healthy older adults compared to healthy young participants. Moreover, it only showed sensitivity to feedback valence in young adults. The P300 component has been linked to inhibition of irrelevant brain activation to focus attention on incoming stimulus information and facilitate memory encoding (Polich, 2007, 2012). Thus, our results are consistent with the inhibition hypothesis of the P300, which also suggests that deficits in cortical processes underlying inhibitory signals might lead to reduced P300 amplitudes with aging and dementia (Polich, 2012). In summary, whereas executive performance monitoring was preserved in healthy older participants and PwAD, a breakdown of cortical inhibitory processes might contributed to impaired awareness of task performance after longer time intervals at least in PwAD.

In addition to this first part, the second section of the present work was dedicated to the exploration of affective processing, which also is potentially influenced by AD and aging. We investigated emotional reactivity to negative, self-relevant, and neutral pictures. Affective ratings, facial expression data, as well as ERP results showed that emotional reactivity was preserved in PwAD. However, impaired cognitive inhibition processes might have led to more intense facial expressions to negative pictures in PwAD and healthy older participants in comparison to young adults. Furthermore, although higher levels of apathy were associated with reduced neurophysiologic responses to negative pictures in PwAD, these were still enhanced in comparison to healthy older controls. It has been suggested that aging is associated with an increased cognitive influence on emotional reactivity (Kunzmann & Richter, 2009; Mather, 2012). Therefore, we speculated that enhanced neurophysiological responses to negative stimuli in PwAD might reflect a lack of cognitive control mechanisms. On top of that, results suggested that neurophysiological responses to self-relevant dementia-related pictures may be increased in PwAD compared to

healthy older and also young participants, and arousal ratings of those pictures were positively correlated with social awareness. The content of the dementia-related pictures was highly social, showing older people in medical and caregiving settings with other persons.

This is supportive of findings suggesting that PwAD are more aware of dementia related problems in other people (Clare, Nelis, Martyr, Whitaker, et al., 2012; Mograbi, Brown, & Morris, 2012), and thus consistent with the notion that knowledge about others is based on knowledge about the self (Decety & Jackson, 2004). An essential ability for understanding the behavior and intentions of others is empathy. This higher order emotional ability is crucial for successful social functioning (Leiberg & Anders, 2006). The ability to empathize relies on emotional, as well as cognitive components that are closely interwoven, whereby affective empathy is built on a bottom-up affective sharing mechanism that distinguishes between the self and the other. On the other hand, the cognitive aspect of empathy reflects top-down control mechanisms such as perspective taking and regulation (Decety, 2011). According to the reviewed literature, affective empathy is largely preserved in PwAD, while aspects of cognitive empathy seem to be impaired, especially when complexity and level of conscious cognitive control demands of the task increase. Moreover, enhanced affective sharing in PwAD could be due to impaired cognitive processes underlying inhibition of emotion (Sturm et al., 2013). Deficits in the overall ability to empathize can be attributed to a general cognitive decline in AD.

In summary, the present work found evidence for different factors influencing different aspects of awareness. Whereas general awareness of the disease was influenced by depressive mood state and general cognitive impairment, both mediated by ADL, awareness of task performance was found to be affected by a failure in updating acquired knowledge into self representations. Factors influencing emotional reactivity were apathy and self-relevance. Although emotional reactivity was largely preserved, impaired cognitive control mechanisms might have led to increased neurophysiological responses and more intense facial expressions. Empathy as a higher emotional ability is likewise affected by the general cognitive decline that accompanies AD, whereby affective aspects might be particularly sensitive to deficits in cognitive inhibition processes. In this context, our work gives

further evidence for how deeply intertwined cognitive and affective processes are (Okon-Singer et al., 2015). Research about affective processing and emotional capacities in AD is still scarce, and so far, it is not clear which cognitive impairments lead to enhanced affective processing in PwAD compared to older controls. Deficits in cortical processes underlying cognitive inhibition could be a possible explanation. Although AD is characterized by a significant impairment of inhibitory processes, inhibition is a very heterogeneous construct and not all its mechanisms are affected by the disease (Amieva et al., 2004). This leaves room for future studies to investigate the nature of emotion-cognition interactions in affective processing and awareness in AD.

Furthermore, our work supports the notion that emotional abilities are relatively preserved in PwAD. This point has considerable importance for clinical implications. Strengthening preserved capacities will lead to larger improvements for PwAD and caregivers than focusing on lost abilities. A review by Zhang and colleagues (Zhang et al., 2015) emphasizes the optimization of preserved emotional abilities to increase positive emotions and improve socio-emotional functioning in PwAD. Promoting positive emotions, e.g. through watching a happy movie, getting a positive surprise or by helping others, can contribute to build psychological resources related to coping, as well as help to prevent negative emotions associated to loss and disease. Interventions like that will not only benefit PwAD, but also their caregivers. Low daily life functionality, anosognosia, and NPS are related to caregiver burden (Clare, Nelis, Martyr, Roberts, et al., 2012; Feast, Moniz-Cook, Stoner, Charlesworth, & Orrell, 2016; Starkstein, 2014). Thus, interventions aimed at ameliorating levels of ADL, awareness and NPS, such as depression and apathy, will indirectly improve quality of life and stress for caregivers. In this context, Di Domenico and colleagues (Di Domenico, Palumbo, Fairfield, & Mammarella, 2016) indicated that an emotional shaping task improved apathy in PwAD. On the other hand, it seems important not only to promote positive emotions, but also to prevent unpleasant situations as much as possible, since lacking cognitive control mechanisms could elevate PwAD's exposure to negative emotions (Sturm et al., 2013). Finally, a detailed diagnostic of domain specific anosognosia could provide additional insight for individual treatment.

Some general limitations of the present work should be mentioned. One point is the generalizability of our results to illiterate PwAD and PwAD with clinical depression, because less than four years of formal education was an exclusion criterion, as well as clinical levels of depression. Additionally, PwAD were recruited from an outpatient unit of a university hospital. Thus, PwAD who did not take part in the studies mostly had difficulties to arrange an additional visit at the hospital due to available time of the caregiver or greater distance. Another point to keep in mind is the assessment of patient variables, such as apathy and awareness, through caregiver reports. While caregiver report is thought to be more reliable because of PwAD's awareness deficits, they are influenced by caregiver well-being and perception of the person with AD (Clare, Nelis, Martyr, Roberts, et al., 2012). A last point we want to mention is the need for cross-validation of our results, on the one hand because of the small sample size included in our experimental studies, on the other hand because of the heterogeneous nature of AD.

To conclude, we would like to present some future directions. Our work demonstrated that the investigation of awareness, as well as of affective processes, benefits from the integration of results from different methodological approaches. Therefore, we recommend that future studies continue to combine behavioral and subjective data with physiological and neuroimaging data to provide additional information on neural mechanisms and structures that contribute to subjective and behavioral changes in AD. Moreover, raising efforts to create large-scale datasets that can be used to model relationships of key variables and influential factors could be beneficial to validate existing models of awareness. Hereby, data from different research groups and centers could be combined with datasets that are available online in open-source projects. Another important point is the implementation of longitudinal studies. Our work found that the underlying structure of awareness in AD varies with progression of the disease. Hence, it is of interest how awareness develops in the course of AD, and to identify the contribution of different factors in the early, as well as in the later stages of the disease. Last but not least, it is necessary to engage in translational research in the field. The question how to implement research findings in specific clinical practice is a key element of successful caregiving.

V. References

Aalten, P., Van Valen, E., Clare, L., Kenny, G., & Verhey, F. (2005). Awareness in dementia: A review of clinical correlates. *Aging & Mental Health*, *9*(5), 414–422. https://doi.org/10.1080/13607860500143075

Aalten, P., Van Valen, E., De Vugt, M. E., Lousberg, R., Jolles, J., & Verhey, F. R. J. (2006). Awareness and behavioral problems in dementia patients: A prospective study. *International Psychogeriatrics*, *18*(1), 3–17. https://doi.org/10.1017/S1041610205002772

Agnew, S. K., & Morris, R. G. (1998). The heterogeneity of anosognosia for memory impairment in Alzheimer's disease: A review of the literature and a proposed model. *Aging & Mental Health*, *2*, 7–19. https://doi.org/10.1080/13607869856876

Alexopoulos, G. S., Abrams, R. C., Young, R. C., & Shamoian, C. A. (1988). Cornell Scale for Depression in Dementia. *Biological Psychiatry*, *23*(3), 271–284. https://doi.org/10.1016/0006-3223(88)90038-8

Alladi, S., Ch, S., Shailaja, M., Santhoshi, C., Nigam, R., & Kaul, S. (2011). Empathy and frontal behavioral patterns discriminate between vascular dementia, Alzheimer's disease and frontotemporal dementia. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *7*(4), 43–44. https://doi.org/https://doi.org/10.1016/j.jalz.2011.09.185

Almeida, O. P., & Almeida, S. A. (1999a). Confiabilidade da versão brasileira da Escala de Depressão em Geriatria (GDS) versão reduzida. *Arquivos de Neuro-Psiquiatria*, *57*(2B), 421–426. https://doi.org/10.1590/S0004-282X1999000300013

Almeida, O. P., & Almeida, S. A. (1999b). Short versions of the Geriatric Depression Scale: A study of their validity for the diagnosis of a major depressive episode according to ICD-10 and DSM-IV. *International Journal of Geriatric Psychiatry*, *14*(10), 858–865. https://doi.org/10.1002/(SICI)1099-1166(199910)14:10<858::AID-GPS35>3.0.CO;2-8

American Psychiatric Association. (2000). *Diagnostic and statistical manual of*

mental disorders (4th ed., T). Washington, DC: American Psychiatric Association.

Amieva, H., Phillips, L. H., Della Sala, S., & Henry, J. D. (2004). Inhibitory functioning in Alzheimer's disease. *Brain*, *127*, 949–964. https://doi.org/10.1093/brain/awh045

Arkin, S., & Mahendra, N. (2001). Insight in Alzheimer's patients: Results of a longitudinal study using three assessment methods. *American Journal of Alzheimer's Disease and Other Dementias*, *16*(4), 211–224. https://doi.org/10.1177/153331750101600401

Armony, J., & Vuilleumier, P. (2013). *The Cambridge Handbook of Human Affective Neuroscience*. (J. Armony & P. Vuilleumier, Eds.), *Choice Reviews Online* (Vol. 50). New York: Cambridge University Press. https://doi.org/10.5860/choice.50-7043

Asendorpf, J. B., & Baudonnière, P. M. (1993). Self-Awareness and Other-Awareness: Mirror Self-Recognition and Synchronic Imitation Among Unfamiliar Peers. *Developmental Psychology*, *29*, 88–95. https://doi.org/10.1037/0012-1649.29.1.88

Baran, Z., Cangöz, B., & Ozel-Kizil, E. T. (2014). The impact of aging and Alzheimer's disease on emotional enhancement of memory. *European Neurology*, *72*(1–2), 30–37. https://doi.org/10.1159/000359924

Barrett, P. (2007). Structural equation modelling: Adjudging model fit. *Personality and Individual Differences*, *42*(5), 815–824. https://doi.org/10.1016/j.paid.2006.09.018

Bartochowski, Z., Gatla, S., Khoury, R., Al-Dahhak, R., & Grossberg, G. T. (2018). Empathy changes in neurocognitive disorders: A review. *Annals of Clinical Psychiatry*, *30*(3), 220–232.

Baune, B. T., Miller, R., McAfoose, J., Johnson, M., Quirk, F., & Mitchell, D. (2010). The role of cognitive impairment in general functioning in major depression. *Psychiatry Research*, *176*(2–3), 183–189. https://doi.org/10.1016/j.psychres.2008.12.001

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). Manual for the Beck depression inventory-II. *San Antonio, TX: Psychological Corporation*.

Bennys, K., Portet, F., Touchon, J., & Rondouin, G. (2007). Diagnostic value of event-related evoked potentials N200 and P300 subcomponents in early diagnosis of Alzheimer's disease and mild cognitive impairment. *Journal of Clinical Neurophysiology*. https://doi.org/10.1097/WNP.0b013e31815068d5

Bertolucci, P. H. F., Brucki, S. M. D., Campacci, S. R., & Juliano, Y. (1994). O Mini-Exame do Estado Mental em uma população geral: impacto da escolaridade. *Arquivos de Neuro-Psiquiatria*, *52*(1), 01–07. https://doi.org/10.1590/s0004-282x1994000100001

Bertrand, E., Dourado, M. C. N., Laks, J., Morris, R. G., Landeira-fernandez, J., & Mograbi, D. C. (2016). Mood-congruent recollection and anosognosia in Alzheimer ' s disease. *Cortex*, *84*, 55–62. https://doi.org/10.1016/j.cortex.2016.09.001

Bertrand, E., Landeira-Fernandez, J., & Mograbi, D. C. (2016). Metacognition and perspective-taking in Alzheimer's disease: A mini-review. *Frontiers in Psychology*, *7*, 1–7. https://doi.org/10.3389/fpsyg.2016.01812

Bird, G., & Viding, E. (2014). The self to other model of empathy: Providing a new framework for understanding empathy impairments in psychopathy, autism, and alexithymia. *Neuroscience and Biobehavioral Reviews*, *47*, 520–532. https://doi.org/10.1016/j.neubiorev.2014.09.021

Blessing, A., Forstmeier, S., & Eschen, A. (2014). Emotionen als wirkfaktoren psychosozialer interventionen bei Alzheimer-demenz. *Zeitschrift Fur Psychiatrie, Psychologie Und Psychotherapie*, *62*(3), 191–199. https://doi.org/10.1024/1661-4747/a000195

Bond, R. L., Downey, L. E., Weston, P. S. J., Slattery, C. F., Clark, C. N., Macpherson, K., … Warren, J. D. (2016). Processing of Self versus Non-Self in Alzheimer's Disease. *Frontiers in Human Neuroscience*, *10*, 1–10. https://doi.org/10.3389/fnhum.2016.00097

Bora, E., Walterfang, M., & Velakoulis, D. (2015). Theory of mind in behavioural-variant frontotemporal dementia and Alzheimer's disease: a meta-analysis.

Journal of Neurology, Neurosurgery & Psychiatry, *86*, 714–719. https://doi.org/10.1136/jnnp-2014-309445

Bradley, M., & Lang, P. J. (1994). Measuring Emotion: The Self-Assessment Semantic Differential Manikin and the. *Journal of Behavior Therapy and Experimental Psychiatry*, *25*(I), 49–59. https://doi.org/10.1016/0005-7916(94)90063-9

Bucks, R. S., & Radford, S. A. (2004). Emotion processing in Alzheimer's disease. *Aging and Mental Health*, *8*(3), 222–232. https://doi.org/10.1080/13607860410001669750

Burton, K., & Kaszniak, A. (2006). Emotional experience and facial expression in Alzheimer's disease. *Aging, Neuropsychology, and Cognition*. https://doi.org/10.1080/13825580600735085

Byrne, B. M. (1998). *Structural equation modeling with LISREL, PRELIS, and SIMPLIS : basic concepts, applications, and programming*. *Multivariate applications book series* (2nd ed.). Mahwah: Routledge.

Caeiro, L., Silva, T., Ferro, J. M., Pais-Ribeiro, J., & Figueira, M. L. (2012). Propriedades métricas da versão portuguesa da escala de avaliação de apatia. *Psicologia, Saúde & Doenças*, *13*(2), 266–282. https://doi.org/10.15309/12psd130209

Caeiro, Lara, Silva, T., Ferro, J. M., Ribeiro, J. L. P., & Figueira, M. L. (2012). Metric properties of the portuguese version of the apathy evaluation scale. *Psicologia, Saúde & Doenças*, *13*(2), 266–282.

Carvalho, V. A., & Caramelli, P. (2007). Adaptação brasileira do Exame Cognitivo de Addenbrooke-Revisado. *Dementia & Neuropsychologia*, *1*(2), 212–216. https://doi.org/10.1590/s1980-57642008dn10200015

Castelli, I., Pini, A., Alberoni, M., Liverta-Sempio, O., Baglio, F., Massaro, D., … Nemni, R. (2011). Mapping levels of theory of mind in Alzheimer ' s disease : A preliminary study. *Aging & Mental Health*, *15*(2), 157–168. https://doi.org/10.1080/13607863.2010.513038

Chen, D., Wu, J., Yao, Z., Lei, K., Luo, Y., & Li, Z. (2018). Negative association

between resilience and event-related potentials evoked by negative emotion. *Scientific Reports*, *8*(1), 1–6. https://doi.org/10.1038/s41598-018-25555-w

Chen, K. H., Lwi, S. J., Hua, A. Y., Haase, C. M., Miller, B. L., & Levenson, R. W. (2017). Increased subjective experience of non-target emotions in patients with frontotemporal dementia and Alzheimer's disease. *Current Opinion in Behavioral Sciences*, *15*, 77–84. https://doi.org/10.1016/j.cobeha.2017.05.017

Christidi, F., Migliaccio, R., Santamaría-García, H., Santangelo, G., & Trojsi, F. (2018). Social cognition dysfunctions in neurodegenerative diseases: Neuroanatomical correlates and clinical implications. *Behavioural Neurology*. https://doi.org/10.1155/2018/1849794

Cines, S., Farrell, M., Steffener, J., Sullo, L., Huey, E., Karlawish, J., & Cosentino, S. (2015). Examining the Pathways between Self-Awareness and Well-Being in Mild to Moderate Alzheimer Disease. *American Journal of Geriatric Psychiatry*, *23*(12), 1297–1306. https://doi.org/10.1016/j.jagp.2015.05.005

Clare, L., Nelis, S. M., Martyr, A., Roberts, J., Whitaker, C. J., Markova, I. S., … Morris, R. G. (2012). The influence of psychological, social and contextual factors on the expression and measurement of awareness in early-stage dementia: Testing a biopsychosocial model. *International Journal of Geriatric Psychiatry*, *27*(2), 167–177. https://doi.org/10.1002/gps.2705

Clare, L., Nelis, S. M., Martyr, A., Whitaker, C. J., Marková, I. S., Roth, I., … Morris, R. G. (2012). Longitudinal trajectories of awareness in early-stage dementia. *Alzheimer Disease and Associated Disorders*, *26*(2), 140–147. https://doi.org/10.1097/WAD.0b013e31822c55c4

Clare, L., Nelis, S. M., Martyr, A., Whitaker, C. J., Marková, I. S., Roth, I., … Morris, R. G. (2012). "She might have what I have got": the potential utility of vignettes as an indirect measure of awareness in early-stage dementia. *Aging & Mental Health*, *16*(5), 566–575. https://doi.org/10.1080/13607863.2011.652594

Coen, R. F., Swanwick, G. R. J., O'Boyle, C. A., & Coakley, D. (1997). Behaviour disturbance and other predictors of carer burden in Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *12*, 331–336. https://doi.org/10.1002/(SICI)1099-1166(199703)12:3<331::AID-

GPS495>3.0.CO;2-J

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum Associates.

Corbett, A., Smith, J., Creese, B., & Ballard, C. (2012). Treatment of behavioral and psychological symptoms of Alzheimer's disease. *Current Treatment Options in Neurology*, *14*(2), 113–125. https://doi.org/10.1007/s11940-012-0166-9

Cuerva, A. G., Sabe, L., Kuzis, G., Tiberti, C., Dorrego, F., & Starkstein, S. E. (2001). Theory of Mind and Pragmatic Abilities in Dementia. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology*, *14*(3), 153–158.

Cummings, J. L., Ross, W., Absher, J., Gornbein, J., & Hadjiaghai, L. (1995). Depressive symptoms in Alzheimer disease: Assessment and determinants. *Alzheimer Disease and Associated Disorders*, *9*(2), 87–93. https://doi.org/10.1097/00002093-199509020-00005

Cuthbert, B. N., Schupp, H. T., Bradley, M. M., Birbaumer, N., & Lang, P. J. (2000). Brain potentials in affective picture processing: Covariation with autonomic arousal and affective report. *Biological Psychology*, *52*(2), 95–111. https://doi.org/10.1016/S0301-0511(99)00044-7

David, A. S. (2004). The clinical importance of insight: an overview. In X. F. E. Amador & A. S. E. David (Eds.), *Insight and Psychosis: Awareness of Illness in Schizophrenia and Related Disorders* (pp. 359–392). New York: Oxford University Press.

de Vignemont, F., & Singer, T. (2006). The empathic brain: how, when and why? *Trends in Cognitive Sciences*, *10*(10), 435–441. https://doi.org/10.1016/j.tics.2006.08.008

De Waal, F. B. M., & Preston, S. D. (2017). Mammalian empathy: Behavioural manifestations and neural basis. *Nature Reviews Neuroscience*, *18*(8), 498–509. https://doi.org/10.1038/nrn.2017.72

Decety, J. (2011). Dissecting the neural mechanisms mediating empathy. *Emotion Review*, *3*(1), 92–108. https://doi.org/10.1177/1754073910374662

Decety, J., & Jackson, P. L. (2004). The Functional Architecture of Human Empathy.

Behavioral and Cognitive Neuroscience Reviews, *3*(2), 71–100. https://doi.org/10.1177/1534582304267187

Decety, J., & Meyer, M. (2008). From emotion resonance to empathic understanding: A social developmental neuroscience account. *Development and Psychopathology*, *20*, 1053–1080. https://doi.org/10.1017/S0954579408000503

Decety, J., & Moriguchi, Y. . Y. (2007). The empathic brain and its dysfunction in psychiatric populations: Implications for intervention across different clinical conditions. *BioPsychoSocial Medicine*, *1*, 22–65. https://doi.org/10.1186/1751-0759-1-22

Decety, J., & Svetlova, M. (2012). Putting together phylogenetic and ontogenetic perspectives on empathy. *Developmental Cognitive Neuroscience*, *2*, 1–24. https://doi.org/10.1016/j.dcn.2011.05.003

Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*. https://doi.org/10.1016/j.jneumeth.2003.10.009

Dermody, N., Wong, S., Ahmed, R., Piguet, O., Hodges, J. R., & Irish, M. (2016). Uncovering the Neural Bases of Cognitive and Affective Empathy Deficits in Alzheimer's Disease and the Behavioral-Variant of Frontotemporal Dementia. *Journal of Alzheimer's Disease*, *53*(3), 801–816. https://doi.org/https://doi.org/10.3233/JAD-160175

Derouesne, C., Thibault, S., Lagha-Pierucci, S., Baudouin-Madec, V., Ancri, D., & Lacomblez, L. (1999). Decreased awareness of cognitive deficits in patients with mild dementia of the Alzheimer type. *International Journal of Geriatric Psychiatry*, *14*(12), 1019–1030. https://doi.org/10.1002/(SICI)1099-1166(199912)14:12<1019::AID-GPS61>3.0.CO;2-F

Desmarais, P., Lanctôt, K. L., Masellis, M., Black, S. E., & Herrmann, N. (2018). Social inappropriateness in neurodegenerative disorders. *International Psychogeriatrics*, *30*(2), 197–207. https://doi.org/10.1017/S1041610217001260

Di Domenico, A., Palumbo, R., Fairfield, B., & Mammarella, N. (2016). Fighting apathyin Alzheimer's dementia: Abrief emotional-based intervention. *Psychiatry Research*, *242*, 331–335. https://doi.org/10.1016/j.psychres.2016.06.009

Di Gregorio, F., Ernst, B., & Steinhauser, M. (2019). Differential effects of instructed and objective feedback reliability on feedback-related brain activity. *Psychophysiology*, *56*(9), 1–10. https://doi.org/10.1111/psyp.13399

Donchin, E. (1981). Surprise!… Surprise? *Psychophysiology*, *18*, 493–513. https://doi.org/10.1111/j.1469-8986.1981.tb01815.x

Dourado, M. C. N., Laks, J., & Mograbi, D. (2016). Functional Status Predicts Awareness in Late-Onset but not in Early-Onset Alzheimer Disease. *Journal of Geriatric Psychiatry and Neurology*, *29*(6), 313–319. https://doi.org/10.1177/0891988716640372

Dourado, M. C. N., Laks, J., & Mograbi, D. C. (2019). Awareness in Dementia: Development and Evaluation of a Short Version of the Assessment Scale of Psychosocial Impact of the Diagnosis of Dementia (ASPIDD-s) in Brazil. *Alzheimer Disease and Associated Disorders*, *33*(3), 220–225. https://doi.org/10.1097/WAD.0000000000000306

Dourado, M. C. N., Mograbi, D. C., Santos, R. L., Fernanda, M., Sousa, B., Sousa, M. F. B., … Laks, J. (2014). Awareness of disease in dementia: factor structure of the assessment scale of psychosocial impact of the diagnosis of dementia. *Journal of Alzheimer's Disease*, *41*, 947–956. https://doi.org/10.3233/JAD-140183

Drago, V., Foster, P. S., Chanei, L., Rembisz, J., Meador, K., Finney, G., & Heilman, K. M. (2010). Emotional indifference in Alzheimer's disease. *Journal of Neuropsychiatry and Clinical Neurosciences*, *22*(2), 236–242. https://doi.org/10.1176/jnp.2010.22.2.236

Duncan-Johnson, C. C., & Donchin, E. (1982). The P300 component of the event-related brain potential as an index of information processing. *Biological Psychology*. https://doi.org/10.1016/0301-0511(82)90016-3

Ecklund-Johnson, E., & Torres, I. (2005). Unawareness of deficits in Alzheimer's disease and other dementias: Operational definitions and empirical findings. *Neuropsychology Review*, *15*(3), 147–166. https://doi.org/10.1007/s11065-005-9026-7

Ekman, P., Friesen, W. V., & Hager, J. C. (2002). *Facial Action Coding System* -

Investigator's Guide. *FACS*.

Eling, P. A. T. M., Maes, J. H. R., & Van Haaf, M. (2006). Processing of emotionally toned pictures in dementia. *International Journal of Geriatric Psychiatry*. https://doi.org/10.1002/gps.1568

Ernst, A., Moulin, C. J. A., Souchay, C., & Mograbi, D. C. (2015). Anosognosia and Metacognition in Alzheimer's Disease. *The Oxford Handbook of Metamemory*, (June 2016), 1–41. https://doi.org/10.1093/oxfordhb/9780199336746.013.12

Farina, E., Baglio, F., Pomati, S., D'Amico, A., Campini, I. C., Tella, S. Di, … Pozzo, T. (2017). The mirror neurons network in aging, mild cognitive impairment, and Alzheimer disease: A functional mri study. *Frontiers in Aging Neuroscience*, *9*, 1–13. https://doi.org/10.3389/fnagi.2017.00371

Feast, A., Moniz-Cook, E., Stoner, C., Charlesworth, G., & Orrell, M. (2016). A systematic review of the relationship between behavioral and psychological symptoms (BPSD) and caregiver well-being. *International Psychogeriatrics*, *28*(11), 1761–1774. https://doi.org/10.1017/S1041610216000922

Feng, C., Li, W., Tian, T., Luo, Y., Gu, R., & Zhou, C. (2014). Arousal modulates valence effects on both early and late stages of affective picture processing in a passive viewing task Arousal modulates valence effects on both early and late stages of affective picture processing in a passive viewing task, (September), 37–41. https://doi.org/10.1080/17470919.2014.896827

Fernandez-Duque, D., Baird, J. A., & Black, S. E. (2009). False-belief understanding in frontotemporal dementia and Alzheimer ' s disease. *Journal of Clinical and Experimental Neuropsychology*, *31*(4), 489–497. https://doi.org/10.1080/13803390802282688

Fernandez-Duque, D., Hodges, S. D., Baird, J. A., & Black, S. E. (2010). Empathy in frontotemporal dementia and Alzheimer's disease. *Journal of Clinical and Experimental Neuropsychology*, *32*(3), 289–298. https://doi.org/http://dx.doi.org/10.1080/13803390903002191

Fischer, A., Dourado, M. C. N., Laks, J., Landeira-Fernandez, J., Morris, R. G., & Mograbi, D. C. (2019). Modelling the impact of functionality, cognition, and mood state on awareness in people with Alzheimer's disease. *International*

Psychogeriatrics, 1–11. https://doi.org/10.1017/S1041610219001467

Fliss, R., Le Gall, D., Etcharry-Bouyx, F., Chauviré, V., Desgranges, B., & Allain, P. (2016). Theory of Mind and social reserve: Alternative hypothesis of progressive Theory of Mind decay during different stages of Alzheimer's disease. *Social Neuroscience*, *11*(4), 409–423. https://doi.org/10.1080/17470919.2015.1101014

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189–198.

Fortier, J., Besnard, J., & Allain, P. (2018). Theory of mind, empathy and emotion perception in cortical and subcortical neurodegenerative diseases. *Revue Neurologique*, *174*(4), 237–246. https://doi.org/10.1016/j.neurol.2017.07.013

Fredericks, C. A., Sturm, V. E., Brown, J. A., Hua, A. Y., Bilgel, M., Wong, D. F., … Seeley, W. W. (2018). Early affective changes and increased connectivity in preclinical Alzheimer's disease. *Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring*, *10*, 471–479. https://doi.org/10.1016/j.dadm.2018.06.002

Freedman, M., Binns, M. A., Black, S. E., Murphy, C., & Stuss, D. T. (2013). Theory of Mind and Recognition of Facial Emotion in Dementia. *Alzheimer Disease & Associated Disorders*, *27*(1), 56–61. https://doi.org/10.1097/WAD.0b013e31824ea5db

Gallese, V., Fadiga, L., Fogassi, L., & Rizzolatti, G. (1996). Action recognition in the premotor cortex. *Brain*, *119*, 593–609. https://doi.org/10.1093/brain/119.2.593

Gomes-Oliveira, M. H., Gorenstein, C., Neto, F. L., Andrade, L. H., & Wang, Y. P. (2012). Validation of the Brazilian Portuguese Version of the Beck Depression Inventory-II in a community sample. *Revista Brasileira de Psiquiatria*. https://doi.org/10.1016/j.rbp.2012.03.005

Goodkind, M. S., Gyurak, A., McCarthy, M., Miller, B. L., & Levenson, R. W. (2010). Emotion Regulation Deficits in Frontotemporal Lobar Degeneration and Alzheimer's Disease. *Psychology and Aging*, *25*(1), 30–37. https://doi.org/10.1037/a0018519

Goodkind, M. S., Sturm, V. E., Ascher, E. A., Shdo, S. M., Miller, B. L., Rankin, K. P., & Levenson, R. W. (2015). Emotion recognition in frontotemporal dementia and alzheimer's disease: A new film-based assessment. *Emotion*, *15*(4), 416–427. https://doi.org/10.1037/a0039261

Gregory, C., Lough, S., Stone, V., Erzinclioglu, S., Martin, L., Baron-Cohen, S., & Hodges, J. R. (2002). Theory of mind in patients with frontal variant frontotemporal dementia and Alzheimer's disease: theoretical and practical implications. *Brain*, *125*(4), 752–764. https://doi.org/10.1093/brain/awf079

Grühn, D., & Scheibe, S. (2008). Age-related differences in valence and arousal ratings of pictures from the International Affective Picture System (IAPS): Do ratings become more extreme with age ? *Behavior Research Methods*, *40*(2), 512–521. https://doi.org/10.3758/BRM.40.2.512

Guo, C., Duan, L., Li, W., & Paller, K. A. (2006). Distinguishing source memory and item memory: Brain potentials at encoding and retrieval. *Brain Research*. https://doi.org/10.1016/j.brainres.2006.08.034

Guzmán-Vélez, E., Feinstein, J. S., & Tranel, D. (2014). Feelings Without Memory in Alzheimer Disease. *Cognitive And Behavioral Neurology*, *27*(3), 117–129. https://doi.org/10.1097/WNN.0000000000000020

Gyurak, A., Gross, J., & Etkin, A. (2011). Explicit and implicit emotion regulation: A dual process framework. *Cognition & Emotion*, *25*(3), 400–412. https://doi.org/10.1080/02699931.2010.544160

Hajcak, G., Macnamara, A., & Olvet, D. M. (2010). Event-related potentials, emotion, and emotion regulation: An integrative review. *Developmental Neuropsychology*, *35*(2), 129–155. https://doi.org/10.1080/87565640903526504

Hajcak, G., Moser, J. S., Holroyd, C. B., & Simons, R. F. (2006). The feedback-related negativity reflects the binary evaluation of good versus bad outcomes. *Biological Psychology*, *71*(2), 148–154. https://doi.org/10.1016/j.biopsycho.2005.04.001

Hajcak, G., & Olvet, D. M. (2008). The Persistence of Attention to Emotion: Brain Potentials During and After Picture Presentation. *Emotion*, *8*(2), 250–255. https://doi.org/10.1037/1528-3542.8.2.250

Hajcak, G., Weinberg, A., MacNamara, A., & Foti, D. (2012). ERPs and the Study of Emotion. In E. S. Kappenman & S. J. Luck (Eds.), *The Oxford Handbook of Event-Related Potential Components*. New York: Oxford University Press. https://doi.org/10.1093/oxfordhb/9780195374148.013.0222

Hamann, S. B., Monarch, E. S., & Goldstein, F. C. (2000). Memory enhancement for emotional stimuli is impaired in early Alzheimer's disease. *Neuropsychology*, *14*(1), 82–92. https://doi.org/10.1037/0894-4105.14.1.82

Hämmerer, D., Li, S. C., Müller, V., & Lindenberger, U. (2011). Life span differences in electrophysiological correlates of monitoring gains and losses during probabilistic reinforcement learning. *Journal of Cognitive Neuroscience*. https://doi.org/10.1162/jocn.2010.21475

Henry, J. D., Rendell, P. G., Scicluna, A., Jackson, M., & Phillips, L. H. (2009). Emotion experience, expression, and regulation in Alzheimer's disease. *Psychology and Aging*, *24*(1), 252–257. https://doi.org/10.1037/a0014001

Holroyd, C. B., & Coles, M. G. H. (2002). The neural basis of human error processing: Reinforcement learning, dopamine, and the error-related negativity. *Psychological Review*, *109*(4), 679–709. https://doi.org/10.1037//0033-295X.109.4.679

Horning, S. M., Melrose, R., & Sultzer, D. (2014). Insight in Alzheimer's disease and its relation to psychiatric and behavioral disturbances. *International Journal of Geriatric Psychiatry*, *29*(1), 77–84. https://doi.org/10.1002/gps.3972

Hsieh, S., Irish, M., Daveson, N., Hodges, J. R., & Piguet, O. (2013). When One Loses Empathy. *Journal of Geriatric Psychiatry and Neurology*, *26*(3), 174–184. https://doi.org/10.1177/0891988713495448

Hu, L. T., & Bentler, P. M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling*, *6*(1), 1–55. https://doi.org/10.1080/10705519909540118

Hughes, J. (2011). *Alzheimer's and other dementias*. New York: Oxford University.

Hurt, C. S., Banerjee, S., Tunnard, C., Whitehead, D. L., Tsolaki, M., Mecocci, P., … Lovestone, S. (2010). Insight, cognition and quality of life in Alzheimer's

disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *81*(3), 331–336. https://doi.org/10.1136/jnnp.2009.184598

Hynes, C. A., Baird, A. A., & Grafton, S. T. (2006). Differential role of the orbital frontal lobe in emotional versus cognitive perspective-taking. *Neuropsychologia*, *44*(3), 374–383. https://doi.org/10.1016/j.neuropsychologia.2005.06.011

Ickes, W. (1997). *Empathic Accuracy*. New York: Guilford.

Ito, T. A., & Cacioppo, J. T. (2000). Electrophysiological Evidence of Implicit and Explicit Categorization Processes. *Journal of Experimental Social Psychology*. https://doi.org/10.1006/jesp.2000.1430

Jackson, A. F., & Bolger, D. J. (2014). The neurophysiological bases of EEG and EEG measurement: A review for the rest of us. *Psychophysiology*, *51*(11), 1061–1071. https://doi.org/10.1111/psyp.12283

Jackson, D. L. (2003). Revisiting sample size and number of parameter estimates: Some support for the N:q hypothesis. *Structural Equation Modeling*, *10*(1), 128–141. https://doi.org/10.1207/S15328007SEM1001_6

Jacus, J. P. (2017). Awareness, apathy, and depression in Alzheimer's disease and mild cognitive impairment. *Brain and Behavior*, *7*(4), 1–8. https://doi.org/10.1002/brb3.661

Johnson, R. J., & Donchin, E. (1978). On how the P300 amplitude varies with the utility of the eliciting stimuli. *Electroencephalography and Clinical Neurophysiology*, *44*, 424–437.

Kalenzaga, S., & Clarys, D. (2013). Self-referential processing in Alzheimer's disease: Two different ways of processing self-knowledge? *Journal of Clinical and Experimental Neuropsychology*, *35*(5), 455–471. https://doi.org/10.1080/13803395.2013.789485

Katada, E., Sato, K., Ojika, K., & Ueda, R. (2004). Cognitive Event-Related Potentials: Useful Clinical Information in Alzheimers Disease. *Current Alzheimer Research*, *1*(1), 63–69. https://doi.org/10.2174/1567205043480609

Kemp, J., Després, O., Sellal, F., & Dufour, A. (2012). Theory of Mind in normal ageing and neurodegenerative pathologies. *Ageing Research Reviews*, *11*(2),

199–219. https://doi.org/10.1016/j.arr.2011.12.001

Kensinger, E. A., Anderson, A., Growdon, J. H., & Corkin, S. (2004). Effects of Alzheimer disease on memory for verbal emotional information. *Neuropsychologia*, *42*(6), 791–800. https://doi.org/10.1016/j.neuropsychologia.2003.11.011

Kiesel, A., Miller, J., Jolicœur, P., & Brisson, B. (2008). Measurement of ERP latency differences: A comparison of single-participant and jackknife-based scoring methods. *Psychophysiology*, *45*(2), 250–274. https://doi.org/10.1111/j.1469-8986.2007.00618.x

Kisley, M. A., Wood, S., & Burrows, C. L. (2007). Looking at the Sunny Side of Life - Age-Related Change in an Event-Related Potential Measure of the Negativity Bias. *Psychological Science*, *18*(9), 838–843. https://doi.org/10.1111/j.1467-9280.2007.01988.x

Klein-Koerkamp, Y., Beaudoin, M., Baciu, M., & Hot, P. (2012). Emotional decoding abilities in Alzheimer's disease: A meta-analysis. *Journal of Alzheimer's Disease*, *32*(1), 109–125. https://doi.org/10.3233/JAD-2012-120553

Klimecki, O., & Singer, T. (2013). Empathy from the Perspective of Social Neuroscience. In J. Armony & P. Vuilleumier (Eds.), *The Cambridge Handbook of Human Affective Neuroscience* (pp. 533–551). New York: Cambridge University.

Kunzmann, U., & Grühn, D. (2005). Age differences in emotional reactivity: The sample case of sadness. *Psychology and Aging*, *20*(1), 47–59. https://doi.org/10.1037/0882-7974.20.1.47

Kunzmann, U., & Richter, D. (2009). Emotional Reactivity Across the Adult Life Span: The Cognitive Pragmatics Make a Difference. *Psychology and Aging*, *24*(4), 879–889. https://doi.org/10.1037/a0017347

Labouvie-Vief, G., Lumley, M. A., Jain, E., & Heinze, H. (2003). Age and gender differences in cardiac reactivity and subjective emotion responses to emotional autobiographical memories. *Emotion*, *3*, 115–126.

Lacerda, I. B., Santos, R. L., Neto, J. P. S., & Dourado, M. C. N. (2017). Factors

Related to Different Objects of Awareness in Alzheimer Disease. *Alzheimer Disease and Associated Disorders*, *31*(4), 335–342. https://doi.org/10.1097/WAD.0000000000000210

Lai, C.-L., Lin, R.-T., Liou, L.-M., & Liu, C.-K. (2010). The role of event-related potentials in cognitive decline in Alzheimer's disease. *Clinical Neurophysiology*, *121*, 194–199. https://doi.org/10.1016/j.clinph.2009.11.001

Laisney, M., Bon, L., Guiziou, C., Daluzeau, N., Eustache, F., & Desgranges, B. (2013). Cognitive and affective Theory of Mind in mild to moderate Alzheimer's disease. *Journal of Neuropsychology*, *7*(1), 107–120. https://doi.org/10.1111/j.1748-6653.2012.02038.x

Lanctôt, K. L., Amatniek, J., Ancoli-Israel, S., Arnold, S. E., Ballard, C., Cohen-Mansfield, J., … Boot, B. (2017). Neuropsychiatric signs and symptoms of Alzheimer's disease: New treatment paradigms. *Alzheimer's and Dementia: Translational Research and Clinical Interventions*, *3*(3), 440–449. https://doi.org/10.1016/j.trci.2017.07.001

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (2008). *International affective picture system (IAPS): Affective ratings of pictures and instruction manual. Technical Report A-8*. Gainesville, FL.

Langeslag, S. J. E., & Van Strien, J. W. (2009). Aging and Emotional Memory : The Co-Occurrence of Neurophysiological and Behavioral Positivity Effects. *Emotion*, *9*(3), 369–377. https://doi.org/10.1037/a0015356

Lawton, M. P., Kleban, M. H., Rajagopal, D., & Dean, J. (1992). Dimensions of affective experience in three age groups. *Psychology and Aging*, *7*(2), 171–184. https://doi.org/10.1037//0882-7974.7.2.171

Le Bouc, R., Lenfant, P., Delbeuck, X., Ravasi, L., Lebert, F., Semah, F., & Pasquier, F. (2012). My belief or yours? Differential theory of mind deficits in frontotemporal dementia and Alzheimer's disease. *Brain*, *135*(10), 3026–3038. https://doi.org/10.1093/brain/aws237

Leclerc, C. M., & Kensinger, E. A. (2011). Neural processing of emotional pictures and words: A comparison of young and older adults. *Developmental Neuropsychology*, *26*, 519–538. https://doi.org/10.1080/87565641.2010.549864

Lehrner, J., Kogler, S., Lamm, C., Moser, D., Klug, S., Pusswald, G., … Auff, E. (2015). Awareness of memory deficits in subjective cognitive decline, mild cognitive impairment, Alzheimer's disease and Parkinson's disease. *International Psychogeriatrics*, *27*(3), 357–366. https://doi.org/10.1017/S1041610214002245

Leiberg, S., & Anders, S. (2006). The multiple facets of empathy: a survey of theory and evidence. *Progress in Brain Research*, *156*, 419–440. https://doi.org/10.1016/S0079-6123(06)56023-6

Levenson, R. W., Carstensen, L. L., & Gottman, J. M. (1994). The Influence of Age and Gender on Affect, Physiology, and Their Interrelations: A Study of Long-Term Marriages. *Journal of Personality and Social Psychology*, *67*(1), 56–68. https://doi.org/10.1037/0022-3514.67.1.56

Levenson, R. W., & Miller, B. L. (2007). Loss of cells - Loss of self: Frontotemporal lobar degeneration and human emotion. *Current Directions in Psychological Science*, *15*, 289–294. https://doi.org/10.1111/j.1467-8721.2007.00523.x

Lopez-Calderon, J., & Luck, S. J. (2014). ERPLAB: An open-source toolbox for the analysis of event-related potentials. *Frontiers in Human Neuroscience*, *8*, 1–14. https://doi.org/10.3389/fnhum.2014.00213

Lopez, O. L., Becker, J. T., Somsak, D., Dew, M. A., & DeKosky, S. T. (1994). Awareness of cognitive deficits and anosognosia in probable alzheimer's disease. *European Neurology*, *34*(5), 277–282. https://doi.org/10.1159/000117056

Luck, S. J. (2014). *An Introduction to the Event-Related Potential Technique* (2nd ed.). Cambridge: MIT Press.

Ludowicy, P., Czernochowski, D., Weis, T., Haese, A., & Lachmann, T. (2019). Neural correlates of feedback processing during a sensory uncertain speech - nonspeech discrimination task. *Biological Psychology*, *144*, 103–114. https://doi.org/10.1016/j.biopsycho.2019.03.017

MacCallum, R. C., & Austin, J. T. (2000). Applications of Structural Equation Modeling in Psychological Research. *Annual Review of Psychology*, *51*(1), 201–226. https://doi.org/10.1146/annurev.psych.51.1.201

Maia, A. L. G., Godinho, C., Ferreira, E. D., Almeida, V., Schuh, A., Kaye, J., & Chaves, M. L. F. (2006). Application of the Brazilian version of the CDR scale in samples of dementia patients. *Arquivos de Neuropsiquiatria, 64*, 485–489. https://doi.org/10.1590/S0004-282X2006000300025

Marin, R. S., Biedrzycki, R. C., & Firinciogullari, S. (1991). Reliability and validity of the apathy evaluation scale. *Psychiatry Research*, *38*(2), 143–162. https://doi.org/10.1016/0165-1781(91)90040-V

Marková, H., Laczó, J., Andel, R., Hort, J., & Vlcek, K. (2015). Perspective taking abilities in amnestic mild cognitive impairment and Alzheimer's disease. *Behavioral Brain Research*, *281*, 229–238. https://doi.org/10.1016/j.bbr.2014.12.033

Mather, M. (2012). The emotion paradox in the aging brain. *Annals of the New York Academy of Sciences*, *1251*(1), 33–49. https://doi.org/10.1111/j.1749-6632.2012.06471.x

Mathewson, K. J., Dywan, J., Snyder, P. J., Tays, W. J., & Segalowitz, S. J. (2008). Aging and electrocortical response to error feedback during a spatial learning task. *Psychophysiology*, *45*(6), 936–948. https://doi.org/10.1111/j.1469-8986.2008.00699.x

Mathieu, N. G., Gentaz, E., Harquel, S., Vercueil, L., Chauvin, A., Bonnet, S., & Campagne, A. (2014). Brain processing of emotional scenes in aging: Effect of arousal and affective context. *PLoS ONE*, *9*(6). https://doi.org/10.1371/journal.pone.0099523

McDonald, R. P., & Ho, M. H. R. (2002). Principles and practice in reporting structural equation analyses. *Psychological Methods*, *7*(1), 64–82. https://doi.org/10.1037//1082-989X.7.1.64

McLellan, T., Johnston, L., Dalrymple-Alford, J., & Porter, R. (2008). The recognition of facial expressions of emotion in Alzheimer's disease: A review of findings. *Acta Neuropsychiatrica*, *20*(5), 236–250. https://doi.org/10.1111/j.1601-5215.2008.00315.x

Meng, X., Yang, J., Cai, A., Ding, X., Liu, W., Li, H., & Yuan, J. (2015). The neural mechanisms underlying th e aging-related enhancement of positive affects:

Electrophysiological evidences. *Frontiers in Aging Neuroscience*, *7*(JUL), 1–15. https://doi.org/10.3389/fnagi.2015.00143

Michon, A., Deweer, B., Pillon, B., Agid, Y., & Dubois, B. (1994). Relation of anosognosia to frontal lobe dysfunction in Alzheimer's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *57*, 805–809. https://doi.org/10.1136/jnnp.57.7.805

Miltner, W. H. R., Braun, C. H., & Coles, M. G. H. (1997). Event-related brain potentials following incorrect feedback in a time-estimation task: Evidence for a "generic" neural system for error detection. *Journal of Cognitive Neuroscience*, *9*(6), 788–798. https://doi.org/10.1162/jocn.1997.9.6.788

Mioshi, E., Dawson, K., Mitchell, J., Arnold, R., & Hodges, J. R. (2006). The Addenbrooke's Cognitive Examination revised (ACE-R): A brief cognitive test battery for dementia screening. *International Journal of Geriatric Psychiatry*, *21*(11), 1078–1085. https://doi.org/10.1002/gps.1610

Mograbi, D. C., Brown, R. G., Landeira-Fernandez, J., & Morris, R. G. (2014). Metacognition and attribution of diffculty for self and others in alzheimer's disease. *Psychology and Neuroscience*, *7*(3), 417–424. https://doi.org/10.3922/j.psns.2014.036

Mograbi, D. C., Brown, R. G., & Morris, R. G. (2009). Anosognosia in Alzheimer's disease - The petrified self. *Consciousness and Cognition*, *18*(4), 989–1003. https://doi.org/10.1016/j.concog.2009.07.005

Mograbi, D. C., Brown, R. G., & Morris, R. G. (2012). Emotional reactivity to film material in alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, *34*(5–6), 351–359. https://doi.org/10.1159/000343930

Mograbi, D. C., Brown, R. G., Salas, C., & Morris, R. G. (2012). Emotional reactivity and awareness of task performance in Alzheimer's disease. *Neuropsychologia*, *50*(8), 2075–2084. https://doi.org/10.1016/j.neuropsychologia.2012.05.008

Mograbi, D. C., Ferri, C. P., Sosa, A. L., Stewart, R., Laks, J., Brown, R., & Morris, R. G. (2012). Unawareness of memory impairment in dementia: A population-based study. *International Psychogeriatrics*, *24*(6), 931–939. https://doi.org/10.1017/S1041610211002730

Mograbi, D. C., & Morris, R. G. (2013). Implicit awareness in anosognosia: Clinical observations, experimental evidence, and theoretical implications. *Cognitive Neuroscience*, *4*(3–4), 181–197. https://doi.org/10.1080/17588928.2013.833899

Mograbi, D. C., & Morris, R. G. (2014). On the relation among mood, apathy, and anosognosia in Alzheimer's disease. *Journal of the International Neuropsychological Society*, *20*(1), 2–7. https://doi.org/10.1017/S1355617713001276

Mograbi, D. C., & Morris, R. G. (2018). Anosognosia. *Cortex*, *103*, 385–386. https://doi.org/10.1016/j.cortex.2018.04.001

Mograbi, D. C., Morris, R. G., Fichman, H. C., Faria, C. A., Sanchez, M. A., Ribeiro, P. C. C. C., & Lourenço, R. A. (2017). The impact of dementia, depression and awareness on activities of daily living in a sample from a middle-income country. *International Journal of Geriatric Psychiatry*, *33*(6), 807–813. https://doi.org/10.1002/gps.4765

Mondragón, J. D., Maurits, N. M., & De Deyn, P. P. (2019). Functional Neural Correlates of Anosognosia in Mild Cognitive Impairment and Alzheimer's Disease: a Systematic Review. *Neuropsychology Review*, 139–165. https://doi.org/10.1007/s11065-019-09410-x

Moran, T. P., Jendrusina, A. A., & Moser, J. S. (2013). The psychometric properties of the late positive potential during emotion processing and regulation. *Brain Research*, *1516*, 66–75. https://doi.org/10.1016/j.brainres.2013.04.018

Moreau, N., Rauzy, S., Viallet, F., & Champagne-Lavau, M. (2016). Theory of Mind in Alzheimer Disease: Evidence of Authentic Impairment During Social Interaction. *Neuropsychology*, *30*(3), 312–321. https://doi.org/10.1037/neu0000220

Moretti, D. V. (2016). Involvement of mirror neuron system in prodromal Alzheimer's disease. *BBA Clinical*, *5*, 46–53. https://doi.org/10.1016/j.bbacli.2015.12.001

Morris, R. G., & Hannesdottir, K. (2004). Loss of "awareness" in Alzheimer's Disease. In R. G. Morris & J. T. Becker (Eds.), *The Cognitive Neuropsychology of Alzheimer's Disease* (pp. 275–296). Oxford: Oxford University Press.

Morris, R. G., & Mograbi, D. C. (2013). Anosognosia, autobiographical memory and self knowledge in Alzheimer's disease. *Cortex*, *49*(6), 1553–1565. https://doi.org/10.1016/j.cortex.2012.09.006

Mroczek, D. K., & Kolarz, C. M. (1998). The effect of age on positive and negative affect: a developmental perspective on happiness. *Journal of Personality and Social Psychology*, *75*(5), 1333–1349. https://doi.org/10.1037/0022-3514.75.5.1333

Narme, P., Mouras, H., Roussel, M., Devendeville, A., & Godefroy, O. (2013). Assessment of socioemotional processes facilitates the distinction between frontotemporal lobar degeneration and Alzheimers disease. *Journal of Clinical and Experimental Neuropsychology*, *35*(7), 728–744. https://doi.org/10.1080/13803395.2013.823911

Nash, S., Henry, J. D., McDonald, S., Martin, I. I., Brodaty, H., Peek-O'Leary, M.-A. A., … Peek-O'Leary, M.-A. A. (2007). Cognitive disinhibition and socioemotional functioning in Alzheimer's disease. *Journal of the International Neuropsychological Society*, *13*(6), 1060–1064. https://doi.org/10.1017/S1355617707071184

Nelson, P. T., Alafuzoff, I., Bigio, E. H., Bouras, C., Braak, H., Cairns, N. J., … Beach, T. G. (2012). Correlation of alzheimer disease neuropathologic changes with cognitive status: A review of the literature. *Journal of Neuropathology and Experimental Neurology*, *71*(5), 362–381. https://doi.org/10.1097/NEN.0b013e31825018f7

Nitta, E., Onoda, K., Ishitobi, F., Okazaki, R., Mishima, S., Nagai, A., & Yamaguchi, S. (2017). Enhanced feedback-related negativity in Alzheimer's disease. *Frontiers in Human Neuroscience*, *11*, 1–12. https://doi.org/10.3389/fnhum.2017.00179

Nobili, A., Latagliata, E. C., Viscomi, M. T., Cavallucci, V., Cutuli, D., Giacovazzo, G., … D'Amelio, M. (2017). Dopamine neuronal loss contributes to memory and reward dysfunction in a model of Alzheimer's disease. *Nature Communications*, *8*. https://doi.org/10.1038/ncomms14727

Okon-Singer, H., Hendler, T., Pessoa, L., & Shackman, A. J. (2015). The

neurobiology of emotion-cognition interactions: fundamental questions and strategies for future research. *Frontiers in Human Neuroscience*, *9*, 1–14. https://doi.org/10.3389/fnhum.2015.00058

Olofsson, J. K., Nordin, S., Sequeira, H., & Polich, J. (2008). Affective picture processing: An integrative review of ERP findings. *Biological Psychology*. https://doi.org/10.1016/j.biopsycho.2007.11.006

Olofsson, J. K., & Polich, J. (2007). Affective visual event-related potentials: Arousal, repetition, and time-on-task. *Biological Psychology*. https://doi.org/10.1016/j.biopsycho.2006.12.006

Ott, B. R., Lafleche, G., Whelihan, W. M., Buongiorno, G. W., Albert, M. S., & Fogel, B. S. (1996). Impaired awareness of deficits in Alzheimer disease. *Alzheimer Disease and Associated Disorders*, *10*(2), 68–76. https://doi.org/10.1097/00002093-199601020-00003

Parra, M. A., Ascencio, L. L., Urquina, H. F., Manes, F., & Ibáñez, A. M. (2012). P300 and neuropsychological assessment in mild cognitive impairment and Alzheimer dementia. *Frontiers in Neurology*, *3*, 1–10. https://doi.org/10.3389/fneur.2012.00172

Patel, V., & Prince, M. (2001). Ageing and mental health in a developing country: who cares? Qualitative studies from Goa, India. *Psychological Medicine*, *31*(1), 29–38. https://doi.org/10.1017/S0033291799003098

Pfeffer, R. I., Kurosaki, T. T., Harrah, C. H., Chance, J. M., & Filos, S. (1982). Measurement of functional activities in older adults in the community. *Journal of Gerontology*, *37*(3), 323–329. https://doi.org/10.1093/geronj/ 37.3.323

Phillips, L. H., Scott, C., Henry, J. D., Mowat, D., & Bell, J. S. (2010). Emotion perception in Alzheimer's disease and mood disorder in old age. *Psychology and Aging*, *25*(1), 38–47. https://doi.org/10.1037/a0017369

Piaceri, I., Nacmias, B., & Sorbi, S. (2013). Genetics of familial and sporadic Alzheimer's disease. *Frontiers in Bioscience - Elite*, *5*, 167–177. https://doi.org/10.2741/e605

Pietschmann, M., Endrass, T., Czerwon, B., & Kathmann, N. (2011). Aging,

probabilistic learning and performance monitoring. *Biological Psychology*, *86*(1), 74–82. https://doi.org/10.1016/j.biopsycho.2010.10.009

Pini, L., Pievani, M., Bocchetta, M., Altomare, D., Bosco, P., Cavedo, E., … Frisoni, G. B. (2016). Brain atrophy in Alzheimer's Disease and aging. *Ageing Research Reviews*, *30*, 25–48. https://doi.org/10.1016/j.arr.2016.01.002

Poletti, M., & Bonuccelli, U. (2013). Alteration of affective Theory of Mind in amnestic mild cognitive impairment. *Journal of Neuropsychology*, *7*(1), 121–131. https://doi.org/10.1111/j.1748-6653.2012.02040.x

Poletti, M., Enrici, I., & Adenzato, M. (2012). Cognitive and affective Theory of Mind in neurodegenerative diseases: Neuropsychological, neuroanatomical and neurochemical levels. *Neuroscience and Biobehavioral Reviews*, *36*(9), 2147–2164. https://doi.org/10.1016/j.neubiorev.2012.07.004

Polich, J. (2007). Updating P300: An Integrative Theory of P3a and P3b. *Clinical Neurophysiology*, *118*(10), 2128–2148. https://doi.org/10.1016/j.clinph.2007.04.019

Polich, J. (2012). Neuropsychology of P300. In E. S. Kappenman & S. J. Luck (Eds.), *The Oxford Handbook of Event-Related Potential Components*. New York: Oxford University Press.

Polich, J., & Corey-Bloom, J. (2005). Alzheimers Disease and P300: Review and Evaluation of Task and Modality. *Current Alzheimer Research*, *2*(5), 515–525. https://doi.org/10.2174/156720505774932214

Portugal, M. G., Coutinho, E. S. F., Almeida, C., Barca, M. L., Knapskog, A. B., Engedal, K., & Laks, J. (2012). Validation of montgomery-Åsberg rating scale and cornell scale for depression in dementia in Brazilian elderly patients. *International Psychogeriatrics*, *24*(8), 1291–1298. https://doi.org/10.1017/S1041610211002250

Potts, G. F., Martin, L. E., Kamp, S.-M., & Donchin, E. (2011). Neural Response to Action and Reward Prediction Errors: Comparing the Error Related Negativity to Behavioral Errors and the Feedback Related Negativity to Reward Prediction Violations. *Psychophysiology*, *48*(2), 218–228. https://doi.org/10.1111/j.1469-8986.2010.01049.x.Neural

Preston, S. D., & de Waal, F. B. M. (2002). Empathy: Its ultimate and proximate bases. *Behavioral and Brain Sciences*, *25*, 1–20. https://doi.org/10.1017/S0140525X02000018

Prince, M., Wimo, A., Guerchet, M., Ali, G.-C., Wu, Y.-T., & Prina, M. (2015). *World Alzheimer Report 2015: The Global Impact of Dementia - An Analysis of Prevalence, Incidence, Cost and Trends*. *Alzheimer's Disease International*. London.

Qiu, J. M., Casey, M. A., & Diamond, S. G. (2019). Assessing Feedback Response With a Wearable Electroencephalography System. *Frontiers in Human Neuroscience*, *13*, 1–14. https://doi.org/10.3389/fnhum.2019.00258

Ramanan, S., Souza, L. C. De, Moreau, N., Sarazin, M., Teixeira, A. L., Allen, Z., … Ad, T. (2017). Determinants of Theory of Mind performance in Alzheimer's disease: A data-mining study. *Cortex*, *88*, 8–18. https://doi.org/10.1016/j.cortex.2016.11.014

Rankin, K. P., Gorno-Tempini, M. L., Allison, S. C., Stanley, C. M., Glenn, S., Weiner, M. W., & Miller, B. L. (2006). Structural anatomy of empathy in neurodegenerative disease. *Brain*, *129*(11), 2945–2956. https://doi.org/10.1093/brain/awl254

Rankin, K. P., Kramer, J. H., & Miller, B. L. (2005). Patterns of cognitive and emotional empathy in frontotemporal lobar degeneration. *Cognitive and Behavioral Neurology*, *18*(1), 28–36. https://doi.org/10.1097/01.wnn.0000152225.05377.ab

Rapoport, S. I. (1989). Hypothesis: Alzheimer's disease is a phylogenetic disease. *Medical Hypotheses*, *29*(3), 147–150. https://doi.org/10.1016/0306-9877(89)90185-0

Reed, B. R., Jagust, W. J., & Coulter, L. (1993). Anosognosia in Alzheimer's disease: Relationships to depression, cognitive function, and cerebral perfusion. *Journal of Clinical and Experimental Neuropsychology*, *15*, 231–244. https://doi.org/10.1080/01688639308402560

Rizzolatti, G., Fadiga, L., Gallese, V., & Fogassi, L. (1996). Premotor cortex and the recognition of motor actions. *Cognitive Brain Research*, *3*, 131–141.

https://doi.org/10.1016/0926-6410(95)00038-0

Rosen, H. J. (2011). Anosognosia in neurodegenerative disease. *Neurocase*, *17*(173), 231–241. https://doi.org/10.1080/13554794.2010.522588

Rosen, H. J., Alcantar, O., Rothlind, J., Sturm, V., Kramer, J. H., Weiner, M., & Miller, B. L. (2010). Neuroanatomical correlates of cognitive self-appraisal in neurodegenerative disease. *NeuroImage*, *49*(4), 3358–3364. https://doi.org/10.1016/j.neuroimage.2009.11.041

Ruby, P., Collette, F., D'Argembeau, A., Péters, F., Degueldre, C., Balteau, E., … Salmon, E. (2009). Perspective taking to assess self-personality: What's modified in Alzheimer's disease? *Neurobiology of Aging*, *30*, 1637–1651. https://doi.org/10.1016/j.neurobiolaging.2007.12.014

Salmon, E., Perani, D., Herholz, K., Marique, P., Kalbe, E., Holthoff, V., … Garraux, G. (2006). Neural correlates of anosognosia for cognitive impairment in Alzheimer's disease. *Human Brain Mapping*, *27*(7), 588–597. https://doi.org/10.1002/hbm.20203

Sandoz, M., Démonet, J.-F., & Fossard, M. (2014). Theory of mind and cognitive processes in aging and Alzheimer type dementia: a systematic review. *Aging & Mental Health*, *18*(7), 815–827. https://doi.org/10.1080/13607863.2014.899974

Saxe, R., & Powell, L. J. (2006). It's the thought that counts: Specific brain regions for one component of theory of mind. *Psychological Science*, *17*(8), 692–699. https://doi.org/10.1111/j.1467-9280.2006.01768.x

Scheltens, P., Blennow, K., Breteler, M. M. B., de Strooper, B., Frisoni, G. B., Salloway, S., & Van der Flier, W. M. (2016). Alzheimer's disease. *The Lancet*, *388*(10043), 505–517. https://doi.org/10.1016/S0140-6736(15)01124-1

Schultz, R. R., De Castro, C. C., & Bertolucci, P. H. F. (2009). Memory with emotional content, brain amygdala and Alzheimer's disease. *Acta Neurologica Scandinavica*, *120*(2), 101–110. https://doi.org/10.1111/j.1600-0404.2008.01132.x

Schupp, H. T., Cuthbert, B. N., Bradley, M. M., Cacioppo, J. T., Ito, T., & Lang, P. J. (2000). Affective picture processing: the late positive potential is modulated by

motivational relevance. *Psychophysiology*, *37*(2), 257–261. https://doi.org/10.1111/1469-8986.3720257

Shamay-Tsoory, S. G., Tibi-Elhanany, Y., & Aharon-Peretz, J. (2006). The ventromedial prefrontal cortex is involved in understanding affective but not cognitive theory of mind stories. *Social Neuroscience*, *1*(3–4), 149–166. https://doi.org/10.1080/17470910600985589

Shany-Ur, T., Lin, N., Rosen, H. J., Sollberger, M., Miller, B. L., & Rankin, K. P. (2014). Self-awareness in neurodegenerative disease relies on neural structures mediating reward-driven attention. *Brain*, *137*(8), 2368–2381. https://doi.org/10.1093/brain/awu161

Sheikh, J. I., & Yesavage, J. A. (1986). Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. *Clinical Gerontologist: The Journal of Aging and Mental Health*, *5*(1–2), 165–173. https://doi.org/10.1300/J018v05n01_09

Shimokawa, A., Yatomi, N., Anamizu, S., Torii, S., Isono, H., Sugai, Y., & Kohno, M. (2001). Influence of deteriorating ability of emotional comprehension on interpersonal behavior in Alzheimer-type dementia. *Brain and Cognition*, *47*(3), 423–433. https://doi.org/10.1006/brcg.2001.1318

Silva, A. R., Pinho, M. S., Macedo, L., Souchay, C., & Moulin, C. (2017). Mnemonic anosognosia in Alzheimer's disease is caused by a failure to transfer online evaluations of performance: Evidence from memory training programs. *Journal of Clinical and Experimental Neuropsychology*, *39*(5), 419–433. https://doi.org/10.1080/13803395.2016.1231799

Smith, M. C. (1995). Facial expression in mild dementia of the Alzheimer type. *Behavioural Neurology*, *8*(3–4), 149–156.

Spalletta, G., Girardi, P., Caltagirone, C., & Orfei, M. D. (2012). Anosognosia and neuropsychiatric symptoms and disorders in mild Alzheimer disease and mild cognitive impairment. *Journal of Alzheimer's Disease*, *29*(4), 761–772. https://doi.org/10.3233/JAD-2012-111886

Starkstein, S. E. (2014). Anosognosia in Alzheimer's disease: Diagnosis, frequency, mechanism and clinical correlates. *Cortex*, *61*, 64–73.

https://doi.org/10.1016/j.cortex.2014.07.019

Starkstein, S. E., Jorge, R., Mizrahi, R., Adrian, J., & Robinson, R. G. (2007). Insight and danger in Alzheimer's disease. *European Journal of Neurology*, *14*(4), 455–460. https://doi.org/10.1111/j.1468-1331.2007.01745.x

Starkstein, S. E., Jorge, R., Mizrahi, R., & Robinson, R. G. (2006). A diagnostic formulation for anosognosia in Alzheimer's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *77*(6), 719–725. https://doi.org/10.1136/jnnp.2005.085373

Starkstein, S. E., Petracca, G., Chemerinski, E., & Kremer, J. (2001). Syndromic validity of apathy in Alzheimer's disease. *American Journal of Psychiatry*, *158*(6), 872–877. https://doi.org/10.1176/appi.ajp.158.6.872

Starkstein, S. E., Sabe, L., Chemerinski, E., Jason, L., & Leiguarda, R. (1996). Two domains of anosognosia in Alzheimer's disease. *Journal of Neurology Neurosurgery and Psychiatry*, *61*(5), 485–490. https://doi.org/10.1136/jnnp.61.5.485

Starkstein, S. E., Vázquez, S., Migliorelli, R., Tesón, A., Sabe, L., & Leiguarda, R. (1995). A single-photon emission computed tomographic study of anosognosia in Alzheimer's disease. *Archives of Neurology*, *52*, 415–420. https://doi.org/10.1001/archneur.1995.00540280105024

Stewart, G., McGeown, W. J., Shanks, M. F., & Venneri, A. (2010). Anosognosia for memory impairment in Alzheimer's disease. *Acta Neuropsychiatrica*, *22*(4), 180–187. https://doi.org/10.1111/j.1601-5215.2010.00463.x

Sturm, V. E. V., Yokoyama, J. S., Seeley, W. W., Kramer, J. H., Miller, B. L., & Rankin, K. P. (2013). Heightened emotional contagion in mild cognitive impairment and Alzheimer's disease is associated with temporal lobe degeneration. *Proceedings of the National Academy of Sciences*, *110*(24), 9944–9949. https://doi.org/10.1073/pnas.1301119110

Sunderaraman, P., & Cosentino, S. (2017). Integrating the Constructs of Anosognosia and Metacognition: a Review of Recent Findings in Dementia. *Current Neurology and Neuroscience Reports*, *17*(3). https://doi.org/10.1007/s11910-017-0734-1

Sutton, S., Braren, M., Zubin, J., & John, E. R. (1965). Evoked-potential correlates of stimulus uncertainty. *Science*, *150*(3700), 1187–1188. https://doi.org/10.1126/science.150.3700.1187

Synn, A., Mothakunnel, A., Kumfor, F., Chen, Y., Piguet, O., Hodges, J. R., & Irish, M. (2018). Mental States in Moving Shapes: Distinct Cortical and Subcortical Contributions to Theory of Mind Impairments in Dementia. *Journal of Alzheimer's Disease*, *61*, 521–535. https://doi.org/10.3233/JAD-170809

Tabachnick, B. G., Fidell, L. S., G. Tabachnick, B., & S. Fidell, L. (2007). *Using Multivariate Statistics* (5th ed.). New Jersey: Pearson Education.

Torres, B., Santos, R. L., Sousa, M. F. B. de, Simões Neto, J. P., Nogueira, M. M. L., Belfort, T. T., … Dourado, M. C. N. (2015). Facial expression recognition in Alzheimer's disease: a longitudinal study. *Arquivos de Neuro-Psiquiatria*, *73*(5), 383–389. https://doi.org/10.1590/0004-282X20150009

Troisi, A., Pasini, A., Gori, G., Sorbi, T., Baroni, A., & Ciani, N. (1996). Clinical predictors of somatic and psychological symptoms of depression in Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *11*, 23–27. https://doi.org/10.1002/(SICI)1099-1166(199601)11:1<23::AID-GPS264>3.0.CO;2-4

Tsai, J. L., Levenson, R. W., & Carstensen, L. L. (2000). Autonomic, subjective, and expressive responses to emotional films in older and younger Chinese Americans and European Americans. *Psychology and Aging*, *15*, 684–693.

United Nations, Department of Economic and Social Affairs, P. D. (2015). *World Population Prospects: The 2015 Revision, Key Findings and Advance - Tables* (No. ESA/P/WP.241).

Vasterling, J. J., Seltzer, B., Foss, J. W., & Vanderbrook, V. (1995). Unawareness of deficit in alzheimer's disease: Domain-specific differences and disease correlates. *Neuropsychiatry, Neuropsychology and Behavioral Neurology*, *8*(1), 26–32.

Verhey, F. R. J., Rozendaal, N., Ponds, R. W. H. M., & Jolles, J. (1993). Dementia, awareness and depression. *International Journal of Geriatric Psychiatry*, *8*, 851–856. https://doi.org/10.1002/gps.930081008

Verhülsdonk, S., Quack, R., Höft, B., Lange-Asschenfeldt, C., & Supprian, T. (2013). Anosognosia and depression in patients with Alzheimer's dementia. *Archives of Gerontology and Geriatrics*, *57*(3), 282–287. https://doi.org/10.1016/j.archger.2013.03.012

Villain, N., Fouquet, M., Baron, J. C., Mézenge, F., Landeau, B., De La Sayette, V., … Chételat, G. (2010). Sequential relationships between grey matter and white matter atrophy and brain metabolic abnormalities in early Alzheimer's disease. *Brain*, *133*(11), 3301–3314. https://doi.org/10.1093/brain/awq203

Vogel, A., Waldorff, F. B., & Waldemar, G. (2015). Longitudinal changes in awareness over 36 months in patients with mild Alzheimer's disease. *International Psychogeriatrics*, *27*(1), 95–102. https://doi.org/10.1017/S1041610214001562

Wang, L., Zang, Y., He, Y., Liang, M., Zhang, X., Tian, L., … Li, K. (2006). Changes in hippocampal connectivity in the early stages of Alzheimer's disease: Evidence from resting state fMRI. *NeuroImage*, *31*(2), 496–504. https://doi.org/10.1016/j.neuroimage.2005.12.033

Wei, G., Irish, M., Hodges, J. R., Piguet, O., & Kumfor, F. (2019). Disease-specific profiles of apathy in Alzheimer's disease and behavioural-variant frontotemporal dementia differ across the disease course. *Journal of Neurology*. https://doi.org/10.1007/s00415-019-09679-1

Weinberg, A., & Hajcak, G. (2010). Beyond Good and Evil: The Time-Course of Neural Activity Elicited by Specific Picture Content. *Emotion*, *10*(6), 767–782. https://doi.org/10.1037/a0020242

West, & Huet. (2020). The Effect of Aging on the ERP Correlates of Feedback Processing in the Probabilistic Selection Task. *Brain Sciences*, *10*(1), 40. https://doi.org/10.3390/brainsci10010040

Wheaton, B., Muthen, B., Alwin, D. F., & Summers, G. (1977). Assessing Reliability and Stability in Panel Models. *Sociological Methodology*, *8*(1), 84–136. https://doi.org/10.2307/270754

Widmann, A., Schröger, E., & Maess, B. (2015). Digital filter design for electrophysiological data - a practical approach. *Journal of Neuroscience*

Methods, *250*, 34–46. https://doi.org/10.1016/j.jneumeth.2014.08.002

Wild-Wall, N., Willemssen, R., & Falkenstein, M. (2009). Feedback-related processes during a time-production task in young and older adults. *Clinical Neurophysiology*, *120*(2), 407–413. https://doi.org/10.1016/j.clinph.2008.11.007

Wilson, R. S., Boyle, P. A., Yu, L., Barnes, L. L., Sytsma, J., Buchman, A. S., … Schneider, J. A. (2015). Temporal course and pathologic basis of unawareness of memory loss in dementia. *Neurology*, *85*(11), 984–991. https://doi.org/10.1212/WNL.0000000000001935

Woodman, G. F. (2010). A brief introduction to the use of event-related potentials (ERPs) in studies of perception and attention. *Attention and Perceptual Psychophysiology*, *72*(8), 1–29. https://doi.org/10.3758/APP.72.8.2031.A

World Health Organization. (2004). *ICD-10 : international statistical classification of diseases and related health problems* (2nd ed., 1). World Health Organization. Retrieved from https://apps.who.int/iris/handle/10665/42980

Wright, C. I. (2011). Emotion and Behavior in Alzheimer's Disease and Other Dementias. In A. E. Budson & N. W. Kowall (Eds.), *The Handbook of Alzheimer's Disease and Other Dementias* (pp. 416–456). Oxford: Blackwell.

Zaitchik, D., Koff, E., Brownell, H., Winner, E., & Albert, M. (2004). Inference of mental states in patients with Alzheimer's disease. *Cognitive Neuropsychiatry*, *9*(4), 301–313. https://doi.org/10.1080/13546800344000246

Zaitchik, D., Koff, E., Brownell, H., Winner, E., Albert, M., Koff, E., & Albert, M. (2006). Inference of beliefs and emotions in patients with Alzheimer's disease. *Neuropsychology*, *20*(1), 11–20. https://doi.org/10.1037/0894-4105.20.1.11

Zaki, J., & Ochsner, K. (2012). The neuroscience of empathy: Progress, pitfalls and promise. *Nature Neuroscience*, *15*(5), 675–680. https://doi.org/10.1038/nn.3085

Zamboni, G., Drazich, E., McCulloch, E., Filippini, N., Mackay, C. E., Jenkinson, M., … Wilcock, G. K. (2013). Neuroanatomy of impaired self-awareness in Alzheimer's disease and mild cognitive impairment. *Cortex*, *49*, 668–678. https://doi.org/10.1016/j.cortex.2012.04.011

Zanetti, O., Vallotti, B., Frisoni, G. B., Geroldi, C., Bianchetti, a, Pasqualetti, P., &

Trabucchi, M. (1999). Insight in dementia: when does it occur? Evidence for a nonlinear relationship between insight and cognitive status. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *54*(2), P100–P106. https://doi.org/10.1093/geronb/54B.2.P100

Zhang, F., Ho, Y. W., & Fung, H. H. (2015). Learning from Normal Aging: Preserved Emotional Functioning Facilitates Adaptation among Early Alzheimer's Disease Patients. *Aging and Disease*, *6*(3), 208–215. https://doi.org/10.14336/AD.2014.0620

Zhao, Q.-F., Tan, L., Wang, H.-F., Jiang, T., Tan, M.-S., Tan, L., … Yu, J.-T. (2016). The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. *Journal of Affective Disorders*, *190*, 264–271. https://doi.org/10.1016/j.jad.2015.09.069