Social cognition in Alzheimer’s disease: A separate construct contributing to dependence

Stephanie Cosentino, Laura B. Zahodne, Jason Brandt, Deborah Blacker, Marilyn Albert, Bruno Dubois, Yaakov Stern

Abstract

The extent to which social cognitive changes reflect a discrete constellation of symptoms dissociable from general cognitive changes in Alzheimer’s disease (AD) is unclear. Moreover, whether social cognitive symptoms contribute to disease severity and progression is unknown. The current multicenter study investigated cross-sectional and longitudinal associations between social cognition measured with six items from the Blessed Dementia Rating Scale, general cognition, and dependence in 517 participants with probable AD. Participants were monitored every 6 months for 5.5 years. Results from multivariate latent growth curve models adjusted for sex, age, education, depression, and recruitment site revealed that social cognition and general cognition were unrelated cross-sectionally and throughout time. However, baseline levels of each were related independently to dependence, and change values of each were related independently to change in dependence. These findings highlight the separability of social and general cognition in AD. Results underscore the relevance of considering social cognition when modeling disease and estimating clinical outcomes related to patient disability.

Keywords: Alzheimer’s disease; Social cognition; Cognition; Dependence

1. Introduction

Social cognition has been described as a set of converging implicit and explicit processes that are engaged to understand or interpret the self in relation to others [1,2]. This set of processes forms the basis of the complex set of behaviors and mutually shared expectations that enable individuals to interact successfully with one another across a range of situations [3]. In contrast to certain presentations of frontotemporal dementia (FTD), early Alzheimer’s disease (AD) is characterized frequently by preserved social cognition [4]. In fact, social cognition often remains intact into the moderate stages of the disease [5,6]. However, a small subset of individuals with AD evidence marked changes in social cognition early during the disease that is sometimes severe enough to elicit misdiagnoses of FTD. Even in cases that fit the typical AD profile, with amnestic deficits being prominent, individuals have been shown to demonstrate impairment on objective social cognitive tests including Theory of Mind (ToM) and emotion recognition [7,8], and in some cases these impairments can be commensurate with those in FTD. See Harciarek and Cosentino [9] for a review.

The extent to which social cognitive deficits represent a component of the disease that is separable from general...
cognitive deficits in AD has not been examined formally. Existing work has demonstrated that functional deficits and psychiatric symptoms (i.e., depression, psychosis, agitation), although related to general cognitive impairment in AD, are separable elements of the disease [10–12]. Social cognitive symptoms may represent yet another specific manifestation of disease pathology that is distinct anatomically and/or behaviorally from general cognitive impairment. For example, social behaviors have been shown to have distinct neural circuitry originating in the orbitofrontal regions of the prefrontal cortex (PFC) and mapping onto specific regions (e.g., ventral vs. dorsal) of subcortical structures, including the striatum, globus pallidus, and thalamus [13,14]. Behavioral evidence for the dissociation between this circuitry and other circuits originating in the PFC can be seen, for example, in the frequent dissociation between social cognition and executive abilities in behavioral variant FTD [15–19]. It has also been suggested that social cognitive deficits may reflect compromise within a network including the PFC, insula, and temporal lobe that is critical for updating and processing contextual cues [20]. This social context network model has been proposed recently as a possible basis for the social cognitive changes in behavioral variant FTD.

Alternatively, it is possible that social cognitive deficits in AD stem from more general cognitive deficits. For example, it has been suggested that impairment on objective tests of emotion recognition and ToM may reflect deficits in visuoperception or executive functioning, for example [21]. The first aim of this study was to examine the cross-sectional and longitudinal associations between subjectively rated social cognitive symptoms assessed with a six-item subscale from the Blessed Dementia Rating Scale (BDRS) and general cognition for the first time in a large cohort of individuals with AD. A second, related aim was to clarify the extent to which subjectively rated social cognitive symptoms, although potentially unrelated to general cognitive symptoms, have relevance to disease severity and course assessed with the Dependence Scale (DS) [22], a measure that has been recommended for modeling AD progression [23]. The DS accounts for more variance in clinical outcomes than cognitive scores alone [23]. Indeed, when compared with other markers of disease including the Mini-Mental State Examination (MMSE), Disability Assessment in Dementia, and Clinical Dementia Rating, the DS accounted for the greatest amount of variance in a variety of economic (e.g., direct medical costs) and quality-of-life outcomes for patients and caregivers. It has thus been recommended for use in models of long-term disease progression in AD.

2. Material and methods

2.1. Participants and procedures

The current sample included 517 patients diagnosed with probable AD and enrolled in the Multicenter Study of Pre-
dictors of Disease Course in Alzheimer’s Disease. Local institutional review boards at all participating sites approved the study. Full study procedures are described elsewhere [24,25]. In brief, patients were recruited in two waves at outpatient clinics and clinical research centers at four sites in the United States and Europe: Columbia University Medical Center (n = 208), John Hopkins School of Medicine (n = 147), Massachusetts General Hospital (n = 124), and the Hôpital de la Salpêtrière in Paris, France (n = 38). Diagnoses of probable AD were made using National Institute of Neurological and Communicable Diseases and Stroke–Alzheimer’s Disease and Related Disorders Association criteria [2] at consensus conferences attended by at least two physicians specializing in dementia and one neuropsychologist. Complete inclusion and exclusion criteria for the study have been described previously [24,25]. All patients were required to have mild dementia defined by a Modified Mini-Mental State Examination (mMMSE) score of 30 points or more (described later), which is approximately equivalent to a Folstein MMSE score of 16 points or more. Exclusion criteria were evidence for a cause of dementia other than AD, Parkinsonism, stroke, alcoholism, schizophrenia, schizoaffective disorder, and electroconvulsive therapy within 2 years preceding study enrollment or a history of 10 or more electroconvulsive treatments in a single course.

2.2. Measures

Social cognitive symptoms were assessed at each occasion on a scale from 0 to 6 points based on a subset of informant-rated items from the BDRS [26] that query whether the patient is (i) more stubborn than before and less able to adapt to change, (ii) more self-centered than before; (iii) unconcerned about others’ feelings, (iv) unable to control emotions, (v) easily angered, and (vi) likely to make strange jokes or laugh at things that are not funny. These items were shown previously to load together on a single factor that was independent from three other factors assessing symptoms related to general cognitive symptoms (e.g., remembering short lists, finding the way around the house), apathy (e.g., less interest in starting new things, less likely to participate in hobbies, decreased emotional reactions), and basic self-care (e.g., eating, dressing, and bladder control) [27].

Global cognitive status was evaluated at each occasion with the mMMSE [28]. In addition to items from the MMSE [29], the mMMSE includes items that allow for more comprehensive assessment of working memory, calculation, recall of the current and four previous presidents of the United States, confrontation naming, repetition, and visuoconstruction. The scale was translated and modified for assessments at the Paris site. Scores range from 0 to 57 points, with higher scores indicating better cognitive functioning.

Depressive symptoms were assessed at baseline with the Columbia University Scale for Psychopathology in AD [30],
which is a semistructured interview conducted with an informant assessing the presence and severity of psychiatric symptoms during the past month. Depressive symptom severity scores were used in the current study to rule out the possibility that elements of the social cognitive index reflected depression. Scores range from 0 to 4 points, with higher scores indicating greater psychopathology. Good interrater reliability for concurrent ratings of the depressive symptoms portion of a single interview has been reported ($\kappa = 0.80$) [30].

The main outcome measure was the DS, a 13-item instrument administered to a caregiver [22]. The DS comprises 11 dichotomous items (e.g., Does the patient need to be watched or kept company when awake?) and two items scored on a 3-point Likert-type scale indicating the frequency of need (e.g., Does the patient need reminders or advice to manage chores, do shopping, cook, play games, or handle money?) Scores range from 0 to 15 points, with higher scores indicating greater dependence. Interrater reliability, internal consistency, convergent validity, criterion validity, and sensitivity to change range from acceptable to excellent [22,31].

2.3. Statistical analysis

Data were analyzed using MPlus version 7 (Muthen & Muthen, Los Angeles, CA) with a special case of structural equation modeling often referred to as latent growth curve (LGC) modeling using maximum likelihood estimation [32,33]. Missing data were managed with the full information maximum likelihood method, which uses all available data for parameter estimation. This approach accumulates and maximizes casewise likelihood functions computed using all available data for each participant. Monte Carlo simulation has shown that the full information maximum likelihood method produces unbiased and more efficient estimates than alternative methods (e.g., listwise deletion, pairwise deletion, and similar response pattern imputation) [34]. Models carry the assumptions of homogeneity of error variance and dependence of errors within each domain (i.e., function, cognition, depressive symptoms). A strength of LGC modeling is that it allows the study of multiple outcomes throughout time in a multivariate framework. The overall level of change (intercept) and amount of change (slope) in each symptom type (i.e., dependence, cognition, social cognition) represented the key parameters. Additional information regarding parameter estimation in multivariate LGC and its application to the study of neurodegenerative disease is available elsewhere [32,35]. Model fit was assessed with the following commonly used statistics: $\chi^2$, root mean square error of approximation (RMSEA), comparative fit index (CFI), and Tucker-Lewis index (TLI). Smaller values of chi square and RMSEA indicate better model fit. Values of CFI and TLI that are closer to 1 indicate better fit. Fit between nested models was compared statistically using the chi square test.

Model building proceeded in two broad stages. First, the trajectories of the three variables of interest were examined separately with unconditional univariate growth curve models.

To characterize the functional forms of social cognitive, general cognitive, and dependence trajectories, models that estimated only linear change were compared statistically with those that estimated both linear and quadratic change. Second, best-fitting univariate models were combined into a single, conditional multivariate model, in which obtained parameter estimates controlled for all included variables. In this model, correlations between initial levels and changes in the symptoms independent of the covariates (i.e., sex, age, education in years, recruitment site, and depression) can be estimated. In addition, covariate effects on both the overall levels of symptoms (intercepts) and on symptom changes (slopes) were examined. Certain covariates were centered to facilitate parameter interpretation. Specifically, values of zero corresponded to the mean sample age of 74 years, to 12 years of education, male sex, enrollment at the Columbia site, and absence of depressive symptoms at baseline.

3. Results

3.1. Descriptives

Participants had an average baseline age of 74.35 ± 8.66 years (standard deviation) and educational level of 13.61 ± 3.58 years. The ethnic distribution of the sample was 93% white, 6% black, and 1% other ethnicities. Five percent of the participants were Hispanic by self-report. A total of 59.8% of the participants were female. Average baseline performance on the mMMSE was 37.63 ± 6.37 points. On average, caregivers reported that participants demonstrated 2.05 of six social cognitive symptoms at baseline, with a range of zero to six. Frequencies of individual symptoms at baseline ranged from 9% (making strange jokes) to 54% (more stubborn). Dependence scores were 5 out of 13 points on average, with a range of 0 to 12 points. See Table 1 for initial and change values of all variables. At least one follow-up assessment was available for 96.9% of the current sample. The average number of assessments was 7.7 ± 3.3, indicating that the average participant was monitored semiannually for more than 4 years. Data from only the first 12 occasions (5.5 years) were included in the current study to maximize covariance coverage.

3.2. Unconditional univariate models

Nested unconditional univariate models were built separately for the three outcome variables. In models allowing only linear change, social cognition (slope estimate = 0.213; $P = .001$), cognition (slope estimate = −1.384; $P < .001$), and dependence (slope estimate = 1.819; $P < .001$) worsened during the study period. Allowing for curvilinear change improved model fit significantly for social cognition ($\Delta \chi^2[4] = −149.15, P < .001$), cognition ($\Delta \chi^2[4] = −503.18, P < .001$), and dependence ($\Delta \chi^2[4] = −201.80, P < .001$). Thus, models including both linear and quadratic slopes were retained for subsequent model building.
Parameter estimates in the best-fitting unconditional univariate LGC models are shown in the upper panel of Table 1. Intercepts (levels) refer to latent variables derived from all 12 occasions that reflect estimated initial levels of the outcomes independent of the growth process, not merely baseline scores. Linear slopes can be interpreted as the constant rates of change over time. Quadratic slopes can be interpreted as changes in the rates of change over time. Variance estimates for both intercepts and slopes represent the degree of individual differences in initial levels and trajectories in each variable. There were significant residual variances in both intercepts and slopes (all, \( P < .001 \)) in all three models, indicating substantial individual differences both in initial levels and trajectories of social cognition, cognition, and dependence. Such residual variance is a precondition for additional model building. As shown in Fig. 1, social cognition, cognition, and dependence worsened during the study period, but leveled out over time. Change in social cognition, although statistically significant, is less prominent than that in the other two variables and may be particularly difficult to appreciate with the representation of the full range of the scale on the y-axis in Fig. 1.

### 3.3. Conditional multivariate model

The three best-fitting univariate LGC models for social cognition, general cognition, and dependence (i.e., the models that allowed for both linear and quadratic change in each of the three variables) were combined into a single multivariate model, and five time-invariant predictors measured at baseline (i.e., age, sex, education, depression, and recruitment site) were added. The model provided the following fit statistics: \( \chi^2(747) = 1253.652 \) (\( P < .001 \)), CFI = 0.96, TLI = 0.95, and RMSEA = 0.037 (0.033, 0.040). Intercepts shown in the lower panel of Table 1 can be interpreted as estimated initial values when all covariates are set to zero (i.e., age is 74 years; education is 12 years; sex is male; site is Columbia; baseline depressive symptoms are zero). As shown, worsening over time was evident for social cognition, cognition, and dependence after controlling for these variables.

Correlations between the factors in the conditional model are shown in Table 2. After controlling for the covariates, initial levels of each variable were related to subsequent change in these domains. Initial levels of both social cognition and cognition were related to initial dependence level, although they were not related to each other. Initial social cognitive status was not associated with subsequent changes in cognition or dependence. However, rates of change in social cognition and change in dependence over time were correlated (Table 2). Rates of change in cognition were also related to rates of change in dependence.

Older age was associated independently with greater initial dependence (standardized parameter estimate = 0.21, standard error [SE] = 0.05, \( P < .001 \)) but slower increase in social cognitive symptoms (standardized parameter estimate = 1.51, SE = 0.06, \( P = .017 \)) and slower general cognitive decline (standardized parameter estimate = 0.24, SE = 0.05, \( P < .001 \)). Female sex was associated with fewer initial social cognitive symptoms (standardized parameter estimate = −0.12, \( SE = 0.05, P = .024 \)) but a more rapid increase in social cognitive symptoms over time (standardized parameter estimate = 0.16, SE = 0.06, \( P = .010 \)) and lower initial cognition (standardized parameter estimate = −0.15, \( SE = 0.05, P = .001 \)). Lower level of education was associated with lower general cognitive status at baseline (standardized parameter estimate = 0.20, \( SE = 0.05, P < .001 \)) but not with the rate of cognitive decline in any domain. Participants enrolled at different recruitment sites did not differ in initial levels or in rates of change in any of the three outcomes.

To examine the role of depression or apathy at any point in time, these variables were entered into an additional model as time-varying covariates. Specifically, depression and apathy

<table>
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<tr>
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<th>Intercept (SE)</th>
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<th>Linear slope (SE)</th>
<th>Variance (SE)</th>
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<th>Model Variance (SE)</th>
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<td>1.929 (0.168)</td>
<td>0.253 (0.056)</td>
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<td>−0.039 (0.011)</td>
<td>0.026 (0.004)</td>
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<td>mMmMSE</td>
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<td>37.874 (2.617)</td>
<td>−5.181 (0.296)</td>
<td>34.209 (2.808)</td>
<td>0.159 (0.057)</td>
<td>0.947 (0.105)</td>
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<td>Dependence</td>
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<td>4.465 (0.421)</td>
<td>1.386 (0.085)</td>
<td>1.896 (0.222)</td>
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<td>38.515 (0.614)</td>
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<td>3.859 (0.377)</td>
<td>1.133 (0.197)</td>
<td>2.004 (0.230)</td>
<td>−0.003 (0.034)</td>
<td>0.045 (0.006)</td>
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Abbreviations: SE, standard error; SC, social cognition (range, 0–6 points); mMmMSE, modified Mini-Mental State Examination (range, 0–30 points)

*Parameters estimated in three separate univariate models.

\( P < .001 \)

\( P < .05 \)

*Parameters estimated in a single conditional multivariate model.
at each visit were allowed to correlate with all three dependent variables (i.e., social cognition, cognition, dependence) at that visit. Apathy was measured with three items from the BDRS that were shown previously to load together on a single factor that was dissociable from the items used to measure social cognition in the current study (See Section 2.2 Measures). Depression was related to social cognition at all but three visits (baseline standardized covariance \(50.17, P = .005\)), and was in general unrelated to cognition or dependence over time. Apathy was related to social cognition at all visits except for the final visit (baseline standardized covariance \(50.29, P < .001\)), unrelated in general to cognition, and related inconsistently to dependence over time. More important, when these variables were included as time varying, the main findings regarding the relationships between social cognition, cognition, and dependence remained unchanged, but the overall fit of the model became poor.

In a final set of analyses, we examined the extent to which the current findings were based on the particular items included in the social cognitive index. To do so, we reran the conditional multivariate model excluding symptoms that might be considered nonspecific (defined as being present in at least one-third of participants at baseline). Results were unchanged when excluding either (i) increase in stubbornness/decreased ability to adapt to change (54%), (ii) very irritable/easily angered (47%), or (iii) unable to control emotions (34%). Exclusion of the fourth most common symptom, increase in self-centeredness (33%), resulted in a correlation of general cognitive symptoms with social cognitive symptoms. Results thus suggest that including self-centeredness in the index bolsters its dissociability from general cognition.

4. Discussion

Social cognitive symptoms, although associated most commonly with FTD, also occur in a subset of individuals with AD. The current study focused on a brief, subjective measure of social cognition as reported by the caregiver, as opposed to an objective assessment of abilities such as ToM or emotion recognition, for example. In the current study, individuals demonstrated an average of two of six social cognitive symptoms on the BDRS at baseline (with a range of zero to six), as reported by a knowledgeable informant. Social cognitive symptoms increased an average of 0.25 point/year. A primary question in this study was whether social cognitive symptoms map on to general cognition or whether they represent a separable component of the disease. Multivariate latent growth curve analysis demonstrated that when controlling for demographic variables, depression and apathy, social and general cognition were unrelated both at baseline and over time, indicating that social cognitive changes in AD are not a by-product of changes in general cognition, but rather reflect a distinct constellation of symptoms.

It is possible that social cognitive deficits reflect damage to specific brain regions or networks that may become compromised during the course of AD, such as the orbitomedial PFC and/or its projecting fibers in the basal ganglia and thalamus [13,14], the anterior cingulate [36], or temporal
regions including the temporoparietal junction (TPJ) [20,37,38]. Changes in personality, here conceived of as social cognitive symptoms, have long been reported in the context of orbitofrontal compromise and ventromedial caudate lesions [39–41]. More recent imaging work in context of orbitofrontal compromise and ventromedial social cognitive symptoms, have long been reported in the [20,37,38]. Changes in personality, here conceived of as regions including the temporoparietal junction (TPJ) [20,37,38]. Changes in personality, here conceived of as social cognitive symptoms, have long been reported in the context of orbitofrontal compromise and ventromedial caudate lesions [39–41]. More recent imaging work in context of orbitofrontal compromise and ventromedial social cognitive symptoms, have long been reported in the [20,37,38]. Changes in personality, here conceived of as

<table>
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<th>SC</th>
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<th>mMMESE</th>
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<tr>
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Abbreviations: SC, social cognition; mMMESE, modified Mini-Mental State Examination.

*P < .001.

Table 2
Standardized between-person associations between the latent factors in the conditional multivariate model

DS items measure nonsocial dependencies (i.e., needs help managing chores, remembering information, bathing, eating, toileting, and so forth). As such, social cognitive symptoms appear to have direct implications for a primary disease outcome via a route that is separate from the effects of general cognitive deficits. This dissociation is consistent with the idea that multiple, discrete factors constitute disease severity and progression [10,11]. Using a latent variable modeling approach in two separate samples of individuals with AD, Tractenberg and colleagues [10] found that the model that best fit the data included a general neurological factor and three symptom factors, including cognition, function, and behavior. That is, although there was a seemingly common underlying disease process accounting for the shared variance across discrete symptom types, each set of symptoms also acted as separate constructs independently relevant for disease severity. Social cognitive impairment may represent another element of disease that should be considered when estimating clinical outcomes related to patient disability, and potentially other important outcomes such as family impact and health care use.

A final issue addressed in this study was whether social cognitive symptoms herald a more aggressive disease course. Existing work has demonstrated that atypical presentations of AD, including those that implicate a disproportionate involvement of frontal and/or subcortical regions, are often associated with more rapid general cognitive and functional decline [43,44]. Moreover, individuals with behavioral variant FTD appear to decline more quickly than those with other subtypes of FTD [45–47], suggesting that involvement of the brain regions and/or genetic factors that underlie social cognitive changes may reflect an aggressive variant of disease, or that frontal lobe involvement could hasten disease course secondary to behavioral problems that may lead to overmedication or other differences in quality of medical care [47]. However, the severity of social cognitive symptoms at baseline did not predict future change in...
dependence in individuals with AD the in current study. Therefore, although such symptoms contribute to and track disease severity over time, their cross-sectional presence in early AD appears to have little prognostic value with respect to future disease course, and this is in contrast to the predictive utility of general cognitive symptoms for change in dependence. The lack of a predictive relationship between social cognitive symptoms and change in dependence was somewhat unexpected, given their association at baseline, and the previously reported prognostic value of frontally mediated symptoms in both AD and FTD. However, as mentioned earlier, it is not necessarily the case that social cognitive symptoms in AD reflect prefrontal compromise, as growing evidence implicates a more widespread network of structures such as the TPJ that appear to be particularly important for supporting aspects of social cognition [20,37].

The current findings highlight the distinct nature of social cognitive and general cognitive changes in AD, and underscore the relevance of each aspect of the disease process for level of dependence. Models of disease should consider social cognitive symptoms and change in these symptoms as a separate process contributing to overall markers of severity such as dependence. Limitations of the current study include use of a retrospective measure of social cognition that is (i) relatively limited in scope, lacking information about a greater range of socially inappropriate behaviors; (ii) subjective and therefore potentially influenced by caregiver bias; (iii) inclusive of several common behaviors in AD that may have limited the specificity of the measure; and (iv) lacking information about specific, objectively measurable aspects of social cognition, including ToM or emotion recognition, for example. However, the social cognitive index compiled for the current study was based on a factor analysis in which these symptoms clustered together and were separable from caregiver-reported symptoms related to general cognition, apathy, and basic self-care. Moreover, although objective measures of social cognition provide nonbiased information, family report is a primary means by which clinicians determine the presence of social cognitive changes in a patient. Furthermore, activation in brain regions that contribute to social cognition, including the orbitofrontal and medial frontal cortex, has been shown to vary parametrically with objective indices of social cognition, including ToM and subjective indices such as an individual’s social network size, suggesting that these different aspects of sociality may share a similar neural basis [48]. Last, although there were several common symptoms included in the scale (e.g., stubbornness, easily angered), item-by-item analysis of the scale suggested that removal of these symptoms did not change the current results. In fact, removal of one common symptom (i.e., self-centeredness) resulted in the association between social cognitive and general cognitive symptoms, suggesting that including this item in the social cognitive index enhanced its independence as a construct. A second limitation of the current study is that autopsy data were not available for all individuals included in the sample. As such, there is a risk that participants with other forms of dementia such as FTD were included in this study [25,49]. However, previous investigations in the Predictors study have demonstrated that the diagnosis of AD was confirmed in as much as 96% of available postmortem diagnostic evaluations [25,49]. The investigation of social cognitive symptoms in this large longitudinal cohort of individuals with AD complements the primarily small experimental and case studies that have examined this topic thus far. It will be important for future work to include social cognitive symptoms in models of disease along with markers of cognition, function, and psychiatric symptoms. Moving forward, it will also be important to determine the extent to which social cognitive symptoms are separable from behavioral (e.g., agitation) and psychiatric symptoms.

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RESEARCH IN CONTEXT

1. Systematic review: The accumulated knowledge related to the focus of the current manuscript was established by a comprehensive PubMed literature search related to social cognition in Alzheimer’s disease and frontotemporal dementia.

2. Interpretation: Current findings suggest that social cognitive changes in Alzheimer’s disease are not by-products of cognitive change, but represent a distinct manifestation of disease. Second, the presence of social cognitive changes relates to higher levels of dependence at individual points in time and over time. These findings implicate a role for social cognition in models of disease.

3. Future directions: To expand these findings, future studies should evaluate the interplay between social cognitive deficits and a range of psychiatric symptoms to determine the extent to which these manifestations of disease are independent. In addition, work evaluating the relationship between subjective and objective social cognitive measures is needed to understand fully whether these different assessments tap into a similar construct or whether they evaluate dissociable abilities.
References


