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Systematic Review

Distinguishing Late-Life Depression and Alzheimer's Disease Based on Memory Impairment and Memory-Associated Biochemical Markers- A Systematic Review

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Abstract

Background: The need to identify Alzheimer's disease and late-life depression increases as the overall age of the population rises. The lack of evidence of the underlying physiopathologies as well as the heterogeneity of both illnesses complicate the distinction, thus increasing the risk of misdiagnosis. Providing the appropriate diagnoses are necessary to ensure the best possible outcome of care and treatment of existing and future treatment. This systematic review examines the role of episodic memory impairment and memory-associated biochemical markers to distinguish between late-life depression and Alzheimer's disease.

Method: 78 articles were included for full-text screening, of which 9 met the inclusion criteria. These criteria are that articles includes both participants with late-life depression and Alzheimer's disease, examining impaired episodic memory and are peer-reviewed. Studies examining genes or having comorbid illnesses were not included.

Results: Late-life depression and Alzheimer's disease can both be characterized by hippocampal atrophy which consequently can lead to impairment of episodic memory (especially coding new information) and changes in memory-associated biochemical markers. Indeed, measures of cerebrospinal fluid (p-tau$_{231}$, AβxMAP&t-tau/Aβ$_{40}$, Aβ1-40/1-42, D-serine and Neprilysin) and urinary samples (AD7c-NTP) are able to distinguish between the two illnesses with a sensitivity and specificity ~80%. Neuropsychological tests (FCSRT, OI) have approximately the same accuracy. Yet, also reflected in the reviewed papers is the fact that late-life depression is not a homogeneous diagnosis, thus subtypes might be particularly difficult to differentiate from Alzheimer's disease. Furthermore, the possibility that subtypes of late-life depression are prodromes to Alzheimer's disease is a pressing issue questioning whether the differentiation is even possible.

Conclusion: Measures of memory impairment can be valid means to distinguish late-life depression from Alzheimer's disease. Both diagnoses can be characterized by impairment of episodic memory, indeed, the degree of the impairment is what can help set the diagnosis. Future studies should study the underlying pathophysiology of both diagnoses, and understand the possible causal relationship between them, to set a more certain diagnosis.

Keywords: *Alzheimer's Disease; Late-Life Depression; Cerebrospinal Fluid; Neuropsychological Tests; Differentiation*

Abbreviations

Aβ: Beta-Amyloid; AD: Alzheimer's Disease; AD7c-NTP: Alzheimer-Associated Neuronal Thread Protein; CSF: Cerebrospinal Fluid; FC-SRT: Free and Cued Selective Reminding Test; LLD: Late-Life Depression; OI: Olfactory Identification. p-tau: Phosphorylated Tau; t-tau: Total-Tau; NEP: Neprilysin

Introduction

Unipolar depression affects approximately 4.4% of the global population in 2017, around 300 million people, and its prevalence has increased by 18.4% from 2005 to 2015 [1]. Moreover, between 9.7% and 13.8% of the elderly population is believed to suffer from late-life depression (LLD) [2-4]. At the same time, in 2015 46.8 million people in the world were diagnosed with dementia [5]. The prevalence of dementia increases with age, and ~40% of people above 90 years old will be diagnosed with dementia [6]. This systematic review focuses on dementia of the late onset Alzheimer's type (AD), which is present in about 42%-60% of dementia cases [7,8]. According to Alzheimer's disease International, AD costs 818 billion USD worldwide every year [5], while in 2000 LLD cost 83.1 billion USD in the States alone [9]. In Denmark, 85.8% of people with AD were diagnosed correctly in 2003. Meaning that 14.2% of people diagnosed with AD do not actually have it [10]. The consequences of misdiagnosing result in not providing the appropriate treatment. LLD is believed to be able to recover with pharmaceutical or psychological treatment, while AD can only be provided with appropriate care and medicine to reduce symptoms. Misdiagnosing a person with AD consequently implies not attempting remission. To improve the differentiation will significantly improve the quality of life of these individuals, since the appropriate care and treatment can be given.

Currently, measures to identify LLD and AD rely mostly on standardized clinical criteria or cognitive profiles, which can be supplemented by neuroimaging or lumbar punctures [11-13]. A certain way of differentiating the two illnesses does not exist, partly because their underlying pathophysiologies are not known. Indeed, this systematic review reveals a more complex and dynamic relationship within and between the diagnoses.

This systematic review examines the role of episodic memory impairment and memory-associated biochemical markers in distinguishing Alzheimer's disease and late-life depression. This is achieved through a systematic analysis of articles examining measures of cerebrospinal fluid (CSF) based biomarkers related to memory, neuropsychological assessments and alternative neurobiological measures related to memory. Increased knowledge about differentiation of LLD and AD could potentially help the clinician provide the correct diagnosis to some of the patients whom are wrongly diagnosed with either of these illnesses. An improved diagnostic setup will allow all patients to benefit better from present and future treatments - thus as far as possible providing the proper care and improved quality of life. On the background of this systematic review clinicians and researchers will be better able to realize which measures are likely best to assist in the differentiation between LLD and AD - and how much one should rely on such measures.

Definition of concepts

Memory

This review will focus on episodic memory impairment and memory-associated biochemical markers as an expression of damage or atrophy to the hippocampus, since the hippocampus is believed to be central for several stages of memory consolidation, which will be elaborated later. This understanding derives from findings of patients with retrograde and anterograde amnesia connected to direct damage to different areas of the hippocampus [14]. It has later been found that the hippocampus is a critical component of episodic memory acquisition and retrieval - meaning the hippocampus itself functions more as a relay station than a site of storage. It is believed that the hippocampus holds capabilities of pattern separation and pattern completion, meaning it is capable of storing different content throughout the brain and is able to retrieve a memory by combining the correct 'strings' without mixing up memories [14]. In this review different measures of memory will be used such as the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). The two batteries measure various cognitive functions (memory, language, attention etc.) to determine cognitive impairment [15]. This review specifically focuses on the memory aspects of such tests.

Late-life depression and Alzheimer's disease

LLD, also called late-onset depression, describes a type of depression in which the first episode occurs in the geriatric age ~65 years old [16]. LLD can be diagnosed through the ICD-, DSM- and CES-D system. LLD is analyzed instead of other types of depression because it correlates with a higher prevalence of dementia and memory impairment [17,18].

AD of the late-onset type is defined by accumulation of senile plaques, formed by Beta-Amyloid (Aβ), and neurofibrillary tangles, comprised primarily of hyperphosphorylated-tau (p-tau), originating in the hippocampus [19] - primarily resulting in anterograde amnesia [20]. It is believed that the changes occurring in the brain are represented in the CSF [21] - and the different measures and accumulations of CSF-based biomarkers affect hippocampal atrophy and memory decline [22].

Methodology

Literature search

A systematic search on PubMed, PsycInfo and Web of Science was executed with the search string [depressi* AND Alzheimer* AND memor* AND biomark*] including articles from inception till February 2019. First, a title/abstract screening was completed of all articles. Only articles fulfilling inclusion criteria [section Selection criteria] proceeded to a screening of the full text. In this full-text screening all articles were weighted independently in agreement with the inclusion/exclusion criteria. Reasons for exclusions are noted for articles in the full-text screening (see appendix 2). A hand search was executed in which references from included articles were screened for supplementary articles. The search strategy used for this systematic review is in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) [23] (See figure 1: PRISMA).

Selection criteria

The PICO framework (Population, Intervention, Comparison, Outcome) was used to define the specific search criteria in the initial search, using the four categories [23]. Inclusion criteria are: (a) clinical trials (b) peer-reviewed (c) include geriatric patients with LLD or AD, (d) compare/differentiate LLD and AD, and (e) examine episodic memory and/or memory-associated biochemical markers. Articles which included patients < 55 years old or had comorbid psychiatric, somatic or neurodegenerative illnesses or patients with current substance or alcohol abuse were excluded. Articles with a primary focus on DNA/genes are also excluded. Lastly, unpublished studies, studies with languages other than English and animal studies were excluded.

Search results

A total of 588 articles resulted from the initial search. Following removal of duplicates and the primary title/abstract screening 78 articles remained for full-text screening. Subsequently, 9 articles remained for final inclusion and are reviewed in this paper. Both authors conducted title/abstract screening and full-text screening independently and ended on a full agreement of the 9 included articles. These articles compare AD and LLD with regard to episodic memory impairment and/or memory-associated biochemical markers. This systematic review used strict inclusion criteria because of size and scope limitations. Therefore, the possibility of excluding some articles which otherwise might have been enlightening for the research question is imaginable.

The data extracted from each study is in accordance with the PRISMA procedure [23]: First, descriptive information is noted. Second, the articles procedure and content are analyzed. Third, each study is reviewed in relation to bias or skewed data. Lastly, each study is weighted independently. It is interesting to note the way the authors evaluate their own method, possible biases, limitations and statistics.

Results

Of the 588 articles from the initial screening, nine have been selected according to the inclusion criteria. The nine articles are divided in three groups (a) CSF-based biomarkers, (b) neuropsychological tests as markers, and (c) alternative neurobiological biomarkers (See table 1). Appendix 1 provides μ and SD for the measures.

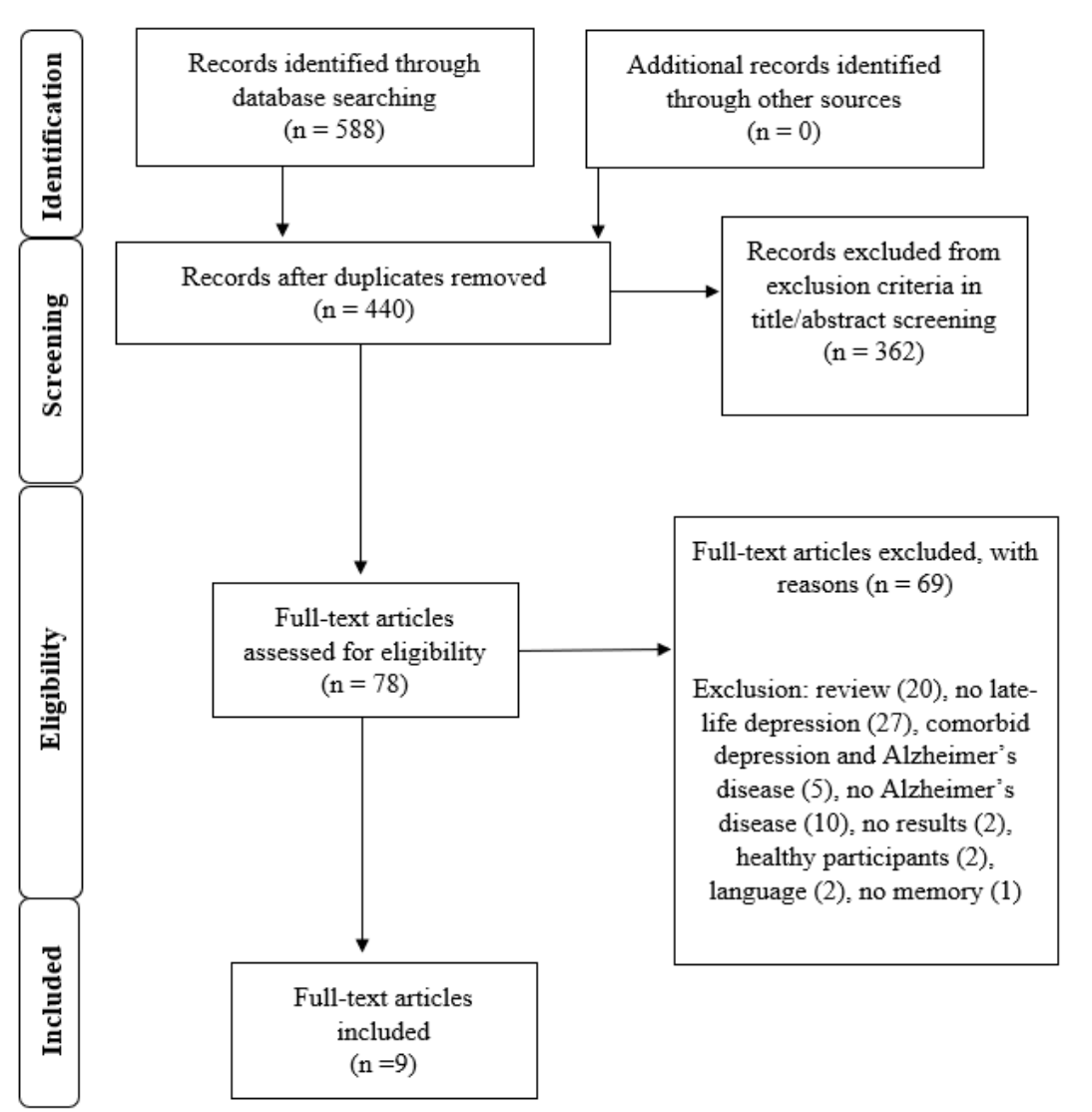

Figure 1: *PRISMA flow diagram.*

Cerebrospinal fluid-based biomarkers

Three articles examined CSF-based biomarkers and memory impairment for differentiating LLD and AD [24-26].

p-tau$_{231}$

Buerger., *et al.* [24] divides AD in probable (N = 64) and possible AD (N = 17) through NINCDS-ADRDA criteria [32]. The article focuses exclusively on tau phosphorylated at the 231-site (p-tau$_{231}$) [33]. Buerger., *et al.* [24] found a significant difference in p-tau$_{231}$-level between LLD and probable and possible AD ($p < .001$). Interestingly using p-tau$_{231}$ as the only differential measurement revealed a sensi-

		LLD			AD			HC	
Citation	**Measure**	**Criteria**	**N**	**Age (SD)**	**Criteria**	**N**	**Age (SD)**	**N**	**Age (SD)**
Buerger., *et al*. [24]	- p-tau$_{231}$ - MMSE	DSM-IV	34	65.4 (12.1)	NINCDS-ADRDA (possible/probable)	81	68.8 (9.7)/71.9 (8.1)	21	57.7 (14.2)
Hertze., *et al*. [25]	- A*β*xMAP and t-tau/ A*β*40 - MMSE	DSM-IV	29	58 (8.4)	DSM-IIIR NINCDS-ADRDA (Probable)	94	77 (7.1)	38	77 (8.2)
Sun., *et al*. [26]	- A*β1-40/1-42* - MMSE - MRI	CES-D	118	N/A	DSM-IV NINCDS-ADRDA	46	N/A	36	N/A
Chen., *et al*. [27]	- OI - MMSE	DSM-IV	125	66.7 (6.2)	NINCDS-ADRDA (probable)	50	71.9 (9.9)	60	65.4 (7.3)
Grön., *et al*. [28]	- MMSE - VEM-AUC	DSM-IV	12	57.6 (4.5)	NINCDS-ADRDA (probable)	12	61.7 (5.0)	12	59.8 (2.6)
Teichmann., *et al*. [29]	- FCSRT - A*β, t/p-tau* - MMSE	MADRS + DSM-V	71	N/A	IWG-2 (AD dementia + prodromal AD)	216	N/A		
Madeira., *et al*. [30]	- D-serine - IATI - MMSE	DSM-IV	9	69.8 (5.8)	DSM-IV NINCDS-ADRDA (probable)	21	72.1 (8.4)	10	70.7 (6.3)
Sorensen., *et al*. [31]	- NEP - A*β, t/p tau*	ICD-10	13	F 54.71 (14.22) M 66.73 (7.32)	DSM-IV NINCDS-ADRDA (probable AD)	20	F 67.44 (9.03) M 66.36 (9.34)		
Zhang., *et al*. [4]	- AD7c-NTP - MoCA	DSM-IV	81	LLD-CI 64.2 (6.2) LLD-NCI 63.1 (5.7)	NINCDS-ADRDA	30	66.5 (6.1)	27	64.5 (5.4)

Table 1*: Descriptive information of primary articles.*

Note: CES-D: Center for Epidemiologic Studies Depression Scale; DSM: Diagnostic and Statistical Manual of Mental Disorders; FCSRT: Free and Cued Selective Reminding test; (f)MRI: (functional) Magnetic resonance imaging; ICD: International Classification of Diseases and Related Health Problems; IWG: International Working Group; MADRS: Montgomery and Åsberg *Depression Rating Scale; MMSE: Mini -Mental Status Examination; MoCA: Montreal Cognitive Assessment; NEP: Neprilysin; OI: Olfactory Identification; VEM-AUC: Verbal Episodic Memory-Area Under the Curve.*

tivity of 92% and a specificity of 85%, meaning 85% of the LLD/healthy control (HC) group would correctly not be allocated with an AD diagnosis. Meanwhile a sensitivity of 82%, and a specificity of 71% with LLD/HC vs. possible AD was found. These results, however, leave 13% - 22% room for false positives. The consequence of such specificity could implicate that 13% - 22% of people with actual depression are given a wrong diagnosis, and thus, not receiving the treatment which potentially might help them [34].

It is important to be aware that the authors compare AD to the compiled score of LLD/HC. The authors have done so because there is no significant difference between LLD and HC regarding p-tau$_{231}$ when matched for age (p = 0.27), although the LLD mean is 5 times

higher than the HC mean (10/2 µl). The consequence of such a compiled score is that the statistical results can only conclude something about LLD and HC together. Interestingly, it is noticeable how the SD in µl p-tau$_{231}$ is large in all groups (See figure 2) [24, p. 6]. The fact that there is such a big variation could explain why the specificity never goes higher than 85%, simply because a big within-group variation of p-tau$_{231}$ is found in all groups [35].

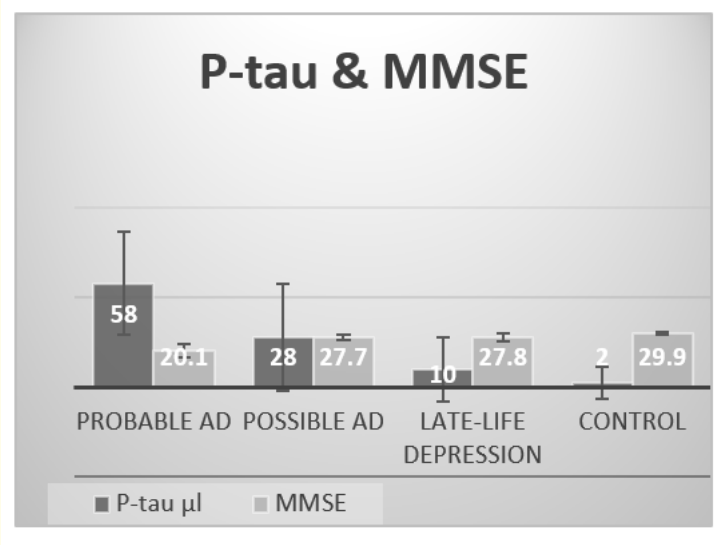

Figure 2: *P-tau and MMSE across groups [24].*

Furthermore, the groups' p-tau$_{231}$ level and their MMSE scores did not correlate [24]. This does not necessarily imply that p-tau$_{231}$ and episodic memory are not associated. MMSE measures several cognitive constructs (e.g. orientation, attention), and therefore, only looking at their measure of memory could potentially reveal an association [36]; however, the article only reports the whole score. Similar results are reported by Mitchell and Brindle [33], who also found that p-tau$_{231}$ and pulled MMSE do not correlate. However, one study supports the hypothesis that p-tau$_{231}$ and memory are associated - and concludes that more p-tau$_{231}$ is associated with decreasing episodic memory and medial temporal lobe atrophy similar to AD [37]. This supports the hypothesis that p-tau$_{231}$ and episodic memory might be associated and that this might be mediated through atrophy of the medial temporal lobe. However, whether episodic memory and p-tau$_{231}$ are associated, and thus is an effective differential measurement of memory cannot be confirmed nor denied from the results of Buerger., *et al* [24].

Aβ$_{42}$xMAP and t-tau/Aβ$_{40}$

Hertze., *et al.* [25] examines the predictive effects of 8 different measures of CSF, MMSE and APOE ε4-gene (APOE ε4 will not be included in this analysis), through a 4.7-year follow-up study. The article finds a significant baseline difference in MMSE scores between AD and LLD, which indicates a significant cognitive difference [36]. When quantifying Aβ$_{42}$ with a technology called xMAP and using that measure with t-tau/Aβ$_{40}$ it resulted in the largest predictive effect with a sensitivity of 88% and a specificity of 92% [AD vs. LLD/HC]. However, as in Buerger., *et al.* [24] the results rely on differentiating probable AD from a compiled score of LLD/HC. From figure 3 it can be observed that HC and LLD scores are similar - however one should take into consideration that these groups are not matched for age. The HC group is on average 19 years older than the LLD group, which might mean that a difference could be observed if matched for age.

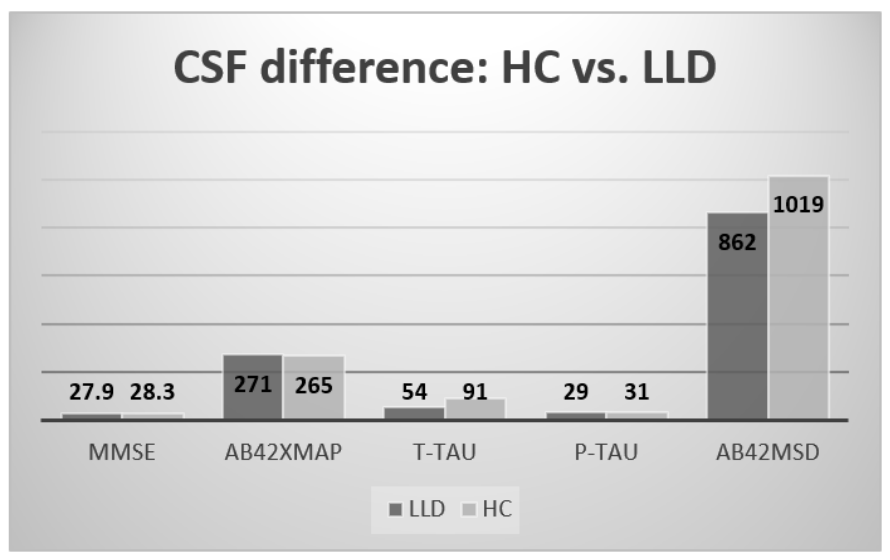

Figure 3: *Graphical representation of CSF-measures on LLD and HC [25].*

Interestingly, both this measure and p-tau$_{231}$ from Buerger., *et al.* [24] reveal large effects. Noticeably, the outcome of p-tau in Hertze., *et al.* [25] is different from Buerger., *et al.* [24] which will be elaborated upon in section of Interim summary.

Aβ1-40/1-42 ratio

The final paper [26] has its primary marker of differentiation as Aβ1-40/1-42 ratio. This specific marker has been confirmed to be linked to memory [38]. The article supplements CSF-based measures with magnetic resonance imaging (MRI), which show that, in LLD high Aβ1-40/1-42 ratio correlates to increased risk of amygdala atrophy and AD [26, p. 599]. The article states that LLD with high ratio and amygdala atrophy are prodromal to AD - thus, complicating differentiation. Figure 4 show how LLD (high vs. low Aβ1-40/1-42 ratio) differs regarding brain area volume. Only amygdala and total brain volume differ between the groups, not hippocampal volume. Thus, indicating that the high Aβ1-40/1-42 group does not have more hippocampal atrophy contrary to main assumption that AD is characterized by atrophy of the hippocampus. This association has been confirmed in another study [39] - nevertheless this study is the first to examine the association in LLD without mild cognitive impairment.

Commentation on the article's statistical use is needed. First, when correlating MCI Aβ1-40/1-42 ratio to hippocampus volume ($r = -0.35$, $p = 0.19$) the authors claim that such a high p-value "… tended to correlate with hippocampus volume" [26, p. 598]. However, a p-value >.05 is usually not perceived as significant [40-42]. Second, in their reporting of descriptive values [26, p. 596], the authors do not report CSF, MMSE scores etc. for the individual groups but just generalized results. This represents a problem since their statistics are impossible to replicate; besides the table does not provide an overview of their results. Third, a significant p-value does not speak to the actual strength of the results, which is why sensitivity and specificity measures are beneficial [43]. The lack of descriptive statistics makes it impossible for an external author to make such calculations.

The second issue concerns bias. The authors refer to the LLD group with high Aβ1-40/1-42 ratio as 'amyloid associated depression', which the authors claim is directly associated to AD [26, p. 599]. This assumption is only supported by an earlier article, by the same

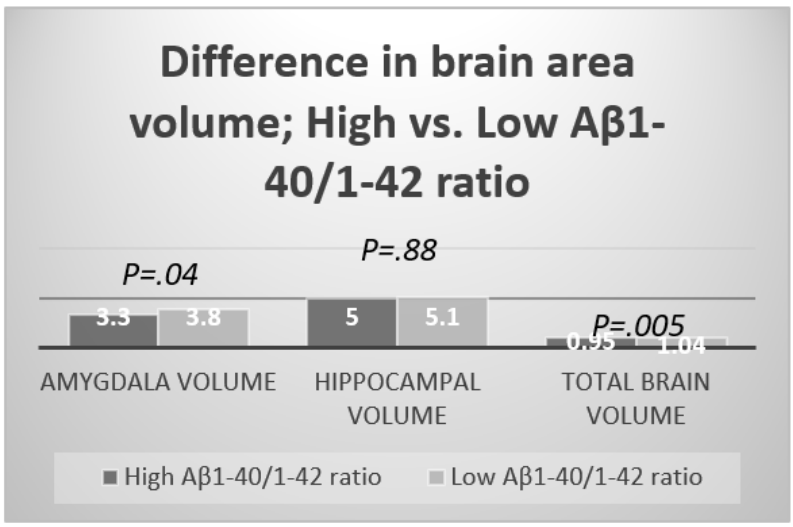

Figure 4: *Brain volume in LLD (High vs. low A Aβ140/1-42 ratio) [26].*

authors in 2008 [38], however independent evidence would decrease the possibility of bias. Furthermore, no conclusive evidence on the relationship between LLD and AD exists [41,44,45]. Hence, this underlying assumption impacts the entirety of the article, and questions its validity. Although their assumption might be correct, it has not been proven sufficiently to draw such conclusions [46].

Interim summary

In summation, these three articles point to the fact that LLD and AD can be distinguished using different CSF-based markers. As pointed out, there are certain complications in each article. It is noticeable that all three articles suggest different CSF based markers as being the most efficient. The problem of the papers prioritizing different measures, and having contradictory statistics has significant consequences for the field. One measure cannot be promoted as the first in line diagnostic tool, and even if one measure had a higher power, if it has not been replicated it is hard to conclude its reliability. This is exemplified when Hertze., *et al.* [25] compares AD to HC/LLD through p-tau the sensitivity is 46%, indicating p-tau is not good at distinguishing. This is not in accordance with the results of Buerger., *et al* [24].

Limitations of general consideration is the fact that LLD and HC are compared together to AD. A consequence of this could be that the specificity measures might drop when only using LLD since it is believed that LLD has similar alterations in CSF as AD, unlike HC [47]. Ultimately, these three studies all provide interesting views upon the differentiation. One single conclusion cannot be reached because of inconsistencies between studies, analyzing LLD and HC as the same group and lack of replications. Studies correcting these issues, could reveal which CSF-based measure is best for differentiation.

Neuropsychological tests

Three articles examine neuropsychological tests as a non-invasive approach to the differentiation of LLD and AD [27-29].

Olfactory identification

Chen., *et al.* [27] examines Olfactory Identification (OI) through the Sniffin' Sticks Screen 16 test [48] as a differential marker. Olfaction is one of the first senses to be affected in the early phases of AD [15] and is found to correlate to episodic memory processes, since it is

interconnected with neural structures such as the olfactory bulb and the hippocampus [49]. A damaged olfactory bulb is correlated to OI impairment and AD [50] and the fact that hippocampus is a part of the secondary olfactory cortex links memory and smell.

The study used neuropsychological tests in multiple cognitive domains (including memory through the Logical Memory Test (LMT)) [27]. Some underwent MRI to measure grey matter volume specifically in the hippocampus and the olfactory bulb. OI correlated positively with memory impairment [27, p. 644].

Chen., *et al.* [27] found that OI scores were significantly different between the three groups (AD > LLD > HC) (Figure 5). A lower OI score is correlated to poorer memory scores and reduced bilateral olfactory bulb and hippocampus volume. Interestingly when dividing HC and LLD in no olfactory impairment (NOII) and olfactory impairment (OII) there was no significant grey matter difference between [HC-NOII and LLD-NOII]; [LLD-NOII and LLD-OII]; [LLD-OII and AD]. Noticeable is that the LLD-OII group had similar structural abnormalities as the AD group, but not the LLD-NOII group, indicating differential associations to the AD diagnosis. Sensitivity and specificity are not reported, however, the authors do refer to other papers who found large effect sizes [51,52].

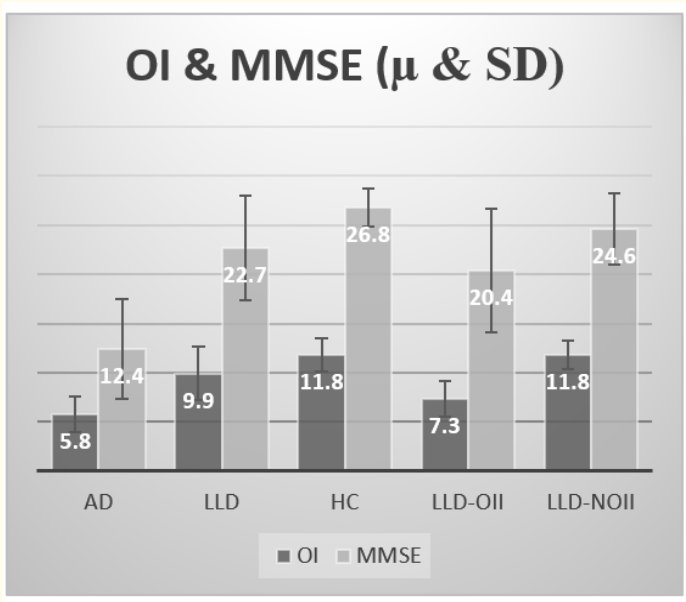

Figure 5: *OI and MMSE across groups (Means and SD) [27].*

Subjective memory complaints

Grön., *et al.* [28] examine the role of subjective memory complaints (SMC) since they hypothesize a correlation to the development of AD. All participants are assessed through neuropsychological tests, along-side with an episodic memory task. The episodic memory task involves learning and recalling different abstract geometric figures [28] - of the 7 measures of the episodic memory test, the verbal episodic memory (VEM) (area under the curve AUC) will be of examination in this review (Figure 6).

The episodic memory task was performed during a fMRI-scan. The fMRI displays several differences between LLD and AD, most significant for memory is the fact that LLD have significantly more activity in their right hippocampal area compared to AD. The study alto-

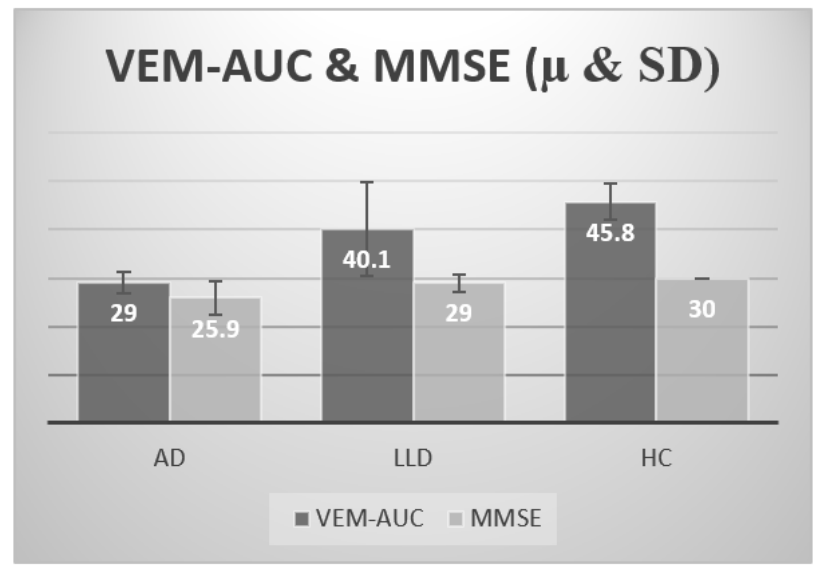

Figure 6: *VEM-AUC and MMSE across groups (means and SD) [28].*

gether concludes, that the differentiation between AD and LLD is "clear-cut on a neural network level" [28, p. 497]. In support, a similar study found that subjective memory decline in HC is associated with $A\beta_{1-42}$ and tangles postmortem [53]. Thus, $A\beta_{1-42,}$ which is normally associated with AD, has a significant correlation with subjective memory decline. Indeed, one study proposes that people with SMC have 9 times higher probability of developing AD [54]. Conversely Buckley., *et al*. [53] found that high $A\beta_{1-42}$ and high subjective memory decline also were correlated to more depressive symptoms. Thus, it appears that subjective memory decline and $A\beta_{1-42}$ is more defining of AD, and that a functioning hippocampal recruitment is defining of LLD. Putting up specific criteria of these could be interesting, in that it could support the differentiating process.

Free and cued selective reminding test

Teichmann., *et al.* [29] examines the Free and Cued Selective Reminding Test (FCSRT) as a measure of an episodic memory impairment called 'amnestic syndrome of the hippocampal type' [55,56]. The syndrome is characterized by a failure to recruit hippocampus and will be identified: "by insensitivity to cueing and by low total recall" [29, p. 914]. The article examines 992 people of which they found that 31% would be diagnosed with AD and 11% with LLD. A thorough neuropsychological examination was carried out along with measures of CSF, multiple neuroimaging scans, MMSE, an assessment battery and the FCSRT. The FCSRT consists of learning a list of 16 words; a free recall and free recall with semantic cue and repeating three times. Then testing again after 30 minutes (free delayed recall and total delayed recall) [29, p. 915].

Specifically regarding LLD, the FCSRT would diagnose 36.6% of the group with the amnestic syndrome of the hippocampal type (Figure 7) - similarly 11.7% would be biomarker positive (looking at p-tau_{181}/$A\beta_{1-42}$ ratio). All together this can indicate two things, either (a) the FCSRT is not sensitive enough, and thus includes people who should not be included, or (b) the FCSRT demonstrates that the LLD group is heterogenous. Underlining the fact that hippocampal atrophy might not only be found in AD, but also in some people with LLD. The discussion will further elaborate on this.

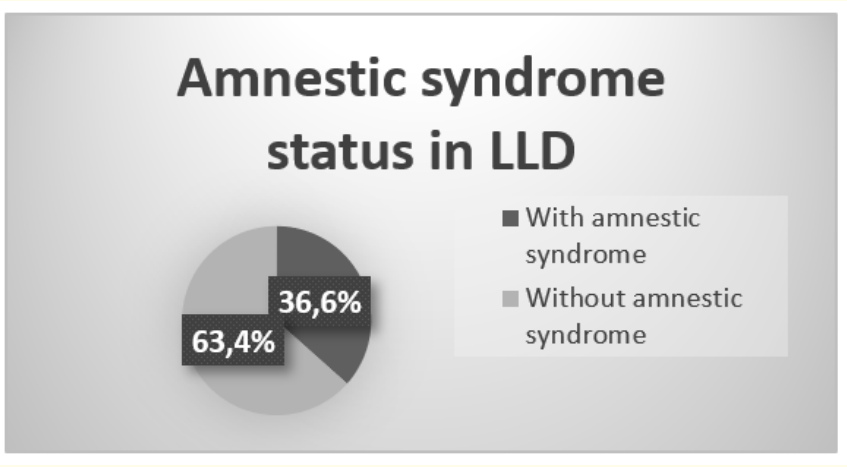

Figure 7: *Percentage of amnestic syndrome in LLD [29].*

Since the FCSRT is a new possible tool it should be explored, mostly because of its non-invasive approach: "Thus, memory tests such as the FCSRT remain indispensable, non-invasive, inexpensive, and easy-to-obtain first-line tools…" [29, pp. 920-921]. Lastly, "CSF biomarkers are not correlated with disease progression" [29, p. 921], thus addressing the advantage of using the FCSRT, since it is correlated to disease progression.

Interim summary

The three analyzed articles all offer valid potential measurement or considerations to the differentiation of LLD vs. AD. They are all non-invasive, easy and affordable to perform, which is preferred from a clinical perspective [57]. Firstly, it is found that OI through Sniffin' Sticks test did significantly distinguish AD from LLD - but also that the LLD-OII group had worse cognitive performance and similar structural abnormalities as the AD group [27]. Secondly, Grön., *et al.* [28] shed light on the potential benefit of using SMC in the diagnosis. They found a clear neural network difference between LLD and AD, based on LLD's ability to recruit the hippocampus. Supporting evidence indicates that SMC (a) is a risk factor of AD, and (b) subjective memory decline is directly correlated with $A\beta_{1\text{-}42}$. Thirdly, the role of the FCSRT was examined. Using FCSRT 36.6% of the LLD group would also be diagnosed with amnestic syndrome of the hippocampal type - explained by either: (a) the FCSRT is not an accurate measure of the amnestic syndrome and therefore co-measure other functions such as attention, or (b) some patients with LLD also have hippocampal damage. The latter is supported in neuroimaging studies [58-60] and studies of excitotoxicity which is elaborated on further in the discussion [6,61].

Alternative neurobiological biomarkers

This segment goes in depth with three articles on alternative neurobiological markers [4,30,31]. These studies examine the effect of D-serine, Neprilysin, and Alzheimer-associated neuronal thread protein.

D-serine

Madeira., *et al.* [30] measures the level of D-serine in the CSF of patients and compares their results to a CSF Aβ/t-tau index (IATI). D-serine is a naturally occurring NMDA-receptor co-agonist, which assist glutamate in the influx of Ca^{2+} into the postsynaptic membrane which can enhance the memory trace [62]. In addition, there is not a clear-cut 1:1 relationship between NMDA-excitation and memory, since a memory trace can be established without the NMDA receptor [14]. D-serine is, however, also associated with excitotoxicity and

atrophy [62]. The article also includes animal studies, these will not be included in this review. The study found that D-serine itself gave a better sensitivity compared to IATI, but not a better specificity. However, combining the two (IATI+D-serine) at cutoff value of 0.14, resulted in a sensitivity of 96.3% and a specificity of 100% [30].

The LLD group and a hydrocephalus (HYD) group (n = 9) have their scores pulled together. The AD group had significantly higher levels of D-serine compared to LLD/HYD. Meanwhile, LDD/HYD had significantly more D-serine compared to HC ($p < .001$). In addition, the authors found that D-serine is negatively correlated to MMSE and IATI-score in all groups - which means that the more D-serine the worse overall cognitive performance, and lower IATI (which is indicative of AD) (See figure 8).

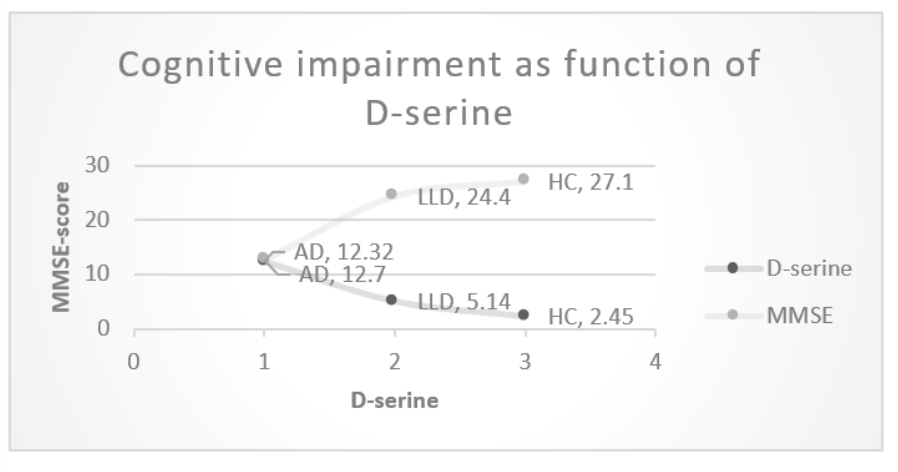

Figure 8: *MMSE as a function of D-serine across groups [30].*

All together the results could indicate that D-serine can be a measure of memory impairment and disease progression, unlike some CSF-based measures [30] and that D-serine might be linked to excitotoxicity and atrophy [63]. D-serine, indeed, appears to be a correlate to cognitive memory functioning, thus expressing a qualitative difference in memory functioning between the diagnoses. Also, the study has a low sample size, thus generalizing the finding can be troublesome.

Neprilysin

The role of Neprilysin (NEP), an Aβ degrading enzyme, and its relation to Aβ, p-tau and t-tau is examined by Sorensen., *et al* [31]. The idea of examining NEP comes from the peripheral sink hypothesis, which states that: "Sequestration and degradation of Aβ outside the brain may shift the balance between soluble and aggregated Aβ in the brain by lowering the total amount of Aβ. Enzymes capable of degrading Aβ outside the brain are therefore of interest" [31, p. 380]. The idea is that the level of NEP in the CSF can be an estimate of neural degradation.

There are two conclusions from their article: First, the results show strong positive correlations between NEP activity and p-tau$_{181P}$ in the LLD and AD group ($R = .764$, $p = .0004$; $R = .800$, $p < .001$). The AD group also had a strong correlation to t-tau ($R = .751$, $p < .001$) [31, p. 384]. Second, the fact that NEP does not correlate with Aβ in AD, which seems counterintuitive, since NEP is a Aβ degrading enzyme. The authors claim that what is characteristic of AD is: (a) the correlation between NEP and t-tau, and (b) "a lack of association between NEP activity and CSF-Aβ$_{42}$ levels" [31, p. 385].

One major problem with such a conclusion is the fact that there is no correlation between Aβ and NEP in LLD either - thus it cannot be characteristic of AD alone. Furthermore, there is no test of sensitivity or specificity in this paper, since it is more explorative in nature. Therefore, the claim of the authors might not be correct, since their sample is small, they are the first to test NEP *in-vivo* to AD and LLD, and their statistics are based on correlations. However, if a unique relationship between AD and NEP can be found, it could potentially break new ground for the differential research.

Alzheimer-associated neuronal thread protein

Zhang., *et al.* [4] examine urinary samples of the Alzheimer-associated neuronal thread protein (AD7c-NTP) as a biomarker for cognitive impairment in LLD, which in turn may increase the risk of developing AD. AD7c-NTP over-expression can lead to cell death and can be associated with the changes in AD [4, p. 1498]. The paper points to the fact that there are abnormal levels of Aβ and tau in LLD - earlier findings suggest that AD7c-NTP is correlated with p-tau in AD - thus this article examines if such an association can be found in LLD as well. In the analysis the authors divide LLD in cognitive impairment (LLD-CI) and no cognitive impairment (LLD-NCI). LLD-CI had a score <26 of the Montreal Cognitive Assessment (MoCA).

The study found that LLD-CI had significantly higher levels of AD7c-NTP compared to LLD-NCI ($p < .001$) and HC ($p < .001$), while AD had higher levels than LLD-CI ($p = .03$) (Figure 9). Comparing AD7c-NTP to the MoCA indicates that concentration of AD7c-NTP increases with worse MoCA scores. This tendency was found in 6 of 7 measures in the MoCA with AD, including delayed recall ($p < .001$). The study demonstrates the potential benefit of separating LLD in two groups based on AD7c-NTP and MoCA. Keeping in mind that LLD might have subgroups, could potentially increase the accuracy of diagnostic measures, since one is aware that all patients cannot be diagnosed in the same fashion [64].

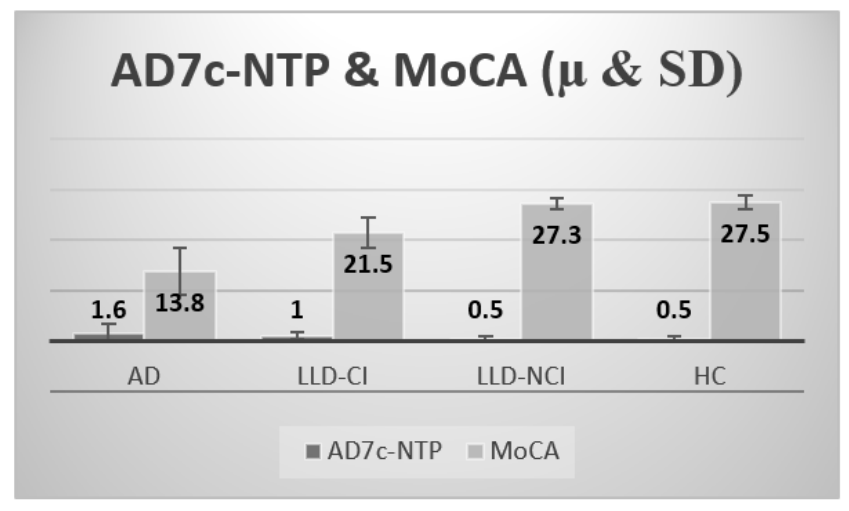

Figure 9: *AD7c-NTP and MoCA across groups (Means and SD) [4].*

The authors themselves point to limitations, among these are a low sample size and a lack of test of efficacy. The fact that a longitudinal design would illustrate "dynamic changes of urinary AD7c-NTP" [4, p. 1501] could be examined. Also, considering the lack of control of the effects of LLD itself on cognition is a limitation. Although the authors claim AD7c-NTP correlates with CSF-based measures, its proposed association is not tested in the article. However, the finding that differences can be found using urinary samples (non-invasive),

and that LLD can be separated into subgroups is promising for future studies in that they can differentiate non-invasively and might indicate which subgroups are of special interest.

Interim summary

The above-mentioned articles all offer different means to distinguish the diagnoses - and could break new ground in the differentiation of LLD and AD.

First, D-serine did have a large effect in line with existing CSF-based measures, and the specificity and sensitivity increased when combining D-serine to IATI. Madeira., *et al*. [30] demonstrates that abnormal levels of D-serine are not only found in AD, but also in LLD to some degree. In addition, unlike several CSF-measures [30], D-serine is correlated to MMSE and disease progression [65]. Second, Sorensen., *et al*. [31] found that the NEP correlation to t-tau and lack of correlation with $A\beta_{42}$ is indicative of AD. The potential of either identifying AD through an association between NEP and tau or a lack of association between NEP and $A\beta_{42}$ would be interesting to test. Lastly, Zhang., *et al*. [4] is the only article examining urinary samples and could open for a different way of identifying AD. The authors found that AD7c-NTP-levels positively correlated with cognitive impairment measured with the MoCA. Furthermore, a higher level of AD7c-NTP seems indicative of AD - although sensitivity and specificity were not tested. Importantly, the authors emphasize the fact that it might be advantageous to divide LLD in at least two groups when differentiating, which will be elaborated upon in the discussion.

These three articles all have a low sample size which increases the possibility of false-positive results [66]. All articles are cross-sectional; hence they cannot determine temporal changes in the measures. Also, all measures were found to be elevated in both LLD and AD compared to HC, which increases the importance of examining why these levels also are increased in LLD. Future studies replicating these measures should elaborate on the differential effect of such new biomarkers.

Discussion

The assumption that it is possible, to some degree, to differentiate LLD and AD has been confirmed by above reviewed studies - however the unclear relationship between LLD and AD is a returning theme throughout the analysis.

Overall findings

Overall the various approaches to the differentiation of AD and LLD each hold their strengths and weaknesses - interestingly they each have a distinctive way of approaching memory as a differentiating factor. One underlying assumption in several of the papers is the fact that the hippocampus is central for memory acquisition and retrieval, which is why atrophy of this should, in theory, lead to memory impairment [14]. As AD is expected to have a degenerating hippocampus because of neurofibrillary tangles and senile plaques, it is surprising that CSF-based measures [24-26] do not correlate to MMSE, although their specificity and sensitivity is >80%. However, one should remember that the MMSE measures several constructs, and thus the item for memory could correlate to CSF-measures, but that is often not disclosed. In addition, the association between CSF-based biomarkers and memory impairment do not always seem to be associated, but might still be, since the accumulation of Aβ is non-linear [22].

D-serine and NEP are different entities entirely [30,31]. D-serine appears to be a measure of cognitive functioning, as well as a correlate to IATI - and appears to be effective in the differentiation. Meanwhile, NEP's lack of association with Aβ and correlation to t-tau might be characteristic of AD. More research might increase the sensitivity and specificity, perhaps combined with other CSF-based measures. Zhang., *et al*. [4] stands out for their use of urinary samples. The authors find that AD7c-NTP correlates with the MoCA and thus can be a measure of memory impairment.

Notwithstanding, four of the nine articles present relevant considerations revolving heterogeneity within the LLD group [4,26,27,29]. These articles argue that one subgroup is more similar to AD, thus shedding doubt on the relevance of comparing AD to LLD as a whole.

The four articles have found similar structural abnormalities, memory impairment, olfactory impairment and hippocampal atrophy in approximately 1/3 of the cases in LLD, hence, when differentiating it might be this subgroup which is misdiagnosed. This similarity can be explained through the concept of excitotoxicity in LLD [14], which can result in atrophy in the hippocampus similar to the ones by neurofibrillary tangles and senile plaques [19]. Nevertheless, Grön., *et al*. [28] argue against this thesis, in that they found that LLD patients are able to recruit their hippocampus unlike AD - although they do not examine subgroups. Because the subgroup difference exists according to some studies it is relevant to examine the potential in separating the LLD group for future differentiation. Because evidence is not conclusive, a discussion of LLD as a prodrome or as a risk factor to AD will link these findings to theories regarding the potential causal role between the diagnoses.

Prodrome/risk factor

Both LLD and AD have a high prevalence and are often comorbid - 15% - 25% have comorbid probable AD and LLD [67]. The relationship between LLD and AD is still unknown, though there are two ideas of thought: (a) LLD is a risk factor of AD, therefore they are independent illnesses [35,41,45,68], or (b) LLD is a prodrome to AD, thus the two are interconnected in a causal way [38,44,58,60,69,70].

It has been established that depressive symptoms often will be seen with cognitive impairment [71] and this impairment affects memory directly, but the type of impairment is not homogeneous [18]. In the following the evidence supporting LLD as a risk factor or as a prodrome will be discussed, and a synthesis of the two will be attempted.

Synthesis

Studies [35,41,45,68] have found that LLD increases the likelihood of later being diagnosed with AD. Even though some inconsistencies exist, the tendency seems clear; "(…) studies of late-life depression have been more conflicting but the majority support an association…" [72, p.1]. While another base of studies claim that instead of increasing the likelihood of AD, LLD is a prodrome and the two illnesses thus are causally linked. Arlt [58] states that "Mood disorders in the elderly are often accompanied by cognitive deficits independent of AD; however, depression may accompany AD as an early symptom, possibly complicating the diagnosis" (page 470) - thus, LLD may be the first symptom of a developing AD. The nine analyzed articles mostly hold the main assumption that the two illnesses can be distinguished - although some recognize the heterogeneity of the relationship between LLD and AD as mentioned in section of Overall findings.

LLD appears more frequently with AD, which might have several causes one of which is age [17]. The picture is, however, more complex. On the one hand the term pseudo-dementia [45] arose as a definition of the cognitive difficulties which can come from LLD: "[Pseudo-dementia] is the clinical condition, which presents, with the picture of a full-blown dementia but actually is a different entity" [45, p. 2]. On the other hand, LLD is unique in the way it relates to AD. A study found that LLD is a prodrome because the later the depressive symptom onset, the higher risk of developing AD, despite genetic influence [44, p. 12]. Similar results were found in Heser., *et al*. [69] who demonstrated that depressive symptoms were predictive of transition to AD. They furthermore claim that LLD might be a reaction to cognitive impairment from the beginning stages of AD [69]. Oppositely, Wright and Persad [70] states that depression is not a reaction to a subtle cognitive decline, but still is a prodrome through the concept of hypercortisolemia, which is touched upon earlier with the upregulation of glucocorticoids in an abnormal HPA-axis [14]. The article claims that because heightened cortisol is found in LLD and AD, that is what links them together. Analyzing LLD as a whole cannot be accomplished, which may lead to speculations regarding different types of LLD.

"Major depressive disorder (MDD) is a heterogeneous syndrome with diverse and complex neurobiological bases" [35, p. 615]. Two interpretations exist. The first interpretation is related to pseudo-dementia [45]. This diagnosis holds the assumption that if the depression remises, then the cognitive deficits will also remiss - indicating a risk factor [17]. The second interpretation can be expressed

through endogenous depression. Endogenous depression appears to be characterized by not remising its cognitive symptoms after recovering from depressive symptoms - indicating a prodrome [41,45]. If the premise that these two categories can co-exist, how would one identify one over the other, since both are characterized by memory impairment? From the included articles at least four different approaches to identify subgroups of AD are suggested [4,26,27,29]. Certainly, that more cognitively impaired subgroups can be identified with OI, CSF-based measures, AD7c-NTP or FCSRT - not addressing the reliability or validity. Since these different subgroups can be characterized with a more impaired cognitive profile, atrophy of the hippocampus and somewhat similar structural changes as seen in AD, it can in part be seen in compliance with endogenous depression. In addition, even though types of LLD might have similar structural abnormalities and hippocampal atrophy as AD, one critical consideration about the cause of such sheds doubt upon the prodromatic nature of types of LLD. With current knowledge LLD is more likely a risk factor, although one type of LLD might be of greater risk for AD than another [35]. That said, identifying a cognitive profile or a particular neural formation of a prodrome to AD can be influenced by everything from a small infection causing delirium to a different neurological illness like Parkinsons. The important thing to notice here is that *for many individuals* it might be the case that a specific type of LLD can be identified. What can be deducted from this complexity is that although subtypes of LLD can be identified, their relation to AD cannot be established because of inconsistencies in theory and practice, meaning the origin of the impairments is incompatible using current knowledge.

Interim interpretation

The research distinguishing LLD as a risk factor or a prodrome is, to this date, still unclear. Although different types of depression which have different impairments of cognition exist [59], a specific type of LLD acting as a prodrome to AD has not been identified although some are suggested. A LLD type with episodic memory impairment [6,14,61], depressive symptoms [73] and hippocampal atrophy [29,74] might be of special interest. However, since the analyzed studies all have a different approach, a specific profile cannot be made - thus, it does not clarify whether subtypes of LLD might be prodromes to AD.

Three interpretations are possible: (a) LLD impairs episodic memory, causing pseudo-dementia, (b) LLD is the first manifestation of AD, making it a prodrome, (c) the two illnesses co-exists independently [75]. These conclusions should not be seen as mutually exclusive, they might be right for different types of LLD - "(…) it is possible that both prodromal and risk factor association may be differentially relevant for different individuals" [44]. Indeed, one should consider the evidence that either endogenous depression, LLD-OII, LLD-CI or Alzheimer-associated depression might be prodromatic to AD, since they have different cognitive and neural underpinnings [4,26,27,29,75]. In addition, identifying which subgroup can be treated will help to give the appropriate treatment. Conclusively, identifying subtypes of LLD, and knowing which leads to a specific outcome, can save money, time and lead to a better quality of life since appropriate measures can be taken.

Strengths and Limitations of the Current Paper

Materials

The main goal of this systematic review is to differentiate AD and LLD on the basis of episodic memory impairment and memory-associated biochemical markers; "A biomarker should be reliable, reproducible, non-invasive, simple to perform and inexpensive" [57, p. 244]. Hence, the invasive, complicated and expensive nature of CSF-based measures [76,77] is in question since they are the last step of the diagnostic process [13,32]. Also, complexities of CSF-based measures have been found [22] and the fact that the articles examine homogenous groups might trouble the implication in general practice [78]. Thus, shedding doubt upon the ecological relevance or validity of CSF-measures. Following guidelines from Hampel., *et al*. [57], more research on neuropsychological tests and perhaps urine-samples might be a better approach. A general critique of the articles is the fact that not all articles perform a power or sensitivity/specificity analysis of their findings, thus not examining the strength of their findings, which makes it hard to compare to other measures of differentiation.

Methodology

Overall one critique applies to the fact that N < 50 in 5 of the 9 papers regarding LLD and AD. In addition, two papers [29,31] do not have a control group. When control groups are a part of the study, the authors often compare AD against a polled score of LLD and HC, which might drag the difference up, thus increasing possibility of significant results (under the assumption that LLD will be more biomarker positive than HC). This could possibly point to publication bias, in which one wishes to provide statistically significant results, also, it does not speak to the direct difference between AD and LLD [79]. Both AD and LLD are dynamic illnesses, and therefore cross-sectional studies are not going to explain causal relationships, consequently longitudinal studies are preferred. Finally, large standard deviations are found, and different scores in the same diagnosis across studies - see appendix 1. This underlines the need for more accurate measures which provide smaller SD and revealing the dynamic elements of AD and LLD.

Conclusion

Differentiation of AD and LLD based on memory impairment and memory-associated biochemical markers is a debated topic, mostly because the underlying pathophysiologies of the diagnoses are not fully understood. Indeed, two fields of knowledge can be identified originating from their underlying assumption revolving LLD as a prodrome or a risk factor to AD. The first, viewing LLD as a prodrome to AD questions whether differentiation is relevant, or whether it's more relevant to identify subtypes of LLD. The second, viewing LLD as a risk factor to AD, claims that differentiation today is possible with a sensitivity and specificity >80%, thus it would rather elaborate on developing more precise equipment. Of consideration is the fact that some non-invasive approaches were as effective as measures of lumbar puncture. A non-invasive, easier and more affordable approach can therefore be promoted.

Despite these different assumptions misdiagnosis will still be expected based on four established facts: (a) big comorbidity - it might not be possible to differentiate them, (b) big SD in most measurements - illustrated in appendix 1 this lack of accuracy complicates the diagnosis, (c) different results and conclusions across studies, even when using the same measurement, and (d) a general lack of knowledge about the underlying nature of LLD and AD. In addition, it is established that subgroups of LLD exist; therefore, their influence should be considered regardless of underlying assumption. If differentiation between the two is difficult, one should treat the depressive symptoms regardless of underlying assumption because a correlation of depressive symptomatology and episodic memory impairment is found.

Most important from this systematic review are suggestions for future research - since an improved understanding of the presently addressed issues is essential to avoid misdiagnosis. Two directions are proposed. On the one hand, one must identify subgroups of LLD and understand their relationship to AD. In this way exposed groups can be of special consideration. On the other hand, one needs to elaborate on existing tools of differentiation. This elaboration should replicate existing measures, so reliability can be established. Differentiation of LLD and AD will only become of greater importance. Undeniably, identifying critical subgroups and improving measurements will help millions in the future through quickly giving appropriate care and treatment to the ever-increasing number of people suffering from these diseases.

Conflict of Interest

Both authors have declared no conflict of interest.

Appendix

Main outcomes in included articles

Citation	Groups	Measure 1: score (SD)	Measure 2: score (SD)
Buerger., *et al*. [24]		**p-tau$_{231}$**	**MMSE**
	Probable AD	58 µl (29)	20.1 (3.8)
	Possible AD	28 µl (30)	27.7 (1.2)
	LLD	10 µl (18)	27.8 (2.3)
	HC	2 µl (9)	29.0 (0.8)
Hertze., *et al*. [25]		**AB42xMAP**	MMSE
	AD	158 (41)	19.0 (3.9)
	LLD	271 (53)	27.9 (2.2)
	HC	265 (74)	28.3 (1.8)
Sun., *et al*. [26]		**AB1-40/1-42 ratio**	**MMSE**
	AD	N/A	N/A
	LLD	N/A	N/A
Chen., *et al*. [27]		**OI**	**MMSE**
	AD	5.8 (1.8)	12.4 (5.1)
	LLD	9.9 (2.7)	22.7 (5.3)
	[LLD-NOII]	11.8 (1.4)	24.6 (3.6)
	[LLD-OII]	7.3 (1.8)	20.4 (6.3)
	HC	11.8 (1.7)	26.8 (1.9)
Grön., *et al*. [28]		**Verbal episodic memory (AUC)**	**MMSE**
	AD	29.0 (2.2)	25.9 (3.5)
	LLD	40.1 (9.7)	29.0 (1.8)
	HC	45.8 (3.7)	30.0 (0.0)
Teichmann., *et al*. [29]		**FCSRT (total delayed recall)**	**MMSE**
	AD	8.6 (0.5)	19.1 (0.5)
	AD (prod.)	8.1 (1.3)	26.1 (1.6)
	LLD	13.4 (0.5)	25.6 (0.7)
Madeira., *et al*. [30]		**D-serine**	**MMSE**
	AD	12.32 (0.44)	12.7 (6.2)
	LLD	5.14 (3.28)	24.4 (2.2)
	HC	2.45 (0.65)	27.1 (1.3)
Sorensen., *et al*. [31]		**NEP**	**MMSE**
	AD	N/A	N/A
	LLD	N/A	N/A
Zhang., *et al*. [4]		**AD7c-NTP**	**MoCA**
	AD	1.6 (1.7)	13.8 (4.7)
	LLD-CI	1.0 (0.7)	21.5 (3.1)
	LLD-NCI	0.5 (0.3)	27.3 (1.1)
	Mean LLD	0.75 (0.5)	24.4 (2.1)
	HC	0.5 (0.3)	27.5 (1.3)

PRISMA - articles at full-text screening and reason for exclusion

	Author (year) Title	Inclusion/exclusion
1	Amariglio., *et al*. (2015) Subjective cognitive concerns, amyloid-β, and neurodegeneration in clinically normal elderly	Excluded: No AD/LLD
2	Arlt, S. (2013) Non-Alzheimer's disease-related memory impairment and dementia	Excluded: Review
3	Bagattini., *et al*. (2017) Neural dynamics of multiple object processing in mild cognitive impairment and Alzheimer's disease: Future early diagnostic biomarkers?	Excluded: No LLD
4	Barca., *et al*. (2017) Trajectories of depressive symptoms and their relationship to the progression of dementia	Excluded: No LLD
5	Baune., *et al*. (2012) Inflammatory biomarkers predict depressive, but not anxiety symptoms during aging: the prospective sydney Memory and Aging Study	Excluded: NO AD
6	Bemelmans., *et al*. (2016) Psychological, behavioral and social effects of disclosing Alzheimer's disease biomarkers to research participants	Excluded: Review
7	Bevan-Jones., *et al*. (2017) Neuroimaging of Inflammination in Memory and Related other disorders (NIMROD) study protocol: a deep phenotyping cohort study of the role of brain inflammation in dementia, depression and other neurological illnesses	Excluded: No results (not finished)
8	Bishnoi., *et al*. (2015) Vitamin D binding protein as a serum biomarker of Alzheimer's Disease	Excluded: No LLD
9	Bittner., *et al*. (2013) Association of 1H-MR spectroscopy and cerebrospinal fluid biomarkers in Alzheimer's disease: Diverging behavior at three different brain regions	Excluded: No LLD
10	Blennow and Galasko (2000) Cerebrospinal fluid biomarkers for Alzheimer's disease: their role in Clinical Chemistry	Excluded: No LLD
11	Blennow and Vanmechelen (1998) Combination of the different biological markers for increasing specificity of in vivo Alzheimer's testing	Excluded: No LLD
12	Blennow and Vanmechelen (2003) CSF markers for pathogenic processes in Alzheimer's disease: diagnostic implications and use in clinical neurochemistry	Excluded: Review
13	Blennow., *et al*. (2001) CSF total tau, a beta 42 and phosphorylated tau protein as biomarkers for Alzheimer's disease	Excluded: Review
14	Borg (2008) Molecular imaging of the 5-HT[1A] receptor in relation to human cognition	Excluded: Review
15	Bos., *et al*. (2017) The frequency and influence of dementia risk factors in prodromal Alzheimer's disease	Excluded: Review
16	Brites and Fernandes (2015) Neuroinflammation and depression: Microglia activation, extracellular microvesicles and microRNA dysregulation	Excluded: Comorbid illnesses
17	Buckley., *et al*. (2016) Subjective memory decline predicts greater rates of clincal progression in preclinical Alzheimer's disease	Excluded: No LLD
18	Buerger., *et al*. (2003) Differentiation of Geriatric Major Depression From Alzheimer's Disease With CSF Tau Protein Phosphorylated at Threonine 231	Included
19	Burke., *et al*. (2016) Neuropsychiatric symptoms and Apolipoprotein E: Associations with eventual Alzheimer's disease development	Excluded: No AD
20	Chang., *et al*. (2016) Clinical Dementia Rating Scales Detects White Matter Changes in Older Adults at Risk for Alzheimer's disease	Excluded: No LLD
21	Chen., *et al*. (2018) Cognitive impairment and Structural Abnormalities in Late Life depression with olfactory identification impairment: an Alzheimer's Disease like pattern	Included

22	Chung., *et al*. (2015) Lifetime history of depression predicts increased amyloid-β accumulation in patients with mild cognitive impairment	Excluded: No LLD
23	Diniz., *et al*. (2012) Reduced serum levels of adiponectin in elderly patients with major depression	Excluded: No AD
24	Do Couto., *et al*. (2016) Depression with melancholic features is associated with higher long-term risk for dementia	Excluded: No LLD
25	Donix., *et al*. (2019) Risk factors for dementia are not associated with cognitive dysfunction in young people with major depressive disorder	Excluded: No LLD
26	Edwards., *et al*. (2014) Combining select neuropsychological assessment with blood-based biomarkers to detect mild Alzheimers disease: a molecular neuropsychology approach	Excluded: No LLD
27	Engelborghs (2013) Clinical indications for analysis of Alzheimer's disease CSF biomarkers	Excluded: Review
28	Engelborghs and De Deyn (2001) Biological and genetic markers of sporadic Alzheimer's disease	Excluded: Review
29	Fjell., *et al*. (2018) Neuroinflammation and Tau interact with amyloid in predicting sleep problems in aging independetly of atrophy	Excluded: No LLD
30	Green., *et al*. (1997) Early detection of Alzheimer disease: methods, markers, and misgivings	Excluded: Comorbid illnesses
31	Grön., *et al*. (2002) Subjective memory complaints: objective neural markers in patients with Alzheimer's disease and Major Depressive Disorder	Included
32	Guest (2019) Early detection and treatment of patients with Alzheimer's Disease: future perspectives	Excluded: Review
33	Hamm., *et al*. (2015) Precocious Alterations of Brain Oscillatory Activity in Alzheimer's Disease: A window of Opportunity for Early Diagnosis and treatment	Excluded: Review
34	Hampel., *et al*. (2003) Advances in the development of biomarkers for Alzheimer's disease: from CSF total tau and A[beta]1-42 proteins to phosphorylated tau protein	Excluded: Review
35	Hampel., *et al*. (2004) Core biological marker candidates of Alzheimer's disease - perspective for diagnosis, prediction of outcome and reflection of biological activity	Excluded: Review
36	Handels., *et al*. (2012) Dianostic and economic evaluation of new biomarkers for Alzheimer's disease: the research of a prospective cohort study	Excluded: No LLD
37	Harrison., *et al*. (2015) Quantitative Magnetization transfer imaging as a biomarker for effects of systemic inflammation on the brain	Excluded: No AD/LLD
38	Hassenstab., *et al*. (2013) Neurobiology of mental illness., 4th ed.	Excluded: Language (not english)
39	Hertze., *et al*. (2010) Evaluation of CSF Biomarkers as Predictors of Alzheimer's Disease: A clinical follow-Up Study of 4.7 Years	Included
40	Hesse., *et al*. (2017) Reduced cGMP levels in CSF of AD patients correlate with severity of dementia and current depression	Excluded: Comorbid illnesses
41	Hollands., *et al*. (2015) Amyloid-[beta] related memory decline is not associated with subjective or informant rated cognitive impairment in Healthy adults	Excluded: No LLD
42	Hori., *et al*. (2015) Demonstrating the role of anticholinergic activity in a mood disorder	Excluded: No AD
43	Javaherian., *et al*. (2018) Examining the complicated relationship between depressive symptoms and cognitive impairment in preclinical AD	Excluded: No LLD
44	Kim., *et al*. (2013) Less depressive symptoms are associated with smaller hippocampus in subjective memory impairment	Excluded: No LLD
45	Kovacs., *et al*. (2013) 5'-nucleotidases, nucleosides and their distribution in the brain: pathological and therapeutic implications	Excluded: Review

46	Lebedeva., *et al*. (2014) Structural brain changes associated with depressive symptoms in the elderly with AD	Excluded: Comorbid illnesses
47	Lederman (2000) What tests are necessary to diagnose Alzheimer disease?	Excluded: No LLD
48	Lee., *et al*. (2016) Altered relaxin family receptors RXFP1 and RXFP3 in the neocortex of depressed Alzheimer's disease patients	Excluded: Comorbid illnesses
49	Lo., *et al*. (2012) Predicting missing biomarker data in a longitudinal study of Alzheimer disease	Excluded: No LLD
50	Madeira., *et al*. (2015) D-serine levels in Alzheimer's disease: implications for novel biomarker development	Included
51	Martin-Harris (2016) Biological and environmental factors impacting risk of cognitive decline: Imaging [beta] amyloid plaques, tau neurofibrillary tangles and the 5HT1A receptor	Excluded: No LLD
52	Mitchell and Brindle (2003) CSF phosphorylated tau - does it constitute an accurate biological test for Alzheimer's disease?	Excluded: Review
53	Sorensen., *et al*. (2013) Neprilysin-Like activity correlates with CSF-tau and phospho-tau in patients with Alzheimer's disease	Included
54	Pluchino., *et al*. (2013) Steroid hormones and BDNF	Excluded: Review
55	Ramakers and Verhey (2017) The difficult distinction between affective disorders and mild cognitive deterioration	Excluded: Review
56	Reichert., *et al*. (2016) The memory education and research initiative	Excluded: No results (Not finished)
57	Robinson., *et al*. (2017) Multiplexing biomarker methods, proteomics and considerations for Alzheimer's disease	Excluded: Review
58	Royall., *et al*. (2015) Serum IGF-BP2 strongly moderates age's effect on cognition: a MIMIC analysis	Excluded: No LLD
59	Sangubotla and Kim (2018) Recent trends in analytical approaches for detection neurotransmitters in Alzheimer's disease	Excluded: Review
60	Schonknecht., *et al*. (2011) Symptoms and imaging diagnostics of neurodegenerative dementia	Excluded: Language (german)
61	Schultz., *et al*. (2010) Transthyretin as a potential CSF biomarker for AD and dementia with LB: effects of treatment with cholinesterase inhibitors	Excluded: No LLD
62	Seo., *et al*. (2017) Association of subjective memory complaint and depressive symptoms with objective cognitive functions in prodromal Alzheimer's disease including pre-mild cognitive impairment	Excluded: No LLD
63	Seidl and Massman (2015) Relationships between testosterone levels and cognition in patients with Alzheimer disease and nondemented elderly men	Excluded: No LLD
64	Smith., *et al*. (2018) Microvascular Endothelial Function and Neurocognition Among Adults With Major Depressive Disorder	Excluded: No AD
65	Sohrabi., *et al*. (2009) Olfactory dysfunction is associated with subjective memory complaints in community-dwelling elderly individuals	Excluded: No AD
66	Somers., *et al*. (2016) A Decade of Cerebrospinal Fluid Biomarkers for Alzheimer's Disease in Belgium	Excluded: Review
67	Stogmann., *et al*. (2016) Activities of daily living and depressive symptoms in patients with Subjective cognitive decline, MCI and AD	Excluded: No LLD
68	Sun., *et al*. (2011) The relationship between plasma amyloid-[beta] peptides and the medial temporal lobe in the homebound elderly	Included

69	Sun., *et al*. (2009) Depression and Plasma amyloid [beta] peptides in the elderly with and without the apolipoprotein E4 Allele	Excluded: No AD
70	Swanwick., *et al*. (1996) Clinical application of electrophysiological markers in the differential diagnosis of depression and very mild Alzheimer's disease	Excluded: No Memory
71	Teichmann., *et al*. (2017) Free and cued selected reminding test - accuracy for the differential diagnosis of Alzheimer's and neurodegenerative diseases: A large-scale biomarker-characterized monocenter cohort study	Included
72	Terry and Katzman (1983) Senile dementia of the Alzheimer type	Excluded: Review
73	Vercruysse., *et al*. (2018) Relevance of Follow-Up in Patients with Core Clinical Criteria for Alzheimer Disease and Normal CSF Biomarkers	Excluded: No LLD
74	Verfaillie., *et al*. (2019) Amyloid[beta] load is related to worries, but not to severity of cognitive complaints in individuals with subjective cognitive decline	Excluded: No AD
75	Wake., *et al*. (2018) The psychological impact of disclosing amyloid status to Japanese elderly: a preliminary study on asymptomatic patients with subjective cognitive decline	Excluded: No LLD
76	Wu., *et al*. (2018a) Plasma Abeta analysis using magnetically-labeled immunoassays and PET (18) F-florbetapir binding in non-demented patients with major depressive disorder	Excluded: No AD
77	Wu., *et al*. (2018b) Diveristy of neurodegenerative pathophysiology in nondemented patients with major depressive disorder: Evidence of cerebral amyloidosis and hippocampal atrophy	Excluded: No AD
78	Zhang., *et al*. (2018) The association between urinary Alzheimer-associated neuranal thread protein and cognitive impairment in late-life depression: a controlled pilot study	Included

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