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Progression of socio-cognitive impairment from healthy aging to Alzheimer's Dementia: A systematic Review and Meta-Analysis

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CONFLICTS OF INTEREST

Andrew K. Martin and Marcus Meinzer are co-authors of one of the reviewed studies (Martin et al., 2019), however, they were not involved in data extraction and quality assessment of this particular study to avoid a potential conflict of interest.

AUTHORSHIP STATEMENT

Mandy Roheger: Conceptualization, Methodology, Formal Analysis, Visualization, Writing -

Original Draft, Writing - Review and Editing

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Abstract

Background: Socio-cognitive processes can be negatively affected in healthy older adults and in pathological aging conditions. However, trajectories of decline across different socio-cognitive domains have not been investigated. This was addressed in the present systematic review and meta-analysis that aimed to determine the degree of socio-cognitive decline in healthy older individuals and those diagnosed with Alzheimer's disease and its precursors.

Methods: MEDLINE, Web of Science Core Collection, CENTRAL, and PsycInfo were searched for studies investigating social cognition across four broad domains (Theory of Mind, ToM; emotion recognition, ER; Social-decision making, SD; visual perspective taking, VPT) in healthy older individuals, individuals diagnosed with subjective and mild cognitive impairment (SCI, MCI) and Alzheimer's disease (AD). Random-effects meta-analyses were conducted. Risk of Bias was assessed using the "Tool to assess risk of bias in cohort studies".

Results: Of the 8,137 studies that were screened, 132 studies were included in the systematic review, 72 studies in pairwise meta-analyses. ToM and emotion recognition showed a clear progression of impairment across the healthy lifespan and from normal aging to AD. Differential patterns of decline were identified for different types of ToM and emotion processing. Only seven studies addressed changes in SMD and VPT and only included healthy individuals.

Conclusion: This systematic review and meta-analysis identified progression of decline of specific socio-cognitive abilities, which is the necessary pre-requisite for developing early and targeted interventions. We also identified important knowledge gaps in this field that need to be addressed. These include a current lack of research on socio-cognitive decline in a number of different population (e.g., middle age, SCD and MCI-subtypes) and domains (SDM, VPT).

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Keywords: social cognition, healthy aging, subjective cognitive decline, mild cognitive impairment, Alzheimer's disease, theory of mind, emotion recognition, meta-analysis

Highlights

- First systematic review on the progression of impairment on socio-cognitive domains in healthy aging, SCD, MCI and AD.
- ToM and emotion recognition showed a clear progression of impairment across the healthy lifespan and from normal aging to AD.
- There is a current lack of research on socio-cognitive decline in a number of different population (e.g., middle age, SCD and MCI-subtypes) and domains (SDM, VPT).

1. BACKGROUND

The success of the human species has been linked to its sophisticated social abilities (Herrmann et al., 2007) and on the individual level, superior emotional and social skills are predictors of relationship and vocational success, and quality of life (Amdurer et al., 2014). In this context, "social cognition" is used as an umbrella term to describe the mental operations critical for interpreting and responding to others' emotions and intentions. Social cognition is a multidimensional construct that comprises lower order processes that are often highly automatized (e.g., basic emotion recognition), but also more complex operations like visual perspective taking, social decision making or theory of mind (ToM, i.e., inferring what others are thinking or feeling). The latter are thought to draw more heavily on other cognitive functions, like executive control (Adolphs, 2009). However, even lower order socio-cognitive processes may require volitional overriding of automatic emotional responses, expressions, or experiences. Thus, many aspects of social cognition depend to some extent on domain general cognitive processes (e.g., Wade et al., 2018). This is mirrored at the neural level and both domain specific and domain general processes support social cognition. For example, rapid and automatic evaluation of emotional stimuli involve the amygdala and a network of brain regions mediating autonomic, motor and cognitive responses to those stimuli (Pessoa, 2011). Cortical networks specifically linked to social decision making and perspective taking include the ventromedial prefrontal and right temporo-parietal cortex (Hiser and Koenigs, 2018; Martin et al., 2020). Domain general regions like the prefrontal cortex are involved in high-level behavioral regulation, learning of contingencies and updating of information in both social and non-social contexts (Adolphs, 2009).

Deficits in social cognition have been studied most extensively in developmental or acquired diseases directly affecting major hubs of the social brain (e.g., autism, schizophrenia or frontotemporal dementia (Christidi et al., 2018; Cotter et al., 2018)). However, the brain networks supporting both social and domain general cognitive operations are subject to change across the healthy human lifespan (Moran et al., 2012) and socio-cognitive impairments have frequently been reported towards the third age (Hayes et al., 2020; Henry et al., 2013). This can have profound negative consequences for older individuals, including reduced social participation, loneliness and poor health (Charles and Carstensen, 2010), which are even more pronounced when neurological and behavioral impairments progress due to age-associated pathology. For example, impaired social cognition has not only been reported in Alzheimer's disease (AD; Christidi et al., 2018), which is the most frequent neurodegenerative dementia and main cause for neurocognitive impairment, but also in prodromal stages of AD like subjective cognitive decline (SCD; Yildirim et al., 2020) and mild cognitive impairment (MCI; Bora and Yener, 2017). Importantly, because the percentage of elderly people in populations worldwide and the incidence of AD and its precursors are constantly increasing in aging societies worldwide (He et al., 2016), a growing interest to study social deficits in these populations has emerged.

To date, however, research on socio-cognitive impairment in these populations has largely focused on specific deficits (e.g., emotion processing, ToM) or comparison of specific sub-groups (e.g., healthy older individuals vs. AD). Therefore, the present systematic review and meta-analysis will include for the first time all studies that investigated changes in four broad socio-cognitive domains (i.e., emotion recognition, visual perspective taking, social decision making, ToM) that have been studied in healthy aging and individuals diagnosed with SCD, MCI and AD. This approach will not only allow identification of research gaps in this field, but also allow to reveal potential impairment progression in specific socio-cognitive abilities, which is the necessary pre-requisite for developing early and targeted interventions in these populations.

2. METHODS

The present systematic review and meta-analysis was pre-registered and the protocol can be accessed at www.crd.york.ac.uk/PROSPERO/ (ID: CRD42020191607). It follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (Moher et al., 2009). The "PRISMA for Abstracts Checklist" and the "PRISMA checklist for systematic reviews" are displayed in **Supplementary Tables 1 and 2**.

2.1 Systematic Review

A systematic review was conducted and key characteristics of each included study that investigated social cognition in healthy aging, SCD, MCI, and AD were summarized, using the highest reporting standards in the field. The following section describes the search methods, study selection and data extraction processes, and quality assessments.

2.1.1 Search and study selection

A comprehensive search of electronic databases without time restrictions for articles written in English or German was undertaken until the 15th of June 2020. An update search was conducted until 6th of July 2021. The following databases were searched: Pubmed/MED-LINE, Web of Science Core Collection, Cochrane Central Register of Controlled Trials (CENTRAL), PsycINFO & PsycArticles. The search strategy used a combination of keywords and filters whenever possible [(e.g., example from Pubmed/Medline search: (((((Social Cognition) OR (Theory of Mind)) OR (Emotion Recognition)) OR (Visual perspective taking)) OR (social decision making) AND ((((((mild cognitive impairment) OR (subjective cognitive decline)) OR (healthy aging)) OR (healthy older adults)) OR (dementia)) OR (Alzheimer)) OR (AD)) NOT ((psychosis) OR (schizophrenia) OR (depression) OR (parkinson))]. For a detailed overview of our search strategy for every data base, see **Supplementary Tables 3 to 6**. The search procedure was supplemented by a manual search of bibliographies in relevant reviews.

A two stage-screening process against pre-defined eligibility criteria (please see below) was carried out independently by two researchers for each study (MR, JB, or SR) using the Covidence screening and data extraction tool. Initially, titles and abstracts of potential studies were screened, followed by full-text screening. Any disagreements were resolved by discussion and a third reviewer (MM) was involved if no consensus could be reached.

2.1.2 Eligibility criteria

A detailed study protocol was developed prior to study commencement, agreed upon by all authors and pre-registered. Only studies published in German or English were considered. All studies were prospective studies without interventions. Studies were limited to female and male participants ≥50 years of age, either healthy or diagnosed with SCD, MCI or AD. Studies also had to include a comparison group including either healthy young (< 50 years of age) or older individuals (≥ 50 years of age), or a different pathological aging condition (i.e., any combination of SCD, MCI or AD). The diagnosis of SCD, MCI and AD had to be made according to validated criteria [e.g. SCD criteria by Jessen et al., 2020 (Jessen et al., 2020); MCI by either Peterson (Petersen et al., 1997) or Internal Work Group Criteria for MCI diagnosis [IWG criteria (Winblad et al., 2004)], AD e.g. according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Associations (NINCDS/ADRDA; McKhann et al., 1984)]. Only studies using standardized assessment of social cognition as outcomes were included.

"Theory of Mind" was defined as the primary outcome, because it is the most frequently studied socio-cognitive process in healthy and pathological aging (Bora and Yener, 2017). Secondary outcomes included emotion recognition, social decision making, and visual perspective-taking. In cases where the included studies did not clearly state which socio-cognitive domain was measured, we classified the outcomes into either ToM, emotion recognition, social decision making or visual perspective-taking, based on the tests or experimental paradigms that were used. This was necessary to reduce heterogeneity due to variability of assessment tools across studies included in the meta-analyses. For the same reason, the outcome "emotion recognition" comprised all emotion recognition and facial emotion recognition tasks, even though several studies labelled these tasks as affective ToM. Studies that had investigated at least one socio-cognitive domain or process were considered for inclusion. If a study reported multiple assessment time points, only the first was considered.

2.1.3 Data Extraction

Independent data extraction was performed by two reviewers for each study (MR, JB, SR.) using the Cochrane Data extraction form (Higgins et al., 2019) to investigate the reporting of studies. Ambiguous or incomplete data were clarified by contacting the authors, if required. A standardized data extraction form was used.

2.1.4 Quality Assessment

Risk of bias (RoB) was assessed using the "Tool to assess risk of bias in cohort studies" (Higgins, 2018) which is comprised of eight questions regarding reporting quality in cohort studies. Each question was rated by three independent reviewers (MR, JB, SR) leading to low/medium/high RoB for each assessed RoB question. If at least one question was rated as "medium RoB", the overall RoB was medium. In cases where at least one RoB question was rated as "high RoB" or three questions were rated as "medium RoB", the whole study was rated as having a high RoB. Yet, we did not exclude any study from our analysis due to the RoB rating, rather, the quality assessment served as a general first quality check.

2.2 Statistical analyses

Random-effects pairwise meta-analyses were conducted to calculate the overall effect for each investigated outcome (ToM [affective, cognitive, and mixed], overall emotion recognition as well basic emotions separately [i.e., happiness, anger, fear, sadness, disgust, surprise, neutral], visual perspective taking, and social decision making) for each group comparison (healthy young vs. older individuals, healthy older individuals vs. patients with MCI, healthy older individuals vs. patients with AD) if sufficient data was available. There was not sufficient data to statistically compare socio-cognitive abilities between healthy individuals and individuals with SCD or between the different patient groups (MCI, AD).

Data analysis was conducted using R. For all analyses, the alpha level was set at .05. Overall, we analyzed four different groups (healthy young and older individuals, individuals with MCI, patients with AD) leading to three group comparisons for each outcome (young vs. old; old vs. MCI; old vs. AD). Dependent variables for the different meta-analyses were: scores on ToM, emotion recognition [overall and all basic emotions separately, displayed in Forest Plots], visual perspective taking, and social decision making. The mean score of the dependent variable, the mean standard variation, and the number of included participants in each group were used to calculate standardized mean differences. As for the systematic review, only baseline data were considered because data on long-term progression was limited and heterogeneous timings were assessed. Data was not always available as required for the meta-analyses and the following adjustments were made: (1) when standard errors were given for each group, standard deviations were calculated using the formula $SD = SE \times \sqrt{N}$, as suggested in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2020). (2) In cases where results for more than one age group within the healthy aging spectrum were provided (e.g., 70 - 75 years and 76 - 80 years), means and standard deviations were pooled, whenever possible. (3) When several tests were conducted to test one outcome in a study, only the test method which was most frequently used in all studies was considered to decrease heterogeneity (Phillips et al., 2011). (4) In cases where statistical data was only presented graphically, "Plot to Data" for Windows was used to estimate means and standard deviations. (5) When statistical data was unclear or studies were incomplete, authors of the studies were contacted and asked to provide the data within the following two weeks. In cases where no sufficient data could be obtained with the above describe methods, studies were excluded from the meta-analyses.

The I² statistic was used to address heterogeneity of the included studies. As recommended in the Cochrane Handbook for systematic reviews of interventions (Higgins et al., 2019), heterogeneity was interpreted as: 0% to 40%: not important/low heterogeneity; 30% to 60%: moderate heterogeneity; 50% to 90%: substantial heterogeneity; 75% to 100%: considerable heterogeneity. A funnel plot for identifying possible publication bias was calculated.

Sensitivity analyses were conducted using fixed effect models. In addition, we further divided studies according to different ToM tasks (i.e., affective, cognitive, and mixed) and the different emotions tested in the emotion recognition tasks, wherever data was available.

3. RESULTS

3.1 Search results

The initial database search yielded 9,155 studies and an additional 41 studies were identified through inspection of relevant reviews. After removal of duplicates 8,137 studies were screened. After abstract and title screening, 181 full-texts were assessed for eligibility and 132 studies were included in the systematic review. Yet, only 72 studies were included in pairwise meta-analyses because no sufficient data was provided in the remaining studies and could not be obtained through the above described means. The PRISMA flow-diagram (Moher et al., 2009) in Figure 1 illustrates the study selection process.

3.2 Systematic Review

References of the 132 studies included in the systematic review are listed in the **Supplementary Materials, Appendix A**. Due to the large number of eligible studies, we limit narrative summaries of specific comparisons to those that could not be considered in the meta-analyses. A detailed overview of all studies and including demographic information of the study populations, procedures, cognitive and socio-cognitive tasks used, and the main results is provided in **Supplementary Table 7**. Overall, 56 studies that compared social cognition in healthy young and older individuals were included, two studies that compared healthy older participants and individuals with SCD, 32 studies that compared healthy older individuals and patients with MCI, and 57 studies that compared healthy older individuals and patients with AD. In addition, ten studies directly compared socio-cognitive processes in individuals with SCD, MCI and AD; those are highlighted in **Supplementary Table 7**.

The most frequently investigated socio-cognitive process in studies that compared healthy young and older adults was emotion recognition (n = 37 studies), assessed with different facial emotion recognition paradigms or the Reading the Mind in the Eyes Tests (RMET, Baron-Cohen et al., 2001). If tasks were not explicitly categorized by the authors (e.g., Baksh et al., 2018) and requests for clarification remained unanswered, we attempted to assign those tasks to the four broad socio-cognitive domains described above. Studies that had labelled facial emotion recognition tasks as affective ToM task, e.g. Duclos et al., (2018), were categorized as "emotion recognition" in our analysis to maintain homogeneity in our meta-analyses. Cognitive and overall ToM were assessed in n = 20 studies; affective ToM in four studies, Social-decision making (n = 7) and visual-perspective taking (n = 3) tasks were only used in studies comparing healthy young and older individuals. Social-decision making was assessed using either the Dictator Game (Person A "the Dictator" receives money and can decide whether or not to split it with another person) or the Ultimatum Game (Person A receives money and can split it with Person B, however, both get the money only if Person B accepts the offer) in four studies (Beadle et al., 2015; Beadle et al., 2012; Girardi et al., 2018; Harlé and Sanfey, 2012; Roalf et al., 2012). These studies suggested that older adults tend to accept unfairer offers but also make fewer unfair offers to others. Furthermore, two studies used Gambling Tasks (Kovalchik et al., 2005; MacPherson et al., 2002) and one study used a Trust Game (a specific form of the Ultimatum Game) to investigate social-decision making (Kocher and Sutter, 2007). There were no significant differences between young and older adults in any of these tasks. Three studies investigating VPT show contradicting results (Baksh et al.,

2020; Martin et al., 2019; Mattan et al., 2017): two studies reported that the relationship between age group and VPT performance was fully or partially mediated by processing speed and updating (Baksh et al., 2018; Martin et al., 2019). Mattan et al., (2017) reported that age modulated the ability to take perspectives primarily when participants' own first-person perspective was task relevant.

Only two studies were identified that investigated participants with SCD and both included a comparison with MCI patients. One study (Pietschnig et al., 2016) also included healthy older individuals. SCD was diagnosed using criteria suggested by Jessen et al., 2020 [i.e., subjectively perceived cognitive decline individual, but normal performance on standardised cognitive tests], MCI was diagnosed using the Petersen criteria (Petersen et al., 1997). Both studies tested emotion recognition. Participants with SCD performed better on Emotion Recognition Tasks compared to MCI patients (Pietschnig et al., 2016; Yıldırım et al., 2020), but worse than healthy controls (Pietschnig et al., 2016). Only one of the studies investigated ToM (assessed by the Faux-Pas Task) and reported comparable performance in participants with SCD and patients with MCI (Yıldırım et al., 2020).

A total of 32 studies investigated socio-cognitive processes in healthy older individuals and patients with MCI. Of these, n = 23 studies used Peterson criteria (Petersen et al., 1997) to diagnose MCI, six studies used IWG criteria (Winblad et al., 2004), and three studies used DSM-5 criteria. 23 studies described their studied sample as patients with amnestic MCI (aMCI). Again, emotion recognition was the most frequently studied socio-cognitive process (n = 23) using both facial recognition tasks and the RMET. Cognitive and overall ToM were assessed in nine studies using first and second order false-belief tasks or the Strange Story task. Of these, two studies did not find a difference in ToM performance between healthy controls and patients with aMCI, seven studies reported impairment in patients with aMCI (n = 5) and MCI (n = 2). Five studies (McCade et al., 2018; McCade et al., 2013b; McCade et al., 2013a; Michaelian et al., 2019; Pietschnig et al., 2016) further differentiated their samples and investigated facial emotion recognition in healthy controls, patients with aMCI and nonamnestic MCI (na-MCI). Patients with aMCI were significantly more impaired in emotion recognition than patients with na-MCI. Performance of na-MCI patients was comparable to healthy controls. Four studies differentiated between patients with single-domain amnestic MCI (sd-aMCI) and multi-domain amnestic MCI (md-aMCI), all reported impaired emotion recognition in patients with md-aMCI, but not in sd-aMCI (Sheardova et al., 2014; Teng et al., 2007; Varjassyová et al., 2013; Weiss et al., 2008). Social-decision making or visual perspective taking were not considered as outcomes in studies investigating patients with MCI.

Socio-cognitive processing in healthy older individuals compared to patients with AD was investigated in 57 studies. AD diagnosis was made using criteria of the National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association: NINCDS-ADRDA (McKhann et al., 1984) (n = 50 studies), DSM IV TR criteria (DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, 2000) (n =5 studies), and the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX; Murphy, 1989) was used in one study (Burnham and Hogervorst, 2004). Two studies reported using a neuropsychological test battery or MMSE scores to determine AD status (Fernandez-Duque et al., 2009; Youmans and Bourgeois, 2010). Emotion recognition was assessed most frequently (n = 31), using the facial emotion recognition test as well as the RMET, followed by ToM (n = 27 studies), assessed with Faux-pas Tasks, False-Belief Tests, and the Metaphoric and Sarcastic Scenario Test. Most studies that assessed emotion recognition or ToM tasks demonstrated impaired performance in the AD samples. Only three demonstrated comparable performance in healthy individuals and AD patients [emotion recognition: (Gregory et al., 2002; Kéri, 2014); ToM: (Gregory et al., 2002; Irish et al., 2014)]. Three studies assessed the "Interpersonal reactivity index", a tool, which measures perspective taking and empathy concern, demonstrating impaired performance in patients with AD (Dermody et al., 2016; Dodich et al., 2014; Nash et al., 2007). Three additional studies could not be assigned to the

specific domains (Duclos et al., 2018; Poveda et al., 2017; Scheidemann et al., 2016) as they used relatively broad and complex assessment tools.

Only one study (Maki et al., 2013) compared all investigated groups, except for individuals with SCD (younger and older individuals, patients with aMCI and AD), on first and second order ToM (i.e., the ability to understand the intentions or thoughts of another person vs. the ability to infer what another person thinks about thoughts or intentions of others (Happé, 1994)). This study demonstrated that only second-order ToM was impaired in older participants, while both tasks were negatively affected in aMCI and in AD, with more pronounced impairment in the latter group.

Ten studies investigated socio-cognitive tasks in older individuals and compared the results to patients with MCI and AD, thus investigating the progression of socio-cognitive skills. Of these, seven studies investigated emotion recognition, two studies investigated ToM (Yamaguchi et al., 2019; Yamaguchi et al., 2012), and one study investigated Story-based Empathy Emotion Recognition (Dodich et al., 2016). Regarding ToM progression, both studies showed a decline of ToM in patients with MCI and an even greater decline in patients with AD. Story-based Empathy Emotion Recognition Recognition was comparable in healthy individuals and patients with MCI, but declined in patients with AD. Six out of seven studies that investigated emotion recognition in patients with MCI and AD showed progressive decline, and one study reported impairment in patients with AD, but not MCI (Bediou et al., 2009). Furthermore, two studies showed selective impairment of emotion recognition in patients with md-MCI, but in those diagnosed with sd-MCI (Sheardova et al., 2014; Weiss et al., 2008)

3.3 Results of meta-analyses

Overall, n = 72 studies were included in the meta-analyses. There was not sufficient information provided in the remaining studies to be included. Those comprised 37 studies

comparing young and healthy older individuals, 18 studies comparing healthy older individuals and patients with MCI, 17 studies comparing healthy older individuals and patients with AD, and four studies comparing patients with MCI and AD.

3.3.1 Meta-Analyses: Primary outcome: Theory of mind

3.3.1.1 Comparison: Young vs. Old

In the pairwise meta-analyses comparing ToM in young vs. older individuals, we included n = 4 studies investigating affective ToM, n = 11 studies investigating cognitive ToM, and n = 13 studies that provided an overall ToM score, not differentiating between affective and cognitive ToM. Results showed that younger individuals performed significantly better in all aspects of ToM (affective ToM: SMD=0.68, 95%CI: 0.19-1.17, I²=71%; cognitive ToM: SMD=1.43, 95%CI: 0.65-2.21, I²=95%; mixed ToM: SMD=0.72, 95%CI: 0.33-1.10, I²=85%) with the largest effect size (meaning the greatest difference between younger and older people) for cognitive ToM. Forest plots for all three outcomes are displayed in **Figure 2**.

3.3.1.2 Comparison: Old vs. MCI

Only three studies provided sufficient data to compare ToM in older individuals and patients with MCI. ToM was not further classified in these studies (e.g. affective or cognitive ToM). Therefore, we calculated an analysis with mixed ToM as outcome. Results showed that older adults performed significantly better (SMD=0.46, 95%CI: 0.18-0.74, I²=0%) than patients with MCI (see also the forest plot in **Figure 3**).

3.3.1.3 Comparison: Old vs. AD

Ten studies provided sufficient data to compare older individuals and patients with AD with mixed (affective and cognitive ToM) as outcome. Results showed that older adults performed significantly better (SMD=-1.19, 95%CI: -1.60-(-0.78), I²=72%) than patients with AD (see also the forest plot in **Figure 4**).

3.3.2 Meta-Analyses: Secondary outcome Emotion Recognition

Meta-analyses were calculated for the following comparisons: young vs. older individuals, older individuals vs. patients with MCI, older individuals vs. patients with AD, and patients with MCI vs. patients with AD. An overview of the results is shown in **Figure 5**. Forests plots for the overall scores of Emotion Recognition (collapsed across different types of emotion processing) for each group comparison, as well as separate analyses for each emotion are displayed in the **Supplementary Figures 1 – 24**.

3.3.2.1 Comparison: Young vs. Old

Analysis of the overall Emotion-Recognition scores indicated that younger people were significantly better in recognizing emotions than older people (n = 16 studies, SMD=0.66, 95%CI: 0.34-0.98, P=88%). Yet, there was substantial heterogeneity and separate analyses of individual emotions demonstrated that younger people had a significant advantage in identifying happiness, fear, sadness and surprise (happiness: n = 9 studies, SMD=0.34, 95%CI: 0.08-0.61, P=70%, fear: n = 8 studies, SMD=0.58, 95%CI: 0.46-0.70, P=0%, sadness: n = 7 studies, SMD=0.72, 95%CI: 0.34-1.09, P=84%, surprise: n = 4 studies, SMD=0.27, 95%CI: 0.03-0.51, P=16%, please see **Supplementary Figures 1 - 7** for details).

3.3.2.2 Comparison: Old vs. MCI

The overall Emotion Recognition score analysis showed a significant advantage for older adults comparted to patients with MCI (n = 14 studies, SMD=0.56, 95% CI: 0.33-0.78, I²=67%). Separate analyses of individual emotions demonstrated that older people were significantly better in recognizing anger (n = 11 studies, SMD=0.31, 95% CI: 0.17-0.64, I²=0%), fear (n = 10 studies, SMD=0.29, 95% CI: 0.14-0.45, I²=0%), sadness (n = 8 studies, SMD=0.26, 95% CI: 0.10-0.42, I²=0%), disgust (n = 7 studies, SMD=0.24, 95% CI: 0.06-0.42, I²=0%), happiness (n = 11 studies, SMD=-0.15, 95% CI: 0.00-0.30, I²=0%), and also of neutral faces (n = 5 studies, SMD=0.41, 95% CI: 0.05-0.78, I²=62%) compared to patients with MCI, but not surprise (n = 5 studies, SMD=0.27, 95% CI: (-0.03)-0.57, I²=49%, **Supplementary Figures 8 – 15**).

3.3.2.3 Comparison: Old vs. AD

Six studies were included in the analysis of Emotion Recognition total scores comparing healthy older individuals and patients with AD. Older individuals were significantly better in recognizing emotions than patients with AD (SMD=1.35, 95%CI: 0.85-1.84, I²=68%). Older individuals also outperformed AD patients in recognizing happiness (n = 5 studies, SMD=0.68, 95%CI: 0.201-1.16, I²=64%), anger (n = 5 studies, SMD=0.92, 95%CI: 0.16-1.65, I²=84%), sadness (n = 5 studies, SMD=0.55, 95%CI: 0.04-1.15, I²=68%), and disgust (n = 5 studies, SMD=0.56, 95%CI: 0.08-1.03, I²=64%, see **Supplementary Figures 16 – 23**).

3.3.2.3 Comparison: MCI vs. AD

Four studies could be included in the analysis of Emotion Recognition total scores investigating the differences between patients with MCI and patients with AD. Results show that patients with MCI perform significantly better on Emotion Recognition tasks than patients with AD (n = 4 studies, SMD=0.42, 95%CI: 0.17-0.67, I²=12%, see **Supplementary** Figure 24).

3.3.3 Meta-Analyses: Secondary outcomes social-decision making

For social-decision making, only a meta-analysis for the comparison between young vs. older individuals was conducted, because there was not sufficient data reported and/or these processes were not assessed in other populations. Four studies demonstrated that older individuals performed better in social-decision making tasks than young individuals, even though the result was not significant (SMD=-0.94, 95%CI: (-2.42)-0.54, I²=95%, for details see **Supplementary Figure 25**).

3.4 Risk of Bias

The results of the risk of bias assessment are summarized in **Supplementary Table 8**. Overall, most studies were rated as "with some concerns", mainly because studies did not match the two groups for all variables that are associated with the outcome of interest and/or statistical analysis did not adjust for these factors (e.g., educational level, cognitive status). Furthermore, information on "usual treatment" of patients with MCI and AD was missing in most studies. Yet, this information is important to evaluate the "standard living environment" of the two comparison groups in the risk of bias assessment. For example, the "usual treatment" of individuals with MCI and AD is likely different and this may impact socio-cognitive skills.

4. DISCUSSION

This systematic review and meta-analysis addressed changes in socio-cognitive abilities across the healthy life span and in individuals diagnosed with SCD, MCI and AD. We aimed to identify possible trajectories of impairment across four major socio-cognitive domains and also to highlight current research gaps in this field. The systematic review included 132 eligible studies and the majority directly compared healthy older individuals with younger control groups (N=56), patients with MCI (N=32) or patients with AD (N=57). Importantly, the vast majority of studies comparing healthy groups only recruited participants from the lower and upper end of the human adult lifespan. Only two studies included middle-aged individuals (Kessels et al., 2013; Calder et al., 2003). Therefore, only limited information about possible early socio-cognitive changes in this age bracket is currently available which needs to be addressed in the future. Few studies compared socio-cognitive performance in healthy older adults with that of more than one patient group (N=10) or directly compared different patient groups (e.g., AD vs. prodromal stages, N=10). Indeed, only one study included all investigated groups, except for individuals with SCI (Maki et al. 2012). Hence, there is a lack of studies assessing progression of impairment in carefully matched groups with the same experimental paradigms. In studies that included patients with MCI, the majority of studies recruited patients diagnosed with amnestic MCI (N=23/32). Only five studies further characterized their samples as single or multidomain aMCI, four comparisons included patients with non-amnestic MCI. Therefore, relatively little research on differential socio-cognitive impairment in MCI sub-types with varying neuropsychological profiles is currently available. We also noted a specific lack of studies investigating possible pre-clinical signs of socio-cognitive decline in SCD, which is likely related to the relative novelty of the concept (Jessen et al. 2014, 2020). With regard to socio-cognitive domains, emotion recognition was most frequently investigated across all groups (Young vs. Old: N=37; SCI vs. Old/MCI: N=2; Old vs. MCI: 23; Old vs. AD: N=31), followed by different types of ToM (e.g., Young vs. Old: N=22; Old vs. MCI: N=7; SCD vs. MCI: N=1, Old vs. AD: N=27). However, only few studies employed other tasks (social decision making: N=7; visual perspective taking: N=3) and only healthy individuals were investigated, which highlights the need for more systematic research in these areas of social cognition.

A total of 72 studies could be included into the different meta-analyses and there was only sufficient data available for two of the four investigated domains (i.e., emotion recognition, ToM) to assess trajectories of socio-cognitive changes. Overall, our results confirmed impairment progression for both ToM and emotion recognition across the healthy groups and the different patient populations. Specifically, young individuals outperformed healthy older individuals in all aspects of ToM. The largest effect size was found for studies that had assessed cognitive ToM; affective ToM was also impaired, but effect sizes were about half the size. This pattern is largely in line with previous research showing higher correlations between cognitive vs. affective ToM and age-associated cognitive decline or more pronounced impairment for ToM tasks that draw more heavily on executive functions (Charlton et al., 2009; Cho and Cohen, 2019). Additional comparisons were only available for mixed ToM. Here, performance of older individuals was significantly impaired compared to younger individuals (with a similar effect size as for affective ToM), but outperformed both patients diagnosed with MCI and AD. However, the magnitude of this effect was twice as large in patients with AD compared to MCI. There was not sufficient data available to conduct meta-analyses including patients with SCD or to compare the different patient populations. Indeed, only one recent study (Yildirim et al. 2020) compared healthy individuals and individuals diagnosed with SCD and reported comparable performance between those groups. However, this study did not differentiate between cognitive and affective components of the task that was used, which would have been of interest to investigate potential early decline of cognitive ToM (Fault-Pax Task, (Bottiroli et al., 2016)). Regarding MCI, insufficient data precluded investigating different diagnostic subgroups, but ToM was impaired in 7 of 9 studies including patients diagnosed with (a)MCI. Only cognitive or mixed ToM were assessed and task difficulty varied substantially between studies, which likely explains these heterogeneous results. Two additional studies confirmed more pronounced ToM impairment in patients with AD compared to MCI, but also progression of impairment in AD at later stages of the disease (Yamaguchi et al. 2012; 2019).

A similar pattern emerged for emotion recognition and scores consistently declined from young age to AD. When considering the different types of emotions that were investigated, happiness, surprise, fear and sadness were significantly impaired even in healthy aging, but not recognition of anger and disgust. This pattern is largely consistent with two studies that investigated emotion recognition across the entire healthy human lifespan (Calder et al. 2003; Kessels et al. 2013). These studies demonstrated gradual decline of happiness, fear, sadness and overall emotion recognition scores across the healthy human lifespan. Anger recognition showed a sharp decline only late in life, recognition of digust even improved in old age (Calder et al. 2003). Progression of emotion recognition impairment was confirmed by comparing healthy individuals and patients with MCI and AD: Here, older individuals outperformed both patient groups in recognizing all investigated types of emotions, except for surprise in MCI. Moreover, the magnitude of impairment compared to healthy older adults was 2-4 times higher in patients with AD than in MCI. This suggests a clear progression of emotion recognition impairment from normal aging to AD, which is in line with results reported by studies that directly compared these patient populations and those showing early impairment of emotion recognition in SCD (Pietschnig et al. 2016; Yildirim et al. 2020), more pronounced impairment in patients with amnestic- vs. non-amnestic MCI (McCade et al. 2013a,b,2018; Michaelian et al. 2019; Pietschnig et al. 2016) and single- vs. multi-domain aMCI (Sheardova et al. 2014; Teng et al. 2007; Varjassyova et al. 2013; Weiss et al. 2008). Hence, our results are in line with and extend a previous study that confirmed early emotion recognition impairment in MCI that was based on only six studies (Bora and Yener et al. 2017). They also challenge the notion that facial emotion recognition is not consistently impaired in AD (Torres Mendoca de Melo Fadel, 2019).

Only few studies investigated social-decision making and visual perspective taking and sufficient data to conduct meta-analyses was only available for the former and the comparison of healthy young and older individuals. While there were qualitative differences between young and older individuals (e.g., older individual may accept unfairer offers, while being fairer themselves) and older individual tended to perform better overall, no significant performance differences were found. This result is to be interpreted with caution because of the small number of included studies (N=4). For studies investigating visual perspective taking (N=3), methods and results showed substantial heterogeneity, preventing any meaningful conclusions at this stage and more research in these areas of social cognition is urgently needed.

5. CONCLUSION

Overall, our analyses confirmed a gradual progression of socio-cognitive impairment from young adulthood to AD for both ToM and emotion recognition. Within those domains, we also highlight the different trajectories of decline for different aspects of ToM and emotion processing. The latter is of high relevance, because intact socio-cognitive abilities are associated with higher quality of life, emotional well-being, and social functioning throughout life (e.g. Bora et al., 2016, Yogarajah et al., 2019). Consequently, identification of early impairment is of utmost importance for developing intervention protocols. We also identified important shortcomings in this field that need to be addressed including lack of research on socio-cognitive decline in several different populations (e.g., middle age, SCD and MCI-subtypes) and domains.

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