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Medical decision-making in Alzheimer's disease

A linguistic approach

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Picture on front page: “Decision-making a summer day on Österlen”, Torgny Wennström, 2018. Rights to use the image have been obtained from both the photographer and the person who is the subject of the image.

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THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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ABSTRACT

Objectives. To explore medical decision-making capacity (MDC) for research participation, in patients with Alzheimer's disease, using a linguistic approach and including comparable groups.

Materials and Methods. The thesis comprises five studies, based upon two separate data collections from three groups of elderly with varied cognitive function: Alzheimer' disease (AD; dataset 1: n= 20 and dataset II: n=21), mild cognitive impairment (MCI; dataset 1: n= 22 and dataset II: n=17) and healthy controls (HC; dataset 1: n= 37 and dataset II: n=17). Studies I-III and V are primarily quantitative studies investigating medical decision-making in research as measured by two different linguistic instruments (LIMD and KIMB) and patients' self-estimation by visual analogue scale (VAS), correlated to demographic factors and cognitive and linguistic abilities. Study IV is a qualitative study, analysing the sense-making of selected utterances by conducting semantic analysis.

Results. *Study I:* A Swedish Linguistic Instrument of Medical-Decision making (LIMD) was developed and demonstrated good psychometric features. *Study II:* Multiple factors are involved in MDC (assessed by LIMD) such as overall verbal knowledge, episodic memory, cognitive speed and working memory. LIMD total score showed highest correlation to the single test Reading Speed (which assesses both rapid reading, inference and understanding). *Study III:* AD patients showed high acceptance to participate in a high-risk trial as well as reduced capability to notify risk. *Study IV:* Irregularly placed, and sporadically used linguistic signs for time, place and person may lead to difficulties interpreting and understanding the meaning of verbal utterances. *Study V:* A brief Swedish reading tool (KIMB-t) was developed to detect patients with reduced capacity to give informed consent.

Conclusions. The linguistic and cognitive functions associated with comprehending, evaluating and communicating a choice, may affect MDC, referred to as the capacity to make decisions in research settings e.g. to give informed consent. Patients, already with mild AD are likely to have reduced capacity to identify and estimate possible risks as well as difficulties in reasoning and to communicate a choice in a clear and logical manner. Evaluating different aspects associated to medical decision-making from a linguistic perspective, in groups with varied cognitive function, contributes to further knowledge in the field. The results indicate that a linguistic approach can contribute not only to further analysis of MDC, but also to a better understanding in the communication with patients with impaired cognitive function, during the decision-making process.

SAMMANFATTNING

Syfte. Undersöka medicinsk beslutsförmåga, definierad som förmågan att fatta beslut vid forskning t.ex. ge informerat samtycke, utifrån ett språkligt perspektiv, hos patienter med lindrig Alzheimers sjukdom, och jämförande grupper.

Material och metoder. Avhandlingen omfattar totalt fem delstudier och är baserad på två separata datainsamlingar som inkluderar tre grupper av äldre med varierad kognitiv funktion: Patienter med lindrig Alzheimersjukdom (AD; datainsamling I: n = 20; och datainsamling II: n = 21), Lindrig kognitiv störning (MCI; datainsamling I: n = 22 och datainsamling II: n = 17) och friska kontroller (HC; datainsamling I: n = 37 och datainsamling II: n = 17). Studie I-III och V är huvudsakligen kvantitativa studier som undersöker beslutsförmåga och resonemang mha olika mätinstrument, korrelerade med demografiska faktorer samt kognitiva och språkliga test. Studie IV redovisas som en kvalitativ studie, vilken analyserar begripligheten i utvalda verbala resonemang mha semantisk analys.

Resultat. *Studie I:* Ett svenskt lingvistiskt test av medicinsk beslutsförmåga, LIMD har utvecklats med goda psykometriska egenskaper. *Studie II:* Flera faktorer är involverade i medicinsk beslutsförmåga (mätt med LIMD) t.ex. verbal kunskap, episodminne, snabbhet och arbetsminne. LIMDs totalpoäng visade starkast samband den enskilda uppgiften: ”Läshastighet”, som mäter både läshastighet och förståelse av text. *Studie III:* AD patienter förefaller ha hög acceptans att delta i hög-riskstudier samt reducerad förmåga att skatta risk. *Studie IV:* Avvikande och sporadiskt använda språkliga markörer för tid, plats och person kan leda till svårigheter att tolka och förstå begripligheten i verbala uttalanden. *Studie V:* En kort svensk läsuppgift (KIMB-t) har utvecklats för att upptäcka patienter med risk för reducerad förmåga att ge informerat samtycke.

Slutsatser. Språkliga och kognitiva förmågor associerade till att förstå, utvärdera och att kommunicera ett val, kan påverka förmågan att fatta beslut vid forskning, t.ex. ge informerat samtycke som är baseras på skriven information. Redan vid lindrig AD kan patienter riskera att ha en påverkad beslutsförmåga. De förefaller också ha nedsatt förmåga att identifiera och uppskatta eventuella risker och att motivera och kommunicera ett beslut på ett tydligt och logiskt sätt. Resultaten indikerar att ett språkligt perspektiv kan bidra, inte bara till analys av MDC, men också till bättre förståelse i kommunikationen med patienter med nedsatt kognitiv funktion, under beslutsprocessen.

PROLOGUE

I have always had a genuine interest in the human mind and communication. During previous work in elderly home care, I developed a certain interest in the elderly as a vulnerable group, enriched with experiences and knowledge from the past. Unfortunately, some have difficulties communicating their stories and their desires due to language disorders, memory loss or other cognitive impairments caused by neurodegenerative diseases. In addition, the interlocutor may have more or less capability (e.g. time or interest) to capture and interpret the meaning of their utterances. My experience in elderly care made me curious to learn more about the brain and communication, which lead me into the study of speech and language pathology and my current employment at Karolinska University Hospital, Stockholm.

In my clinical work as a speech and language pathologist, I had the opportunity to be involved in a major research network; Swedish Brain Power, where numerous researchers worked together to improve the situation of patients with neurodegenerative diseases. My entrance into the network was to explore issues concerning medical decision-making. The linguistic perspective of medical decision-making, originated from the discipline of speech and language pathology, formed the base of my PhD-project. Nevertheless, an interdisciplinary approach is necessary in order to fully explore the complexity of decision-making. I have attempted to merge different perspectives throughout my studies and for this effort I am most grateful for the collaboration with my supervisors, co-authors and colleagues, who contributed with their extensive knowledge in speech and language pathology, neuropsychology, medicine, linguistics, and ethics.

Evaluating the decision-making procedure and the capacity is about identifying various signs, more or less visible or audible. I am convinced that an interdisciplinary collaboration and discussion can improve and facilitate the decision-making procedures, for the exposed and fragile group of patients with neurodegenerative diseases. I am most grateful to have been part of past and ongoing interdisciplinary discussions which have empowered both my research in medical decision-making and clinical work, evaluating language and communication disorders among patients with impaired cognitive function.

LIST OF SCIENTIFIC PAPERS

The thesis includes five studies as shown below. The studies are referred to in the text by their Roman numeral. Reprints of studies I, II and III, were made with permission from the publisher.

I. Tallberg I.M., **Stormoen S.,** Almkvist, O., Eriksdotter-Jönhagen M. & Sundström, E. (2013). Investigating medical decision-making capacity in patients with cognitive impairment using a protocol based on linguistic features. *Scandinavian Journal of Psychology, 54*(5): 386-92. doi.org/10.1111./sjop.12068.

II. **Stormoen S.,** Almkvist, O., Eriksdotter, M. & Sundström, E., & Tallberg I.M. (2014). Cognitive predictors of medical decision-making capacity in mild cognitive impairment and Alzheimer's disease. *International Journal of Geriatric Psychiatry, 29*(12), 1304-1311. doi: 10.1002/gps.4114.

III. **Stormoen S.,** Almkvist, O., Eriksdotter, M., Sundström E. & Tallberg I.M. (2017). Decisions and attitudes regarding participation and proxy in clinical trials among patients with impaired cognitive function. *Dementia,* doi: 10.1177/1471301217737413. [Epub ahead of print]

IV. **Stormoen, S.** & Tallberg, IM. Semantic analysis of sense-making in a hypothetical clinical trial. *Manuscript.*

V. **Stormoen, S.***, Thalén, L.*, Almkvist O., Eriksdotter M., Heimann Mühlenbock, K., Sundström E. & Tallberg I.M. * *equal contribution*. Validation of a brief test to detect impairment in medical decision-making capacity. *Manuscript.*

CONTENTS

ABBREVIATIONS

AD	Alzheimer's disease
ADRDA	The Alzheimer's Disease and Related Disorders Association
ANOVA	Analysis of variance
BeSS	Assessment of subtle language disorders (bedömning av subtila språkstörningar)
BNT	Boston Naming Test
C	Controls
CCTI	The Capacity to Consent to Treatment Instrument
DLS	Assesments of reading and writing function (diagnostiskt material för analys av läs- och skrivförmåga)
ES	Erik Sundström
FAS	Phonemic verbal fluency test: FAS (letters: f, a, s)
FTD	Frontotemporal dementia
HC	Healthy Controls
HCP	Health care proxy
HD	Huntington disease
HDM	Health care decision-making
ICD-10	The International Statistical Classification of Diseases and Related Health Problems, a medical classification list by the World Health Organization.
IMT	Ing-Mari Tallberg
KHM	Katarina Heimann Mühlenbock
KIMB	Kliniskt Instrument för Medicinsk Beslutsförmåga
KIMB-q	KIMB questionnaire
KIMB-t	KIMB target word task
LIMD	The Swedish Linguistic Instrument of Medical Decision-making Linguistic
LS	Legal Standards
LT	Liv Thalén
MacCAT-CR	MacArthur Competence Assessment Tool for Clinical Research
MACCAT-T	MacArthur Competence Assessment Tool for Treatment
MANOVA	Multivariate analysis of variance
MCI	Mild Cognitive Impairment
MDC	Medical decision-making capacity (referred to in current PhD-project as capacity in research context)

MDMC	Medical decision-making capacity (referred to in current PhD-project as capacity in research context)
ME	Mia Eriksdotter
MMSE	The Mini Mental State Examination
MoCA	The Montreal Cognitive Assessment
NIA	The National Institute on Aging
NIA-AA	The Alzheimer's Association published revised guidelines
NIH	National Institute of Health
NINCDS	The National Institute of Neurological and Communicative Disorders and Stroke
OA	Ove Almkvist
PD	Parkinson's disease
Q	Question, referred to as questions in LIMD or KIMB.
R-O	Rey-Osterrieth test (copy and retention)
RAVL	Rey Auditory Verbal Learning Test
RAVLT	Rey Auditory Verbal Learning Test Total learning
S	standards (e.g. standards for consent)
SS	Sara Stormoen
STROOP	Stroop Color and Word Test
TCC	Treatment consent capacity
TL	Test leader
TMT	Trail Making Test (A and B)
UBACC	The University of California Brief Assessment of Capacity to Consent
VAS	Visual analogue scales (0-100mm) used in study IV to estimate e.g. risk/benefit.
WAIS-R	Wechsler Adult Intelligence Scale Revised
WMA	World Medical Association

INTRODUCTION

"Everything we see hides another thing, we always want to see what is hidden by what we see. There is an interest in that which is hidden and which the visible does not show us. This interest can take the form of a quite intense feeling, a sort of conflict, one might say, between the visible that is hidden and the visible that is present" Rene Magritte (1965), about his painting: Le fils de l'homme.

Reasoning and decisions may not always be communicated clearly and concisely. Sometimes the true sense of an utterance may be difficult to interpret and the extent of a person's capability to make an autonomous decision may be in question. Comprehension, reasoning and ability to communicate a choice may be reduced or lacking completely due to several causes, for example the cognitive decline caused by a neurodegenerative disease such as Alzheimer's. Several studies have investigated the medical decision-making procedure from a neuropsychological perspective and it is well-recognized that numerous of cognitive functions are correlated to the decisional capacity. It has been reported that language and communication abilities have impact on decisional capacity, although the linguistic perspective seems to have earned less attention within the field. The discipline of speech and language pathology formed the theoretical foundation of the thesis, from which an interface between neuropsychology and medical ethics was created and constituted an exploratory approach to the study of medical decision-making capacity (MDC) in research settings such as to give informed consent. The overall aim of the PhD-project was to explore medical decision-making in patients with Alzheimer's disease, by use of a linguistic approach.

Three key assumptions formed the starting point for the studies: (1) patients with Alzheimer's disease have to some extent reduced capacity to comprehend, evaluate and communicate a choice as well as reason in a logical manner; (2) linguistic abilities are central in order to obtain informed consent and (3) exploring the decision making from a linguistic perspective in AD in comparison to groups with varied cognitive function, may add further knowledge to field of MDC. Notable, the studies included in the current thesis, are referring to MDC as the capacity to make decisions for research, such as the ability to give informed consent. Yet, the capacity is described and discussed also from other reference points in the theoretical background of the thesis and in respectively study.

1 BACKGROUND

Medical-decision making capacity and associated elements have been widely discussed in the last decades among researchers from different disciplines (e.g. medical ethics and neuropsychology). Following sections in the background are reporting some previous findings, disagreements and consensus of different aspects of medical decision-making, that are considered central for the PhD-project (but the thesis does not aim to review the overall intradisciplinary debate of medical decision-making in neither research or treatment settings).

1.1 INFORMED CONSENT

Informed consent can be described as an individual's valid authorisation or refusal of a medical intervention. Informed consent serves to protect patients' autonomy, as the consent refers not only to being *informed* but in addition also to *voluntary* and *competent*. In other words, medical and research settings should provide the patient with adequate information, so that the patient can make an authentic decision. The Declaration of Helsinki is a key set of guidelines for medical ethics adopted by the 18th World Medical Association (WMA) General Assembly in Helsinki, Finland in June, 1964 and revised repeatedly since. The Declaration has had impact on medical ethic and national legalisation for example concerning informed consent. One of its fundamental principles is that concern for the individual is superior to the interests of science and society (World Medical Association, Declaration of Helsinki, 2013).

It has been suggested that informed consent to research should contain some fundamental elements concerning information, voluntarism and capacity to make a decision such as (1) ensure safety, (2) allow the patient or potential subject to be autonomous, (3) entail information of the total procedure as well as (4) report potential benefits and risks. A common difference between consent procedures for research in comparison to treatment is that participants enrolling a clinical trial need to understand the difference between possible interventions within the research project such as placebo as well as the terms and conditions of the research protocol (e.g. Appelbaum & Roth. 1982; Roberts, 2002; Gupta & Kharawala, 2012).

The term *health literacy*, has strengthened the individual perspective of inherit control of own health, such as for example the importance of making an autonomous decision (Nutbeam, 2008). Ringsberg, Olander and Tillgren (2017) discussed healthy literacy and emphasized that individuals have different conditions to take independent responsibility for their own health and Sarvimäki and Stenbock-Hult (2017) implied that elderly may risk to face challenges in health

literacy, as cognitive impairment is associated with several age-related diseases. Furthermore, Montalvo and Larson (2014) implied that there is an overall inconsistency in the degree of health literacy among research participants, meaning for example that the participant could face difficulties in capturing given key information concerning for example placebo, benefit and risk. Charles, Lidz, Appelbaum, Grisso, and Renaud (2004) implied that patients may risk to have only modest ability to appreciate the given risks when signing a consent to participate in a clinical trial. The authors imply that insufficient ability to identify and differentiate the consequences described in a research protocol undermines the informed consent procedure.

1.2 MEDICAL DECISION-MAKING CAPACITY

Palmer and Harmell (2016) implied in a recent paper, that consensus on a clear and overall definition concerning the capacity of healthcare decision-making seems difficult to reach. Intradisciplinary discussions of medical decision-making capacity have struggled with for example ethical issues, applicability in law, definition of the capacity and critical standards as well as its associated cognitive functions and neuroanatomic correlates. In addition, the decision-making capacity has in previous literature been referred to by different definitions and abbreviations. Yet, it is worth noting, that competence or incompetence is a legal term and is, if needed, the outcome of a formal legal procedure.

In the 80's, Appelbaum and Grisso (1988), among others, have discussed certain functional abilities, central for decision-making: (1) communicating a choice, (2) understanding relevant information, (3) appreciating current situation and its consequences and (4) manipulating information rationally. These have been referred to as e.g. standards for competence and are well established in the overall field of decision-making but have also been the target for discussion throughout the years. One general discussion concern that the model is mostly "cognitive", not attending to other issues, such as patient values and emotions, that could affect the capacity.

Another topic of discussion has concerned to include and merge standards into fewer or different categories. The functional standards understanding, reasoning and appreciation have been discussed and problematised in several previous studies (e.g. Marson, Cody, Ingram & Harrell, 1995 and Moye, Karel, Gurrera and Azar, 2006). Okonkwo et al. (2008), among others, explored medical decision-making capacity by including an experimental standard "making a reasonable choice" when evaluating the ability to communicate a choice as a consent capacity.

Yet, the authors pointed out that this additional standard is not generally accepted, as the degree of "reasonable" in a choice is difficult to measure in an objective and standardized manner, i.e. making a reasonable choice may be associated with appreciation and a reflection of the information to one's self and one's own situation. In addition, the reasonableness in utterances may sometimes be ambiguous or unexpected due to for example personal attitude and ethical considerations. Also, Grisso and Appelbaum (1998) were discussing the standard "expressing a choice", emphasizing a *clear and consistent* choice, since individuals may be able to communicate but unable to choose.

Further on, "the understanding" standard has been problematized by for example Dunn and Jeste (2001) underscored the difficulty of knowing what the measurement of "understanding" actually is referring to. Functions like comprehension, knowledge, and recall have been used to describe the "understanding" standard. Another aspect is the issue of what abilities the participant needs to require to truly comprehend the context of given research protocol. The authors underscored that neither knowledge nor recall do necessary imply understanding. Buckles et al. (2003) were investigated decision-making capacity for research participation among patients with mild to moderate AD, by an exploratory approach: only evaluating one dimension of the capacity: "understanding" (i.e. capacity to comprehend consent information in a relatively simply research protocol). Yet, they found, in line with previous studies that the patients showed reduced capacity. The authors implied that the capacity to provide rational reasons for choice or to actually understand the given context may presumable be more cognitive demanding in comparison to for example the standards: "communicate a decision" or "appreciating the consequences of participation".

An additional angle to the discussion was raised in a recent study, which explored psychiatrists' judgements and interpretation of decision-making. They reported that decisional capacity can be considered not only depending on previously well-established standards, but also to the actual choice. The authors implied that patients who made irrational decisions were considered to be "irresponsible" for the listener, although they were perhaps yet capable of making a decision (Sjöstrand, Karlsson, Sandman, Helgesson, Eriksson & Juth, 2015).

1.2.1 Associated cognitive and linguistic functions

In decision-making, a certain level of cognitive and linguistic function is needed, in order to acquire information to identify, understand and evaluate different options, and to finally communicate a choice. Several previous studies have reported certain cognitive characteristics as being associated with the different standards and dimensions of decisional-making capacity (assessed by different instruments and among different groups). Gurrera, Moye, Karel, Azar, & Armesto (2006) emphasized that verbal retrieval, among others, is an important cognitive correlate to decision-making capacity among patients with mild to moderate dementia. Furthermore, Gurrera, Karel, Azar and Moye (2014) underscored that the overall capacity to make a decision depends on numerous of interactions between different cognitive functions, rather than on any single function alone. Cognitive models based on performance in tests of executive function, semantic memory and delayed recall could serve to examine aspects of decisional capacity. Nevertheless, performance in cognitive tasks can serve to predict decisional capacity only to some extent. Several previous studies (e.g. Gerstenecker et al., 2015; Grisso & Appelbaum, 1998; Dunn & Jeste, 2001) have showed that verbal function is associated to the decision-making capacity.

Palmer and Savla (2007) underscored certain central abilities associated with the cognitive process of consent capacity, such as short-term memory (e.g. encode information for further processing), language comprehension (e.g. understand information), conceptualization and executive function (e.g. processing of information), judgment and reasoning (rational evaluating and weighting information), expressive language (e.g. communicating a choice). It was also reported that the ability to understand (as a component of decision-making in research) may be associated to several elements such as (1) knowledge of a participation in the study, (2) ability to remember information as well as (3) a general understanding of the meaning of randomization procedures (e.g. placebo treatments). Furthermore, Palmer and Harmell (2016) reported association between certain neurocognitive domains and healthcare decision-making, such as episodic memory, naming, working memory, executive functions and speed. The authors also summarised previously findings of what cognitive abilities appear to be correlated to different components of decision-making capacity:

- **The 'understanding' component** –executive function (Dymek, Atchison, Harrell, & Marson, 2001), processing speed, episodic memory (Okonkwo et al., 2008a), verbal function, fluency and memory (Gerstenecker et al., 2015).
- **The 'appreciation' component** –working memory (Palmer, Dunn, Appelbaum & Jeste, 2004), episodic memory and mental speed (Okonkwo et al., 2008a).
- **The 'reasoning' component** –working memory (Palmer et al., 2004), executive function (Dymek et al., 2001; Marson, Chatterjee, Ingram, and Harrell, 1996), episodic memory and expressive language function (Okonkwo et al., 2007).

1.2.2 Neuroanatomical correlates

Medical decision-making capacity is complex and depends, as we have seen, on several cognitive and linguistics functions. Consequently, the capacity cannot be associated with only one isolated part of the brain but can rather be considered as a result of several neurological processes. Despite this complexity, researchers have tried to localise and describe the key neurological systems involved in decision-making. For example, Kable and Glimcher (2009), identified two basic stages in the neurobiological mechanism for choice: (1) The multicomponent valuation, which is suggested to be associated with the prefrontal cortex and parts of the striatum, and (2) The choice, associated with activity in the lateral prefrontal and parietal areas. Hsu, Bhatt, Adolphs, Tranel and Camerer (2005) suggested that activity in the prefrontal cortex is associated with random choices, commonly noted among individuals with AD. Gleichgerrcht, Ibanez, Roca, Torralva & Manes (2010) reviewed neuroanatomical patterns of decision-making among those with neurodegenerative diseases (AD, frontotemporal dementia, FTD, Parkinson's disease, PD and Huntington's disease, HD). Three central neurological systems for decision-making were identified: (1) A stimulus encoding system, associated with the orbitofrontal and ventromedial prefrontal cortex, (2) An action selection system, related to the anterior cingulate cortex and the lateral prefrontal and parietal cortices and (3) An expected reward system, associated with basal ganglia, amygdala and insula.

1.2.3 Assessments

Researchers seem to agree upon that the capacity to make a valid decision is not static but changeable, due to both individual factors (e.g. patient's status) and contextual factors (e.g. the complexity of decision-making situation and time restrictions) (e.g. Palmer & Harmell, 2016). Hence, sufficient or insufficient capacity must always be assessed on an individual basis. Braun,

Gurrera, Karel, Armesto and Moye (2009) investigated whether clinicians are biased in their conclusions on the decision-making capacity of elderly patients. They reported that unstructured determinations of the capacity may be problematic, as even the most skilled medical professionals may find it difficult to determine the capacity. Unstructured estimations may lead to disagreements as well as questionable validity and inter-rater reliability. They reported also that the estimations were associated to the clinicians' idea of how the patient was involved in decisions such as for example emotional reactions. Sessum, Zembrzuska and Jackson, (2011), were also reporting difficulties among physicians to recognize decision-making incapacity in patients determined (through more formal assessments) insufficient to make health care decisions. The authors emphasized the use of standardized measurement tools, based on predefined key criteria when estimating medical decision-making capacity. Pennington, Davey, Ter Meulen, Coulthard and Kehoe (2018) emphasize that several approaches e.g. individual and cultural perspective as well as medical status must be considered when estimating decision-making capacity in dementia. The authors also pointed out that it does not exist any gold standard for capacity instruments, which stress the importance for both clinicians and researchers to apply different approaches when evaluating the capacity. Finally, Buckles et al., (2003) implied that brief tools to evaluate if patients understand the context of a research protocol would be beneficial to apply when enrolling patients with dementia in a consent process.

1.2.3.1 Tests

Estimation of cognitive severity by for example Mini Mental State Examination (MMSE; Folstein, Folstein & McHugh, 1975) or Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), can serve to give an initial assumption of the patient's cognitive status. Yet, specific valid tests are acquired to evaluate decision-making capacity. Several instruments have been developed and validated to examine different dimensions of the capacity and should preferable be used when the capacity needs to be examined in detail. Several reviews have reported assessments tools of decision-making capacity in different health care and research settings. Notable, objectives, design, administration, scoring procedures, validity and usefulness differ among the assessment tools (for details see for example reviews and papers by Karlawish, 2017; Palmer and Harmell, 2016; Lamont, Jeon & Chiarella, 2013; Pennington et al., 2018). Some well-established instruments to assess different aspects of the capacity are: the MacArthur Competence Assessment Tool for Treatment (MacCAT-T), the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) (Grisso, Appelbaum and

Hill-Fotouhi, 1997; Grisso and Appelbaum, 1998, Appelbaum and Grisso, 2001), the Capacity to Consent to Treatment Instrument (CCTI) (Marson, Ingram, Cody & Harrell, 1995a) and the University of California Brief Assessment of Capacity to Consent (UBACC) (Jeste et al., 2007). Most instruments can be divided into two general test designs: "decision-at-hand" and "vignettes", described in short below (Palmer and Harmell, 2016):

- **Decision-at-hand**. Some instruments are designed to assess the capacity tailored to the decision at hand (i.e. current, real information). These assessments often consist of structured or semi-structured interview formats based on the current situation (for example decisions concerning a certain treatment or other health care issues) in addition to scoring guidelines. Since the responses are specific to the situation at hand, the assessment procedure and questions must be adjusted to the explored situations. This can cause difficulties with standardisation, reliability and validity. Dunn, Nowrangi, Palmer, jeste & Saks (2006) noted that the contextual impact needs to be further investigated and that tools of this type need to undergo further research.

- **Vignettes**. The so-called vignette-method is a common approach, which assesses the decisional capacity based on hypothetical situations. As these instruments by their nature include fictional information, for example concerning a certain disease and/or clinical trial, the method is generalisable among both situations and patients, but also requires a certain level of ability in figurative thinking and hypothetical reasoning. A possible concern is uncertainty about whether the participants would make the same choice in a real situation.

1.2.3.2 Linguistic analysis

Semantics and pragmatics are concerned with the study of meaning, such as for example how linguistic signs in the speech (e.g. words) are associated with meaning. Johansson and Manninen (2012) proposed that "the meaning of meaning" can be studied from a referential perspective (i.e. meaning is derived from the link between linguistic signs and objects that exist or might exist in the real world) or from a mental perspective (i.e. assuming that a word has a meaning because it activates a concept in the mind of the speaker/listener). The authors also discuss different kinds of meaning: linguistic versus encyclopaedic, literal versus associative and literal versus non-literal meaning. The study of meaning is of interest not only for linguistic semantics, but also studied among philosophers, psychologists and computational scientists.

Examining the linguistic signs for person, place and time in the speech adds further knowledge about the meaning of the utterances. Time can be expressed by verbal tense or by time adverbials (e.g. then, now). Place relates to the speaker's perception of his/her position in space/room (e.g. here, there). Person may concern the speaker (e.g. personal pronouns such as I, you, he or she). Signs of misperception and confabulations in patients' speech can be explained as a disturbance of her/his self- image in relation to time and space. For example, the pronoun 'I' may risk losing its actual meaning (e.g. whom it is referring to) if it is presented as a self without a connection to time and place (Tallberg, 1999).

An interview is a complex process during in which the interviewer and responder may display various clear or subtle linguistic and communication features. Clark and Schaefer (1989) proposed a theoretical linguistic model to help identify whether successful exchange of information has occurred in the decision-making conversation. This model structures a hierarchy of evidence of understanding and can contribute to an overall assessment of decision-making capacity. The model was modified in a recent study by Brauner and Merel (2006) as the "Modified Hierarchy of Evidence of Decision-Making Capacity" and includes well-defined core features such as: (1) Continued attention, (2) Acknowledgment (backchanneling, for example, nodding, saying "yeah" or "uh-huh" and (3) Next relevant contribution; (3a) single word answers (yes, no, maybe etc.), (3b) single word answers plus confirmatory language (yes, I think so), (3c) paraphrases, (3d) new idea (that signals understanding of previous contribution). Brauner and Merel conducted a linguistic analysis based on the modified model, of semi-structured interviews concerning different hypothetical research texts, as well as the four previously defined functional abilities (Appelbaum & Grisso, 1988). Brauner and Merel (2006) explored these functional standards by their linguistic model summarized as followed:

- **Communicateing a choice** - e.g. continued attention, eye contact, acknowledgement: back channelling.
- **Understanding information related to the options** – e.g. paraphrasing, anaphora, need for repair, response to repair.
- **Appreciating the context, including its consequences** – e.g. reference to one´s disease, "*Aha"* contribution.
- **Reasoning about the information rationally** – e.g. recognisable reason.

The model also considered that confusing language can be a sign of questionable decisional capacity. Yet, thoughtful actions by the interviewer, such as successfully “repairing” confused language in the interaction, can result in the participant being able to improve their capability to answer the questions.

1.3 DEMENTIA

The term "dementia" does not constitute a disease in itself, but rather a set of symptoms whereby an acquired cognitive impairment significantly affects functional ability and declines over time. Cognitive failure may occur in a variety of conditions and diseases. Even at high age, cognitive ability may be affected by other more common diseases where the combination of high age and multiple illness may lead to significant cognitive impairment. In order for the criteria for dementia to be met, the cognition should have declined over time, during more than six months, and must be pronounced and lowered in comparison to previous level as well as affect work or social life. Dementia is more common among the elderly, prevalence > 65 years has been reported as 8% in Swedish population. Around 160 000 people have dementia in Sweden today (24 000 newly diagnosed persons per year). It is not possible to cure dementia, but the health and social services can contribute to facilitate everyday life and contribute to quality of life in the various stages of the disease. The National Board of Health recommends an interprofessional approach to provide best possible efforts in dementia care (Guidelines for Dementia; The National Board of Health, Rev. 2017).

1.4 ALZHEIMER’S DISEASE

Alzheimer’s disease (AD) is the leading cause of dementia, accounting for 50–70% of cases. The primary risk factor for AD is of age (Winblad et al., 2016). The clinical diagnosis of AD in Sweden is defined according to the ICD-10 classification. AD is recognized by for example (1) impaired function in multiple cognitive domains: memory impairment is obligatory, as well as any other interference such as aphasia, apraxia, agnosia or impaired executive function; (2) the impairments lead to a significant decline in social or occupational functions and (3) the course is characterised by a gradual onset and continuous deterioration. Both in the clinic and in research often the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer´s Disease and Related Disorders Association (ADRDA) criteria from 1984 have been used, but the criteria was recently updated by the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease NIA-AA criteria (McKhann et al. 2011), including new categories such as proof of the AD

pathophysiological process using biomarkers of AD pathophysiology reflecting amyloid β-deposition and neurodegeneration. However, due to the need of standardisation and availability of quantitative analytical techniques, the use of biomarkers is still not recommended in the clinical setting, but often included in the diagnostic process when available. There is increasing evidence to show that AD starts many years before symptoms occur (Winblad et al., 2016).

Typical examples of communication deficits in AD is an inadequate ability to follow the "thread" of conversation. Furthermore, morphological, syntactic and lexical discrepancies of language function and general vocabulary difficulties have been observed. Reading capacity is also commonly impaired in AD, such as reduced ability identifying and reading out the words, decoding texts and to actually processing and comprehend the content, which requires additional cognitive functions such as semantic and episodic memory. In addition, the impaired reading function in AD could be reduced due to a disturbed visual processing (e.g. Emery & Olga, 2000; Glossera, et al., 2002; Fernandéz, Schumacher, Casstro, Orozco & Agamennoni, 2015; Obler and Gjerlow, 1999). In a study by Tallberg and Almkvist (2001), it was noted that impaired cognitive function in AD can be related to an increased number of confabulations. The authors highlighted the relevance of listening to what may be perceived as irrelevant speech and attempting to understand what the person with AD is trying to convey. Automated verbal pronouncements and the syntactic structure can be relatively well-maintained far into the disease development. When cognitive, communicative and pragmatic functions are disturbed, it usually means a need for a specially adapted environment (Penn, 1999). Impaired language functions, such as the ability to recall words, may be noted even in the early stages of the gradual cognitive degeneration of AD and when the disease progresses the ability to express and comprehend language decreases (Bayles, Tomoeda, Cruz & Mahendra, 2000). Furthermore, de Lira, Ortiz, Camanha, Bertolucci and Minett (2011) explored fluctuations in the speech of AD patients and found that both lexical and syntactic performance were lower than expected. Individuals with AD may be relatively adept at finding strategies to conceal their difficulties, thus possibly giving a distorted picture of their functional ability. For example, they may have sustained the capacity to read as an automatic process, although comprehension of the text is reduced or completely lacking (Emery, 2000).

1.5 MILD COGNITIVE IMPAIRMENT

Mild cognitive impairment (MCI), refers to the clinical state of a minor impairment in cognitive function, typically memory, but with normal performance in other domains and not meeting the criteria for clinically probable AD. Some patients with MCI show *amnestic* MCI characterized by memory loss, with a high rate (10-15%) of progression to AD, in comparison to healthy elderly (converting at a rate of 1-2% per year). However, there are multiple sources of heterogeneity in MCI as some patients may develop AD, while others may progress to other dementia diagnoses, or never progress to a significant extent (Winblad et al, 2004).

1.6 DECISION-MAKING CHARACTERISTICS IN IMPAIRED COGNITIVE FUNCTION

Palmer and Harmell (2016) implied that cognitive impairment seems to be highly associated with impaired health care decision-making capacity, also including patients with other dominant symptoms. Age-related diseases involving cognitive impairment may impact decision-making capacity (Petersen et al., 2007; Mata, Schooler & Rieskamp, 2007) and it is well-recognised that reduced decision-making capacity can be found in patients with various neurodegenerative diseases. In a study by Okonkwo et al. (2008b), people with cognitive impairments were found to have significantly lower ability to evaluate, reason and understand compared to healthy controls and impaired decisional capacity has been noted even in mild AD (Gurrera et al., 2006). Jefferson et al., (2008) used the Maccat-CR to examined decisional-capacity for research participation among patients with MCI. Their results indicated, in line with previously findings, that also patients with MCI show impaired decision-making capacity. In addition, the patients who failed to provide informed consent for a hypothetical clinical trial, which they were exposed to in the exploratory study, were less educated. However, the characteristics of decision-making deficit vary between diagnoses and change over time, as the cognitive impairment progressively worsens (Buckles et al., 2003; Gleichgerrcht et al., 2010). A different communication style such as “a silently agreeing manner” for research participation has been identified among patients with dementia (Sugarman et al. 2007), which may risk to be falsely interpreted as for example a willingness to participate. The authors imply that, not only the cognitive status of the patient, but in addition social and emotional considerations should be considered in the discussion concerning proxy and consent in dementia.

1.7 ETHICAL ISSUES

A debated issue in dementia research concerns obtaining informed consent from patients with impaired cognitive function (e.g. Peterson and Wallin, 2003; Slaughter, Cole, Jennings, & Reimer, 2007). Critical ethical issues associated with medical decision-making concern for example patient autonomy. Autonomy is a loaded word and considered as a fundamental human right, in Sweden as well as in numerous of other countries (see e.g. World Medical Association, Declaration of Helsinki, 2013). Determination of sufficient or insufficient decision-making capacity may lead to ethical and medical consequences for the patient. One ethical issue is the important responsibility of finding the right balance between autonomy for individuals as well as protections for those with reduced capacity to make autonomous decisions (Berghmans & Widdershoven, 2003). Furthermore, Johansson (2017) underscores the importance of being sensitive to what the patients communicates, even when decisional capacity is considered insufficient, i.e. not to listen to individuals, whatever their identity or status is to adopt an attitude towards the other as an object rather than a subject, which is not consistent with good medical ethics. Proxy consent may be needed if certain decisional capacity is considered insufficient (e.g. White & Seery, 2009). Dubois et al. (2011) underscored that attitude toward proxy seem to vary in relation to the potential risk associated to the situation, such as for example it seems to be a higher willingness to accept proxy regarding possible engagement to low-risk research. This stress the importance of discussing patient's attitude and choice of proxy preferably before the decisional capacity is significantly reduced. Furthermore, Moye, Sabatino and Weintraub et al (2013) emphasize the importance of exploring possible similarities and differences between different type of capacity, such as to consent to treatment or to appoint a future proxy and Kim, Caine, Currier, Leibovici and Ryan (2001) were reported that patients with questionable decision-making capacity may to some extent have sufficient capacity to appoint a proxy to make decisions on their behalf. Smebye, Kirkevold and Engedal, (2012) point out that families are essentially already in the initial phase of a dementia disease, to pursue shared or supported decision-making, e.g. facilitate information and guide through different options, but leave the final decision to the patient. Swedish law states that researchers must apply for permission from regional ethical vetting board for any research that affects a human being. A Swedish act of Future Proxy came into force, to allow to designate a future proxy. The powers and selection criteria of a future proxy can be in general or specified to certain situations (https://www.riksdagen.se/sv/dokument-lagar/dokument/svensk-forfattningssamling/lag-2017310-om-framtidsfullmakter_sfs-2017-310).

1.8 AIMS OF THE PROJECT

The overall objective of the PhD-project was to explore various aspects of medical decision-making for research involving patients with mild AD, by applying a linguistic perspective and include comparable groups of interest. The different objectives of each study are summarised below:

I. To develop and validate a Swedish linguistic instrument of medical decision-making capacity for research, among groups of patients with Alzheimer's disease (AD) and mild cognitive impairment (MCI) and comparable healthy elderly individuals (HC).
II. To examine the association between cognition and MDC in research (by LIMD) using a comprehensive battery of cognitive and linguistic tests
III. To evaluate how groups with various cognitive functions (AD, MCI and HC) reason and estimate risks and benefits in the context of possible participation in hypothetical clinical trials.
IV. To explore the meaning of utterances concerning a hypothetical clinical trial by conducting semantic analysis of time, person and place.
V. To develop and validate a Swedish brief task to detect compromised informed consent to research among patients with AD.

2 METHODS

2.1 PROCEDURES

Medical decision-making capacity in the PhD-project is abbreviated as MDC or MDMC, which is referring to the capacity to make decisions for research, such as the ability to give informed consent. Yet, results from previous research referring to other definitions and aspects of the capacity are reported and discussed to some extent within the thesis and in respectively study (I-V).

The studies are derived from two separate data collections: data collection I (studies I-IV), data collection II (study V). Each participant was only participating in one of the two data collections.

The first collection (studies I-IV) was conducted between 2009-2010 (by SS). Data collection one contained in addition to the new instrument LIMD a large test battery including neuropsychological and linguistic tests and VAS. The total test procedure was durable approximately 3-4 hours per participant (including breaks). The data was analysed by several evaluators (IMT, OA and SS).

The second data collection (study V) was conducted between 2015-17 (by SS and LT) and by students of speech and language pathology (RH and EL). Data collection two contained in addition to the new tool KIMB some cognitive and linguistic tests and was durable approximately 1.5 hours per participant. The data was analysed by two evaluators (SS and LT).

In addition to the test design of LIMD and KIMB, a large number of scientific methods were applied in order to analyse the data in studies I-V such as (1) assessment of cognitive and linguistic tests, (2) structured interviewing (regarding three hypothetical clinical trials as part of LIMD) (3) orthographical transcription of audio recorded speech, (4) standardised scoring of verbal responses by LIMD protocol, (5) blinded analysis of test results, (6) manually measuring participants self-estimations by VAS, (7) statistical analyses, (8) semantic analyses of transcribed speech. The test design of LIMD and KIMB was settled before initiating the data collections to enable a standardized assessment and scoring procedure.

The results emanated from two scientific approaches: (1) quantitative (study I-III and V), by reporting the scores of neuropsychological and linguistic tests as wells as the scores by different measurements of MDC and self-estimations by VAS and (2) qualitative (study IV), by semantic analysis of the speech. The qualitative approach in study IV aim to contribute to a deeper understanding of the speech and can be viewed upon as an extension of study I-III as theses four studies report from the same data collection (I).

2.2 PARTICIPANTS

The two data collections included different individuals but groups with similar diagnostic clinical features (enrolled by similar inclusion and exclusion criteria): (1) Patients with *mild* Alzheimer's disease (AD) and (2) Mild Cognitive Impairment (MCI) as well as an age matched group of (3) Healthy individuals (HC).

All patients (AD and MCI) were recruited from the Karolinska University Hospital memory clinic. The diagnosis of AD followed NINCDS-ADRDA criteria (McKhann, Drachman, Folstein, Katzman, Price & Stadlan, 1984) and ICD-10, while diagnoses of MCI followed clinical criteria including subjective cognitive complaints, objective verification of cognitive impairment and maintained activities of daily living (Winblad et al., 2004). The inclusion criteria from the clinical investigation at the Memory clinical were for the patients the patients (MMSE: AD>20) and those with a mild cognitive impairment (MCI) (MMSE: MCI>25), (Folstein et al., 1975), Cornell Scale for Depression in dementia ≤9 (Alexopoulos, Abrams, Young & Shanoian, 1988) and diagnosed within the last 12 months.

HC were recruited through spouses to patients, extended networks and advertisements in public areas e.g. library, churches and hospitals. The main inclusion criteria for the HC group was absence of depression or other psychiatric condition, neurological disease, dementia or other diagnosis that could affect language or cognitive ability. Additional inclusion criteria for *all* three groups (AD, MCI and HC) were: (1) Swedish as (one or one of several) first language(s), (2) no reported dyslexia and (3) no substantial hearing or visual impairment which cannot be corrected by aids.

Demographic characteristics were reported at group level: studies I-III (age, gender and education) and study V (age and education). Study IV did not include and compare demographic characteristics but included data (transcribed verbal utterances) from data

collection I. Overall cognitive severity was an inclusion criterion (MMSE ≥20) as investigated as part of the clinical examination but was also re-tested as part of the two data collections (by MMSE in data collection I and by MoCA in data collection II) and it was the score from the data collections, which was used in the analyses.

2.2.1 Study I

Data collection I: Three groups: (1) patients with dementia of the Alzheimer type (AD, n=20), (2) patients with mild cognitive impairment (MCI, n=22), and (3) healthy controls (HC, n=37). Groups differed significantly ($p<.001$) in overall cognitive function by the Mini-Mental Status Examination (MMSE; Folstein et al., 1975): AD: 24.1±3.3, MCI: 26.7±2.4 and HC: 29.1±1.0). No significant group effects (all $p>.10$) for demographic features (gender, age and education).

2.2.2 Study II

Three groups were selected from data collection I: (1) patients with dementia of the Alzheimer type (AD, n=20), (2) patients with mild cognitive impairment (MCI, n=21) and (3) healthy controls (HC, n=33). Significant groups differences ($p <.001$) by the Mini-Mental Status Examination (MMSE; Folstein et al., 1975; AD: 24.1±3.6, MCI: 26.6±2.4 and HC: 29.1±1.0). No significant group effects (all $p>.10$) for demographic features (gender, age and education).

2.2.3 Study III

The same three groups as in Study II (see above, section 2.2.2)

2.2.4 Study IV

The analysis includes responses from four participants (AD, n=2 and HC, n=2), taken from data collection I. Note, the result does not reveal the total sum of utterances from one individual but presents a mixture of responses (taken from the LIMD-interview) from the four selected individuals, and the utterances were reported by the two groups (AD and HC).

2.2.5 Study V

Data collection II: Three groups: (1) patients with dementia of the Alzheimer type (AD, n=21), (2) patients with mild cognitive impairment (MCI, n=17) and (3) healthy controls (HC, n=17) from data collection II. Groups differed significantly in overall cognitive severity as measured by The Montreal Cognitive Assessment Battery (MoCA; Nasreddine et al., 2005; $p <.001$; AD: 19.72±3.37, MCI: 24.00±2.15 and HC: 26.88±2.13) and showed non-significant group effects ($p>.10$) for age and years of education.

2.3 MATERIAL AND ASSESSMENTS

The cognitive and language tests used in the different studies are listed below according to an associated cognitive or linguistic domain. Free English translations and abbreviations of Swedish tests/tasks have been carried out when necessary.

- **Overall cognitive function.** Mini-Mental Status Examination (MMSE) (Folstein et al., 1975) and The Montreal Cognitive Assessment Battery (MoCA) (Nasreddine et al., 2005).
- **Language production.** Boston Naming Test (BNT) (Kaplan, Goodglass & Weintraub, 1983), Word fluency tests: Phonemic fluency: FAS (letters: f, a, s) and Semantic fluency: Noun and Verb (Tallberg et al., 2008), Repetition of long sentences (subtest of Assessment of Subtle Language Impairment; BeSS) (Laakso, Brunnegård, Hartelius & Ahlsén, 2000; Holmbro & Olsson, 2000) and Forward and Backward recall of automatic word sequences (Östberg, Farnaeus, Bogdanović &Wahlund, 2008).
- **Language comprehension.** Inference and Logico-grammatical sentences (subtests of Assessment of Subtle Language Impairment; BeSS) (Laakso et al., 2000; Holmbro & Olsson, 2000), Information and Similarities (subtests of WAIS-R, Wechsler, 1981).
- **Reading capacity.** Reading Speed (subtest of diagnostic read and write test; DLS) (Järpsten, 2002) and Read aloud words and non-words (subtest of read and write test; LS) (Johansson, 2002).
- **Memory.** Digit Span; forward and backward (subtest of WAIS-R, Wechsler, 1981), Corsi Blocks, Rey Auditory Verbal Learning test (RAVL); total learning (RAVLT) and retention and Rey-Osterrieth test (R-O); retention (Lezak, Howieson & Loring, 2004; Schmidt, 1996)
- **Spatial ability.** Block Design (subtest of WAIS-R, Wechsler, 1981) and Rey-Osterrieth test (R-O); copy (Lezak et al., 2004).
- **Executive function, attention and cognitive speed.** Digit Symbol (subtest WAIS-R) (Wechsler, 1981), Trail Making Test; A and B (TMTa+b) and Stroop (Lezak, et al., 2004; Golden & Freshwater, 2002).

The overall intention with the test batteries was to cover a broad spectrum of cognitive and linguistic domains. The tests above were chosen as they are commonly included as valid and reliable tools as part of the clinical assessments of cognitive and language functions at the

Memory clinic / cognitive unit at Karolinska university hospital. The linguistic test battery has been validated among healthy elderly and patients at the Memory clinic, Karolinska University Hospital and is presented in a Swedish manual (SLUM; Tallberg, 2017).

2.3.1 Study I

2.3.1.1 The Swedish Linguistic Instrument of Medical Decision-making (LIMD)

The vignette method was applied in the design of the Swedish Linguistic Instrument of Medical Decision-making (LIMD), which comprises three essential parts: (1) three vignettes (texts describing hypothetical clinical trials, both writing and orally), (2) Interview (orally) and (3) scoring protocol (based on linguistic features related to three LIMD-criteria: comprehension, evaluation and intelligibility). The participants received the vignettes, one at a time (same order for each participant) and kept the vignette ahead while answering the questions. The interviews (described below) were audio recorded and orthographically transcribed, which allowed different linguistic analyses (reported as a result in LIMD, study I and II as well as an analysis of certain responses reported in study III and IV). Test assessment, audio-recording and transcriptions were conducted by one test-leader (SS). The scoring of LIMD was conducted in two steps and by the same evaluator (IMT), who was blinded to the identity and diagnosis of each participant. IMT did not participate in the interviews. MDC according to LIMD was scored one vignette at a time and included both reading the transcription and listening to the audiotaped interview. No formal comparisons among the three vignettes were made during the scoring procedure, which followed the protocol accounted for below and included in total 79 participants and standardised questions based upon the three vignette interviews (= 227 interviews in total). A second scoring by IMT, to check reliability, using the same transcriptions and audio recordings, was performed after three months (blinded to identity and group).

Vignettes

The three vignette texts included in LIMD were produced from scratch by one of the paper's co-authors (ES), an experienced researcher with knowledge in both biomedicine and medical ethics and were written in a style similar to texts used in patient information forms in Swedish ethical permits but condensed to not exceed two pages. The texts were then discussed and adjusted together with others clinicians and researchers in the field. The texts describe three different hypothetical clinical trial involving three different diseases: kidney disease, skin disease and hypertension. The three were chosen to include chronic diseases (as this is the case of AD) and diseases of different degrees of severity and risk. The language used in the vignette texts was chosen to reflect real informative texts used to recruit patients for clinical trials. The

three vignettes deliberately vary with regard to presumed risk and benefit. The two vignettes deliberately varied with regard to the presumed risks and benefits of participation. The content of the vignettes is summarised as follows:

- **The kidney disease vignette** (241 words; *high* benefit and *low* risk)
  The fictive subject suffers from a serious progressive disease of the kidneys and is informed on the prognosis which implies extensive dialysis with a high probability of future kidney transplantation. The subject is invited to participate in a trial for a medical treatment which could stop the disease from further progress, with no expected serious side effects.
- **The skin disease vignette** (587 words: *low* benefit and *low* risk)
  The fictive subject has a moderately severe inflammatory dermatological disease with stable symptoms. The subject is invited to participate in a trial for a new treatment that is rather inconvenient (drug infusion), with no hope for a permanent cure, and some risk of moderately severe skin effects (persistent skin lesions). However, another group of patients with very severe dermatological disease could be helped if the trial is successful.
- **The hypertension vignette** (528 words, *low* benefit and *high* risk)
  The fictive subject has hypertension that is satisfactorily managed with standard antihypertensive medication. The subject is presented with a drug trial, and if she/he choose to participate, will change antihypertensive medication from the one presently used to a treatment that offers no better effect for the subject than the presently used drug, but could possible help other patients. The new drug has significant possible side effects, including the risk of one very severe (liver cancer) but with a low probability of occurring. (This vignette was designed to describe a trial that most likely would not be accepted by the ethical vetting board or the Swedish Medical Product Agency ("Läkemedelsverket") due to this risk)

Interview

A standardized interview was performed on each participant and for each vignette. The interview considered the participants' understanding, evaluation and choice regarding the three hypothetic clinical trials. The questions in the interview were asked by one individual (SS). The entire interview was audio reordered and orthographically transcribed. The LIMD interview included eight questions:

1. *Describe in your own words what the text is about.*
2. *Is the text about research or treatment?*
3. *What disease is the text about?*
4. *What is the doctor asking you about?*
5. *Are there any risks associated with participation in the study?*
6. *Are there any benefits of participating in the study?*
7. *Why is the study important?*
8. *Would you choose to participate?*

8.1.(If "yes") Why would you choose to participate? / What would be the reasons for your participation?

8.2.(If "no") Why would you choose not to participate?/ What would be the reasons for not participating?

Scoring protocol

The LIMD scoring protocol was constructed in order to allow a wide distribution of scores, including three criteria: comprehension, evaluation and intelligibility and three vignettes with varied implied risks and benefits (kidney disease, skin disease and hypertension), resulting in a total LIMD score with a range from 0 to 27 points for each participant. To measure the total LIMD score of each individual, the test evaluators (IMT and SS) both read at least twice the entire transcribed interview and also listened to the interview by the audio recorded file. Also, it was important that all responses from the entire interview was used as a basis for the assessment since the score should be based upon the sum of the overall responses (i.e. not based upon one single response to one particular question). Using a linguistic analysis, based on both transcribed and oral data, as well as taking the listener's perspective, the intention was to analyse the verbal utterances rather than trying to interpret the thought of the respondents. Therefore, the procedure was based on a systematic predefined protocol to analyse different linguistic signs in their utterances (e.g. syntax, vocabulary), prosody (e.g. strength of voice) and pragmatics (e.g. meta-linguistic devices like irony, consistency in the speech). Particular attention was paid to linguistic markers for estimation in subjects' reasoning such as '*bad, good, very and small'*, which could be signalling if risks and benefits had been adequately addressed. When measuring MDC by LIMD, it was considered important to capture the subjects' actual comprehension of the given context, i.e. the capacity to verbally describe and reason about the information in her/his *own* words, rather than the mere ability to automatically repeat the words

from the vignette. In other words, the score was affected by whether the subject was reading on the inside or whether she/he used own words.

The scoring for each vignette; (1) kidney disease trial, (2) skin disease trial and (3) hypertension trial, was calculated in the same order for all subjects. The principles for scoring in each respective vignette were based on three criteria; comprehension, evaluation and intelligibility of choice. Each criterion received a separate score in the range between 0-3 points/criteria based on what the participant actually communicated during the entire interview, each vignette evaluated separately. The sum of the score, including all three criteria in all three vignettes (3 criteria x 3 vignettes x 0-3 points = range 0-27 score) equaled the total LIMD score per participant. The LIMD scoring protocol defined the requested features for each respective scoring point, 0,1,2 and 3, for each respective criterion. An illustrative extract from the LIMD scoring protocol, concerning score 0 (minimum) and score 3(maximum), is presented below (categorized within each criteria).

- **Comprehension** - ability to perceive, understand and account for the content**.**
  Scoring was based on the assessor's estimation of how closely the subject's responses corresponded to the content of the vignette. Linguistic features such as independence of utterances (i.e. not word-for-word replays), accuracy, inferences, relevance (if utterances were adding new information or not), coherence and specificity.
  0 points – The content of the vignette was not communicated i.e. the evaulater was most certain that the vignette's information had *not* been perceived by the participant (e.g. does *not* answer fully on several questions about the content such as answers incompletely to the majority of questions about the content of the vignette and / or the answers contain "error response" and/or "misunderstanding" and/or answering "I do not Know" and/or "I do not Remember" and/or the participant is reading aloud, i.e. no own language use).
  3 points – The content of the key information of the vignette was communciated well-defined and distinct i.e. the evaulater was most certain that the vignette's information had been *well* perceived by the participant (e.g. does answer fully on several questions about the content. No "error response", "misunderstanding" nor any phrases like "I do not know", "I do not remember". The participant uses own words when retelling about the content).

- **Evaluation** - ability to perceive and value risks and benefits.

  Scoring was based on the extent to which it was shown in the utterances that the participant had evaluated the risks and benefits of the fictive clinical trials, and how these identified risks and benefits were described. The scoring was also considering coherence between utterances, how key words occurred, use of evaluating language, specificity and prosodic elements.

  0 points – The implied risk and benefit described in the vignette was not communicated i.e. the evaulater was most certain that the risk and benefit described in the vignette information had *not* been perceived by the participant (e.g. neglects to explain either the risks or the benefits, occourence of "error response", signs of "misunderstanding" or respnses like "I do not remember", unreasonable or lack of reasoning or non-balance of risk and benefit to each other. Does not take into account the complete context).

  3 points - The implied risk and benefit described in the vignette was communicated in a well-defined and distinct manner i.e. the evaulater was most certain that the risk and benefit described in the vignette information had been *well* perceived by the participant (e.g. explains and evaluate well the given risk and benefit. Balance risk and benefit to each other. Taking into account the full context).

- **Intelligibility of choice** -ability to express and formulate a decision and its motivation.

  *S*coring was based on the assessor's estimation of how far the participants was able to communicate choie and its motivation in an itelligible and relevant way (in relation to the participant's previous utterances as well as to the content of the given information). Language features considered to be relevant to interpret the decision were for example prosodic elements, vocabulary, specificity, occurrence of contradictive utterances and/or words for vagueness.

  0 points – Lack of ability to communciate a choice based on the vignette information and previously reasoning i.e. the evaulater was most certain that the participant's communicated decision (if it was at all communicated) *not* could be considered as a well informed consent. (e.g. absence or partial lack of hypothetical reasoning: giving responses contradictory to own evaluation, motivation and/or based upon a clear misunderstanding of the content of the vignette and/or not answering the question, giving an answer not appropriate to the context or to her/his previous utterances).

  3 points - Ability to communciate an informed consent in a well-defined and distinct manner i.e. the evaluater was most certain that the participant's communicated decision

could be considered as a *well* informed consent. (e.g. good ability in hypothetical reasoning, transfers the vignette's information to herself/him and answers clearly based on the current hypothetical context. Answers clearly and with a well-founded "yes" or "no", the decision is clearly stated and coherent to the participants' own motivation and also to the content of the vignette).

2.3.1.2 Screening of cognitive function

Mini-Mental Status Examination (MMSE; Folstein et al., 1975).

2.3.2 Study II

2.3.2.1 The Swedish Linguistic Instrument of Medical Decision-making (LIMD)

See above (study I).

2.3.2.2 Test battery

Cognitive and linguistic functions were assessed, using in a total of 27 test measurements. See section above: material and assessments (2.3), excluding MoCa.

2.3.3 Study III

2.3.3.1 Screening of cognitive function

Mini-Mental Status Examination (MMSE; Folstein et al., 1975).

2.3.3.2 The Swedish Linguistic Instrument of Medical Decision-making (LIMD)

See above (from data collection I, *see* study I: 2.3.1.).

2.3.3.3 *Vignettes*

Two vignettes (from data collection I, *see* study I: 2.3.1. were chosen to illustrate greatest contrast in probable risk and benefit (kidney disease; low risk and hypertension high risk).

2.3.3.4 Questionnaire

Four standardized questions were used Q1-2 (from data collection I, *see* study I: 2.3.1., numbered as 8 and 8.1) and Q3-4 (were not included in the LIMD, but performed within the same data collection I). The questions were given orally and the total interview was audio-recorded followed by an orthographical transcription which enabled analysis of the responses. Q1 and Q3 were asked to all participants. Q2 and Q4 were open follow-up questions, asked to participants responding "yes" to Q1 and Q2.

1. *Would you be willing to participate?*
2. *Why would you be willing to participate?*
3. *If you were unable to make your own decision, would it be acceptable for someone else to make the decision regarding your participation?*
4. *Who would you prefer to make the decision in your place?*

After transcription and analysis, the different reasons for participation were divided into five informal subcategorizes by the test leader (SS) to facilitate a comparison between groups and/or trials. Co-author (IMT) gave a second opinion on the analysis and sub-categorisations of answers. If the willingness to participate (answer to Q1) was verbalised unclearly, the choice to participate or not was controlled by the follow-up question Q2: "Why would you be willing to participate?" (giving the participant the chance to deny an interpreted willingness). No response options were given.

2.3.3.5 VAS

Visual analogue scales (VAS, 0-100 mm) were handed out to the participant (one at a time) by the test leader (SS) after the interview of each vignette. The VAS served to estimate the participant's evaluation of perceived personal risk ("risk"), personal benefit ("own-benefit") and benefit for others ("other-benefit") involved in the two trials. SS performed the test procedure and analysis (blinded to group).

2.3.4 Study IV

Study IV (work in progress) is a qualitative study, applying semantic analysis of selected utterances (which were considered to be illustrative examples of meaning and lack of meaning) based on previously collected material (data collection I) in the form of recorded interviews and transcripts: (1) one vignette, (2) a standardised interview (Q1-8 from the LIMD)

2.3.4.1 The vignette

The kidney disease vignette describes a hypothetical clinical trial that offers a potentially high degree of benefit at a low degree of risk (see study one; 2.3.1.1. vignettes).

2.3.4.2 Standardized interview

The interview included the eight questions from the LIMD-interview, covering three criteria of MDC (questions 1-8 from the LIMD, see study I; 2.3.1.1). The interview was given orally (based upon information given both in written form and orally) and lasted approximately four minutes per participant. The interview was audio recorded and orthographically transcribed (as

part of data collection I). Note, the interviewer closely followed the script of the standardised questionnaire, i.e. no spontaneous interaction between interviewer and participant was permitted. The participants were allowed to reread the text (vignette) while answering the questions. Answering the questions called for sufficient comprehension and the ability to distinguish between the hypothetical (vignette) and other situations in addition to being able to respond orally to the questions in a rational manner.

2.3.4.3 Semantic analysis of selected utterances

The inclusion of the four participants, in study IV was based on a qualitative selection among transcribed data from data collection I (the LIMD-interview) to represent speech acts from both conditions of impaired cognition due to AD and presumed normal cognitive functioning in the group of HC, respectively. Selected utterances from each participant were examined word-by-word and line-by-line. The selection of utterances was based on the aim of capturing illustrative examples of sense-making and figurative speech based on the reasoning for possible participation in the fictive clinical trial.

The analysis considered sense-making and the way linguistic signs (e.g. words, literal concepts) of time, place and person occurred. This linguistic approach was influenced by previous studies of irrelevant speech in dementia (Tallberg, 1999; Tallberg, 2000), but from a somewhat new perspective as the utterances were the product of an experimental context in which the participant was instructed to take the perspective of a hypothetical self (an individual with a kidney disease described in the vignette text) in a hypothetical situation (the fictive clinical trial described in the vignette text) at an unspecified time. It was presupposed that these participants would, to various degree, move cognitively between predefined cognitive situations, as described by Tallberg (2001) as: “the contexts a speaker constantly moves between, including the present context and memories of the past and the future”. Based upon this presumption, five cognitive situations associated to the context of the current experimental study, were defined:

- **The vignette situation**. A hypothetical situation, clearly stated as fictive in terms of person, time and place. The characters were a doctor working with clinical trials and a patient with a kidney disease, invited to participate in a clinical trial. The text is worded in the present tense and is intended for and addressed to the reader of the text (with the pronoun *you* referring to the hypothetical patient, i.e. the participant in current study).

- **Other imagined situation**. Any invented situation, imagined by the participant, probably totally or partly unknown to the listener, assumed to be constructed from the participant's previously experiences or somewhat related to other predefined situations (the vignette, the participant's own life, experimental and the situation at hand).
- **The own life situation**. The participant's actual real-life situation (current and past), which may or may not bear similarities to the vignette situation.
- **The experimental situation**. This situation began before the interview took place, when the participant agreed to the terms of the current experimental study, which included two speakers: the participant (the subject for the interview, either AD or HC) and the interviewer (test leader; TL) who reads the vignette aloud. The TL began the interview with the words *"Imagine that you…"* followed by the standardised questions.
- **The speech situation.** A shared present situation, referring to the ongoing interview situation, agreed upon by both speakers (*me* and *you*) occuring in present time.

Linguistic signs in the verbal utterances such as choice of pronoun and tense can be valuable clues for the listener who is trying to interpret the meaning of the utterances and what the speech act is referred to as followed (a) from what mental situation *(e.g. here/there and this/that),* (b) from what person *(noun – e.g. she/he, I, you and them)* and (c) from what time *(tense-e.g. current, past or future*). To distinguish different situations (hypothetical and other), the speech is preferably also underscored by additionally linguistic explicit signs such as the conjunctive conditional, *if* or verbally terms emphasising the mental situation from which the speech is derived, such as *hypothetically* or *supposing that.*

2.3.5 Study V

Different assessment tools were included in current version of study V (work in progress): (a) a test battery including cognitive and linguistic tasks and (b) KIMB, including the target word task (KIMB-t; measured by score and time in seconds) and a questionnaire (KIMB-q; measured by score and time in second). The tasks are presented in short below (but *only* the results of KIMB-t score will be reported and discussed in the current thesis).

2.3.5.1 Cognitive test battery

Six cognitive tests / tasks were included. Four of the tests had strong association to MDC (measured by LIMD in study II):

- **Rey Auditory Verbal Learning Test** (RAVLT, Lezak et al., 2004; Schmidt, 1996).
- **Repetition of Long Sentences** (BeSS; Laakso et al., 2000; Holmbro & Olsson, 2000).
- **Inference** (BeSS; Laakso et al., 2000; Holmbro & Olsson, 2000).
- **Reading Speed** (Järpsten, 2002).

Screening test of overall cognitive function:

- **Montreal Cognitive Assessment Battery** (MoCA, (Nasreddine et al., 2005).

One cognitive task we hypothesized would *not* correlate to KIMB:

- **Word sequence production** (Östberg et al., 2008).

2.3.5.2 Kliniskt Instrument av Medicinsk Beslutsförmåga (KIMB, English "clinical instrument of medical deicision-making capacity)

KIMB, target word (KIMB-t). The design of the KIMB target word task (abbreviated in the current thesis as KIMB-t) is similar to the Reading Speed task (DLS; Järpsten, 2002) as it consists of a text (written by SS and LT) including several sets of embedded brackets […] each containing three possible words, where the one correct *target word* should be underlined as fast as possible. However, the text of KIMB-t differed from the Reading Speed task in that it describes a fictive clinical trial and has lower number (13 versus 36) of embedded brackets (i.e. the participant is expected to read through the entire text). The text describes a fictive individual who is suffering from a fictive disease and is offered participation in a clinical trial with presumed high risk and low personal benefit. The text includes information regarding i.e. the procedure as well as the possible risks and benefits of a participation. The text in KIMB has approximately the same number of words (n= 327) as the vignette texts used in LIMD. The KIMB-text, was during its construction, analysed with the SVIT language model (by KHM, Heimann Mühlenbock, 2013) to study its readability and to ensure that it was constructed with similar language characteristics as the text of the Reading Speed task (DLS; Järpsten, 2002), which previously has shown high predictive value for assessing MDC by LIMD (Stormoen, et al., 2014). The SVIT model includes analysis of a combination of linguistic properties such as for example vocabulary (i.e. incidence of difficult word) as sentence structure (i.e. mean length of utterance) (Heimann Mühlenbock, 2013).

The scoring procedure for KIMB-t was to count the correct responses (max 13) and measure total time (in seconds) taken to complete the task. Each correctly identified word earned one

point, whereas wrong choice of the word, no word or several words chosen within the same brackets earned no points. Several different cognitive and linguistic skills were required to identify the correct target word in each bracket, such as reading capacity, word and language comprehension, inference and working memory. The instruction was to read the text and underline one target word in each bracket as fast as possible. An excerpt from KIMB-t is given below:

"…We are investigating and testing the effect of a new drug, Auxilium, which is expected to alleviate the symptoms of the Dolor disease. To participate in this [surgery study contest] the participant will be assigned to one of two trial groups, where one group will try Auxilium and the other will receive a substance with no therapeutic effect, so-called [water caffeine placebo]…"

KIMB, questionnaire (KIMB-q).

The KIMB questionnaire was composed of six written questions with multiple-choice answers: 1) *What is the text about, 2) What are the risks associated with participating in the study? 3) What are the benefits if participating in the study?* 4) *Estimate the risks of Kim's participation, 5) Estimate the benefits of Kim's participation*, 6) *Would you advise Kim to participate in the study?* The participants were allowed to re-read the text while answering the questions to lessen the burden on memory capacity. The instruction was to complete the task as quickly as possible. Each correct chosen answer earned one point, while a wrong answer, no answer or multiple answers earned no points. The scoring procedure of KIMB-q was to count the correct responses (range 0-6 scores) and measure the total time taken (in seconds) to complete the task.

2.4 STATISTICAL ANALYSIS

Statistical analysis was conducted using SPSS™ version 22 (studies I-III) and version 23 (study V). The rejection level was set to $p<0.05$. Descriptive statistics (mean ± standard deviation) were used to present characteristics and test results for the three groups of participants (studies I-III and V).

Principle Component Analysis (PCA)

PCA was conducted in studies I and II and presented and discussed in terms of *component/factor scores* and/or *loadings* as follows:

- *Study I.* The correlation matrix, using eigen-values >1 as criteria for number of components and varimax rotation in order to find a simple structure of all 27 items

(measurment scores) in LIMD. To find out if LIMD-total score represents a uni-dimensionsal variable, independent of criteria and vignettes.

- *Study II.* PCA was performed to find a simple structure of the cognitive tests battery (lessen the number of measurments into independent components including as much as possible of the total variance). Eigen values >1 were used to select number of components (all components should have high loadings; meaning >.70, in at least two test measures). Varimax rotation was applied to identify a parsimonious structure.

Stepwise linear regression

- *Study II.* Stepwise linear regression was used to examine the association (common variance, r^2) between the total LIMD score and the four identified PCA components. The degree of importance for each component toward LIMD was presented as β weights. The first regression analysis was performed with total LIMD score as dependent variable and the four PCA components: (1) verbal knowledge, (2) episodic memory, (3) cognitive speed and (3) working memory. Further regression analyses added demographic characteristic (age, gender and education) and dementia severity (MMSE) to the four components.

The Pearson correlation coefficient

The Pearson correlation coefficient (PCC) also referred to as Pearson's *r*, was conducted in studies I, II and V as follows:

- *Study I.* **(**1) interrelationship between LIMD and demographic characteristics as well as cognitive severity by MMSE within groups (AD, MCI and HC), (2) reliability: (2a) correlation between evaluations by two different examiners and (2b) correlation between two evaluations by the same examiner and (3) validity: interconcistency between the three LIMD criteria (comprehension, evaluation and communication of a choice) and the three vignettes (nine variables).
- *Study II.* Correlations among pairwise variables (test-test and test-component) of LIMD.
- *Study V.* Correlations between KIMB-t and six cognitive tests.

Analysis of variance (ANOVA)

One-way ANOVA (to compare means of two or more diagnostic groups), followed by Tukey's post-hoc t-test (conducted to confirm where the differences of test results occurred between groups) was applied in study I, II, III and V as followed:

- *Study I.* (1) Examination of groups (AD, MCI and C) was comparable in demographic characteristics as demonstrated by non-significant group effects (all p>.1) according to one-way (group) ANOVAs, (2) Investigation the differential diagnostic power by means of ANOVA using total LIMD score as dependent variable and diagnostic group as independent variable and (3) investigation of differential pattern due to vignettes by a repeated measure (three vignette scores) two-way ANOVA with the three diagnostic groups as independent variables and mean LIMD score for each vignette as dependent variable.
- *Study II.* Analysis of group differences in age, education, LIMD, MMSE and all cognitive test measures. Tukey's post hoc t-test was used to analyse possible pairwise group differences. The effect size was reported as degree of explained variance in ANOVA's (eta, η^2).
- *Study III.* (1) Investigation of whether the factor group (AD, MCI and HC) and willingness to participate (acceptance to participate or not) had an influence on cognitive severity (MMSE) and MDC (by LIMD) in the two clinical trials (with varied applied risk and benefit) and (2) analysis of the pattern of results regarding trial, estimate and group in each trial and type of estimation.
- *Study V*. Analysis of possible differences between the groups AD, MCI and HC regarding age, educational level and score on KIMB.

Multivariate analysis of variance (MANOVA)

- *Study III.* **(**1) Two-way (type of trial and type of estimation as within-subject factors) MANOVAs were used to determine whether there were any differences between diagnostic groups (independent variable, between-subjects factor) on two continuous dependent variables: trial and estimation), followed by Tukey's post-hoc t-test (to confirm where the differences occurred between groups), (2) VAS estimation of risk and benefits (risk, own-benefit and other-benefit) in the two hypotetical trials as within-participants' dependent variables and groups as independent variable was analysed and (3) acceptance to participate (answering "yes" to Q1) in the two trials and acceptance

of a proxy as decision maker ("yes" to Q3) in the two trials as within-participants' dependent variables and groups as independent variable.

2.5 ETHICAL CONSIDERATIONS

The studies included in the thesis were approved by The Regional Ethics board at Karolinska Institutet, Stockholm: Dnr. 2008/1276-31/2, 2009/1764-32 and 2015/1516-32. All participating individuals, regardless of group, were given oral and written information about the study and gave their own informed consent to participate.

3 RESULTS

3.1 STUDY I

3.1.1 Scoring

All results are presented on group level (AD, MCI and HC) and the LIMD score refers (if nothing else is specified) to the *mean* and *total* LIMD score (mean value between two ratings by the same examiner (IMT) of total LIMD score, including all three vignettes and all three MDC criteria; minimum score 0 and maximum score 27). The mean and standard deviation on LIMD score in the different groups were; AD= 8.0±7.1 (range 0.5-22), MCI= 17.1±6.1 (range 2-27) and HC= 22.4±4.8 (range 9-27).

3.1.2 Reliability

Test reliability was calculated as inter-rater reliability (the degree of agreement of total LIMD score among two different examiners, IMT and SS) and intra-rater reliability (the degree of agreement of total LIMD score among repeated ratings by a single examiner IMT). Both inter- and intra-reliability were found to be good ($r = .89$, $p < .01$ vs 0.94, $p < .001$). Furthermore, the correlation between first and second evaluation within groups were all at high levels (AD, $r = .92$; MCI, $r = .90$; HC, $r = .88$, all $p < .001$).

3.1.3 Validity

3.1.3.1 Internal consistency

The associations between the three LIMD-criteria and the three vignettes of LIMD (in sum nine variables), were all high, between 0.64 and 0.94, and strongly significant (all $p < .001$). One single component accounted for approximately 80 % of the total variance. All variables were strongly loaded in this component (in range between $r = .86$ and $r = .93$).

3.1.3.2 Differential diagnostic power

Group differences on total LIMD score were strongly significant ($F = 40.60$, $df = 2/76$, $p < .001$, $eta^2 = .52$) and groups differed significantly ($t = 4.51$, $df = 40$, $p < .001$; $t = 3.71$, $df = 57$, $p < .001$; AD vs. MCI and MCI vs. HC). The interrelationship between LIMD score and demographic characteristics (age, gender and education) and MMSE score within groups was not significant between LIMD score, age or gender in any group, but a positive correlation was found between level of education and total LIMD score in HC ($r = .54$, $p < .001$) and a significant association between total LIMD score and MMSE in all groups.

No significant differences pattern (F=1.03, df=1/76, p>.1) was found among total LIMD score, the three vignettes (Kidney disease, Skin disease and Hypertension) and the three groups (AD, MCI and HC). Furthermore, the interaction between vignettes and diagnostic groups was not significant (F=1.98, df=2/76, p>.1), although the groups were clearly separated across vignettes (F=39.46, df=2/76, p<.001).

The three groups differed significantly in total LIMD score including after exclusion of possible confounding demographic factors (age, gender and education) and cognitive severity (by MMSE; F=7.76, df=2/70, p<.001). Three of the four covariates were significantly associated with total LIMD score: age (F=8.32, df=1/70, p<.01), education (F=7.43, df=1/70, p=<.01), and cognitive severity (MMSE; F=17.82, df=1/70, p<.001), though gender was not a dependable covariate. The analysis was repeated also considering the three criteria measured by LIMD (comprehension, evaluation and intelligibility of choice) and possible confounding factors (age, gender, education and MMSE) and no significant effect was found. However, the effect of diagnostic group remained significant (F=4.92, df=2/70, p<.01.).

3.2 STUDY II

3.2.1 Scoring

Descriptive statistics of LIMD and the 27 cognitive and linguistic measurements were reported as followed: AD performed worse than MCI and HC (and MCI performed worse than HC). Significant group differences were shown total LIMD score and the measurement of cognitive and linguistic functions (p<.05).

AD and HC differed significantly in all tests (p<.05). AD and MCI differed significantly on LIMD and several cognitive test measures (e.g. language production and comprehension, reading capacity and episodic memory; p<.05). MCI and HC differed significantly on LIMD and several cognitive tests (e.g. language production, reading capacity, spatial ability, short-term memory, episodic memory, executive function, attention and speed; p<.05).

3.2.2 LIMD versus cognitive and linguistic tests

The 27 cognitive measurements were found to aggregate into four components corresponding primarily to overall verbal knowledge, episodic memory, cognitive speed and working memory and accounted for approximately 70% of the variance in LIMD. Total LIMD score correlated

significantly to the four components (possible predictors) (multiple r=.86, adjusted r^2=.73, F=40.23, df=4/55, p<.001) as followed: the "verbal knowledge" component (beta=.66; p<.001), the "episodic memory" component (beta=.43; p<.001), the "cognitive speed" component (beta=.32; p<.001) and the "working memory" component (beta=.23; p<.01).

The single tests measure with highest correlation to LIMD total score was the language task: "Reading Speed" (included in "the verbal component"), which evaluates e.g. reading capacity, comprehension, speed and inference based on a written context (r=.77, beta=.38; p<.001). The second strongest correlation between LIMD and single tests was "RAVLT" (=total score; included in "the episodic memory component"; r=.71; beta=.26, p<.001), which evaluates e.g. short-term auditory-verbal memory. Inclusion of additional measurements showed significant contribution by the single tasks: "Inference" (included in "the verbal knowledge component", r=.75; beta=.23; p<.001), which evaluates e.g. ability to comprehend and draw a conclusion based on an orally and written context and "Sentence Repetition" (included in "the verbal knowledge component"; r=.67; beta=.22; p<.001), which evaluates e.g. verbal repetition of long sentences, attention and working memory.

3.3 STUDY III

3.3.1 Acceptance to participate

The study reported significant difference between the two hypothetical trials in terms of overall willingness to participate in the hypothetical trials (who accepted answered "yes" to question 1, regardless of diagnostic group; F=44.1, df=1/71, p<.001, ε^2=.38) as followed:

Higher willingness to participate in the *low*-risk trial, Kidney disease trial (approximately 90%) compared to the *high*-risk trial, Hypertension trial (approximately 40%). No significant difference was found among groups regarding willingness to participate in each trial (p>.1) and no significant interaction among groups and trials was shown (p>.1). Significant difference in MDC (measured by LIMD) was found between those participants who accepted to participate (who answered "yes" to Q1, regardless of diagnostic group) in the *low*-risk trial (F=6.60, df=1/73, p<.01, ε^2=.09) in comparison to those who accepted to participate in the *high*-risk trial (F=3.86, df=1/73, p<.01, ε^2=.05).

- Individuals who accepted to participate in the *low*-risk trial (n=66) showed stronger MDC (by LIMD; 18±8) than individuals who did not accept to participate (n=8; LIMD; 10±9).
- Individuals who accepted to participate in the *high*-risk trial (n=31) showed lower MDC (by LIMD; 14±8) in comparison to individuals who did not accept to participate (n=43, LIMD; 18±8). Notable, no significant difference in cognitive severity (by MMSE) was shown between individuals who accepted or not to participate in each trial ($p>0.1$).

3.3.2 Reasons for participation

The reasons for participating in each trial were analyzed for all participants who communicated willingness to participate (the *low*-risk trial, n=66/74 and the *high*-risk trial, n=31/74). Hypothetical participation was motivated by the response to question 2: *"Why would you be willing to participate?"*. After transcription the different reasons for participating were divided into five subcategories, listed below, with some examples of responses within each category):

- **Own-benefit:** (the *low*-risk trial, n=26/66; the *high*-risk trial, n=5/31)
  "...because I want to feel good…" / *"...I like to take advantage from medical controls within the research project, which may be beneficial for myself* (the *low*-risk trial,
- **Help other:** (the *low*-risk trial, n= 12/66; the *high*-risk trial, n= 14/31)
  "...contribute to a better treatment for others in the future"/ "...by participation in a research project one can possible make a difference for others…"
- **Own benefit and Help other:** (the *low*-risk trial, n= 16/66; the *high*-risk trial, n=0/31)
  "...well for my own benefit as I hopefully can get avoid a Kidney transplantation and so that I maybe can contribute to help other in the future…" / "...one reason to participate is that me, myself can benefit from it and in addition one can also contribute to help others…"
- **Support research and Make good:** (the *low*-risk trial, n=4/66; the *high*-risk trial, n=10/31)
  "...the reason is to move forward with research and all those things…" / "...I believe one has a duty… by participating and in that way contribute to research…"
- **Other reason:** (the *low*-risk trial, n=6/66; the *high*-risk trial, n=2/31)
  "... yes well I guess I do not have not much to lose…" / "...it is difficult to explain why…"

The overall primarily reason to participate in the *low*-risk trial was reported as "own-benefit" (approximately frequency across groups 40%), while "help others" was the most commonly identified reason for participation in the *high*-risk trial (approximately frequency across groups 50%).

3.3.3 Estimations of risk and benefit

A significant difference was found between the two trials across groups ($p<.001$) as well as of types of estimations (by VAS; 0-100 mm) across groups ($p<.001$). No significant group differences were found between MCI and HC concerning estimations of benefits or risk in either trial (all $p>0.1$).

- In the *low*-risk trial, significant group differences concering mean VAS score were shown regarding "other-benefit" ($F=5.38$, $df=2/71$, $p<.01$) as followed: AD estimated "other-benefit" lower than MCI and HC ($p<.05$; AD (70), MCI (84) and HC (85)).
- In the *high*-risk trial significant group differences on mean VAS score were shown for "own-benefit" ($F=5.05$, $df=2/71$, $p<.01$) and "risk" ($F=8.96$, $df=2/71$, $p<.001$) as followed: AD estimated "own-benefit" *higher* than MCI and HC ($p<.05$; AD (50), MCI (26) and HC (26)) and estimated "risk" *lower* than MCI and HC ($p<.05$; AD (33), MCI (62) and HC (66)).

3.3.4 Attitude toward proxy

Significant difference was observed between the two trials regarding overall willingness to accept to a future proxy between the two trials ($p<.001$): Higher acceptance of proxy in the *low*-risk trial (approximately 70%) compared to the *high*-risk trial (approximately 40%). AD patients were more willing to accept proxy in the *high*-risk trial compared to HC ($p<.001$; AD (60%) vs. HC (22%)). No group difference was shown regarding acceptance of proxy in the low-risk/high-benefit trial ($p>.1$). Also, AD patients showed an overall positive attitude to proxy and no difference in acceptance to proxy between the two trials ($p>.1$), while acceptance to proxy differed between trials in the groups of MCI ($p<.01$) and HC ($p<.001$). As shown in the transcriptions and analyses of the responses to: *"Who would you prefer to make the decision in your place?"* several different choices of future proxy were communicated among all participants (who accepted a proxy in either trial; the *low*-risk trial, n=52/74 and *high*-risk trial, n= 28/74). Their responses were divided into three informal subcategories listed below with some examples:

- **Family member:** (*low*-risk trial, n=45/52; *high*-risk trial, n=26/28)
  "...my wife or son..." / "...my daughter or son in law…" / "...my husband or daughter.."
- **Physician:** (*low*-risk trial, n=3/52; *high*-risk trial, n=1/28)
  "...some doctor…".
- **Family member and Physician:** (*low*-risk trial, n=4/52; *high*-risk trial, n=1/28).
  "...my partner or son together with a physician…" / "...close family in consultant with a physician…"

The study was reported that "a family member" was the most common identified response (considered each and the sum of the two trials) when the participants were asked who they preferred hypothetically would make the decision in their place (approximately 90%).

3.4 STUDY IV

The AD patients demonstrated fluent but perseverative and unspecific speech displaying some semantic abnormalities. It was unclear to some extent which cognitive situations (as described by Tallberg, 2001) they were moving between (suggesting difficulties to mentally transform themselves within and between given situations; the vignette, other imagined, own life, experimental, and the on-going speech situation). A tendency or preference to remain in the present own-life situation, not taking the perspective of the fictive subject in the hypothetical text, was noted. Hence, the individuals with AD seemed to struggle to separate the hypothetical situation from their own present reality such as motivating a choice to participate in the hypothetical trial due to the real-life situation (e.g. "many children and grandchildren"). Use of linguistic signs for time and place, conditional tenses and conjunctions was very sparse. Also, general use of pronouns did not clearly show a distancing between their own real selves and their hypothetical selves for the purpose of the information given in the vignette. The analysis could also show that the responses by the HC were fluent and more informative, detailed and moved logically and concisely between the different cognitive situations. This movement was conveyed by the use of linguistic signs for time and conditionals expressed through both tense and the conjunction word *If*, which reveals a distance between the individuals real and hypothetical self.

3.5 STUDY V

3.5.1 KIMB-t

3.5.1.1 Comparison of groups

One-way ANOVA showed a significant group difference on KIMB-t ($p < .05$). Tukey's post-hoc test revealed that KIMB-t score was significantly higher for HC than AD group ($p < .05$) while no significant difference was found between HC and MCI nor between AD and MCI. There was also a significant difference between the groups regarding time to complete the task ($p < .01$). Tukey's post-hoc test showed that the time to complete the task was significantly longer for AD than HC ($p < .01$) and MCI ($p < .05$), while no significant difference was found between HC and MCI.

3.5.1.2 Sensitivity and specificity

The significant differences on group level by the combined group (AD + MCI) were a prerequisite for the calculations on sensitivity, specificity and predictive values. If KIMB-t cut-off value was set to 12 points (allowing one error), the sensitivity was low (37 %) but specificity was high (94 %).

3.5.1.3 In comparison to cognitive and linguistic tasks

The Pearson product-moment correlation coefficient was calculated to investigate associations between scores of KIMB-t task and results of the six comparable tests (including all individuals), (effect sizes, calculated as r^2). KIMB-t score correlated significantly and positively to to cognitive severity by MoCA ($p < .01$; $r = .46$; $r^2 = .21$) and to the four cognitive and linguistic tasks previously associated to MDC (by LIMD, see study II): Repetition ($p < .01$; $r = .48$; $r^2 = .23$), Inference ($p < .01$; $r = .45$; $r^2 = .20$), Reading Speed ($p < .01$; $r = .45$; $r^2 = .21$) and RAVLT ($p < .05$; $r = .30$; $r^2 = .09$).

3.6 IN SUM

I. LIMD, the Swedish linguistic instrument of medical decision-making has demonstrated good psychometric features, which high-lights the impact of including communicative and linguistic features when assessing the decision-making capacity for research in patients with cognitive impairment.

II. Multiple factors are involved in MDC as measured by LIMD, but the components of overall verbal knowledge, episodic memory, cognitive speed and working memory were strongly correlated to the capacity and the Reading Speed task, which assesses both rapid reading and understanding of a text, showed the strongest correlation to total LIMD score.

III. Medical decisions by the patients should be interpreted with caution already in early stages of AD as their acceptance to participate in high risk trials may be due an insufficient decisional ability to estimate risk.

IV. Irregularly used linguistic signs for referring to time, place and person may lead to difficulties in interpreting and understanding the sense-making in speech.

V. Preliminary results indicate that KIMB-t could serve as a brief Swedish reading tool to detect patients with reduced capacity to give informed consent (based on written information).

4 DISCUSSION

4.1 METHODOLOGICAL TOPICS

4.1.1 Procedure

The PhD-project is based upon empirically research and includes five studies, which all, by different approaches take a linguistic approach to the topic of medical decision-making among patients with impaired cognitive function: (1) developing two new linguistic tools (LIMD and KIMB) for evaluating different aspects of MDC (studies I and V); (2) investigating cognitive and linguistic correlates of MDC as measured with LIMD (study II and V) and (3) analysing of verbal utterances in terms of choices and decisional reasoning (studies III and IV). The scientific complexity of medical decision-making in dementia can be discussed from two central themes:

1) **Inconsistency -** Estimation of decision-making is per fact limited to the individual's ability to make a decision and reason at one specific occasion (the exact time and context in which the capacity is being assessed). The capacity may fluctuate depending on what cognitive situation the participant is referring to in relation to the hypothetical situation from which the questions are based upon. If the capacity was considered another day or in another context, the result might have been different. Also, the capacity is expected to constantly change due to the progressive cognitive decline following the neurodegenerative disease. Hence, the capacity is not static but changeable, due both to individual causes (e.g. patients' status) and contextual causes (e.g. complexity of decisional situation and time given). Sufficient or insufficient capacity must always be assessed on an individual basis and sometimes needs to be reconsidered.
2) **Interdisciplinary -** The field is multidisciplinary and determination of capacity must be viewed upon in the light of a broad and deep discussion including several research areas such as linguistics (e.g. semantics and pragmatics), speech and language pathology (e.g. language disorder), medicine (e.g. differential diagnosis and neuropathological processes), neuropsychology (e.g. cognitive predictors), medical ethics (e.g. issues related to autonomy and protection) and law (e.g. national laws and guidelines).

Noteworthy, the choice to investigate certain aspects of decision making in research from a linguistic perspective among AD patients, should be considered as a complement, not a supplement, to previous evaluations of MDC. Yet, multidisciplinary aspects and concerns are

intercepting the linguistic perspective of the thesis and are concisely to some extent discussed in the light of the results.

Possible scientific uncertainties such as for example definition of critical key words like MDC, inclusion criteria of groups and possible methodological concerns of both the qualitative semantic analysis as well as the test design and results will be addressed even more distinctly in the two papers still in progress (study IV and V). Yet, methodological choices such as participants, measurements, analyses and results of the five studies will be brought up and discussed in the following sections. Finally, future implications and conclusions will be summed up.

4.1.2 Participants

All participants were given both written and oral information about the research project. It was ensured that all patients had been diagnosed (during the past 12 months) with either AD or MCI at the Memory clinical at Karolinska university hospital before being recruited. By including patients with mild to moderate dementia (MMSE: AD>20) and those with a mild cognitive impairment (MCI) (MMSE: MCI>25) but no dementia, we hoped to capture subtle diversity between groups. Another option may have been to include a larger group of AD patients in place of the MCI group, but in so doing we would have missed the opportunity to compare subtle changes in MDC, cognition and linguistic functions, between the two groups of patients. Another reason to include MCI patients was that they represent a group of subjects with impaired cognitive function, at risk of progressing to AD.

The overall ambition of both data collections was to recruit approximately 20 participants in each group. In the first data collection we included in sum 79 participants (AD, n=20; MCI, n=22; and HC, n=37) and in the second data collection we included 55 participants (AD, n = 21, MCI, n = 17 and HC, n = 17) to serve the purpose of current version of study V. In study II and III, five participants were excluded (one MCI and four HC) from data collection I, in order to match the groups even better in terms of demographic factors (age and education). Study IV was a qualitative report (semantic analysis) of different verbal utterances (participants responses from the standardized interview), and not designed to include a large number of participants.

One inclusion criterion was overall cognitive function measured by the patients clinical score

on MMSE, chosen for reasons of convenience as it this score was reported in a standardised manner within the clinical examinations of all patients (in comparison to for example MoCA, which at the time had not been examined in all patients at the memory clinic). However, MoCA served the purpose to measure cognitive severity in data collection II (study V). It may possible have been beneficial to instead include both MMSE and MoCA to measure overall cognitive severity in both data collections, as the two tests differ in some respect – for example MoCA covers more spatial exercises in comparison to MMSE.

The inclusion criteria for the healthy elderly subjects (HC) were age (>55 years), Swedish as a native language and no dyslexia or hearing/visual impairments (glasses and/or hearing aids was accepted) that could negatively affect their test performance. These criteria were important since all studies were based on the ability to read and comprehend the Swedish language.

Approximately one third of all patients who matched the inclusion criteria accepted to participate. Reasons for not participating were not formally registered. Study III revealed an overall surprisingly high willingness to participate in the hypothetical clinical trials as approximately 90% of all participants expressed that they were willing to participate in the *low*-risk trial, and approximately 40% were willing to participate in the *high*-risk trial (which was written to exaggerate side-effects beyond what would be accepted by an ethical committee for this type of treatment). To examine decisional capacity and attitudes toward research within and between groups - which already had a presumed average positive attitude on average toward research participation since they had volunteered to participate in current experimental research project - must be considered when interpreting the results in each study (especially study III). It is also important to consider that presumable other factors, besides group affiliation or cognitive and language impairment, may affect the results of the studies. For example, current emotional status, family situation, general knowledge of research and medical terms and previous experiences were not considered as part of the studies but could have had some impact on how the participants performed in the assessments of MDC by LIMD (study I) and KIMB (study V) and on how they reasoned and made decisions (studies III and IV). Additionally, it must be considered if the patient has interpreted the given information accurately. Finally, in practice some individuals may have difficulties to verbally express their thoughts and choices, without having an affected decisional capacity. These individuals may instead use other ways to communicate such as written communication, sign language or augmentative and alternative communication. Groups of individuals dependent communication other than verbal, were

however not included in any of the data collections. Hence, alternative ways of reasoning and communicating a choice was not evaluated in either of the studies but would be interesting to explore in a future study.

The results in studies I-V could to some extent be generalized into other neurodegenerative diseases with compromised cognitive functions, but this hypothesis need to be examined systematically in a future study before any conclusions can be drawn. Impaired ability to make a reasonable decision could possibly be a result of an inability or unwillingness to actually "bother" rather than due to a reduced cognitive function. I imagine this could for example be the case for patients with depression or frontal injuries.

It should be noted that, although the groups differ in diagnostic classification and significantly differ in terms of cognitive and linguistic measurements, a wide range of scores within groups was noted concerning for example measurements of general cognitive level (by MMSE or MoCA). Moreover, it is likely that other causes differ to some extent between the individuals in each group, such as emotional status and sleep disorders (which were not covered by the inclusion or exclusion criteria), which could affect the results of the studies.

LIMD and KIMB were validated in a Swedish population with Swedish as native language, which lessens their usability in practice. Assessment of MDC in non-native speaking Swedish individuals entails further complexity to the field. Insufficient Swedish language capacity must not be valid reason for questioning decision-making capacity, but rather give cause to adapt the current situation (i.e. interpreter or language adapted information).

Finally, all healthy adults are presumed to have sufficient decisional capacity, meaning they have the right to make their own decisions autonomously. Hence, age itself does not imply diminished decisional capacity, but age-related diseases such as dementia show a high correlation with reduced MDC. Along with an elderly population, society faces medical, ethical and health literacy challenges in dealing with age-related diseases such as dementia.

4.1.3 Material and Assessments

The cognitive and linguistic tests in study II were chosen on the basis of what tests that are routinely conducted in the clinical investigations by neuropsychologists and/or speech and language pathologists. The test battery (in total 14 tests, 27 measurements), was composed to

cover essential overall cognitive and linguistic functions by valid instruments and to match the clinical assessments. The categorisation of the tests by their measured capacities (overall cognitive function, language production, language comprehension, reading capacity, memory, spatial ability, executive function, attention and cognitive speed) presented in study II was a theoretical construction within the research project. It may be reasonable to discuss whether it was justifiable to include such a comprehensive test battery within the data collection I. It is possible that the participants may have found the high number of tasks challenging and may not have been performing consistently to the best of their abilities for the duration of 3-4 hours. However, it must firstly be mentioned that all participants were offered several pauses and coffee breaks throughout the test procedure, although it is still reasonable to imagine that their mental energy decreased after some time. Secondly, all tests were conducted in the same order, which at least partly enabled a comparison of results between groups (study II).

Study IV contributes with an additional qualitative perspective, by analysing the responses by a detailed descriptive approach; a strength to the PhD-project. The semantic analysis of the utterances reported in study IV may be used for continued theorisation on how to evaluate the reasoning during a decision-making procedure.

Finally, it should be emphasized that the methodology sections and results presented in study IV and V are work in progress and only selected parts from the papers are reported and discussed in the current thesis. The methodological choices, results and conclusions will to some extent be adjusted and discussed further out in revised versions of the papers.

4.1.4 Statistics

Correlations between groups, demographics and measurement scores were analysed by Pearson correlations (studies I-III and V). The literal terms high and strong versus low and weak were used to describe the output of the analyses. The correlations have sometimes also been described as “associations”. The statistical analyses were based upon parametric tests (Pearson’s correlation coefficient and ANOVA), which is considered powerful. However, as our sample sizes in each group were rather small and the choice of tests often depends on whether the mean or median more accurately represents the centre of our data’s distribution it may be argued that non-parametric tests would have been an appropriate choice. To “check” the credibility of previously published results, analyses of correlations have currently been re-calculated by non-parametric tests (Spearman and Kruskal-Wallis, one-way non-parametric

ANOVA). The re-calculation showed results overall in consistency with previously published results. This means that no significant differences of relevance were found to report between the output of parametric and non-parametric analyses.

4.2 THE LINGUISTIC APPROACH

Speech and language pathologist are well trained to assess and analyse language and communication functions using numerous of tools and methodological procedures. Exploring different perspectives of language in the light of MDC evaluation, as done in current PhD-project, is an innovative research approach, but perhaps also a future challenge for the discipline of speech and language pathology to exercise further out, in both clinical and research settings. Also, some previous studies raised from other scientific fields have indicated the significance of verbal knowledge in the MDC process, which are of great inspiration to current research.

The linguistic approach in the five studies is summed as followed:

I. Use of *linguistic features* (e.g. semantics and pragmatics) in the scoring protocol of MDC by the Swedish linguistic instrument of medical decision-making (LIMD), developed within the research project.
II. Exploring how LIMD is correlated to different cognitive and *linguistic components and single test* (measuring e.g. speed, episodic memory, naming, word fluency, reading, comprehension, inference and repetition).
III. Investigating what the participants actually are *verbally responding* (e.g. the meaning of their utterances) concerning acceptance to participate in hypothetical clinical trials and attitudes toward proxy and *how they estimate risk and benefit*.
IV. Conducting *a semantic analysis* (identify signs of time, place and person) to explore the sense-making in verbal utterances concerning hypothetical contexts.
V. Examining how a new brief *reading task, KIMB-t* (developed within the research project) can be useful to detect reduced capacity to give informed consent.

The choice of prioritizing a linguistic aspect of decision-making did not intend to diminish other central impacts of decision-making capacity, rather contribute with an additional approach and high-lighting the complexity of the capacity.

Note, in some of the methodological sections within the studies, cognition and language are presented in a parallel manner, e.g. “cognitive and linguistic tests” while for example the results

section in study II reports the linguistic function "verbal knowledge" as one of several cognitive components highly associated with MDC measured by LIMD. This might raise concerns about how to interpret the relationship between cognition and language. However, the thesis intention was to describe language as one of several functions within the wider overall term "cognition", which indeed encompasses several mental processes such as thinking, attention, memory, learning, awareness, problem solving and decision-making. Hence, cognition is per this description linked to both language and decision-making, which is in coherence with previous findings (e.g. Okonkwo et al., 2007; Gerstenecker et al., 2015). Nevertheless, the general study of linguistics covers a number of elements, discussed by for example Johansson and Manninen (2012). They described the nature and properties in the human language and present different subfields of linguistics such as: *morphology* (study of internal structure of words and their parts), *syntax* (study of how words can be combined to form larger entities such as phrases and sentences), *semantics* (study of the meaning(s) of words, phrases and sentences) and pragmatics (study of how the speaker uses words, phrases and sentences). Studies I-V explore linguistic performance primarily within the sub-field of semantics such as investigating the meaning of linguistic elements like exploring how different linguistic features are usable to estimate MDC and analysis of sense-making in verbal utterances. In addition, other linguistic perspectives such as pragmatic and prosody were considered to some extent as part of the scoring protocol of LIMD.

Furthermore, Johansson and Manninen (2012) discussed different perspectives regarding "the meaning of meaning" such as referential, mentalistic and different kinds of meaning from a linguistic approach. One literal key concept, among others, from the vignettes is "clinical trial". The study of meaning from a referential approach would consider *how* the speaker talks about the concept such as "clinical trial" in an actual speak situation. If the study of the meaning of the concept "clinical trial" is approached from a psychological standpoint, questions may include *how* it is related to representations of mental images and how the speaker and listener interpret the world through these representations of the object. Further on, the meaning of "clinical trial" looked up in dictionary may be described something like "observations of actual patients in comparison to laboratory studies". If we search instead for the encyclopaedic meaning, we will learn more about clinical trials in general as well as its associated terms. However, while semantics focuses on the *literal* meanings of words, phrases and sentences, which may be similar among speaker and listeners and in line with the definition given in a dictionary. meaning explained in a dictionary. Yet, individuals are for several reasons likely to

have different personal associations to the same concept or word. Some people may focus primarily on the risks associated to the concept of "clinical trials", others on the benefits, and this may be based on the individual's memory of previous experiences, current life situation and/or future plans, which presumable affect their verbal reasoning and decision. This assumption would be interesting to explore further in a study of semantics. The non-literal meaning of a concept, refers to the figurative language; how we use words, phrases and sentences to denote something different from their literal meaning, such as the use of metaphors, irony and hypothetical reasoning.

In the present PhD-project, when (a) analysing the sense-making of speech (studies IV), (b) measuring the decisional capacity by ability the ability to comprehend, evaluate and communicate a choice (study I) and (c) analysing how groups estimated risks and benefits (study III), it was not primarily a matter of appreciating the participants' ability to communicate the meaning of a word or concept such as "clinical trial". Their utterances were based upon hypothetical information and their reasoning was analysed and considered regarding their ability to capture this fictive situation (by LIMD; study I; semantic analysis; study IV and VAS; study III). Yet, their speech might have reflected their general knowledge and/or associations with "clinical trial" from previous experiences.

The linguistic features used for scoring by LIMD are somewhat similar to those presented in the Modified Hierarchy of Evidence of Decision-making Capacity (Brauner and Merel, 2006) such as *prosody* (oral signs of continued attention e.g. "uh-uh") and *verbal elements* (identification of single word answers and/or confirmatory language e.g. "yes, I think so" and "words signalling understanding of previous contribution"). This model by Brauner and Merel (2006) includes the decisional criteria "appreciation" (the ability to appreciate/"grasp" the given information and its consequences), which was not included as a separate standard in LIMD (rather embedded to some extent in the criteria of "evaluation and understanding"). The ability to appreciate the given information was explored further on in study III, in the sense of measuring self-estimated risk and benefit in various hypothetical trials by visual analogue scale (VAS; 0-100 mm).

In a study by Tallberg (1999), the author emphasized the importance of recognising signs of misperception in patients with dementia. The individual's self-image can be studied by analyzing how linguistic elements for referring to person, time and place are used in various

decisional situations. Furthermore, Brauner and Merel (2006) suggested that thoughtful actions by the interviewer, such as successfully repairing confusing language, can result in the participant being able to improve their decisional capability. The linguistic elements of person, time and place, were further explored by semantic analysis, as they were noted as absented or commonly used in some speech sequences of individuals in the AD and HC groups (study IV). Verbal reasoning may be incomprehensible if the elements of time, person and place in the reasoning are not used in a logical way, and difficulties in interpreting utterances may lead to assigning a patient impaired capacity of verbal reasoning and drawing the conclusion that the patient has insufficient MDC.

The semantic analysis conducted in study IV was an analysis of the participants' responses and not a result of the interaction between test leader and participant. One may discuss the actions of the test leader during the strict interview as part of LIMD, which had a strict standardised format (i.e. did not allow any additional interaction and / or conversation between the test leader and the participant). If the test leader had instead facilitated a somewhat freer conversation, it may have helped the respondent to better and more easily answer the given questions. Participants' requests for verbal clarification, such as "what", could in a free dialogue have been recognized and "picked up" by the researcher and responded to with clarification of the given information. Moreover, the analysis did not report on overall communication or analysis of non-verbal language like eye-movement and gestures, which could have been captured by a video recorder and have contributed to additional central communicative elements in the analysis of patient's sense-making. In sum, a linguistic perspective can provide valuable information about how and when different phenomena occur in speech and may also help to distinguish different pattern in terms of linguistic phenomena that may indicate an impaired ability to reason rationally.

4.3 LIMD AND KIMB-T

In order to understand the strengths and limitations regarding the test designs of LIMD and KIMB as well as to avoid unnecessary confusions it is important to define certain key words and concepts in the thesis. In the current thesis one key concept, among others can be identified as medical decision-making capacity, abbreviated in the different studies as MDC or MDMC. Each study targeted what the capacity actually was referred to by their objectives and descriptions in the methodology sections such as: "capacity to make decisions in medical contexts, based on text information concerning possible participating in hypothetical clinical

trials" (i.e. MDC for research settings). But, although this definition was well settled within the research project, it could perhaps have been defined more stringent throughout the total text of each study. For example, MDC/MDMC could in some cases, isolated from its overall context be misinterpreted as referring to "overall capacity" or "capacity to treatment". Also, definitions of the capacity and standards from external references, could in some cases have been clarified yet more stringent. For example, in the introduction section of study I, the text was referring to legal standards (LS) for MDMC by Okonkwo et al, (2008), who examined the capacity by the Capacity to Consent to Treatment Instrument (CCTI, Marson et al., 1995a), which covers the four treatment consent standards: (S1) *expressing choice*, (S3) *appreciation*, (S4) *reasoning*, and (S5) *understanding*, as well as one experimental standard (S2) *reasonable choice*.

It is a challenge to develop standardised, reliable and valid instruments for measuring MDC as the latter may be defined by various criteria and examined using different scientific approaches. The two instruments LIMD and KIMB-t, contribute an additional linguistic perspective to the field of MDC assessment. The tests show certain similarities, yet some differences in-between and in comparison, to other well recognized previously developed instruments. For instance, LIMD serves to assess certain linguistic features of MDC, while KIMB-t serves to detect possible reduced capacity for research participation, e.g. to give informed consent. No clear diagnostic "gold standard" or specific cut off values have been clearly settled to define insufficient decisional capacity, which is a key complication when developing valid and reliable new instruments to assess MDC. The validity of LIMD, as well as some preliminary results of KIMB-t score, are discussed in following sections.

4.3.1 Diagnostic validity

The diagnostic validity of LIMD and KIMB-t was investigated by comparing the test results among the three groups with varying in degrees of cognitive function (AD, MC and HC). The analyses were based on two separate data collections (carried out on similar groups but with different individuals). Study I reported strong diagnostic validity of LIMD, based on significant group differences of LIMD score ($p<.001$) and post-hoc t-test analyses of pair-wise group differences showed that the LIMD score significantly separated the three groups respectively ($p<.001$). Study V showed that KIMB-t had diagnostic validity only to some degree, as KIMB-t did not capture the subtle decline in MDC between patients with varied cognitive function (AD and MCI). A significant group difference ($p < 0.05$) and Tukey's post-hoc t-test revealed

that the KIMB-t score was significantly higher for the HC group than the AD group ($p < 0.05$) while no significant difference was found between HC and MCI nor between AD and MCI.

4.3.1.1 General concerns

The AD and MCI patients included in the studies were all diagnosed according to standardised diagnostic criteria at the same memory clinic, and there were no significant demographic differences among groups regarding age or educational level in any study. However, it is difficult to ensure the homogeneity of the groups concerning other aspects not considered such as emotional state. In addition, it is well recognised that a diagnosis in itself is rarely enough to determine decisional capacity. An individual with a cognitive impairment due to dementia may have insufficient capacity in relation to complex decisional contexts, but still sufficient capacity in certain medical settings, such as low-risk treatment decisions (Appelbaum & Grisso 1988). It is worth noting that LIMD was not intended to serve the purpose of categorising individuals as having sufficient or insufficient overall capacity, rather it sought to examine degree of MDC for research based on linguistic features. LIMD was also intended to serve as a research instrument to investigate possible cognitive and linguistic correlates to MDC by LIMD. KIMB-t, on the other hand was designed for possible clinical use to detect individuals with reduced capacity to give informed consent (based on written information). These individuals could presumable need a more comprehensive assessment of MDC and/or facilitating aids during the decisional procedure.

4.3.2 Construct validity

4.3.2.1 *LIMD*

The construct validity of LIMD was explored with a fundamental and detailed scoring procedure (study I) of three criteria of MDC (comprehension, evaluation and intelligibility of choice). In addition, LIMD-total score was correlated with the results to overall cognitive components as well as single tests (study II).

Study I showed high and significant correlations between LIMD and three criteria of decision-making. The overall validity was approximately 80% defined as the degree of variance in LIMD accounted for by group in one-way (groups) ANOVA on LIMD. The LIMD-criteria were inspired by previously well-recognized consent standards (S) (derived from legal standards (LS) for competence): S1) expressing choice; S2) making a reasonable choice; S3) appreciating choice; S4) providing rational reasons for choice; and S5) understanding information relevant of a choice, which have been discussed and evaluated in several previous studies (e.g.

Appelbaum & Grisso, 1988; Marson et al., 1995; Okonkwo et al., 2008a) and discussed in the light of LIMD below:

- **Comprehension** (how the responses correspond to the content of the vignettes, in line with S5: understanding information relevant of a choice). In order to understand the information required to answer the standardized LIMD questions, which were given orally, the participant needed to first comprehend the given information (the vignettes), which was given both orally and in written form. To master the task the participant needed fundamental abilities such as (a) receipt of information, likely depending on attention and receptive language skills) as well as (b) active consciousness and working memory (Palmer & Harmell, 2016). However, to ease the burden on the memory function, and to increase the chances that you actually measure the "right thing", which in this case is the ability to understand and to simulate a real situation, the participant was allowed to keep the vignette text ahead and was invited to reread the text while answering the questions if needed. It is, not possible to exclude the impact of memory when assessing the dimension of understanding, although the linguistic aspect is central when it comes to genuine comprehension (beyond the mere ability to "parrot" the words back to the examiner). Also, Amalraj, Starkweather, Nguyen and Naeim (2009) argue that preserved verbal knowledge and health literacy are core functions in true comprehension.

- **Evaluation** (how utterances reveal the way subjects evaluate and weight the risks and benefits of participation, in line with S3: appreciating consequences of choice and S4; providing rational reasons for choice). Palmer and Harmell (2016) have suggested that the reasoning process involves the ability to envision and compare the potential consequences of various options. In order to answer the LIMD interview questions, the participant needed to reason about the content of the vignette in addtion to to comprehending the given hypotetical situation (vignettes). Also, in order to previse a future event, such as the potential risks involved in a clinical trial (whether real or hypothetical), the participant needed both sufficient working memory, and executive functions such as abstraction and planning (Grisso & Appelbaum, 1998). Making a reasonable choice, associated to appreciation was considered difficult to operationalize in a reliable manner. We preferred to merge appreciating and rational reasons into one overall criteria entitled "evaluation". The choice to exclude appreciation from the

scoring protocol of LIMD was not an action to diminish its actual relevance in relation to the capacity. Appreciating and rational reasons were instead further explored by a different methodological approach in study III (self-estimation of risk and benefit by VAS, verbalized reasons to participate and attitudes toward proxy).

- **Intelligibility of choice** (how decisive utterances are expressed and formulated, in line with S1, expressing a choice and the exprimental standard S2: making the reasonable choice). The ability to communicate a choice, was primarily examined by questions 8: "Would you choose to participate?" and 8.a: "Why would you participate?/What would be the reasons for you participatation?". In order to answer these questions i.w. to come to a conclusion and give informed consent rather than randomly answering yes or no, the participant needed (a) certain degree of contextual comprehension, (b) ability to mentally process the information and (c) to finally communicate a choice, which within the LIMD assessment requires a sufficient expressive oral language function. However in real clinical settings the reasoning and decisions could, if needed, be communciated differently, i.e. sign language and/or alternative and augmentative communciation. Furthermore, executive function i.e. mental flexibility and poor inhibition are likely critical abilities when communicating different choices (regardless if it's based on a real or hypothetical contexts).

Study II reported strong association between LIMD score and several cognitive and linguistic tests measures which are commonly included in the clinical assessments by neuropsychologists and speech and language pathologists in a clinical investigation of cognitive function. The study reported that the results of four single, cognitive and linguistic measurements were significant strongly correlated to total LIMD score: (1) Reading Speed (Järpsten, 2002), measuring e.g. reading capacity, speed and comprehension; (2) RAVLT (Lezak et al., 2004; Schmidt, 1996), measuring e.g. verbal episodic memory; (3) Inference (BeSS; Laakso et al., 2000; Holmbro & Olsson, 2000), measuring e.g. ability to draw conclusions from given information, and (4) Sentence Repetition (BeSS; Laakso et al., 2000; Holmbro & Olsson, 2000), measuring e.g. verbal repetition. The single test that best could predict MDC by LIMD was Reading Speed ($R=.77$; $p<.001$), included in the "verbal component". The result of study II supports the attempt of developing an instrument which captures linguistic characteristics of medical decision-making.

Sufficient verbal ability is essential in the process of medical decision-making in order to comprehend spoken and/or written language, to communicate decisions and to do so in an intelligible way. The impact of verbal ability e.g. verbal retrieval to the decisional capacity has been showed also in previous studies (e.g. Marson et al. 1995 and Gurrera et al., 2006). However, subtle changes of the language function and its correlation to decisional capacity in different contexts should preferable be further specified. For example, sufficient reading capacity is crucial in the decision-making process *if* the context is text-based (but its need yet to be explored how it is applicable in different texts with varied complexity as well as when the information is given with or without orally support). Information provided in order to give informed consent may well be written in academic language and include unfamiliar medical terminology. Eltorai et al. (2015) investigated readability in certain consent forms and found that in order to read (and comprehend) such a text, the reader likely needs to master a higher level of education. They suggest that adjustments to the readability of consent forms could enhance patient comprehension during the decision-making process, a finding in line with the previously stated importance of health literacy (e.g. Nutbeam, 2008). However, it may be suggested that the strong correlation between linguistic capacity and MDC as measured with LIMD could be to the fact that MDC in research contexts is parse a critical linguistic process. In any case, one can conclude with relative certainty that several aspects of verbal ability are crucial for medical decision-making in research settings. Finally, it must be noted that the construction validity of LIMD and possible predictors of MDC as measured by LIMD, was restricted to the choice of criteria, standardised questions and scoring protocol as well as which cognitive and linguistic tests were included in the correlation analysis of study II (as well as how these tests were subcategorized into different cognitive components).

4.3.2.2 *KIMB-t*

When investigating if the tests actually catches what they were aimed to capture it is crucial to define what they are valid to measure. For example, KIMB-t is not constructed to measure universal decision-making, but rather to detect reduced capacity to give informed consent (by assessing the ability to read quickly with sustained understanding and ability to draw conclusions from written information.) The construct validity of KIMB-t was explored in Study V by correlating the task to different cognitive tests with assumed high correlation to MDC by LIMD (according to study II). It would naturally have been beneficial to also include a comprehensive test battery (including LIMD) also in study V. However, the four tests were chosen as a golden middle way between the wish to investigate the construct validity as thoroughly as possible, and the wish to moderate the study's demands on the subjects' time and effort. KIMB-t is

neither based upon the well-recognised vignette method, nor designed to measure decision capacity tailored to the current decisional situation or overall capacity. The construction of KIMB-t was filtered down to assess certain linguistic functions (reading speed and reading comprehension) with presumable high association to MDC assessed by LIMD. The validity of KIMB-t was based on the fact that the task correlated significantly ($p < 0.05$) to the four cognitive tests previously associated with MDC as measured by LIMD. As expected, it did not correlate significantly to the task (word sequence production (Östberg et al., 2008) with assumed no association with MDC.

4.3.2.3 General concerns

It is widely recognised that medical decision-making is a complex process, associated with several cognitive and linguistic abilities and may fluctuate and change in time for several reasons, not limited to cognitive function (e.g. emotional or medical condition). Gurrera et al. (2014), indicated that, when evaluating decision-making, it may be important to attend not only to the patient's level of cognitive function but also to intra-individual in performance on neurocognitive tests. The complexity of MDC is such that neither LIMD nor KIMB can be used to determine MDC as the capacity may vary and is associated to multiple factors. A possible new title in a revised version of study V could be, for example: "A brief Swedish reading tool to detect reduced capability to give informed consent in dementia".

4.3.3 Ecological validity

Ecological validity refers to whether chosen methods, materials and settings approximate the relevant real-world situation and/or environment (but must not necessarily be equal to the overall validity of a study). The test design of LIMD and KIMB were based upon texts which imitated a decisional-making situation, but presented in a hypothetical manner, describing hypothetical clinical trials. A notable difference between the texts of LIMD and KIMB, is that the fictive patient described in LIMD is referred to as second person, "*Imagine that you…*", which might be confusing for patients with cognitive impairment while the fictive subject in the KIMB text is described in third person as the unisex subject "Kim". It is not well-investigated what impact such an innovative test design, like KIMB might have on the overall ecological validity of the task, in comparison to other.

Both LIMD and KIMB include tasks which present written fictive information (the information is also given orally within LIMD). The tests do not genuinely involve the patient's perspective, i.e. in terms of "*me, myself here and now*", but rather require consideration of: "*me or another person at another place and time*". It may be argued that this hypothetical approach could have

a negative influence on the ecological validity, and it is therefore necessary for the researcher/clinician to consider the possible limitations of the conclusions drawn from the results. Palmer and Harmell (2016) note that a disadvantage of the use of vignette-instruments; is that they primarily serve to assess overall capacity, rather than to define whether or not the patient can give consent to a suggested *specific* medical issue. Hence, it may be argued that the vignette method is more suitable for research settings, for example to evaluate the different factors affecting the capacity (rather than the patients actual and overall decisional capacity, generalisable to any clinical setting). However, numerous of valid instruments which assess healthcare decision making are based upon the vignette method (e.g. Grisso et al., 1997; Marson et al. 1995a; Moye et al., 2008).

4.3.4 Usefulness

LIMD is considered a valid and reliable research instrument to assess linguistic features of medical decision-making in research settings and is suitable to capture subtle changes among groups. Yet, the test is not suitable for clinical practice, which diminish its usefulness. KIMB on the other hand is applicable to be used in clinical settings e.g. when patients' capacity for consent to clinical research based on written information needs to be briefly estimated in a standardized and objective manner. Yet, it seems difficult to capture subtle changes among groups by KIMB. Neither of the two tools are valid to assess universal medical decision-making capacity or capacity based on oral information.

4.4 ETHICAL ISSUES

Dementia is a growing and serious challenge in health care and society. Research is necessary and important for achieving success in curing neurodegenerative diseases such as AD. In order to eventually achieve the goal of curing diseases, highly specialized research and voluntary participation in clinical trials are required, but this must not happen at the expense of the individual's interests. It is well known that research involving patients with impaired cognitive function may imply ethical challenges concerning for example how to best protect the individual's interest and autonomy without compromising medical safety. The overall objective of the five studies concerns the challenge to evaluate and analyse medical decision-making from a linguistic perspective i.e. the objective of the thesis was not to explore and discuss MDC from the discipline of medical ethics. Yet, some ethical concerns associated to the PhD-project are emphasised and problematized in the thesis.

Are AD patients capable of giving informed consent? Perhaps, perhaps not: perhaps in some contexts, but not in others. Ethical issues associated with the results of the studies can be discussed from two major perspectives: (1) *patient's perspective* (e.g. how to make and communicate a genuine and well-thought-out and independent decision about one's own (hypothetical) future and considerations and thought associated to the choice of a future proxy) (2) *clinician's perspective* (e.g. how to make a valid interpretation of a patient's decision-making capacity/ to estimate consent capacity).

Sullivan (2008) has reported a general lack of dementia awareness amongst the general population, despite the fact that many people know at least one person with dementia. Insufficient public knowledge about dementia may result in an absence of reflection by friends and family members on the consequences of reduced MDC for patient's autonomy. Excluding individuals with dementia from the decision-making process may lead to increased levels of depression and frustration for the patients (Smebye et al., 2012). This accords a particular responsibility to include the patient as much as possible in all decisions concerning her/his own situation. Yet, it is a challenge to ensure that patients with presumable reduced MDC have understood the actual message of assigned information. According to the Declaration of Helsinki (World Medical Association, Declaration of Helsinki, 2013) it is critical that the specific information needed for potential subjects should be adapted during the informed consent process. Hug and Johansson (2017) emphasize that the researcher should aim to improve the understanding for the research candidate and stress that it is critical to consider *what* information should be obtained in addition to *how* it is provided. For ethical reasons, the inclusion criteria of the data collections (I and II) did not include patients with severe dementia, as they would have had high risk of critically reduced MDC. It was taken into account that some of the participants may have had weak health literacy and possible, to some extent reduced decisional capacity regarding the decision whether to participate in the study. However, participation was not associated with any obvious risks for the participant and the studies were accepted by the ethical vetting board.

Furthermore, according to the results reported by study III, the acceptance of proxy is different depending on the potential risk following participation in the hypothetical clinical trial. However, it is difficult to in an objective manner take into account presumed risk (as this may be a subjective matter) when applying for a proxy, which could be considered an ethical issue. In reality, if a proxy maker is considered necessary and entrusted to act deputy in medical

matters, such as proxy consent to clinical trials, it is the case regardless of degree of assumed risk and benefit of the study. Another issue concerns the fact that decisional capacity may be investigated and discussed only in situations when the patient refuses the recommended medical action, if at all. Also, if a patient with questionable (but not obviously impaired) MDC makes a deviant decision contrary to the clinician's professional suggestion, the clinician may query the patients' decisional capacity rather than simply accepting the decision. Strong autonomy and self-determination are based on the person's capacity to be responsible for her / his own actions and requires that the choices are both voluntary and rational. Hence, to truly respect a patient, one must preferably know which decision the patient would have made before her / his decisional capacity was reduced. Defining the criteria for MDC and using instruments that assess this ability requires a high level of ethical responsibility on the part of the clinician or researcher. It is important not to violate the rights of those who can actually make their own decisions in attempt to protect those with reduced decision-making capacity. It must be noted that an assessment of decision-making capacity by any scoring protocol is the assessor's own interpretation of the test used. It is of ethical importance to always maintain the human value as a central concept. No simple solution nor an absolute truth exists of when and how to estimate MDC nor how to know if the patients informed consent is really based on true health literacy. Finally, the risk of abuse as well as misinterpretation of the result must be taken into account when developing new measurement tools. For example, LIMD should primarily be used for research purposes and KIMB-t ought to be used to identifying patients in need of further examination or support in order to be able to exercise their autonomy. The studies investigated linguistic aspects of MDC in groups with variable cognitive function. Consequently, the participants were assumed to have different degree of decision-making capacity. Johansson (2017) discussed some key principles that ought to protect individuals who have insufficient decisional capacity. One issue to consider in current PhD-project is whether it was in accordance with good ethical practice to perform data collections (I and II). The data collections can be acceptable according to the principle of risk minimisation and insignificant risk as the participants in our research project were not exposed to any intervention or analysis that deliberately exposed them to any obvious risk of being harmed physically or psychologically. It could perhaps be argued that the patients may have been exposed to mental stress (i.e. being subject to a number of tests) that may have been experienced as disappointing or stressful. For this reason, the participants were (a) clearly informed that it was voluntary and that they were allowed to exit the research project at any time and (b) welcomed to pause the test procedure and take a coffee break or talk a walk between the tests. Furthermore, we strived for that the

overall research project was in accordance with the principle of utilitarianism, and that the principles of necessity and population were met, since the studies aimed to contribute with exploratory results to the field of decision-making and in addition benefit the fragile group of elderly with possible reduced decisional capacity. Finally, for ethical reasons, the entire transcriptions showing of the total amount of verbal responses from each participant were not reported in any study, which may otherwise have risked identification. In sum, we believe that the overall study design and objectives conformed to ethical standards for research.

5 CONCLUSIONS

In comparison with healthy individuals and those with MCI, individuals with mild AD showed reduced MDC, measured as the capacity to give informed consent for research participation by LIMD. The total LIMD score, including the criteria; comprehension, evaluation and intelligibility, were highly associated to the component of overall verbal knowledge, counting the single measurements of Reading speed and Inference, as well as the components of episodic memory, cognitive speed and working memory. In addition, patients, already with mild AD seemed to have reduced capacity to estimate possible risks associated with participation to a clinical trial, as well as having difficulties to reason and communicate a choice in a clear and logical manner.

The results indicate that a linguistic approach of MDC among patients with AD, contributes not only to an additional analysis of the capacity, but also to a better understanding in the communication with patients during the decision-making process. Hence, evaluating different aspects associated to medical decision-making from a linguistic perspective in AD and other groups with impaired cognitive function, complements the research field, which hopefully and eventually will benefit the patients.

6 FUTURE DIRECTIONS

A longitudinal study of MDC by LIMD on groups of patients with AD and MCI would be an interesting follow-on from the present study, as the patients' decisional capacity is at risk of becoming impaired over time due to the cognitive and linguistic effects of the disease, neither is it well-recognized if and how patients' estimations of risk and benefit, and their decisions to participate in for example high-risk trials would change over time and how the sense-making of their verbal reasoning may differ. Additionally, several international instruments to assess medical decision-making show good reliability and validity. A future suggestion would be to translate and validate a previously established instrument that measures MDC for research participation into Swedish and compare its results to LIMD score among different groups, for example HC and patients with mild and severe AD, MCI and FTD.

Furthermore, it would be of interest to explore how estimation of MDC could be conducted as part of a standardized clinical investigation, as well as how such an approach could possible benefit the patient in both research and clinical settings. Finally, it would be valuable to investigate how to communicate, in best possible ethical manner, with dementia patients during their medical decision-making process i.e. standardized dialogue concerning decision-making abilities such as comprehension, estimation of risk and benefits, willingness to participate and choice of proxy, during different stages of their diseases.

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