Journal of Alzheimer's Disease xx (20xx) x–xx
DOI 10.3233/JAD-180311
IOS Press

Medical and Research Consent Decision-Making Capacity in Patients with Alzheimer's Disease: A Systematic Review

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Accepted 10 July 2018

Abstract. The capacity to make decisions is an important feature of daily living, which is closely linked to proper cognitive functioning. In conditions in which cognitive functioning becomes compromised, such as in Alzheimer's disease (AD), decision-making capacity can also get affected. Especially in AD, this has important implications, since over the course of the condition many important clinical decisions have to be made. For caregivers as well as physicians, it is sometimes difficult to determine how and when to intervene in the decision-making process. The aim of this systematic literature review was to identify studies that have evaluated medical and research consent decision-making capacity in patients with AD. Studies consistently show that decision-making capabilities are impaired in patients with AD. The cognitive and neuronal correlates of this process are, however, poorly studied. The few studies that investigated correlations have shown worse cognitive performance, mainly on the MMSE, to be related to poorer decision-making capacity. As most of these correlations have been performed in groups combining patients and controls, it remains unknown if these associations are disease specific. There is a need to study more systematically the decision-making process in relation to cognitive functioning and neural correlates to be able to develop a framework of decision-making capacity in AD, ultimately aiding clinicians and caregivers to understand and evaluate those capabilities in patients.

Keywords: Alzheimer's disease, cognition, decision-making, neuroimaging, systematic review

INTRODUCTION

Making decisions means that people choose between different options based on their own ideas or based on suggestions from others. These decisions can have direct consequences, such as what to eat or what to wear, can have direct consequences with impact in the future, including decisions about medical treatments, or they can be decisions in advance with only future consequences. Such decisions with future consequences usually depend on the integration of novel information received. Making an informed decision with future consequences thus

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depends on understanding spoken and written information provided, logical reasoning capacity about this novel information, appreciation of the (future) consequences of the decision, and the ability to communicate the decision. These 5 cases have been labeled as the legal standards in decision-making, and have been used extensively in decision making research [1]. However, what is or not a reasonable decision is ambiguous and subjective. Therefore, this legal standard is little used in decision-making instruments and studies [1, 2].

In turn, these 5 legal standards, and thus the decision-making process, depend heavily on cognitive functions. Novel information that forms the basis of the decision needs to be ordered and evaluated, which is associated with more frontally mediated executive functions, including planning, working memory, and manipulating information, but also with emotions and attitudes toward the subject [1, 3, 4]. It also depends on temporarily storing the novel information and creating new longer-term memories about the decision. Lastly, understanding written and verbal information and communicating with the caregiver or with medical personnel requires intact language skills [3, 4]. In patients with temporary or permanent cognitive deficits, however, such cognitive functions can be affected and therewith the decision-making process can become compromised [5]. Alzheimer's disease (AD) is one of the major diseases that affects memory and executive functions, whereas these patients need to make important medical, research-related, and sometimes also other major life-changing decisions [5].

Given the progressive loss of cognitive abilities in patients with AD [6], the decision-making process will slowly become affected until patients are unable to make informed decisions. However, as the progression of the disease continues multiple important decisions have to be made. These include, for example, decisions about beginning, continuing, or terminating medical treatment, about driving a car, cooking, doing one's own finances, and living independently. Gradually, caregivers will have to start making the decisions for the patients, which can lead to tensions between the patient and the caregiver, especially in combination with impaired insight in patients, which is often the case in AD [7]. Determining when patients are no longer capable of making informed decisions is very difficult. Several legal standards have been proposed as guidelines for proper medical decision-making capacity. The patient should be able to verbally express a choice, making a reasonable decision, appreciate the consequences of the choice, provide rational reasons for the decision, and understand the information that is relevant to the decision [2, 8]. Since establishing what constitutes a reasonable decision can be very subjective, this guideline is little used [1, 2]. Given the expected increase in the prevalence of AD in the coming decades [9], it is of vital importance to understand the decision-making process in this population in terms of expected decline in capabilities, the influence of cognitive decline over time, and the neuronal correlates involved.

Decision making capacity can be measured in many different ways, using different instruments that each aim to measure different fields of decision-making. For instance, the Iowa Gambling Task is one of the more traditional tests used to measure decision-making capacity under ambiguity. In this test, participants will receive some virtual money when choosing a card from one of the 4 decks, but occasionally will lose some money [10]. The amount of loss-cards differs per deck, leading to 'good' and 'bad' decks in terms of gaining money [10]. Although that is a classical task when it comes to measuring capacity to make beneficial choices under ambiguity, the results cannot be generalized to other fields of decision-making that are important in AD, such as medical and research consent decision-making capacity. An extensive systematic review of literature published between 1980 and 2004 identified 15 different instruments measuring medical decision-making capacity [11]. Those included the MacArthur Assessment Tool for Treatment (MacCAT-T) [12], Capacity to Consent to Treatment Instrument (CCTI) [13], and linguistic instruments for decision-making [8]. Although all were based on some legal standard, only 9 of the 15 instruments included all 4 above mentioned legal standards. In general, all instruments have been found reliable, most with an interrater reliability above 0.80, and they are all structured or semi-structured interviews. The association with cognitive functions showed mixed results, with only some studies finding correlations [11]. In this paper, 10 instruments that measure research consent capacity were discussed, including the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) and other vignettes methods [11]. They all had a reasonable reliability, but there is a variability in application. Some instruments have pre-specified information and response possibilities, whereas others are semi-structured interviews, such as the MacCAT-CR. Overall, the MacCAT-T and MacCAT-CR showed to

have the most empirical support, not ruling out the quality of other instruments.

Despite the importance of understanding changes in the medical and research consent decision-making process in AD, there seems to be little information available, which has not been reviewed systematically. Even less is known about the cognitive and neuronal correlates of the decision-making process in this disease. Therefore, the aim of this systematic literature review was to provide an overview of medical and research consent decision-making capacity in patients with AD, by performing a systematic search in different databases. When available, information on the neural and neuropsychological correlates of the decision-making process were summarized as well.

MATERIALS AND METHODS

This study was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines, as published by [14].

Literature search

A comprehensive systematic search of the literature was performed through PubMed, PsycInfo, and Web of Science for articles published between 01-01-2000 and 01-01-2018. The year 2000 was chosen 1) to only include contemporary research based on the most modern diagnostic criteria, and 2) because before this date neuroimaging analysis techniques were less developed and not widely available. The key search criteria were "decision making" in combination with "Alzheimer's disease". There were no *a priori* restrictions in the type of decision making categories, e.g., financial, medical, research consent, etc. The searches were restricted by using filters, selecting only papers reporting on experiments conducted in humans and written in English within the given time frame. After the removal of doubles and non-English literature, two authors (EvD and JF) independently performed the initial screening of abstract and title and the full-text assessment. In the case of a different decision on including or excluding an article, a third author (DCM) made the final decision.

Inclusion and exclusion criteria

Of the original articles that were retrieved from the searches, the title and abstract were screened after exclusion of non-English and double articles. For articles to be included, two main criteria needed to be fulfilled. First, articles had to report data of participants with AD and of a reference group (e.g., participants with mild cognitive impairment, participants without cognitive impairments, or caregivers and clinicians). Second, these articles had to quantify a form of decision making (e.g., medical, research, or financial decision making). Articles with a group of AD patients only, without a reference group, or which did not quantify decision making, were excluded from the screening, as were manuscripts that solely reported on caregiver or medical professional decision-making. Furthermore, book chapters, abstracts, reviews and meta-analyses were also excluded, as were articles on research conducted in animals. Of the included manuscripts, the full text was obtained and read. In this step, articles that were not about medical or research consent decision-making capacity were excluded. To be included, both medical and research consent decision-making capacity had to be measured in a standardized way, such as by use of a validated instrument. Lastly, the references were checked for other potentially eligible articles that were not retrieved through the database searches.

RESULTS

Literature search

The search retrieved a total of 1,609 published works between January 2000 and October 2017. The flowchart, which is prepared according to the PRISMA guidelines [14], is presented in Fig. 1 and shows the work process. After removal of 429 duplicates and articles that were not written in English, 1,180 articles were screened on their title and abstract, and inclusion/exclusion criteria were applied. Of these 1,180 articles, 39 articles were about a form of decision making in AD. After assessing the full-text articles, 19 were additionally excluded as they covered forms of decision-making other than medical or research-consent capacity decision-making. Additionally, checking the reference lists yielded 2 more manuscripts. In total, 22 articles were included in this review. After the full-text assessment the authors disagreed on 3 articles, one about semantic decision-making capacity, one about recall of features of previously reached decisions, and the last about information gathering the reach a decision. All three were excluded by the third author. Thirteen articles

were about medical decision-making capacity and 9 were on research consent capacity. The studies varied widely in terms of sample size. Some studies were small, whereas other studies included up to 200 patients (Table 1). Several studies also included a group of subjects with mild cognitive impairment (Table 1). The age-range also varied widely, but all studies included patients above the age of 65 years, although control groups were sometimes younger than 65 years.

Medical decision-making

The 13 articles that assessed medical decision-making capacity in AD are summarized in Table 1 [2, 15–26]. AD was diagnosed based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). Disease severity was based on evaluation by the Clinical Dementia Rating (CDR) or Dementia Rating Scale (DRS) in 7 articles and 4 studies used the Mini-Mental State Examination (MMSE). In two articles, disease severity was not specified, but these articles reported MMSE scores. The studies that have assessed medical decision-making in AD have used a variety of measurements to study this capacity. The most commonly used were the CCTI [2, 15, 17, 19, 20], and the MacCAT-T [18, 21, 23, 24]. These instruments were based on the legal standards previously formulated. For the other 4 articles, different approaches were used. A total of 10 studies have included healthy control groups to contrast patient performance [2, 15, 17, 19–22, 24–26]. The other 3 studies have included caregivers as a comparison group [16, 18, 23], and 1 also included referring physicians [23]. Thus, all studies can be considered case-control studies. Of the 13 studies, 5 also included individuals with mild cognitive impairment [2, 20, 22, 24, 26], and one included both participants with mild cognitive impairment and AD without specifying participants' status [23], allowing for a comparison of medical decision-making capacity along the continuum of compromised cognitive functioning. One study included patients with AD and Parkinson's disease next to healthy controls [17]. In all studies, decision-making capacity has been found to be lower in patients than in controls or subjects with mild cognitive impairment. This was a general decline on virtually all legal standards, including verbally expressing a choice, making a reasonable decision, appreciating the consequences of the choice, providing rational reasons for the decision, and understanding the information that is relevant to the decision. Ten of the 13 studies included 50 patients or less with AD and one did not differentiate between mild cognitive impairment and AD. Thus, only 2 articles had sufficient sample size to differentiate scores according to dementia severity. The article by Hirschman and colleagues did not directly assess the patients decision-making capabilities, but did show that in patients with moderate AD (i.e., MMSE < 20), patients' involvement in the medical decision-making process declined [16]. The other study included only patients with mild AD [24]. In studies that have included subjects with mild cognitive impairment, results show that these participants usually have decision-making scores in between AD patients and controls on all legal standards [2, 20, 22–26]. This shows that decision-making capacity gradually decreases with increasing impairments in functionality and cognitive performance and that it should not be considered an all-or-nothing principle.

The majority of the studies, 8 in total, have included neuropsychological tests other than the MMSE, but only 5 have performed correlation analyses between neuropsychological outcomes and medical decision-making capacity [2, 15, 21, 25, 26]. Unfortunately, these correlations were usually performed in the whole sample and thus are not specific to AD. The general pattern is that better MMSE scores, episodic/working memory, executive functions, and linguistic abilities are related to better decision-making capacity. These are functions on which the legal standards rely, making these correlations intuitive.

One study performed a longitudinal assessment, in which declining decision-making capacity was demonstrated over the course of 2 years in AD patients compared with controls [19].

Three studies have included caregivers and/or referring physicians, showing that patients commonly have a higher preference of participation in the decision-making process than caregivers or physicians are willing to grant them [16, 18, 23], which may generate frustration and problems in the patient-caregiver/physician relationship.

Research consent capacity

All of the 9 articles that have assessed the capacity to give informed research consent have used the MacCAT-CR (clinical research), which is an adaptation of the MacCAT-T, specifically to determine

Table 1
List of articles included in the systematic review ordered by decision-making category

	N	Age	Diagnostic criteria	Disease stage	MMSE	Materials	Brief conclusion
Medical decision making							
Earnst et al., [15]	21 AD / 10 HC	71.3 ± 8.1 / 67.1 ± 6.5	NINCDS-ADRDA	MMSE: ≥20 (mild), 10–20 (moderate)	AD: 19.1 ± 4.8 / HC: 29.3 ± 1.1	CCTI / MMSE / neuropsychology	Poorer decision-making competency was related to various neuropsychological functions.
Hirschman et al., [16]	77 AD-caregiver dyads	74.2 ± 8.9 / 59.9 ± 12.2	NINCDS-ADRDA	MMSE: ≥20 (mild), 12–19 (moderate), <12 (severe)	AD: 23.0 ± 4.8	5 statement question / MMSE / SCB	MMSE < 20, older age, and mounting caregiver burden resulted in more caregiver dominated decision making.
Griffith et al., [17]	22 AD / 17 PD / 18 HC	70.2 ± 8.3 / 74.2 ± 7.6 / 67.2 ± 6.6	NINCDS-ADRDA	CDR / DRS	–	CCTI / DRS	AD showed impaired consent ability of understanding the medical treatment situation and choices relative to the other groups.
Karlawish et al., [18]	48 AD / 102 caregivers	78.7 ± 7.2 / 61.4 ± 13.2	NINCDS-ADRDA	MMSE: ≥11 (very mild to moderate)	AD: 20.4 ± 4.8 / Caregivers: 28.9 ± 1.8	MacCAT-T / MMSE / Caregiver interview	Patients with moderate AD and lack of awareness have impairments in the ability to make AD treatment decisions.
Huthwaite et al., [19]	20 AD / 15 HC	68.7 ± 8.6 / 68.2 ± 6.2	NINCDS-ADRDA	CDR 0.5 or 1.0	AD: 24.3 ± 2.5 / HC: 29.5 ± 0.6	CCTI / MMSE / DRS / CDR / GDS	AD has impaired medical decision making at baseline, which deteriorates over 2 years in appreciation, reasoning, and understanding.
Okonkwo et al., [20]	31 AD / 60 MCI / 56 HC	74.5 ± 8.6 / 68.1 ± 6.8 / 64.6 ± 8.5	NINCDS-ADRDA / Petersen/Mayo (MCI)	CDR / DRS	AD: 24.8 ± 3.0 / MCI: 28.4 ± 1.5 / HC: 29.6 ± 0.8	CCTI / MMSE / DRS / CDR/ GDS neuropsychology	Significant impairments in medical decision making in MCI, but AD patients performed poorest on these measures.

(Continued)

Table 1
(*Continued*)

	N	Age	Diagnostic criteria	Disease stage	MMSE	Materials	Brief conclusion
Okonkwo et al., [2]	31 AD / 60 MCI / 56 HC	74.5 ± 8.6 / 68.1 ± 6.8 / 64.6 ± 8.5	NINCDS-ADRDA / Petersen/Mayo (MCI)	CDR / DRS	AD: 24.8 ± 3.0 / MCI: 28.4 ± 1.5 / HC: 29.6 ± 0.8	CCTI / MMSE / DRS / CDR/ GDS neuropsychology	In AD, executive functions and processing speed predicted medical decision making. In MCI this was executive functions and short-term verbal memory.
Lui et al., [21]	50 AD / 42 HC	80.0 ± 7.0 / 75.0 ± 7.0	NINCDS-ADRDA	CDR 0.5 or 1.0	AD: 22.0 ± 5.0 / HC: 28.0 ± 2.0	MacCAT-T / MMSE / CDR / neuropsychology	AD had lower decision making capacity, which correlated with MMSE, total ADAS-cog and category fluency performance.
Zamarian et al., [22]	18 AD / 18 / MCI / 18 HC	77.8 ± 4.8 / 75.4 ± 4.9 / 75.4 ± 6.4	NINCDS-ADRDA / Petersen/Mayo (MCI)	Not specified, but MMSE included	AD: 20.9 ± 3.2 / MCI: 26.5 ± 2.0 / HC: 28.1 ± 1.0	Framing tasks / MMSE / HADS-D / neuropsychology	Health-related decision-making may be relevantly biased by positive and negative formulations in conveying the information.
Hamann et al., [23]	100 AD/MCI / 99 relatives / 93 referring physicians	72.3 ± 8.3 / 65.7 ± 11.6 / –	NINCDS-ADRDA / IWG-MCI	CDR 0.5 or 1.0	AD/MCI: 23.7 ± 3.2	MacCAT-T / MMSE / API	High participation preference in AD/MCI, but relatives and physicians poorly predicted this and preferred to attribute less decision-making power to patients.
Lui et al., [24]	95 AD / 99 MCI / 97 HC	82.3 ± 6.6 / 78.2 ± 7.0 / 74.2 ± 6.5	NINCDS-ADRDA / Petersen/Mayo (MCI)	CDR / DRS	AD: 19.5 ± 2.7 / MCI: 25.3 ± 2.5 / HC: 26.6 ± 2.4	MacCAT-T / ACED / MMSE / neuropsychology	Abilities related to decisions on medication management are impaired in AD and MCI relative to HC.
Tallberg et al., [25]	20 AD / 22 MCI / 37 HC	72.4 ± 7.7 / 68.7 ± 8.7 / 68.5 ± 6.6	NINCDS-ADRDA / Petersen/Mayo (MCI)	Not specified, but MMSE included	AD: 24.1 ± 3.3 / MCI: 26.6 ± 2.4 / HC: 29.1 ± 1.0	LIMD / MMSE / neuropsychology	AD patients performed poorest, and communicative ability has an impact on the competence for autonomous decision-making.

Stormoen et al., [26]	20 AD / 21 MCI / 33 HC	72.5 ± 7.6 / 69.1 ± 8.8 / 69.2 ± 6.5	NINCDS-ADRDA / Petersen/Mayo (MCI)	MMSE: ≥20	AD: 24.1 ± 3.6 / MCI: 26.6 ± 2.4 / HC: 29.1 ± 1.0	LIMD / MMSE / neuropsychology	Lower LIMD scores were predicted poorer verbal and working memory.
Research consent capacity							
Kim et al., [27]	37 AD / 15 HC	78.7 ± 5.8 / 75.5 ± 4.7	NINCDS-ADRDA	MMSE: 16–28	AD: 22.9 ± 3.8 / HC: 28.9 ± 1.1	MacCAT-CR / MMSE	Up to 84% of the patients were rated as incapable on at least 1 consent capability. This was 62% based on expert judgement.
Karlawish et al., [28]	15 AD / 15 caregivers / 15 HC	72.0 ± 8.1 / 64.9 ± 12.4 / 77.0 ± 4.5	NINCDS-ADRDA	MMSE: 25–30 (very mild), 20–24 (mild), 12–19 (moderate)	AD: 21.3 ± 5.4 / caregivers: 29.3 ± 1.2; HC: 29.0 ± 1.8	MacCAT-CR / MMSE /	AD had lower scores and many were incompetent to make decisions, whereas a minority of patients was deemed competent.
Kim et al., [29]	34 AD / 14 HC	78.5 ± 6.0 / 75.3 ± 4.9	NINCDS-ADRDA	MMSE: 16–28	AD: 23.3 ± 3.7 / HC: 29.0 ± 1.7	MacCAT-CR / MMSE / 4 research vignettes with varying risk/benefit	No differences in willingness to participate in the hypothetical research presented by the vignettes. Poorer MacCAT-CR scores tended to predict lower willingness in AD.
Palmer et al., [30]	30 AD / 35 schizophrenia / 36 T2DM	77.0 ± 6.6 / 65.7 ± 5.2 / 70.9 ± 6.2	Not specified	MMSE: ≥18	AD: 23.0 ± 3.0 / schizophrenia: 27.1 ± 2.1 / T2DM: 28.2 ± 1.8	MacCAT-CR / 3-item questionnaire / MMSE	AD performed poorest, then schizophrenia and T2DM patients, with large heterogeneity in the groups. A lower MMSE score was the best predictor for lower decision-making capacity in all groups.
Karlawish et al., [31]	59 AD / 60 relatives	–	NINCDS-ADRDA	MMSE: 12–26	AD: between 12 and 26	MacCAT-CR / MMSE	The MacCAT-CR understanding scale can help judging about consent capacity.

(Continued)

Table 1
(*Continued*)

	N	Age	Diagnostic criteria	Disease stage	MMSE	Materials	Brief conclusion
Karlawish et al., [32]	59 AD / 60 relatives	72.2 ± 9.2 / 64.3 ± 12.1	NINCDS-ADRDA	MMSE: 12–26	–	MacCAT-CR / MMSE / 4 questions	Patients participated in the decision to participate in the study and proxy consent was deemed appropriate.
Rubright et al., [33]	40 AD-1 / 40 AD-2 / 30 HC	76.5 ± 6.6 / 74.4 ± 9.5 / 78.1 ± 6.2	NINCDS-ADRDA	MMSE: 18–27	AD-1 : 23.6 ± 2.9 / AD-2 : 23.3 ± 2.7 / HC: 29.5 ± 0.9	MacCAT-CR / MMSE / Informed consent with or without memory / organization aid	The intervention group (AD-2; informed consent with aids) were more likely to be judged competent to consent than the AD-1 group. MacCAT-CR understanding scores benefited the most from the intervention.
Kim et al., [34]	188 AD	75.9 ± 8.9	NINCDS-ADRDA	MMSE: ≥12	20.8 ± 5.0	MacCAT-CR low/high risk scenario / MMSE / CAPA	A substantial proportion of AD patients deemed incapable of consenting to the low/high risk scenario was capable of appointing a proxy.
Palmer et al., [35]	77 AD	74.8 ± 9.8	NINCDS-ADRDA	MMSE / DRS	20.5 ± 5.1	MacCAT-CR / MMSE / DRS / CAPA	60% was deemed capable appointing a proxy, 43% consenting to the low risk and 16% to the high-risk research scenario.

ACED: Assessment of Capacity for Everyday Decision-Making; ADAS-cog: Alzheimer Disease Assessment Scale-Cognitive subscale; AD: Alzheimer's disease; API: Autonomy Preference Index; CAPA: Capacity to Appoint a Proxy Assessment; CCTI: Capacity to Consent to Treatment Instrument; CDR: Clinical Dementia Rating Scale; DRS: Dementia Rating Scale; HADS-D: Hospital Anxiety and Depression Scale; HC: healthy controls; IWG-MCI: International Working Group – Mild Cognitive Impairment; LIMD: Linguistic Instrument for Medical Decision-making; MacCAT-T/CR: MacArthur Competency Assessment Tool for Treatment/Clinical Research; MCI: Mild Cognitive Impairment; MMSE: Mini Mental State Examination; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association; PD: Parkinson's disease; T2DM: type 2 diabetes mellitus.

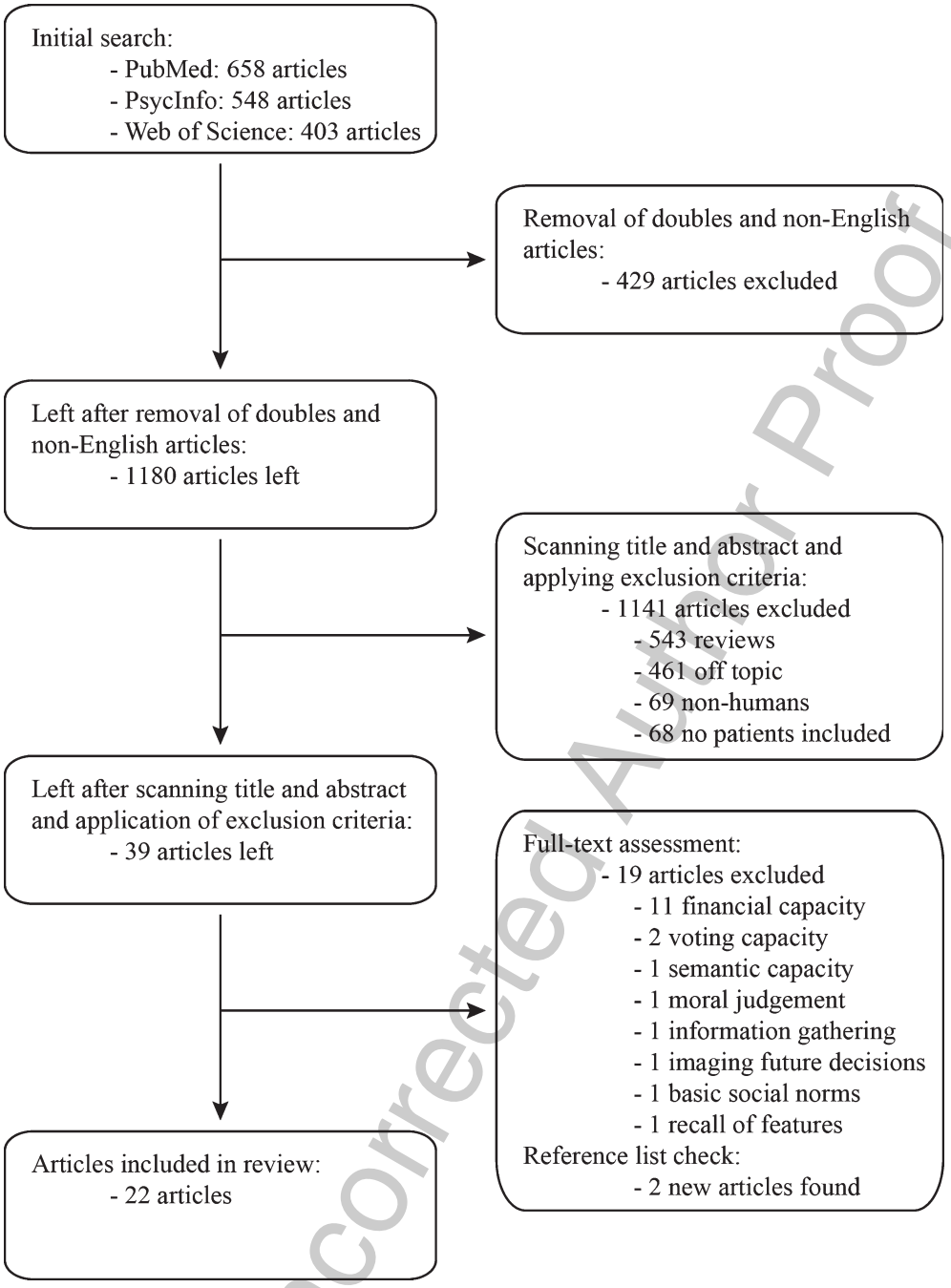

Fig. 1. Flow chart of the systematic literature review process.

research related decision-making capacity [27–35]. One study did not specify diagnostic criteria, whereas all other studies used the NINCDS-ADRDA criteria. All studies used the MMSE to determine disease severity and 1 additionally used the DRS. Without an exception, all studies found that patients with AD scored on average lower on the MacCAT-CR than control subjects did. However, the variety in performance was large within patients, with sometimes a substantial minority of the AD patients having scores comparable to those of control participants. Many of these patients were subsequently deemed capable of

consenting to research participation. There was also considerable variation between studies. Upon closer evaluation, the studies have included patients with different disease stages. This indicates that, comparable to medical decision-making capacity, capacity to give research consent is best represented as a continuum, and is not an all-or-nothing process. This was further underscored by a study by Palmer and colleagues. They showed that patients with AD are better capable to consent to low risk research than to high risk research [35]. That is, as studies have a higher risk for the patient these projects are usually more complex, require more information exchange and thus depend more heavily on cognitive functions than lower risk studies do. Moreover, the only study assessing the correlation between MMSE score and research consent capacity showed that lower MMSE scores (i.e., worse cognitive performance) was related to poorer capacity [30]. Furthermore, appointing a proxy to decide for the patient was preserved in the majority of patients in this study. In one study, two groups of AD patients were included. One group received small memory and organization aids next to the regular informed consent form, the other did not. The results showed that these aids significantly improved the capability to make informed research decisions [33].

DISCUSSION

In this systematic literature review, papers were reviewed that have assessed medical and research consent decision-making capacity in patients with AD. The results show that the 22 articles that adhered to our inclusion criteria assessed decision-making capabilities in many different ways. In general, the results show that decision-making capacity is diminished in patients with AD when compared to control subjects. However, especially for research consent capacity, a sometimes substantial minority of patients had scores comparable to those of controls and were deemed capable of making informed decisions. Some studies have tried to correlate decision-making capacity to neuropsychological functioning, but all have done so in all participants and not specifically in the AD patients alone. Poorer decision-making capabilities were related to lower MMSE scores, lower cognitive capabilities, and older age. No studies have applied neuroimaging methods in order to evaluate the cerebral correlates of decision-making.

Instruments used to evaluate decision-making capacity

The instruments that have been used to evaluate decision-making capacity in the studies vary widely between the different categories, but also within some categories. Some studies that have assessed medical decision-making capacity have been using the MacCAT-T. This list has 4 subscales: the understanding, appreciation, reasoning, and expression scales. These scales are based on the legal standards that have been formulated, that patients need to be able to verbally communicate, appreciate the consequences of their decisions, understand the written and spoken information and logically reason about the novel information [1]. The MacCAT-T was used in 4 of the 13 included studies on medical decision-making capabilities. Five of the 13 studies have used the CCTI. This instrument is somewhat similar to the MacCAT-T in that it also measures the four legal standards. Both questionnaires are based on vignettes, short stories of a medical situation in which a decision needs to be made. After being told the story, the patients are then asked several questions that assess the legal standards. Other studies have used linguistic instruments for medical decision-making or regular vignettes, but all studies and questionnaires have in common that the try to assess the capabilities of patients to come to logical conclusions regarding the legal standards. All included studies on research consent capacity have used the MacCAT-CR (clinical research). These studies, on the other hand, have included patients within a wide range of disease severity, which makes it somewhat difficult to compare the results between studies.

There are challenges related to the use of these instruments [36]. First, standardization or tailoring of the vignettes used. Some instruments, such as the MacCAT-T and MacCAT-CR allow tailoring of the vignettes [11, 36, 37]. Although this can be considered an advantage as various disease specific vignettes can be created, it also raises concern about the reliability and validity of the vignettes. Second, the definition of standards, such as reasoning or understanding, can defer between instruments and as such can measure slightly different concepts [11, 38]. The MacCAT instruments are the most widely used and adopted in AD research and provide a good flexibility to be adapted to the specific requirements of research in this type of dementia [11, 36]. Downsides of this instrument that should be incorporated into the choice of instrument include the lack of validation

and information about the psychometric properties of each adapted version and the extensive training that professionals need to properly use the instruments. Also, for specific situations other lists might be more appropriate. More information on properties of many used instruments to measure decision-making capacity can be found in other reviews [11, 36, 38].

Clinically significant differences

Without exception, all studies show that patients with AD have lower decision-making capacities. The studies that have considered disease severity show that patients with mild cognitive impairment and mild AD have higher scores than those in the moderate to severe stages [2, 16, 20–25]. However, none of the instruments provides a clinical cut-off score that physicians could use to determine if a patient has sufficient decision-making capabilities or not. One can imagine that for a high-risk treatment or study one needs a higher level of decision-making capabilities than for a low(er)-risk study or treatment [11]. Although control data (means and standard deviations) provide a potential comparison value, setting a cut-off would make the instrument less flexible and useful. Not having a pre-defined cut-off is also in line with the thought that the capability to make decisions is not an all-or-nothing process, although it may complicate a physician's or caregiver's ability to evaluate and weigh the input of the patient. Ultimately, even with the help of the current standardized instruments, whether or not a patient is capable of making decisions remains a matter of clinical judgement.

Cognitive correlates of decision-making capacity

In order to fully understand the decision-making process in patients with AD, it is important to investigate which cognitive functions are relevant in this context. Several studies that have evaluated medical decision-making capacity have also incorporated neuropsychological tests and performed correlation analyses. Earnest and colleagues showed in their article that poorer short-term memory, semantic knowledge and simple reasoning were related to higher levels of medical decision-making incompetence [15], whereas Okonkwo et al., showed that measures of executive functioning and processing speed were related to medical decision-making capabilities [2]. Other studies have found medical decision-making capacity to be related to the total score of the Alzheimer's Disease Assessment Scale – Cognition (ADAS-Cog), category fluency, and executive functions [21, 24], and to episodic and working memory, processing speed, and verbal knowledge [25, 26]. Studies on consent capacity to research have not included neuropsychological tests.

These differences in cognitive correlates of decision-making capacity in patients with AD could have various different reasons. First, the neuropsychological tests that have been used in these studies varied widely. Although different tests may be considered to measure attention, memory, or any other cognitive function, they always measure slight different constructs, and never one construct alone [39]. This will automatically lead to differences in correlations. Another reason is the use of different instruments to evaluate decision-making. As each instrument is different from the other instrument, it will generate different correlations. Lastly, studies have used different patient populations, with different age categories and different stages of AD. This all may explain the differences between studies in correlations and call for meta-analyses to identify shared neuropsychological constructs of decision-making in AD. However, a meta-analysis on the 4 studies that have incorporated correlations is not feasible. Because of this heterogeneity it is difficult to identify main cognitive contributors that affect decision-making capabilities.

Another question is whether or not cognitive test could be used to measure decision-making capacity. There are tests that seem correlated with various aspects of decision-making capacity. However, besides a correlation, it is important that the function that cognitive tests assess has a close relationship at a conceptual level with the standard of competence that it is aimed to measure [37]. We do not feel that any of the currently available cognitive tests bare close enough resemblance to any standard of competence to substitute instruments specifically designed to measure decision-making capacities. Hence, cognitive tests have low validity when it comes to these competences [11], and it would be better to incorporate a decision-making instrument into clinical care, than to rely on cognitive tests.

Aids to improve the decision-making process

There is a correlation between declining cognitive functions and decision-making capacity, although it is not clear whether this correlation is also present in AD patients alone. This raises the question whether or not aids that circumvent the cognitive difficulties

help improve the decision-making process. Of the reviewed literature, there was 1 study that used small memory and organizational aids and measured research consent decision-making capacity in patients who used and did not used these aids [33]. Due to the use of aids, the number of patients deemed capable of making an informed decision by themselves increased from 7 (out of 40) to 19 (out of 40), demonstrating a clear advantage when using these techniques. It might also suggest that the decision-making capacity in itself is not affected, but rather the cognitive functions it relies on. More research is needed to study the usefulness of aids in more complex decision-making processes and also in patients with moderate to severe ADsease. Such research should also consider the usability in clinical practice, where physicians generally have limited time to attend patients.

Neural correlates of decision-making capabilities

None of the studies included in this systematic review have incorporated neuroimaging techniques to identify the neuronal underpinnings of the medical or research consent decision-making process in patients with AD. However, there are some studies available that have assessed other aspects of decision-making capacity in relation to neuroimaging that are worth mentioning, because these capacities could rely on similar brain regions as medical decision-making and research consent capacity do. In one study, Rinne and colleagues used ^{15}O PET to measure cerebral perfusion in 9 patients with AD and 8 healthy controls performing a semantic decision-making task consisting of 3 conditions [40]. Compared to the baseline condition, both groups activated the left frontal lobe and the right cerebellum. The patients with AD, however, also activated parts of the midbrain, left cerebellum, right occipital cortex, and other parts of the left frontal region [40], showing that the AD brain is less efficient. Lebreton and colleagues used an intertemporal choice task during functional MRI scanning and also measured grey matter volume [41]. The results of this study showed that the hippocampus, both activation and volume, plays a crucial role in imagination of future reward and with that in the decision-making process, as that partly depends on imagination of future outcomes. The last study to utilize MRI in combination with decision-making is the study by Kloeters and colleagues [42]. They used the Iowa Gambling Test and correlated the outcomes of this test to gray matter volume indices calculated using voxel-based morphometry. In patients with AD, atrophy of the temporal and parietal lobes was related to poorer gambling performance, which resembles the hallmark of brain atrophy in this disease. Combined, these studies seem to suggest a pivotal role for the frontal, temporal, and parietal regions in various tasks about decision-making. Future research should focus on determining the neuronal correlates of medical decision-making and research consent capacity.

Limitations

Some limitations are worth mentioning. First, as mentioned above, there is a large variability in instruments that different studies have used to assess decision-making capacity. Some instruments, such as the MacCAT questionnaires, seem to have high ecological validity. Comparing studies using a variety of instruments can be difficult and should be performed with caution. Another limitation of the current literature is that the studies included in this review do not differentiate between the different stages of AD. Differentiating is important as it might be expected that patients in the earlier stages of the disease have better decision-making capabilities than patients in the later stages do. Thus that decision-making capacity is not an all-or-nothing principle, but rather a continuum along which patients move. The studies including mild cognitive impairment subjects have shown intermediate scores for this group, and positive associations were found between MMSE/cognition and decision-making capacity, indeed suggesting a gradual decline. However, without analyzing capacity in patients in different stages of the disease, preferably through longitudinal follow-up, this cannot be established. Such distinctions are important when one aims to aid clinicians and caregivers in determining how much weight they should give a patient's opinion and wishes. Sample size seems to be another limitation of the studies reviewed. Many studies have relatively small sample sizes, especially the studies that have also included measures of cognition. In order to be able to determine meaningful correlations a relatively large sample size is needed, i.e., $n = 30$ or higher. The smaller sample sizes make it more difficult to assess and value such correlations.

Conclusions and future directions

Decision-making capacity is affected by AD and seems to worsen with disease progression. Relatively little attention has been awarded to the relationship

between decision-making capacities and neurocognitive functions. Those studies that have done so show correlations between decision-making and a wide variety of cognitive domains and sub-tests, including executive functions and verbal memory. Neuronal correlates of medical and research consent decision-making capacity are unknown, but studies in AD testing other forms of decision-making capacity suggest temporal, frontal and parietal involvement. Future studies should focus on the crossroad between decision-making capabilities, neurocognitive functioning and brain structure and functioning in sufficient sample sizes. These studies will help building a theoretical framework of decision-making in patients with AD. It is important to understand how patients come to their decisions, what cognitive functions they rely on and how brain atrophy or alterations in the brain's functional connections affect the entire process. This will help clinicians and the caregivers to better understand patients' decisions and may help to make a more informed decision about when to assist in or entirely take over the decision-making process. The ultimate goal is to ease the transition from independence of the patients to dependence on caregiver and physician, a process that is often met with great hostility.

ACKNOWLEDGMENTS

EvD and JF performed the literature search and separately performed the selection. EvD wrote the manuscript. DCM supervised the literature review and decided on articles on which EvD and JF made different decisions. All authors have made critical revisions to the manuscript. The authors declare no conflict of interest regarding this manuscript. EvD was supported by a personal grant received from the Brazilian National Counsel for Scientific and Technological Development (CNPq). The sponsor was not involved in the design of the study, writing the manuscript, or in the decision to publish.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/18-0311r2).

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