

The link between apathy and Alzheimer's Disease: The role of psychometric tools and the possible implications for treatment

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Abstract

Alzheimer's Disease (AD) represents a critical challenge because of its increasing neuropsychological impairment with progressive cognitive decline accompanied by Behavioral and Psychological Symptoms of Dementia (BPSD) in almost 90% of patients. BPSD represent relevant clinical problems, leading to a worsening in the general conditions of patients. More specifically, apathy is often associated with a poor response to treatment, a faster cognitive and functional decline and an increased mortality rate.

Apathy can be considered as a common symptom of AD and as an early marker of cognitive decline and transition from mild cognitive impairment to dementia. Recent studies have shown different neurobiological and clinical links between apathy and AD. Evidence discussed in the present article suggests a strong clinical link between apathy and AD as well as the relevance of psychometric tools, such as the Apathy Evaluation Scale (AES), to better diagnose and treat apathy in patients with AD. The aim of this review was thus to provide a general overview of the neurobiological and clinical links between apathy and

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AD, with the purpose of evaluating the impact of apathy on the health of AD patients, focusing on the role of psychometric tools and the possible implications for treatment. A multimodal intervention should be promoted as an innovative approach for the future treatment of apathetic AD patients.

Keywords: Apathy; Alzheimer; Psychometric tools; Treatment.

1. Introduction

Alzheimer's Disease (AD) can be defined as a progressive and remediless neurodegenerative disease that affects an increasing number of subjects over the age of 65 (Albert, 2007). It is the most common form of dementia (Herrera, Caramelli, Silveira, & Nitrini, 2002; Hirtz, Thurman, Gwinn-Hardy, Mohamed, Chaudhuri, & Zalutsky, 2007) and in recent years it has been demonstrated (Isaacson, Ganzer, Hristov, Hackett, Caesar, Cohen *et al.*, 2018) that late-onset AD begins decades before a diagnosis, with a long preclinical and prodromal phase often beginning in midlife (Frisoni, Winblad, & O'Brien, 2011). AD represents a critical challenge to the health care system with the aging population (Robert, Ferris, Gauthier, Ihl, Winblad, & Tennigkeit, 2010) because of its increasing neuropsychological impairment with a progressive decline of memory, language, executive function and visuospatial skills (Cummings & McPherson, 2001). The characteristics of the disease, of cognitive and functional decline, are accompanied by Behavioral and Psychological Symptoms of Dementia (BPSD) in almost 90% of patients (Guimarães, Levy, Teixeira, Beato, & Caramelli, 2008). BPSD are symptoms of disturbed perception, thought content, mood, and behavior that occur frequently in patients with dementia; they are common precipitators of institutional care

(Mitchell, Herrmann, & Lanctôt, 2011) and significantly contribute to decreasing the quality of life of caregivers (Lyketsos, Lopez, Jones, Fitzpatrick, Breitner, & Dekosky, 2002; Banerjee, Smith, Lamping, Harwood, Foley, Smith *et al.*, 2006). BPSD, including apathy, agitation, delusion, irritability, anxiety, disinhibition and hallucinations (Cummings & McPherson, 2001), represent significant clinical problems, leading to an accelerated functional decline, the distress of caregivers and aggression towards patients and possibly to an increased mortality rate, as reviewed by Guimarães and colleagues (2008).

Apathy can be defined as a specific dimension of behavior, characterized by a lack of motivation (Marin, Firinciogullari, & Biedrzycki, 1993), in which motivation is a superordinate concept referring to the psychological structure and the determinants of goal-directed behavior (Bindra, 1959; Madsen, 1973). Apathy is often associated with a poor response to treatment, the reliance on caregivers to start activities, a more rapid cognitive and functional decline and an increased mortality rate (Ruslan, Teerenstra, Smalbrugge, Vernooij-Dassen, Bohlmeijer, Gerritsen *et al.*, 2013). For clinical purposes apathy is often considered as a symptom of

other syndromes, such as depression or dementia (Marin *et al.*, 1993). However, it can be considered as a syndrome in itself and conceptualized as a syndrome of reduced motivation in which the lack of motivation is not attributable to a reduced level of consciousness, emotional distress, or cognitive deficits (Marin, 1991). Apathy is a multidimensional construct that can include both the emotional and the social sphere and presents three separate dimensions consisting of cognitive, affective and behavioral symptoms (Robert, Onyike, Leentjens, Dujardin, Aalten, Starkstein *et al.*, 2009) although there is heterogeneity in the degree in which each dimension could be present. The prevalence of apathy is well documented in different neuropsychiatric disorders (Padala, Frederick, & Subhash, 2005), especially in Mild Cognitive Impairment (MCI) and AD. In fact, from an epidemiological point of view, apathy can be considered as a common symptom of AD (Rea, Carotenuto, Fasanaro, Traini, & Amenta, 2014). Recent studies have shown that the higher the level of apathy, the more it is a predictor of the transition to dementia (Lanctôt, 2017). Most of the epidemiological studies on apathy in the context of AD refer to studies on the prevalence or change of apathy symptoms over time (Brodaty, Altendorf, Withall, & Sachdev, 2010). Apathy is predominant both in MCI and dementia and its prevalence is positively related to the severity of dementia (Lanctôt, 2017). It can determine high levels of distress in caregivers (Samus, Rosenblatt, Steele, Baker, Harper, Brandt *et al.*, 2005) and, as in the case with AD, it can provoke several conflicts and unpleasant emotions, like anger and exhaustion, between patients and caregivers. On the basis of this evidence apathy can be considered as an early marker of cognitive decline and transition to dementia. This has prompted the field to flag it as a high-value neuropsychiatric state of risk, as has been highlighted in the latest guidelines for preclinical AD from the National Institute on Aging (Sperling, Aisen, Beckett, Bennett, Craft, Fagan *et al.*, 2011). But already in 2008, The European Alzheimer's Disease Consortium had drawn guidelines for the diagnosis of apathy (Winbald, Frisoni, Frolich, Johannsen, Johansson, Kehoe *et al.*, 2008). To make a correct diagnosis of apathy the reduced motivation clinical picture must persist for no less than four weeks, and two of the following three dimensions should be present: (I) reduced goal-directed behavior, (II) reduced goal-directed cognitive activity, and (III) reduced emotions. In a recent work, Robert and collaborators (Robert, Lanctôt, Agüera-Ortiz, Aaltend, Bremonda, Defrancesco *et al.*, 2018) proposed new diagnostic criteria for apathy to be adopted both in the clinical and the research domain (see Tab. 1).

Table 1 – *New diagnostic criteria for apathy in both the clinical and research domain (Robert et al., 2018)*

CRITERION A: A quantitative reduction of goal-directed activity either in the behavioral, cognitive, emotional or social dimensions in comparison to the patient's previous level of functioning in these areas. These changes may be reported by the patient him/herself or by the observation of others.

CRITERION B: The presence of at least 2 of the 3 following dimensions for a period of at least four weeks and present most of the time.

1. B1. BEHAVIOR & COGNITION: Loss of, or reduced, goal-directed behavior or cognitive activity as revealed by at least one of the following:
 - General level of activity: the patient has a reduced level of activity either at home or at work, he/she makes less effort to initiate or accomplish tasks spontaneously or needs to be prompted to perform them.
 - Persistence of activity: the patient is less persistent in maintaining an activity or conversation, finding solutions to problems or thinking of alternative ways to accomplish them if they become difficult.
 - Making choices: the individual has less interest or takes longer to make choices when different alternatives are presented (e.g., selecting TV programs, preparing meals, choosing from a menu, etc.).
 - Interest in external issues: the subject has less interest in or reacts less to news, either good or bad, or has less interest in doing new things.
 - Personal well-being: the patient is less interested in his/her own health and well-being or personal image (general appearance, grooming, clothes, etc.).

 2. B2. EMOTION: Loss of, or reduced, emotion as revealed by at least one of the following:
 - Spontaneous emotions: the patient shows less spontaneous (self-generated) emotions regarding his/her own affairs, or appears less interested in events that should matter to him/her or to people that he/she knows well.
 - Emotional reactions to the environment: the subject expresses less emotional reaction in response to positive or negative events in his/her environment that affect him/her or people he/she knows well (e.g., when things go well or bad, responding to jokes, or events on a TV program or a movie, or when disturbed or prompted to do things he/she would prefer not to do).
 - Impact on others: the individual is less concerned about the impact of his/her actions or feelings on the people surrounding him/her.
 - Empathy: the patient shows less empathy to the emotions or feelings of others (e.g., becoming happy or sad when someone is happy or sad, or being moved when others need help).
 - Verbal or physical expressions: the individual shows less verbal or physical reactions that reveal his/her emotional states.
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3. B3. SOCIAL INTERACTION: Loss of, or reduced, engagement in social interaction as highlighted by at least one of the following:
 - Spontaneous social initiative: the patient takes less initiative in spontaneously proposing social or leisure activities to family or others.
 - Environmentally-stimulated social interaction: the individual participates less, or is less comfortable or more indifferent, to social or leisure activities suggested by people around him/her.
 - Relationship with family members: the subject shows less interest in the family members (e.g., to know what is happening to them, to meet them or to make arrangements to contact them).
 - Verbal interaction: the patient is less likely to initiate a conversation, or he/she immediately withdraws from it.
 - Homebound: the individual prefers to stay at home more frequently or longer than usual and shows less interest in getting out to meet people.

CRITERION C: The symptoms (A - B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning.

CRITERION D: The symptoms (A - B) are not exclusively explained or due to physical disabilities (e.g. blindness and loss of hearing), to motor disabilities, to a reduced level of consciousness, to the direct physiological effects of a substance (e.g. drug abuse, medication), or to major changes in the patient's environment.

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The recent evidence thus suggests a key role of apathy in AD. Along this line the aim of this review was to provide a general overview of the neurobiological and clinical links between apathy and AD, with the purpose of giving the clinicians the opportunity to evaluate the impact of apathy on the health of AD patients, focusing on the role of psychometric tools and the possible implications for treatment.

2. Neurobiological links between apathy and Alzheimer's Disease

In recent years, apathy has been deeply investigated, due to its high prevalence in neuropsychiatric disorders, especially in AD. Several studies

have demonstrated its anatomical and neuropsychological correlates, in particular through neuroimaging studies. An association was found, for example, between apathy and the dysfunction in both the dorsolateral and orbitofrontal areas of the prefrontal regions and sub-regions within the basal ganglia (Eslinger, Moore, Antani, Anderson, & Grossman, 2012). In particular, an association between apathy and atrophy was revealed in AD concerning many different frontal regions, such as the anterior cingulate cortex (ACC) (Apostolova, Akopyan, Partiali, Steiner, Dutton, Hayashi *et al.*, 2007; Bruen, McGeown, Shanks, & Venneri, 2008; Grambaite, Selnes, Reinvang, Aarsland, Hessen, Gjerstad *et al.*, 2011; Tunnard, Whitehead, Hurt, Wahlund, Mecocci, Tsolaki *et al.*, 2011; Mori, Shimada, Shinotoh, Hirano, Eguchi, Yamada *et al.*, 2014), the medial frontal cortex (Apostolova *et al.*, 2007; Mori *et al.*, 2014), the orbitofrontal cortex (Holthoff, Beuthien-Baumann, Kalbe, Lüdecke, Lenz, Zündorf *et al.*, 2005; Tunnard *et al.*, 2011; Mori *et al.*, 2014), the pars triangularis and insula (Tunnard *et al.*, 2011; Moon, Moon, Kim, & Han, 2014; Mori *et al.*, 2014), the lower inferior temporal cortical thickness (Donovan, Wadsworth, Lorus, Locascio, Rentz, Johnson *et al.*, 2014; Guercio, Donovan, Ward, Schultz, Lorus, Amariglio *et al.*, 2015), as well as the fronto-parietal control network connectivity (Munro, Donovan, Guercio, Wigman, Schultz, Amariglio *et al.*, 2015). Moreover, as recently reviewed by Starkstein and Brockman (2018), the decreased density of grey matter in the right superior frontal gyrus, in the bilateral middle and inferior frontal gyrus, the ACC and the basal ganglia (bilateral putamen and head of the caudate) has found to be correlated to an increased risk to develop apathy. These areas are critically involved in affective modulation and in sensory and emotional information processing (Tekin & Cummings, 2002; Levy & Dubois, 2006). A great attention has been given to the anterior cingulate cortex because it is involved in the systems of motivation and reward as a part of a frontal striatal circuit; moreover, it has been demonstrated that this circuit is correlated with symptoms of apathy (Tekin & Cummings, 2002; Blundo & Gerace, 2015). Levy and Dubois (2006) examined the correlation between the dimensions of apathy (emotional, affective, cognitional and auto-activation) and the anatomical regions of the brain. They found that three different areas of the brain could be attributed to their physiopathology; emotional-affective apathy was found to be typically associated with the damage of circuits linking the orbito-medial prefrontal and limbic cortex to the basal ganglia. Cognitive apathy was, instead, generally correlated to the dysfunction of the dorsolateral prefrontal cortex and related portions within the basal ganglia,

while auto-activation apathy was related to the associative and limbic territories of the internal portion of the globus pallidus.

Finally, the hypofunction of the dopaminergic system should also be taken into consideration as a relevant neurobiological link between apathy and AD. As reviewed by Mitchell and colleagues (2011), in AD patients there seems to be a correlation between the pathophysiological changes to the DAergic neurons in the reward system and the onset of apathy. Indeed, DA mediates feelings of motivation, but it has been shown that there is a dysfunction of the dopaminergic system at an early stage of the pathogenesis of AD with a central role in the pathophysiology of memory deficits and apathy in AD (D'Amelio, Puglisi-Allegra, & Mercuri, 2018).

3. Psychometric tools to evaluate apathy in AD

Whereas apathy can be considered as a preclinical manifestation of the disease and AD patients can have a more rapid cognitive decline (Starkstein, Jorge, Mizrahi, & Robinson, 2006) and a more rapid loss of autonomy in the activities of daily life, a rapid recognition and diagnosis are needed to plan an appropriate treatment. An accurate assessment is essential to improve the management of apathy and its associated symptoms and conditions. Several psychometric tools for apathy are present in the literature, but we will describe the ones, which are most widely adopted (Clarke, Ko, Kuhl, van Reekum, Salvador, & Marin, 2011) and that have been validated on the AD population (Radakovic, Harley, Abrahams, & Starr, 2015; Mohammad, Ellis, Rau, Rosenberg, Mintzer, Ruthirakuhan *et al.*, 2018; see Tab. 2 for details).

Table 2 – Selection of validated psychometric tools to assess apathy in AD

Full name	Abbreviation	Item n.	Authors
Apathy Evaluation Scale	AES (AES-C; AES-I; AES-S)	18	Marin, 1991
Apathy Scale	AS	14	Starkstein, 1992, 1995
Short Version Of The Apathy Evaluation Scale		10	Lueken <i>et al.</i> , 2007
Neuropsychiatric Inventory – Apathy Subscale	NPI – Apathy Subscale	8	Cummings <i>et al.</i> , 1994
Apathy Inventory	AI	3	Robert <i>et al.</i> , 2002
Dementia Apathy Interview and Rating	DAIR	16	Strauss & Sperry, 2002

The Apathy Evaluation Scale (AES) was developed by Marin and colleagues (Marin, Biedrzycki, & Firinciogullari, 1991), on the basis of the definition of apathy according to Marin, which describes a syndrome of loss of motivation as reflected by the acquired changes in affection (mood), behavior and cognition (Marin *et al.*, 1991). It is measured through a four-point Likert-scale, composed of 18 items that assess and quantify the emotional, behavioral and cognitive aspects of apathy. There are three different ways of measuring the scale: through a self-report (AES-S), an informant report (AES-I) or a clinician interview (AES-C). The AES-C, in particular, includes a semi-structured open-ended interview that helps the clinician to collect information from the patient concerning his/her typical day activities, hobbies and interests, which reveals the degree of the subject's motivation and directs the clinician in providing his/her own rating of the individual's level of apathy on each item. Every item is rated on a 4-point response scale (0 = not at all true/characteristic to 3 = very much true/characteristic). Higher scores indicate more severe apathy (Marin *et al.*, 1991). The AES-C version takes between 10-20 minutes to be completed (Marin *et al.*, 1991).

Different studies (Mohammad *et al.*, 2018) demonstrated good to excellent internal consistency of all the versions of the AES, varying the values for convergent validity and good discriminant validity. However, as Marin and colleagues noted (Marin, Biedrzycki, & Firinciogullari, 1991; see also Mohammad *et al.*, 2018), only the AES-C and AES-S versions were able to discriminate apathy from depression. Moreover, the AES has been employed in three Randomized Clinical Trials (RCTs) as a primary outcome in patients with apathy and AD (Herrmann, Rothenburg, Black, Ryan, Liu, Busto *et al.*, 2008; Rosenberg, Lanctôt, Drye, Herrmann, Scherer, Bachman *et al.*, 2013; Padala, Padala, Lensing, Ramirez, Monga, Bopp *et al.*, 2018).

Two different scales were developed on the basis of the first version of the AES. Starkstein and colleagues (Starkstein, Mayberg, Preziosi, Andrezejewski, Leiguarda, & Robinson, 1992) developed a 14-item Apathy Scale, which is a short and slightly modified version of Marin's AES, and they validated it on the stroke, Parkinson's and AD population (Starkstein, Migliorelli, Manes, Teson, Petracca, Chemerinski *et al.*, 1995; Starkstein, Jorge, & Mizrahi, 2006). Lueken and co-workers (Lueken, Seidl, Volker, Schweiger, Kruse, & Schroder, 2007), instead, developed an abbreviated version of Marin's instrument, reducing the items from 18 to 10. This scale demonstrated a moderate convergent validity with the Neuropsychiatric Inventory (NPI)-apathy and an excellent internal consistency (Mohammad *et*

al., 2018). The aforementioned authors reduced the items considered to be redundant (Starkstein *et al.*, 1992) or inappropriate (Lueken *et al.*, 2007) according to experts with a special knowledge of the population being assessed. As with the original Apathy Evaluation Scale, each item is measured with a four-point Likert scale.

The NPI was developed by Cumming (Cummings, Mega, Gray, Rosenberg-Thompson, Carusi, & Gornbein, 1994; Cummings, 1997) as a multidimensional instrument to assess neurobehavioral disorders in dementia. The NPI has a specific 8-item subscale to measure apathy, which lies in a general screen item rated on a yes-versus-no basis. Its scores have a scale ranging from 0 to 12, and higher scores indicate a more severe presence of apathy (Cummings *et al.*, 1994; Cummings, 1997). The NPI and NPI-apaty subscale were used and validated on multicultural sample patients with dementia and AD (Clarke *et al.*, 2011).

The Apathy Inventory (AI) (Robert, Clairot, Benoit, Koutaich, Bertogliati, Tible *et al.*, 2002) is based on Marin and colleagues' diagnostic criteria of apathy (Marin, 1991; Marin *et al.*, 1991), which means lack of emotional response, self-initiated actions, and interest in things. This is why the AI includes 3 different items for the assessment of emotional blunting, lack of initiative, and symptoms of loss of interest. The AI involves two versions: a clinician-administered interview to the caregiver (AI-caregiver) or the patient (AI-patient). The frequency is rated on a four-point Likert scale and the severity on a three-point Likert scale. The AI validation was carried out in a mixed sample consisting of normal controls, MCI patients and AD patients (Robert *et al.*, 2002). The internal consistency reported for the caregiver-based version is of good quality and the between-rater and test-retest reliability were excellent and demonstrated favorable values for all three items on the scale (Robert *et al.*, 2002; Mohammad *et al.*, 2018).

The Dementia Apathy Interview and Rating (DAIR) (Strauss & Sperry, 2002) is an informant-based unidimensional 16-item clinician-administrated scale to measure changes in motivation, engagement, and emotional response in MCI patients with apathy. The scale is administered to a caregiver using a structured interview with questions concerning apathy in the patient over the past month. Each item is rated on a 4-point scale (0 = no or almost never to 3 = yes or almost always) with higher scores corresponding to a greater severity in apathy. Only items representing a change in behavior are included in the final apathy score. The DAIR has very good internal consistency and the two-month test-retest reliability and

the inter-rater reliability also demonstrated to be very good (Strauss & Sperry, 2002).

The presence of valid and reliable apathy scales are essential to assess and plan treatment of the apathy syndrome in the AD population. As we have seen and thoroughly described, there are a lot of well-structured, valid and reliable psychometric tools for the evaluation of apathy that can be used in conjunction with other clinical tools of assessment and that provide altogether a more complex and complete clinical evaluation of the subject. However, a gold standard of apathy assessment is still lacking.

4. Pharmacological treatment of apathy in AD

The pharmacological treatment of apathy appears to be essential to take care and manage AD patients, although it still represents an unmet clinical need. Different studies have investigated the role of different psychotropic drugs on the pharmacological treatment of apathy. Concerning donepezil and rivastigmine, evidence from Randomized Clinical Trials (RCTs) suggests that cholinesterase inhibitors can improve apathy (Winblad, Engedal, Soininen, Verhey, Waldemar, & Wimo, 1999; Cummings, Koumaras, Chen, & Mirski, 2005) and delay its onset (Waldemar, Gauthier, Jones, Wilkinson, Cummings, Lopez *et al.*, 2011). In a recent RCT, the authors compared the apathy scores of 113 mild to moderate AD patients treated for 24 months with donepezil plus a cholinergic precursor (choline alfoscerate) with those of patients who were administered to donepezil alone (Rea, Carotenuto, Traini, Fasanaro, Manzo, & Amenta, 2015). The results demonstrated that the combination of donepezil with choline alfoscerate was more effective than donepezil alone in reducing apathy in AD patients. Lopez and colleagues (Lopez, Mackell, Sun, Kassalow, Xu, McRae *et al.*, 2008) conducted a multi-center, open-label, 12-week study to evaluate the efficacy and safety of the administration of donepezil in 106 mild to moderate AD Hispanic patients treated with donepezil 5 mg/day for 6 weeks followed by 10 mg/day for another 6 weeks. The authors demonstrated that the NPI “apathy/indifference” subdomain showed a statistically significant improvement in donepezil-treated patients. Other studies confirmed that donepezil could improve apathy symptoms in patients with mild-severe AD (Drijgers, Aalten, Winogrodzka, Verhey, & Leentjens, 2009). A validation of the hypothesis that the rescue of the cholinergic system can be a useful approach for the treatment of apathy comes from other relevant studies conducted with cholinesterase inhibitors, such as

rivastigmine and galantamine. In an open-label, multi-center study (Gauthier, Juby, Dalziel, Rehel, Schecter, & EXPLORE Investigators, 2010) the efficacy of rivastigmine on apathy was evaluated in a sample of 4460 AD patients, demonstrating that the percentage of patients showing an improvement vs. a deterioration in apathy at month 6 was in the order of 42.8 vs. 7.2%, respectively. Galantamine can also be used for the treatment of apathy in AD. In 2004, Cummings and colleagues (Cummings, Schneider, Tariot, Kershaw, & Yuan, 2004) assessed the efficacy of galantamine at different doses (8, 16, or 24 mg/day) in a 21-week, multi-center RCT in 978 patients with mild to moderate AD. This study demonstrates a significantly less appearance of apathy in patients treated with galantamine and without specific behavioral symptoms. Monsch and colleagues (Monsch, Giannakopoulos, & GAL-SUI Study Group, 2004) investigated the effects of galantamine (escalated from 8 to 24 mg/day over 8 weeks) in a 3-month, open-label, multi-center study conducted on 124 AD patients. The authors demonstrated a 27% reduction in the apathy score, as assessed by the NPI at the end of the period of treatment. Freund-Levi and co-workers (Freund-Levi, Jedenius, Tysen-Backstrom, Larksater, Wahlund, & Eriksson, 2014) recruited subjects with diagnoses of probable dementia (88%) or MCI (12%) from a memory clinic. The aim of the randomized, open-label trial, was to explore the effects of the administration of galantamine and risperidone on the overall neuropsychiatric symptoms (NPS) and global function. Both galantamine and risperidone treatments were able to produce a small non-significant reduction of apathetic behaviors, as measured by the NPI-aphathy subscale, also over time.

In 2006 (Cummings, Schneider, Tariot, & Graham, 2006) an exploratory analysis of a 24-week, double-blind, placebo-controlled trial was conducted in order to compare memantine (20 mg/day) treatment with placebo in 404 moderate to severe AD patients, which were already treated with donepezil; the authors did not detect significant effects on apathy as assessed with the NPI, whereas an improvement in the NPI-aphathy score (-11.3%) was observed following treatment with memantine by Schmidt and colleagues (Schmidt, Baumhackl, Berek, Brücke, Kapeller, Lechner *et al.*, 2010) in a 16-week, open label study conducted on 53 AD patients.

Moreover, a recent 6-week, multi-center, double-blind, placebo-controlled RCT, investigating the treatment of low-dose methylphenidate (20 mg/day) for apathy in patients with mild-moderate AD, reported a significant improvement in apathy in the group of active treatment vs. placebo on a modified AD Cooperative Study – Clinical Global Impression

of Change (Rosenberg *et al.*, 2013). Padala and colleagues (2018) conducted a 12-week, double-blind, randomized, placebo-controlled survey on 60 elderly veterans in a community dwelling. They used the AES-C to assess apathy as well as to evaluate the impact of the treatment on apathy. The authors demonstrated that the methylphenidate group experienced a significantly greater improvement than the placebo, both in terms of apathy (at 4, 8, and 12 weeks) and in terms of cognition, functional status, caregiver burden and depression (not until 12 weeks).

Pharmacological challenge has shown that AD patients with apathy have a blunted subjective reward following the administration of the dopaminergic agent dextroamphetamine (Lancôt, Herrmann, Black, Ryan, Rothenburg, Liu *et al.*, 2008), suggesting that a hypofunction of the dopaminergic system can contribute to the pathophysiology of apathy in the AD brain. Antidepressant drugs have not been found to improve apathy (Berman, Brodaty, Withall, & Seeher, 2012) although no specific studies have been conducted with second-generation antidepressant drugs, such as fluoxetine and bupropione, to evaluate the impact of these drugs alone or in combination with cholinesterase inhibitors.

5. Non-pharmacological treatment of apathy in AD

As discussed above, pharmacological therapies have demonstrated their efficacy in the management of apathy associated with AD. More specifically, donepezil and methylphenidate have demonstrated to be the most efficient drugs in reducing the level of apathy in the AD population. But alongside pharmacological treatment, several studies have investigated alternative types of interventions. Non-Pharmacological Treatment (NPT), also defined “ecopsychological intervention” (Zeisel, Reisberg, Whitehouse, Woods, & Verheul, 2016), has been recently considered as a new essential path (Theleritis, Siarkos, Politis, Katirtzoglou, & Politis, 2018) to be explored for the management of apathy. Non-pharmacological treatment includes interventions on cognitive, social, psychological, and relational aspects of the subject, using different methods, such as group activities, therapeutic dialogs, meditation, and sensory, physical, and physiological stimulation. The aim of this type of intervention is to improve the quality of life of the patient by strengthening his/her cognitive, psycho-affective, and social skills, reducing the psycho-behavioral symptoms, preserving the patient's social activity, restoring confidence and self-esteem, and promoting autonomy (Zuchella, Sinforiani, Tamburin, Federico, Mantovani,

Bernini *et al.*, 2018). A multiplicity of NPTs has shown to be effective on the treatment of apathy in AD. Occupational therapy and physical activity, inserted within a multidisciplinary intervention, have revealed to be effective in the treatment of apathy in patients suffering from dementia compared with pharmacological treatments alone (Treusch, Majic, Page, Gutzmann, Heinz, & Rapp, 2015). Maci and colleagues (Maci, Pira, Quattrocchi, Di Nuovo, Perciavalle, & Zappia, 2012) conducted an interesting study in a 14-patient RCT, which included physical activity as NPT, in order to assess the effect of a 3-month program of physical activity, cognitive stimulation and socialization versus usual activities at home. Maci and collaborators (2012) demonstrated a significant improvement in the AES scores. Moreover, in 2015, Telenius and co-workers confirmed that a high intensity functional exercise program in nursing home patients with dementia decreased the level of apathy following the intervention versus a control group (Telenius, Engedal, & Bergland, 2015). Several recent studies have considered the key role of exercise in the treatment of various neuropsychiatric disorders (Guerrera, Furneri, Grasso, Caruso, Castellano, Drago *et al.*, 2020). Physical activity, associated with drug treatment, allows to expand the range of rehabilitation interventions dedicated to demented patients.

Furthermore, art therapies are also used as NPTs due to their efficacy in improving the levels of apathy compared with learning therapy (Hattori, Hattori, Hokao, Mizushima, & Mase, 2011). Raglio and colleagues (Raglio, Bellelli, Traficante, Gianotti, Ubezio, Villani *et al.*, 2008) conducted a study in which they included 60 participants: a music therapy experimental group ($n = 30$) and a control group ($n = 30$). After 4 weeks, the NPI scores for apathy were significantly improved in the experimental group. Moreover, Ferrero-Arias and colleagues conducted a RCT, which included 146 patients, divided into two groups: an intervention group, with music, art therapy and psychomotor activity, opposed to a control group, which were simply asked to perform free activities in a room during the day. They used the DAIR scale to assess apathy and they found a significant difference between the intervention and control groups, especially in patients with moderated apathy. They thus came to the conclusion that a structured, non-pharmacological, short-term occupational therapy intervention can improve apathy in mild or moderate dementia patients (Ferrero-Arias, Goñi-Imízcoz, González-Bernal, Lara-Ortega, da Silva-González, & Díez-Lopez, 2011).

More recently, it has been demonstrated that a multi-component psychological intervention after 6 months allows to register an improvement

in the apathy NPI score versus a standard occupational therapy intervention (Fischer-Terworth & Probst, 2012).

In 2016, Di Domenico and colleagues recruited 26 AD patients and 26 healthy controls (Di Domenico, Palumbo, Fairfield, & Mammarella, 2016). The experimental group followed a brief emotional shaping intervention, which was developed to reduce apathy (assessed with the AES) and increase the “willingness to do” in AD patients. The results demonstrated that the patients of the experimental group showed a significant increase in motivation.

Finally, great relevance has been recently given to Information and Communication Technologies (ICT) with the aim to train cognitive functions, promote communication, reduce loneliness, improve physical functions and the emotional state in apathetic and non-apathetic patients (Manera, Abraham, Agüera-Ortiz, Bremond, David, Fairchild *et al.*, 2020). An interesting study (Manera, Petit, Derreumaux, Orvieto, Romagnoli, Lyttle *et al.*, 2015) had the aim of demonstrating the efficacy of employing serious games (SGs), in this case "Kitchen and Cooking", for the assessment and rehabilitation of elderly people with MCI and AD. Twenty-one patients were recruited and results demonstrated that apathetic participants were motivated and interested in the activities, as the non-apathetic group, confirming that this game was useful in the case of presence of apathy. Moreover, Moyle and colleagues (Moyle, Cooke, Beattie, Jones, Klein, Cook *et al.*, 2013) conducted a pilot cross-over RCT with 18 demented patients and used the AES to assess apathy; the authors found no improvement of apathy with the use of a robot companion. In contrast, other studies (Valentí Soler, Agüera-Ortiz, Olazarán Rodríguez, Mendoza Rebolledo, Pérez Muñoz, Rodríguez Pérez *et al.*, 2015) demonstrated that the use of social robots in 60 patients with dementia resulted in an improvement in the NPI apathy scores.

6. Conclusions

The neurobiological and clinical links between apathy and Alzheimer's Disease are essential when considering apathy as one of the main common neuropsychiatric symptoms of AD. Apathy was initially considered only as a symptom of the Major Depressive Disorder, but today, more than ever, it seems important to investigate apathy as a syndrome in itself, in order to be able to specifically intervene promptly on it and improve patients' quality of life. The connection between brain regions involved in both apathy and

Alzheimer's is quite clear and the common involvement of the cholinergic system can explain why drugs currently used in AD patients (i.e. cholinesterase inhibitors) can also be effective in the treatment of apathy. Evidence discussed in the present review suggests a strong clinical link between apathy and Alzheimer's Disease as well as the relevance of psychometric tools, such as the AES, to better diagnose and treat apathy.

We believe that only by considering every single aspect of the patient's clinical picture can the clinician plan a multi-component intervention that has effects on health, defined as a state of complete physical, mental and social well-being (World Health Organization). In fact, several studies have shown the efficacy in reducing apathy also through non-pharmacological treatments centered on individual autonomous, psychological and social functioning, but a major unmet question remains open as to how we can better integrate pharmacological and non-pharmacological treatments. A multimodal intervention is the innovative approach that we believe might be proposed in the next future for the treatment of apathetic AD patients.

References

Albert, M. S. (2007). Changing the trajectory of cognitive decline? *The New England Journal of Medicine*, 357, 502-503.

Apostolova, L. G., Akopyan, G. G., Partiali, N., Steiner, C. A., Dutton, R. A., Hayashi, K. M., Dinov, I. D., Toga, A. W., Cummings, J. L., & Thompson, P. M. (2007). Structural correlates of apathy in Alzheimer's Disease. *Dementia and Geriatric Cognitive Disorders*, 24 (2), 91-97.

Banerjee, S., Smith, S. C., Lamping, D. L., Harwood, R. H., Foley, B., Smith, P., Murray, J., Prince, M., Levin, E., Mann, A., & Knapp, M. (2006). Quality of life in dementia: More than just cognition. An analysis of associations with quality of life in dementia. *Journal of Neurology, Neurosurgery and Psychiatry*, 77, 146-148.

Berman, K., Brodaty, H., Withall, A., & Seeher, K. (2012). Pharmacologic treatment of apathy in dementia. *The American Journal of Geriatric Psychiatry*, 20 (2), 104-122.

Bindra, D. (1959). *Motivation: A Systematic Reinterpretation*. New York: Ronald Press.

Blundo, C., & Gerace, C. (2015). Dopamine agonists can improve pure apathy associated with lesions of the prefrontal-basal ganglia functional system. *Neurological Sciences*, 36 (7), 1197-1201.

Brodsky, H., Altendorf, A., Withall, A., & Sachdev, P. (2010). Do people become more apathetic as they grow older? A longitudinal study in healthy individuals. *International Psychogeriatrics*, 22 (3), 426-436.

Bruen, P. D., McGeown, W. J., Shanks, M. F., & Venneri, A. (2008). Neuroanatomical correlates of neuropsychiatric symptoms in Alzheimer's disease. *Brain*, 131 (9), 2455-2463.

Clarke, D. E., Ko, J. Y., Kuhl, E. A., van Reekum, R., Salvador, R., & Marin, R. (2011). Are the available apathy measures reliable and valid? A review of the psychometric evidence. *Journal of Psychosomatic Research*, 70 (1), 73-97.

Cummings, J. L. (1997). The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurology*, 48 (5 Suppl. 6), S10-S16.

Cummings, J. L., Koumaras, B., Chen, M., & Mirski, D. (2005). Effects of rivastigmine treatment on the neuropsychiatric and behavioral disturbances of nursing home residents with moderate to severe probable Alzheimer's disease: A 26-week, multicenter, open-label study. *The American Journal of Geriatric Pharmacotherapy*, 3 (3), 137-148.

Cummings, J. L., & McPherson, S. (2001). Neuropsychiatric assessment of Alzheimer's disease and related dementias. *Aging Clinical and Experimental Research*, 13, 240-246.

Cummings, J. L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D. A., & Gornbein, J. (1994). The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*, 44 (12), 2308-2314.

Cummings, J. L., Schneider, E., Tariot, P. N., & Graham, S. M. (2006). Memantine MEM-MD-02 Study Group. Behavioral effects of memantine in Alzheimer disease patients receiving donepezil treatment. *Neurology*, 67 (1), 57-63.

Cummings, J. L., Schneider, L., Tariot, P. N., Kershaw, P. R., & Yuan, W. (2004). Reduction of behavioral disturbances and caregiver distress by galantamine in patients with Alzheimer's disease. *American Journal of Psychiatry*, *161* (3), 532-538.

D'Amelio, M., Puglisi-Allegra, S., & Mercuri, N. (2018). The role of dopaminergic midbrain in Alzheimer's disease: Translating basic science into clinical practice. *Pharmacological Research*, *130*, 414-419.

Di Domenico, A., Palumbo, R., Fairfield, B., & Mammarella, N. (2016). Fighting apathy in Alzheimer's dementia: a brief emotional-based intervention. *Psychiatry Research*, *242*, 331-335.

Donovan, N. J., Wadsworth, L. P., Lorius, N., Locascio, J. J., Rentz, D. M., Johnson, K. A., Sperling, R. A., & Marshall, G. A. (2014). Regional cortical thinning predicts worsening apathy and hallucinations across the Alzheimer disease spectrum. *The American Journal of Geriatric Psychiatry*, *22*, 1168-1179.

Drijgers, R. L., Aalten, P., Winogrodzka, A., Verhey, F. R., & Leentjens, A. F. (2009). Pharmacological treatment of apathy in neurodegenerative diseases: a systematic review. *Dementia and Geriatric Cognitive Disorders*, *28*, 13-22.

Eslinger, P. J., Moore, P., Antani, S., Anderson, C., & Grossman, M. (2012). Apathy in frontotemporal dementia: behavioral and neuroimaging correlates. *Behavioral Neurology and Neuropsychiatry*, *25* (2), 127-136.

Ferrero-Arias, J., Goñi-Imízcoz, M., González-Bernal, J., Lara-Ortega, F., da Silva-González, A., & Díez-Lopez, M. (2011). The efficacy of nonpharmacological treatment for dementia-related apathy. *Alzheimer Disease and Associated Disorders*, *25* (3), 213-219.

Fischer-Terworth, C., & Probst, P. (2012). Effects of a psychological group intervention on neuropsychiatric symptoms and communication in Alzheimer's dementia. *Journal of Gerontology and Geriatrics*, *45* (5), 392-397.

Freund-Levi, Y., Jedenius, E., Tysen-Backstrom, A. C., Larksater, M., Wahlund, L. O., & Eriksson, M. (2014). Galantamine versus risperidone treatment of neuropsychiatric symptoms in patients with probable dementia: an open randomized trial. *American Journal of Geriatric Psychiatry*, 22, 341-348.

Frisoni, G. B., Winblad, B., & O'Brien, J. T. (2011). Revised NIA-AA criteria for the diagnosis of Alzheimer's disease: a step forward but not yet ready for widespread clinical use. *International Psychogeriatrics*, 23, 1191-1196.

Gauthier, S., Juby, A., Dalziel, W., Rehel, B., Schecter, R., & EXPLORE Investigators (2010). Effects of rivastigmine on common symptomatology of Alzheimer's disease (EXPLORE). *Current Medical Research and Opinion*, 26 (5), 1149-1160.

Grambaite, R., Selnes, P., Reinvang, I., Aarsland, D., Hessen, E., Gjerstad, L., & Fladby, T. (2011). Executive dysfunction in mild cognitive impairment is associated with changes in frontal and cingulate white matter tracts. *Journal of Alzheimer's Disease*, 27, 453-462.

Guercio, B. J., Donovan, N. J., Ward, A., Schultz, A., Lorusso, N., Amariglio, R. E., Rentz, D. M., Johnson, K. A., Sperling, R. A., & Marshall, G. A. (2015). Apathy is associated with lower inferior temporal cortical thickness in mild cognitive impairment and normal elderly individuals. *Journal of Neuropsychiatry and Clinical Neurosciences*, 27, 22-27.

Guerrera, C. S., Furneri, G., Grasso, M., Caruso, G., Castellano, S., Drago, F., Di Nuovo, S., & Caraci, F. (2020). Antidepressant Drugs and Physical Activity: A Possible Synergism in the Treatment of Major Depression? *Frontiers in Psychology*, 11: 857.

Guimarães, H. C., Levy, R., Teixeira, A. L., Beato, R. G., & Caramelli P. (2008). Neurobiology of apathy in Alzheimer's Disease. *Arquivos de Neuropsiquiatria*, 66 (2-B), 436-443.

- Hattori, H., Hattori, C., Hokao, C., Mizushima, K., & Mase, T. (2011). Controlled study on the cognitive and psychological effect of coloring and drawing in mild Alzheimer's disease patients. *Geriatrics and Gerontology International*, 11 (4), 431-437.
- Herrera, E. Jr, Caramelli, P., Silveira A. S., & Nitrini, R. (2002). Epidemiologic survey of dementia in a community-dwelling Brazilian population. *Alzheimer Disease and Associated Disorders*, 16, 103-108.
- Herrmann, N., Rothenburg, L. S., Black, S. E., Ryan, M., Liu, B. A., Busto, U. E., & Lanctôt, K. L. (2008). Methylphenidate for the treatment of apathy in Alzheimer disease: Prediction of response using dextroamphetamine challenge. *Journal of Clinical Psychopharmacology*, 28 (3), 296-301.
- Hirtz, D., Thurman, D. J., Gwinn-Hardy, K., Mohamed, M., Chaudhuri, A. R., & Zalutsky, R. (2007). How common are the "common" neurologic disorders? *Neurology*, 68, 326-337.
- Holthoff, V. A., Beuthien-Baumann, B., Kalbe, E., Lüdecke, S., Lenz, O., Zündorf, G., Spirling, S., Schierz, K., Winiecki, P., Sorbi, S., & Herholz, K. (2005). Regional cerebral metabolism in early Alzheimer's disease with clinically significant apathy or depression. *Biological Psychiatry*, 57, 412-421.
- Isaacson, R. S., Ganzer, C. A., Hristov, H., Hackett, K., Caesar, E., Cohen, R., Kachko, R., Meléndez-Cabrero, J., Rahman, A., Scheyer, O., Hwang, M. J., Berkowitz, C., Hendrix, S., Mureb, M., Schelke, M. W., Mosconi, L., Seifan, A., & Krikorian, R. (2018). The clinical practice of risk reduction for Alzheimer's disease: a precision medicine approach. *Alzheimer's & Dementia*; 14 (12), 1663-1673.
- Lanctôt, K. L. (2017). Apathy associated with neurocognitive disorders: Recent progress and future directions. *The Journal of Alzheimer's Association*, 13 (1), 84-100.
- Lanctôt, K. L., Herrmann, N., Black, S. E., Ryan, M., Rothenburg, L. S., Liu, B. A., & Busto, U. E. (2008). Apathy associated with Alzheimer disease: use of dextroamphetamine challenge. *The American Journal of Geriatric Psychiatry*, 16 (7), 551-557.

Levy, R., & Dubois, B. (2006). Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. *Cerebral Cortex*, *16* (7), 916-928.

Lopez, O. L., Mackell, J. A., Sun, Y., Kassalow, L. M., Xu, Y., McRae, T., & Li, H. (2008). Effectiveness and safety of donepezil in Hispanic patients with Alzheimer's disease: a 12-week open-label study. *Journal of the National Medical Association*, *100* (11), 1350-1358.

Lueken, U., Seidl, U., Volker, L., Schweiger, E., Kruse, A., & Schroder, J. (2007). Development of a short version of the Apathy Evaluation Scale specifically adapted for demented nursing home residents. *The American Journal of Geriatric Psychiatry*, *15* (5), 376-385.

Lyketsos, C. G., Lopez, O., Jones, B., Fitzpatrick, A. L., Breitner, J., & Dekosky, S. (2002). Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: Results from cardiovascular health study. *JAMA*, *288*, 1475-1483.

Maci, T., Pira, F. L., Quattrocchi, G., Di Nuovo, S., Perciavalle, V., & Zappia, M. (2012). Physical and cognitive stimulation in Alzheimer disease. The GAIA project: a pilot study. *American Journal of Alzheimer's Disease and other Dementias*, *27* (2), 107-113.

Madsen, K. B. (1973). Theories of Motivation. In B. Wolman (Ed.), *Handbook of Psychology*. Prentice-Hall: New Jersey.

Manera, V., Abraham, S., Agüera-Ortiz, L., Bremond, F., David, R., Fairchild, K., Gros, A., Hanon, C., Husain, M., König, A., Lockwood, P. L., Pino, M., Radakovic, R., Robert, G., Slachevsky, A., Stella, F., Tribouillard, A., Trimarchi, P. D, Verhey, F., Yesavage, J., Zeghari, R., & Robert, P. (2020). Recommendations for the Nonpharmacological Treatment of Apathy in Brain Disorders. *The American Journal of Geriatric Psychiatry*, *28* (4), 410-420.

Manera, V., Petit, P. D., Derreumaux, A., Orvieto, I., Romagnoli, M., Lyttle, G., David, R., & Robert, P. H. (2015). "Kitchen and cooking", a serious game for mild cognitive impairment and Alzheimer's disease: a pilot study. *Frontiers in Aging Neuroscience*, *7*: 24.

Marin, R. S. (1991). Apathy: A neuropsychiatric syndrome. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 3 (3), 243-254.

Marin, R. S., Biedrzycki, R. C., & Firinciogullari, M. S. (1991). Reliability and Validity of the Apathy Evaluation Scale. *Psychiatry Research*, 38, 143-162.

Marin, R. S., Firinciogullari, S., & Biedrzycki, R. C. (1993). The sources of convergence between measures of apathy and depression. *Journal of Affective Disorders*, 28, 7-14.

Mitchell, R. A., Herrmann, N., & Lanctôt, K. L. (2011). The Role of Dopamine in Symptoms and Treatment of Apathy in Alzheimer's Disease. *CNS Neuroscience & Therapeutics*, 17 (5), 411-427.

Mohammad, D., Ellis, C., Rau, A., Rosenberg, P. B., Mintzer, J., Ruthirakuhan, M., Herrmann, N., & Lanctôt, K. L. (2018). Psychometric Properties of Apathy Scales in Dementia: A systematic review. *Journal of Alzheimer's Disease*, 66 (3), 1065-1082.

Monsch, A. U., Giannakopoulos, P., & GAL-SUI Study Group. (2004). Effects of galantamine on behavioural and psychological disturbances and caregiver burden in patients with Alzheimer's disease. *Current Medical Research and Opinion*, 20 (6), 931-938.

Moon, Y., Moon, W. J., Kim, H., & Han, S. H. (2014). Regional atrophy of the insular cortex is associated with neuropsychiatric symptoms in Alzheimer's disease patients. *European Neurology*, 71, 223-229.

Mori, T., Shimada, H., Shinotoh, H., Hirano, S., Eguchi, Y., Yamada, M., Fukuhara, R., Tanimukai, S., Zhang, M. R., Kuwabara, S., Ueno, S. I., & Suhara, T. (2014). Apathy correlates with prefrontal amyloid beta deposition in Alzheimer's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, 85, 449-455.

Moyle, W., Cooke, M., Beattie, E., Jones, C., Klein, B., Cook, G., & Gray, C. (2013). Exploring the effect of companion robots on emotional expression in older adults with dementia: a pilot randomized controlled trial. *Journal of Gerontological Nursing*, 39 (5), 46-53.

Munro, C. E., Donovan, N. J., Guercio, B. J., Wigman, S. E., Schultz, A. P., Amariglio, R. E., Rentz, D. M., Johnson, K. A., Sperling, R. A., & Marshall, G. A. (2015). Neuropsychiatric symptoms and functional connectivity in mild cognitive impairment. *Journal of Alzheimer's disease*, *46*, 727-735.

Padala, P. R., Frederick, P., & Subhash, C. B. (2005). Methylphenidate may treat apathy independent of depression. *The annals of Pharmacotherapy*, *39* (11), 1947-1949.

Padala, P. R., Padala, K. P., Lensing, S. Y., Ramirez, D., Monga, V., Bopp, M. M., Roberson, P. K., Dennis, R. A., Petty, F., Sullivan, D. H., & Burke, W. J. (2018). Methylphenidate for apathy in community-dwelling older veterans with mild Alzheimer's disease: A double-blind, randomized, placebo-controlled trial. *American Journal of Psychiatry*, *175*, 159-168.

Radakovic, R., Harley, C., Abrahams, S., & Starr, J. M. (2015). A systematic review of the validity and reliability of apathy scales in neurodegenerative conditions. *International Psychogeriatrics*, *27* (6), 903-923.

Raglio, A., Bellelli, G., Traficante, D., Gianotti, M., Ubezio, M. C., Villani, D., & Trabucchi M. (2008). Efficacy of music therapy in the treatment of behavioral and psychiatric symptoms of dementia. *Alzheimer Disease and Associated Disorders*, *22*, 158-162.

Rea, R., Carotenuto, A., Fasanaro, A. M., Traini, E., & Amenta, F. (2014). Apathy in Alzheimer's Disease: Any Effective Treatment? *The Scientific World Journal*, *2014*: 421385.

Rea, R., Carotenuto, A., Traini, E., Fasanaro, A. M., Manzo, V., & Amenta, F. (2015). Apathy Treatment in Alzheimer's Disease: Interim Results of the ASCOMALVA Trial. *Journal of Alzheimer's Disease*, *48* (2), 377-383.

Robert, P. H., Clairet, S., Benoit, M., Koutaich, J., Bertogliati, C., Tible, O., Caci, H., Borg, M., Brocker, P., & Bedoucha, P. (2002). The apathy inventory: assessment of apathy and awareness in Alzheimer's disease, Parkinson's disease and mild cognitive impairment. *International Journal of Geriatric Psychiatry*, *17* (12), 1099-1105.

Robert, P., Ferris, S., Gauthier, S., Ihl, R., Winblad, B., & Tennigkeit, F. (2010). Review of Alzheimer's disease scales: is there a need for a new multi-domain scale for therapy evaluation in medical practice? *Alzheimer's Research & Therapy*, 2, 24.

Robert, P., Lanctôt, K. L., Agüera-Ortiz, L., Aaltend, P., Bremonda, F., Defrancesco, M., Hanong, C., Davidh, R., Dubois, B., Dujardin, K., Husaink, M., Könige, A., Levyl, R., Mantuam, V., Meulienn, D., Millero, D., Moebius, H. J., Rasmussen, J., Robertr, G., Ruthirakuhanb, M., Stellas, F., Yesavaget, J., Zegharia, R., & Manera, V. (2018). Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018 international consensus group. *European Psychiatry*, 54, 71-76.

Robert, P., Onyike, C. U., Leentjens, A. F. G., Dujardin, K., Aalten, P., Starkstein, S., Verhey, F. R. J., Yessavage, J., Clement, J. P., Drapier, D., Bayle, F., Benoit, M., Boyer, P., Lorca, P. M., Thibaut, F., Gauthier, S., Grossberg, G., Vellas, B., & Byrne, J. (2009). Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *European Psychiatry*, 24, 98-104.

Ronsenberg, P. B., Lanctôt, K. L., Drye, L. T., Herrmann, N., Scherer, R. W., Bachman, D. L., Mintzer, J. E., & ADMET Investigators (2013). Safety and efficacy of methylphenidate for apathy in Alzheimer's disease: A randomized, placebo-controlled trial. *Journal of Clinical Psychiatry*, 74, 810-816.

Ruslan, L., Teerenstra, S., Smalbrugge, M., Vernooij-Dassen, M. J. F. J., Bohlmeijer, E. T., Gerritsen, D. L., & Koopmans, R. T. C. M. (2013). More insight into the concept of apathy: a multidisciplinary depression management program has different effects on depressive symptoms and apathy in nursing home. *International Psychogeriatric Association*, 25 (12), 1941-1952.

Samus, Q. M., Rosenblatt, A., Steele, C., Baker, A., Harper, M., Brandt, J., Mayer, L., Rabins, P. V., & Lyketsos, C. G. (2005). The association of neuropsychiatric symptoms and environment with quality of life in assisted living residents with dementia. *Gerontologist*, 45 (1), 19-26.

Schmidt, R., Baumhackl, U., Berek, K., Brücke, T., Kapeller, P., Lechner, A., Rainer, M., & Stögerer, E. M. (2010). Memantine for treatment of behavioural disturbances and psychotic symptoms in moderate to moderately severe Alzheimer dementia: a naturalistic study in outpatient services in Austria [in German]. *Neuropsychiatrie: Klinik, Diagnostik, Therapie und Rehabilitation: Organ der Gesellschaft Österreichischer Nervenärzte und Psychiater*, 24 (2), 125-131.

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., Iwatsubo, T., Jack, C. R. Jr, Kaye, J., Montine, T. J., Park, D. C., Reiman, E. M., Rowe, C. C., Siemers, E., Stern, Y., Yaffe, K., Carrillo, M. C., Thies, B., Morrison-Bogorad, M., Wagster, M. V., & Phelps, C. H. (2011). Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, 7 (3), 280-292.

Starkstein, S. E., & Brockman, S. (2018). The neuroimaging basis of apathy: Empirical findings and conceptual challenges. *Neuropsychologia*, 118, 48-53.

Starkstein, S. E., Jorge, R., & Mizrahi, R. (2006). The prevalence, clinical correlates and treatment of apathy in Alzheimer's disease. *European Journal of Psychiatry*, 20 (2), 96-106.

Starkstein, S. E., Jorge, R., Mizrahi, R., & Robinson, R. G. (2006). A prospective longitudinal study of apathy in Alzheimer's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, 77 (1), 8-11.

Starkstein, S. E., Mayberg, H. S., Preziosi, T. J., Andrezejewski, P., Leiguarda, R., & Robinson, R. G. (1992). Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 4 (2), 134-139.

Starkstein, S. E., Migliorelli, R., Manes, F., Teson, A., Petracca, G., Chemerinski, E., Sabe, L., & Leiguarda, R. (1995). The prevalence and clinical correlates of apathy and irritability in Alzheimer's disease. *European Journal of Neurology*, 2, 540-546.

Strauss, M. E., & Sperry, S. D. (2002). An informant-based assessment of apathy in Alzheimer disease. *Neuropsychology, Neuropsychiatry, and Behavioral Neurology*, 15 (3), 176-183.

Tekin, S., & Cummings, J. L. (2002). Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. *Journal of Psychosomatic Research*, 53 (2), 647-654.

Telenius, E. W., Engedal, K., & Bergland, A. (2015). Effect of a high intensity exercise program on physical function and mental health in nursing home residents with dementia: an assessor blinded randomized controlled trial. *PLoS One*, 10 (5): e0126102.

Theleritis, C., Siarkos, K., Politis, A. A., Katirtzoglou, E., & Politis, A. (2018). A systematic review of non-pharmacological treatments for apathy in dementia. *International Journal of Geriatric Psychiatry*, 33, 177-192.

Treusch, Y., Majic, T., Page, J., Gutzmann, H., Heinz, A., & Rapp, M. A. (2015). Apathy in nursing home residents with dementia: results from a cluster-randomized controlled trial. *European Psychiatry*, 30 (2), 251-257.

Tunnard, C., Whitehead, D., Hurt, C., Wahlund, L. O., Mecocci, P., Tsolaki, M., Vellas, B., Spenger, C., Kłoszewska, I., Soininen, H., Lovestone, S., & Simmons, A. (2011). Apathy and cortical atrophy in Alzheimer's disease. *International Journal of Geriatric Psychiatry*, 26, 741-748.

Valentí Soler, M., Agüera-Ortiz, L., Olazarán Rodríguez, J., Mendoza Rebolledo, C., Pérez Muñoz, A., Rodríguez Pérez, I., Osa Ruiz, E., Barrios Sánchez, A., Herrero Cano, V., Carrasco Chillón, L., Felipe Ruiz, S., López Alvarez, J., León Salas, B., Cañas Plaza, J. M., Martín Rico, F., Abella Dago, G., & Martínez Martín, P. (2015). Social robots in advanced dementia. *Frontiers in Aging Neuroscience*, 7: 133.

Waldemar, G., Gauthier, G., Jones, R., Wilkinson, D., Cummings, J., Lopez, O., Zhang, R., Xu, Y., Sun, Y., Knox, S., Richardson, S., & Mackellett, J. (2011). Effect of donepezil on emergence of apathy in mild to moderate Alzheimer's disease. *International Journal of Geriatric Psychiatry*, 26 (2), 150-157.

Winblad, B., Engedal, K., Soininen, H., Verhey, F., Waldemar, G., & Wimo, A. (1999, Aug 15-20). *Donepezil enhances global function, cognition and activities of daily living compared with placebo in a one-year, double-blind trial in patients with mild to moderate Alzheimer's disease* [Poster presentation]. *Ninth Congress of the International Psychogeriatric Association*, Vancouver, Canada.

Winblad, B., Frisoni, G. B., Frolich, L., Johannsen, P., Johansson, G., Kehoe, P., Lovestone, S., Olde-Rikkert, M., Reynish, E., Vasser, P. J., & Vellas, B. (2008). EADC (European Alzheimer Disease Consortium) recommendations for future Alzheimer disease research in Europe. *Journal of Nutrition, Health and Aging*, *12* (10), 683-684.

Zeisel, J., Reisberg, B., Whitehouse, P., Woods, R., & Verheul, A. (2016). Ecopsychosocial interventions in cognitive decline and dementia: a new terminology and a new paradigm. *American Journal of Alzheimer's Disease and other Dementias*, *31*, 502-507.

Zuchella, C., Sinforiani, E., Tamburin, S., Federico, A., Mantovani, E., Bernini, S., Casale, R., & Bartolo, M. (2018). The multidisciplinary approach to Alzheimer's disease and dementia. A narrative review of non-pharmacological treatment. *Frontiers in Neurology*, *9*: 1058.