Alzheimer's disease and Mild Cognitive Impairment under a linguistic lens

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Abstract

Linguistic measures in spontaneous speech have shown promise in detecting Alzheimer's disease (AD), but it remains unknown which specific linguistic variables show sensitivity. We selected candidate variables in a hypothesis-driven fashion based on the neurocognitive profile of AD. Speech samples were obtained from a picture description. 105 participants were split into Mild Cognitive Impairment (MCI), Mild-to-Moderate AD, and healthy controls (HC), for between-group comparisons and correlations with MMSE scores. AD and MCI had fewer embedded adjunct clauses relative to HC and MCI vs. HC had fewer adverbial adjuncts. AD used less verbal Aspect marking than HC and differed in the distribution of noun phrase types and their anomalous use. Linguistic variables correlated with and predicted MMSE scores. These linguistic changes reveal cognitive differences relating to specificity in referencing objects and events. They support the potential of fine-grained linguistic variables in detecting and tracking pathological cognitive decline.

Keywords: Alzheimer's Disease, memory, spontaneous connected speech, reference, specificity

1. Background[1]

Language is a universal aspect of human cognition and deeply intertwined with other cognitive domains including memory. Thus, processing any utterance involves the retrieval of lexical concepts stored in long-term semantic memory, which codify our general knowledge about the world (Binder, Rutvik, Graves, & Conant, 2009). These lexical concepts are processed as parts of grammatical structures, in which thoughts are articulated. In sentences of certain types, e.g. *A car was passing by*, these thoughts connect with personal memory directly, semantic or episodic. Language also plays a well-established role in working memory (Baddeley, 2003) and in long-term memory encoding and retrieval (Feist & Cifuentes Férez, 2013; Feist & Gentner, 2007; Lee, 2018). Beyond memory, there is rich evidence that language interfaces with cognitive domains such as perceptual categorization, problem-solving, and mind-reading (Farrar, Benigno, Tompkins, & Gage, 2017; Novack & Waxman, 2019; Zettersten & Lupyan, 2020), and it has been argued to be uniquely linked to the origin of specific kinds of meaning and thoughts, e.g. narrative meaning (Bruner, 1990) or declarative reference (Hinzen, 2017).

These connections make it desirable to de-compartmentalize research on neurocognitive domains in neurological disorders, focusing on relations *between* them, as provided through an overarching and integrative system such as language, which necessarily involves all other cognitive domains in its normal functioning. Language could have high potential for detecting cognitive change and decline and trace it over time across pathologies, as evidence from a range of neurodegenerative and neuropsychiatric diseases already suggests (Cokal et al., 2018; Cokal et al., 2019; Hinzen et al., 2018; Tovar et al., 2020). In Alzheimer's disease (AD), memory is a core clinical symptom and

[1] Abbreviations: AD = Alzheimer's disease, MCI = Mild Cognitive Impairment, HC = healthy controls, MMSE = Mini-Mental State Examination, EM = episodic memory, NP = noun phrase, VP = verb phrase

early language decline as revealed by verbal fluency tests is widely documented (Taler & Phillips, 2008), though the connection between language and memory has been barely explored (but see Irish, Kamminga, & Addis (2015); Schacter & Addis, (2007)). Evidence from hippocampal amnesia suggests that the same processes involved in the hippocampal declarative memory system, such as relational binding of items into integrated representations and their flexible use and online maintenance, are also involved in language processing (Duff & Brown-Schmidt, 2012).

To explore the potential of language as a measure of cognitive decline and disease progression, linguistic studies need to go beyond verbal fluency tasks at the single word-level. Studies of spontaneous connected language in AD have already shown, in the case of written text, that language decline can precede and predict a final diagnosis with AD by years if not decades (Garrard, Maloney, Hodges, & Patterson, 2005; Snowdon et al., 1996; van Velzen & Garrard, 2008). Linguistic analyses of spoken connected language in patients with probable or autopsy-proven AD have revealed language deficits in early stages, particularly in the areas of semantics (Forbes-McKay & Venneri, 2005; Ahmed et al., 2013a; Ahmed, de Jager, & Haigh, 2013b) and syntax (Emery, 2000). A downward path starts at least at the stage of Mild Cognitive Impairment (MCI) (Ahmed et al., 2013a; Taler, Klepousniotou, & Phillips, 2009). Language measures extracted from spontaneous language have some power to predict conversion to MCI (Oulhaj, Wilcock, Smith, & de Jager, 2009), and machine learning classifiers have shown promise in identifying probable AD linguistically as well (Fraser, Meltzerb, & Rudzicza, 2016).

A critical issue is how to measure language in this context. Domains of language typically investigated in studies of spontaneous connected language in AD have been: (i) speech production (e.g. speech rate), (ii) syntactic complexity (e.g. mean length of utterances, syntactic errors), (iii) lexical content (e.g. pronoun-noun ratio), (iv) semantic content (e.g. idea density), and (v) fluency (e.g. pauses). Within these domains, many measures have tended to be linguistically not very specific – e.g. the mean length of utterance in words is only a very crude approximation of syntactic complexity; and a semantic content measure like idea density, which identifies the number of propositional information units per total number of words, tells us something about the efficiency of information packaging, but little about the specific linguistic variables involved.

We here aimed to select measures of cognitive change in language that are integrated with linguistic theory, fine-grained, and selected in a hypothesis-driven fashion with a view to the specific neurocognitive profile of AD. In this regard, the language-memory connection is of particular interest. Episodic memory (EM) impairment is a core feature of AD, and includes memory of personal experiences that are specific for when and where they occurred, and who was involved (Tulving, 2002). Specificity is also a key dimension of language, requiring particular grammatical resources to be put in place. Thus, referencing objects through noun phrases (NPs) can be non-specific (e.g. *I like dogs*), indefinite (*Somebody came*), or definite-specific (e.g. *The dog barked*). NPs exhibiting the forms of reference in question differ systematically in their formal grammatical properties and distribution (Hinzen & Sheehan, 2015) and are thus a suitable target of linguistic analyses in AD. Similar distinctions apply at the verbal level, where event reference can be generic (e.g. *I eat meat*; *I go by car to the university*), non-specific (e.g. *I have gone to Paris*), or more specific through spatio-temporal adjuncts (e.g. *I went to Paris in the summer of 2013*), Aspect marking (e.g., *I was cleaning the house*), or embedded clauses relating one event to another (e.g. *I was frightened when the bell rang*). This was the theoretical basis of the present study. We hypothesized that cognitive change in AD and MCI might reveal itself particularly in changes in the specificity of referencing objects and events, at the level of nouns, verbs, and clauses, in spontaneous speech.

2. Methods

2.1 Sample

The initial sample selected for the present study were fifteen participants with autopsy-proven AD from the study of Ahmed et al. (2013), for whom clinical and neuropsychological evaluation had also supported a diagnosis of MCI before the first assessment that had led to a classification of probable AD. These participants and their age, education, and gender-matched healthy elderly controls were recruited as part of the Oxford Project to Investigate Memory and Ageing (OPTIMA), a longitudinal study of the clinical, neuropsychological, biochemical and imaging correlates of ageing in community dwelling elderly persons with and without dementia. For the cross-sectional aims of the present study, the original participants of Ahmed et al. (2013) were added to the MCI group, while further participants with MCI and AD, as well as matched controls, were added to the control, MCI and AD groups so as to obtain three groups of N=35 each, which were matched for age, education and gender. These additional participants were recruited as part of an ongoing in-house study at St. George's University of London (controls, MCI, and AD participants), and the Pitt corpus of the Dementia bank (MCI and AD participants only), both of which employed similar speech elicitation protocols. The final sample is described in Table 1.

Table 1: Participant demographic data

	HC (N = 35)		MCI (N = 35)		AD (N = 35)	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	68.114	9.11	68.514	8.133	68.629	9.277
Education(years)	14.871	3.003	14.343	3.253	14.2	2.576
Sex (f:m)	23 : 12		12 : 23		15 : 20	
MMSE	29.114	0.758	26.114	3.169	21.6	4.031

2.2 Speech elicitation and transcription

Data from spontaneous spoken language were uniformly obtained through the Cookie Theft picture description task from the Boston Diagnostic Aphasia Examination (Kaplan, Goodglass, & Weintraub, 1983), (SGUL participants used the novel Cookie Theft task, see (Berube et al., 2019) and transcribed in CLAN (MacWhinney, 2000) using the speech from participants (as opposed to examiners) only. Definitions of 'utterance' are critical for transcription in CLAN and further analysis. Here the following definition was used (see Table 2): An utterance is a syntactically independent unit of propositional information providing new information. Utterances in this sense differ from clauses, which are configurations of subjects and predicates (usually verbs), and can be syntactically dependent or independent. Transcriptions were anonymized and linguistic raters were blind to participant data and diagnosis. 20% of each participant group were double-annotated by a second rater who was not otherwise involved in this study, to assess reliability of the first rating. Final reliability was calculated by dividing the total point-by-point agreements by the sum of total points possible, resulting in 92.6% reliability.

Table 2: Linguistic variable definitions and examples.

Variable	Definition	Examples
Formal-grammatical errors	Violations of grammatical well-formedness	1. Now he's looking out the window and the stool. 2. And then there was so the two this.
NP domain		
Definite NP	All definite lexical NPs, divided total NPs	Definite NPs: *The boy* is standing on *the stool.* Indefinite NP: There are *some cookies* in *a cookie jar.*
Pronoun	Total number of pronouns, divided by total NPs.	Pronouns: *He/she/it, you, I, this/that, these/those, there.*
Definite NP anomaly	Formally definite referential NP that is anomalously used (vague, unclear or ambiguous reference, referent mis-identified or not introduced before).	1. *The stuff* is flowing out of the sink. 2. I bet she hasn't got *them* down there. 3. And *this one* picks *it* up.

Indefinite NP anomaly	Formally indefinite NP that is anomalously used (vague, re-introduced referent, or incorrect referent).	1. And *bits* literally falling out of there. 2. She wants *something* from a high place. 3. He's got his hand on *a thing* on the shelf.
VP domain		
Aspect	Grammatical category encoding how an event extends over time in relation to the point of speech.	1.The boy is *falling*. 2.The water *has* spilled. 3.He *stole* the cookies.
Tense	Grammatical category encoding the contextual embedding of an event in time relative to the time of speech.	The dog *ate* the cookies.
Modals	Grammatical devices expressing whether an event is possible, probable, certain or permitted.	She *must* be their mother.
Prepositional adjunct	VP adjunct providing additional information, particularly spatio-temporal.	The water is spilling *onto the floor*.
Adverbial adjunct	Adjunct (non-clausal) attaching to a VP or clause, encoding manner, circumstance, or epistemic aspect of an event.	*Apparently*, the kids are stealing some cookies.
VP composite score	Total composite score comprising all measures of spatio-temporal event specificity (aspect, tense, modals, prepositional adjuncts, adverbial adjuncts).	The mother is *washing* dishes *at the sink* and *apparently* doesn't see that the water is *overflowing.* [4 points total]
VP anomaly	Verb phrases which are vague, incorrectly connect or name actions, or insufficiently describe events.	The stuff is *footle-ing* not *making notion* that this is *falling out.*
Clausal domain		
Argument clause	Dependent clauses specifying information that is grammatically required by a subordinating verb, divided by total number of clauses.	The girl wants *her brother to hand her a cookie.*
Adjunct clause	Dependent clauses specifying further information that is not grammatically required, divided by total number of clauses.	The boy is standing on a stool *which is tipping*.
Coordinated clause	Grammatically independent clauses connected by a conjunction, divided by total number of clauses.	The mother is washing dishes *and the kids are stealing cookies.*
Independent simple clause	Clauses with no embedding or coordination, divided by total number of clauses.	The scene takes place in a kitchen.

2.3 Linguistic annotation

Table 2 lists all linguistic variables assessed in this study. These variables fell into three broad syntactic domains: nominals (NPs), verb phrases (VPs), and clauses. Within these three domains, we distinguished grammatically distinct configurations that play a crucial role for the specificity of the referential information conveyed: e.g., whether a particular lexical NP is definite (e.g., *the girl on the stool*) or indefinite (e.g. *there is a mother*), events are characterized using verbal Aspect (e.g. *the stool is tipping over*), or embedded clauses are added to relate events (e.g. *the stool is tipping over as she is reaching for the cookie*). The variable 'formal grammatical errors' was added to also assess the formal integrity of speech.

2.4 Data analysis

We performed between-group analysis using the non-parametric Kruskal-Wallis H test due to non-normal distribution of the data in at least one group, followed by post-hoc pairwise comparisons, using Dunn's (1964) procedure in SPSS. To assess sensitivity of our linguistic variables to a continuous measure of cognitive decline, a combined correlational analysis was performed for all of these variables and MMSE scores (or their equivalent, converted from ACE exam scores), followed by a regression model with MMSE as dependent variable. Variables that had values of zero for more than half of the participants were dichotomized and compared between groups using Fisher's Exact tests. Bonferroni correction for multiple comparisons was applied in all cases, by multiplying p-values by the number of comparisons or correlations, keeping a uniform significance threshold (α) of 0.05. All p-values are reported in their already corrected form.

3. Results

Two-tailed results from between group analyses for all linguistic variables are displayed in Table 3. Significant group differences in the nominal, verbal, and clausal domains, are displayed in Figures 1-3, respectively.

Table 3: Comparisons of linguistic variables across groups

Variable		Means ± SD	Test	P-values			
					HC-MCI	HC-AD	MCI-AD
Utterances	HC	12.886 ± 1.418	Kruskal-Wallis H	0.788			
	MCI	12.886 ± 1.292					
	AD	12.971 ± 1.115					
Formal-grammatical errors	HC	0.1289 ± 0.005	Fisher's Exact		1.000	1.000	1.000
	MCI	0.0095 ± 0.003					
	AD	0.0179 ± 0.007					
% Definite	HC	66.138 ± 16.71	Kruskal-Wallis H	0.036*	1.000	0.048*	0.14
	MCI	67.307 ± 14.115					
	AD	75.768 ± 10.81					
% Indefinite	HC	33.862 ± 16.71	Kruskal-Wallis H	0.036*	1.000	0.048*	0.14
	MCI	32.667 ± 14.11					
	AD	24.205 ± 10.81					
Pronoun ratio	HC	23.765 ± 1.682	Kruskal-Wallis H	0.007*	1.000	0.011*	0.080
	MCI	25.091 ± 2.075					
	AD	33.091 ± 2.410					
Definite anomaly	HC	2.81 ± 0.732	Fisher's Exact		1.000	0.153	1.000
	MCI	4.26 ± 0.715					
	AD	8.18 ± 1.494					
Indefinite anomaly	HC	3.371 ± 1.056	Fisher's Exact		1.000	0.435	0.075
	MCI	2.871 ± 1.061					
	AD	16.269 ± 4.325					
Aspect	HC	0.773 ± 0.037	Kruskal-Wallis H	0.040*	0.529	0.034*	0.712
	MCI	0.703 ± 0.043					
	AD	0.639 ± 0.040					
Tense	HC	0.017 ± 0.037	Fisher's Exact		1.000	0.891	0.318
	MCI	0.034 ± 0.097					
	AD	0.045 ± 0.070					
Modals	HC	0.035 ± 0.045	Fisher's Exact		1.000	1.000	1.000
	MCI	0.050 ± 0.065					
	AD	0.063 ± 0.076					
Prepositional adjunct	HC	0.404 ± 0.156	Kruskal-Wallis H	0.120			
	MCI	0.385 ± 0.246					
	AD	0.461 ± 0.185					

Adverbial adjunct	HC	0.146 ± 0.017	Kruskal-Wallis H	0.016*	0.020*	1.000	0.085
	MCI	0.081 ± 0.016					
	AD	0.141 ± 0.020					
VP composite score	HC	1.378 ± 0.262	Kruskal-Wallis H	0.249			
	MCI	1.255 ± 0.346					
	AD	1.351 ± 0.288					
VP anomalies	HC	4.98 ± 0.998	Kruskal-Wallis H	0.059			
	MCI	9.02 ± 1.311					
	AD	11.55 ± 2.122					
Argument clause ratio	HC	16.33 ± 1.845	Kruskal-Wallis H	0.188			
	MCI	16.17 ± 1.858					
	AD	20.71 ± 2.059					
Adjunct clause ratio	HC	30.2 ± 1.828	Kruskal-Wallis H	0.001*	0.003*	0.004*	1.000
	MCI	20.15 ± 2.028					
	AD	20.71 ± 2.453					
Coordinated clause ratio	HC	27.5 ± 2.224	Kruskal-Wallis H	0.027*	0.066	0.053	1.000
	MCI	36.26 ± 2.922					
	AD	37.08 ± 3.357					
Independent simple clause ratio	HC	25.98 ± 2.778	Kruskal-Wallis H	0.281			
	MCI	27.43 ± 3.841					
	AD	21.51 ± 3.442					

(*) indicates significance at $\alpha = 0.05$ (all p-values corrected).

Generic measures

Global measures of language (number of utterances and formal grammatical errors) did not distinguish groups ($p > 0.05$).

Nominal domain

Percentages of the ratios of definite and indefinite NPs out of total NPs differed significantly between groups. Post-hoc pairwise comparisons showed that AD differed significantly from HC in producing more definite NP ($H(2) = -17.529$, $p = 0.048$) and fewer indefinite NPs ($H(2) = 17.529$, $p = 0.048$). The ratio of pronouns to lexical NPs showed a significant increase between HC and AD ($H(2) = 9.844$, $p = 0.007$) (Figure 1). A subsequent more fine-grained analysis additionally revealed that this was due to a significant increase only in second person pronouns in the AD group compared to controls (p = 0.039), while no significant differences were seen in first and third-person pronouns.

Finally, the rate of anomalies in indefinite NPs also increased from HC to MCI to AD, with a statistically significant difference between HC and AD (Figure 2).

Figure 1: Distribution of NP types across groups

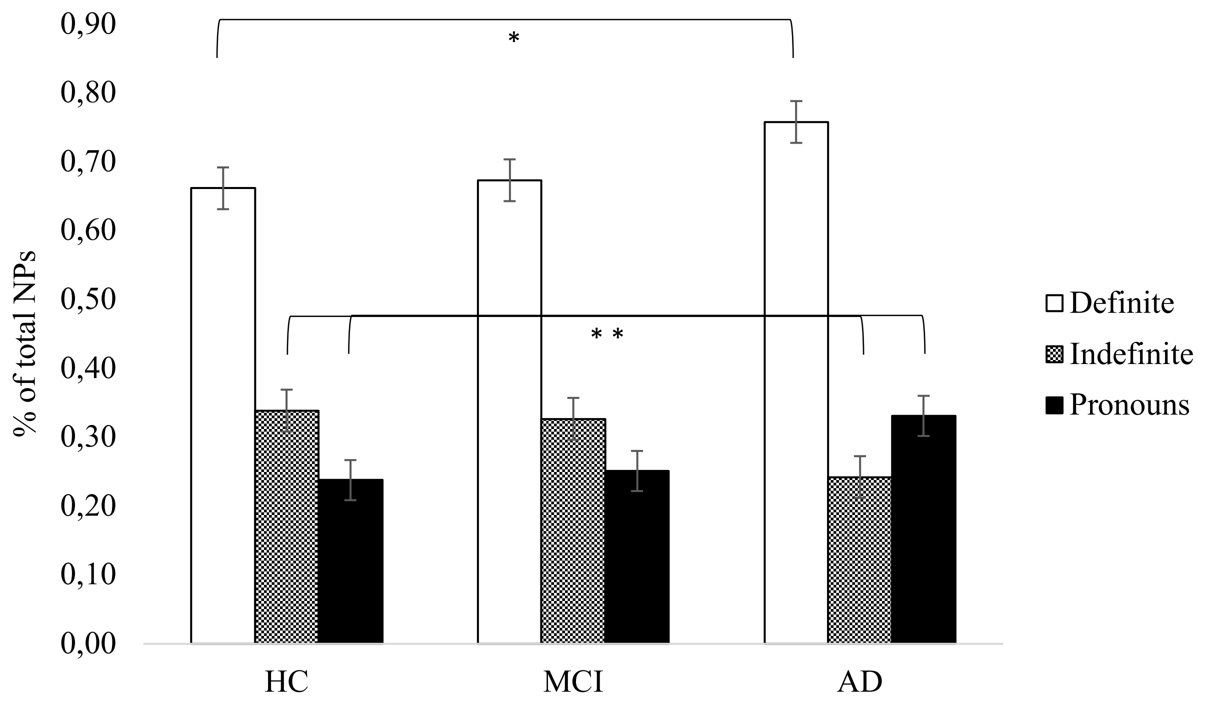
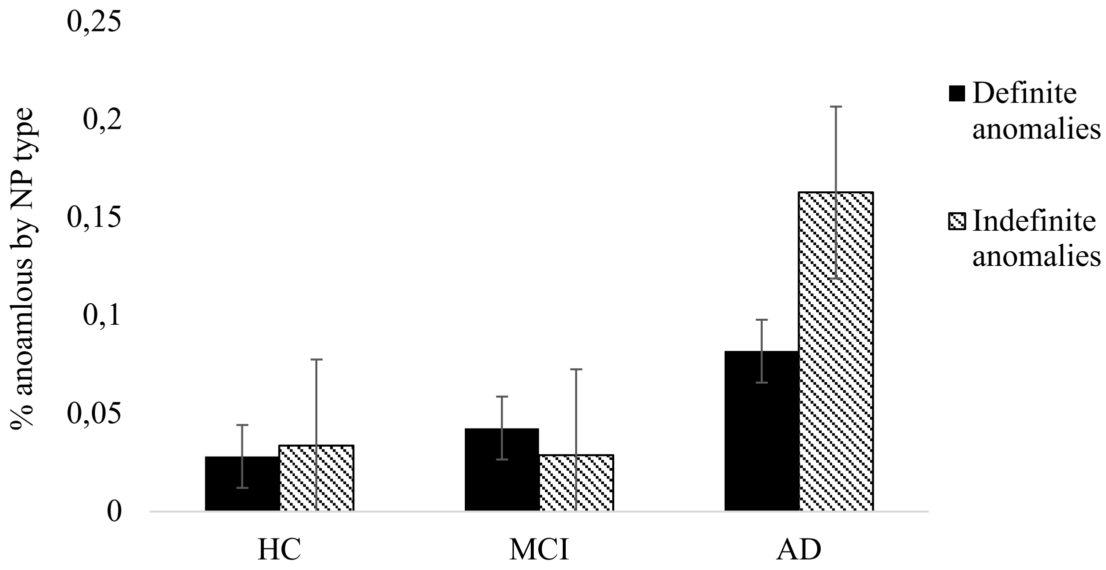


Figure 2: Anomalous NPs by type (definite, indefinite) across groups



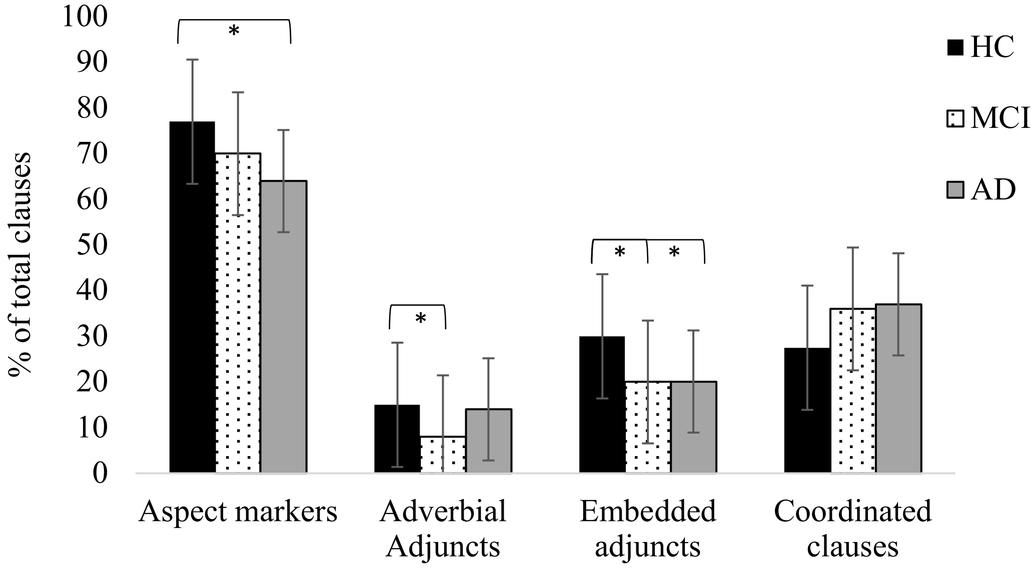
Verbal domain

Aspect scores decreased linearly from HC to MCI to AD, and differences were significant between HC and AD ($H(2) = 18.443$, p = 0.034). In addition, MCI produced significantly fewer adverbial adjuncts than HC ($H(2) = 19.629$, p = 0.020). VP anomalies approached significance in the group comparisons ($H(2) = 5.673$, p = 0.059) (Figure 3).

Clausal domain

Measures of clausal connectivity showed a decrease in the proportion of embedded adjunct clauses from HC to both MCI and AD, with both MCI and AD differing significantly from HC ($H(2) = 24.129$, p = 0.003; $H(2) = 23.357$, p = 0.004, respectively). Coordinated clauses, on the other hand, increased from HC to MCI to AD, with borderline significant differences between HC and both MCI and AD ($H(2) = 7.257$, p = 0.027) (Figure 3).

Figure 3: Group differences in linguistic variables from verbal and clausal domains.



Correlations and regressions

A Spearman's rank order correlation revealed that of all linguistic variables, two of these variables showed significant correlation after correction: Pronoun ratio (r_s = -.349, p = 0.001) and Definite anomalies (r_s = -.367, p = 0.001), while other variables significant in the between-group analysis showed trend level values: Adjunct clause ratio (r_s = .267, p = 0.096), and VP anomaly rate (r_s = -269, p = 0.096). An additional regression analysis was run to determine which linguistic variables could best predict cognitive decline as measured by the MMSE. The four variables with the strongest tendencies in the correlational analysis were selected as predictor variables: Pronoun ratio, Definite anomalies, VP anomaly rate, and Adjunct clause ratio. Adding all four of these as independent variables into a linear regression model with MMSE scores as dependent variable yielded a model explaining 33.5% of the variance (F(4, 100) = 14.080, p < 0.0005).

4. Discussion

These results provide a new window into language changes in both MCI and AD, measured at the level of spontaneous speech. They show that language changes do not appear at the level of generic or coarse-grained linguistic variables such as number of utterances or the formal-grammatical integrity of utterances. Instead, at every level of grammatical complexity distinguished here – NPs, VPs, and clausal configurations – differences emerged in specific and fine-grained linguistic variables.

These are informative for the cognitive changes involved. In the domain of NPs, we confirmed our hypothesis that AD would show differences relating to specificity in referencing objects. These showed quantitatively – in a significant increase of definite and decrease of indefinite NPs in AD relative to HC – and qualitatively, in a trend-level result ($p = 0.037$ before correction) for an increase in anomalous indefinite NPs in AD relative to HC, and a negative correlation between definite anomalies and MMSE scores. This pattern likely relates to a difference in the cognitive functions of these different NPs. The function of indefinite NPs is to introduce new referents into the discourse (e.g. *A boy is stealing some cookies*, *There is a man standing at the sink*), which can then be picked up in the subsequent discourse through definite NPs (e.g. *The boy's sister is watching*; *He does not notice*). Production of both fewer (and, at a trend level, more often anomalous) indefinite NPs in AD therefore suggests a difficulty in setting up new discourse referents and creating referential connections across a narrative: more definite NPs will have referents not introduced before by an indefinite, and thus more likely to be anomalous themselves and to obtain their reference directly from the context, i.e. the visually presented objects in the picture as shared with the interlocutor. Testing the distribution of definite and indefinite NPs with speech elicitation tasks not based on picture descriptions (where referents are always visually present) is needed to confirm this result and identify possible task effects.

In the domain of VPs, two variables showed an effect of group: Aspect marking, which decreased from HC to MCI to AD, and adverbial adjuncts, which decreased from HC to MCI. This result is interpretable in terms of the specificity in the referencing of events, which both Aspect and adverbial adjuncts imply: describing a stool as *tipping over* is to depict an event as happening or ongoing, as and when the speech event takes place. Similarly, describing an action through an adverbial adjunct like *forgetfully* or *quickly* provides further descriptive information for a given event. Reduction of such grammatical elements therefore suggests a cognitive difference in conceptualizing events and in the specificity of event referencing.

In the domain of clauses, which is the most complex (since it includes NPs and VPs as proper parts), highly significant group differences emerged in how clauses are connected, between both AD and MCI in relation to HC. Again, this linguistic difference is interpretable as reflecting cognitive differences: clauses embedded as adjuncts (e.g. *while the water is flowing, the stool is tipping*, *The boy is stealing the cookie, without his father noticing*) play the crucial cognitive role of relating one event to another, creating a connection between them through relations such as simultaneity or cause and effect. Therefore, a reduction in such grammatical elements depicts a further reduction in specificity when referencing events. An increase in coordinated clauses is congruous with this conclusion, as coordination of clauses (with *and* or *or*) serves to depict several events as well, but without one being conceptualized as a part of the other. An increase in coordination and decrease of clausal embedding in spontaneous speech has been noticed in several other clinical groups before, including Huntington's disease (Hinzen, 2017; Hinzen et al., 2018; Tovar et al., 2020) and schizophrenia (Cokal et al., 2018), and there is evidence of problems of comprehension of embedded clauses as well, in schizophrenia (Cokal et al., 2019), and aphasia (Zimmerer, Deamer, Varley, & Hinzen, 2019). Within AD, the present findings are, to our knowledge, novel, and patterns of clausal embedding are an important area for future research.

Importantly, while the rate of pronouns out of total NPs increased from HC to AD, subsequent investigation showed that third person pronouns did *not* do so, and that only second person pronouns (typically addressing the interlocutor) did. What is common to all pronouns is that they lack lexical descriptive content. However, third person pronouns are crucially different in that they can be anaphoric (i.e. picking out a previously mentioned discourse referent) or deictic (picking out a visually present and salient referent shared in the context with the interlocutor), while first and second person pronouns tend to be deictic only. The fact that third person pronouns did *not* increase from HC to AD suggests that there is no problem in AD with retrieving lexical descriptive content *per se*, which would be naturally reflected in an over-use of referential devices such as pronouns (as previously reported: Ahmed et al., 2013a), which lack such a content. On the other hand, the fact that referents are visually present in a picture description task may hide such semantic retrieval difficulties, suggesting again that analyses of spontaneous speech in other tasks are needed.

Finally, correlational results further confirmed that the values of most of our linguistic variables correlated with an established continuous measure of cognitive decline, the MMSE, at significant or near-significant levels. Remarkably, a combination of the four most closely correlated variables explained a third of the population variance of cognitive performance based on MMSE values.

In summary, this study reveals a more fine-grained linguistic profile of spontaneous speech in MCI and AD as elicited with a picture description task. Significant group differences were seen in individual linguistic variables relating to aspects of the specificity of referencing objects and events, a defining feature of episodic memory, rather than in generic linguistic variables. It is imperative to confirm and expand this sensitivity in further studies of spontaneous speech using elicitation tasks requiring more creative use of reference than picture descriptions, and in other languages. Language measures based on spontaneous speech are easy to obtain and analyses can, in part, be automated, providing a promising avenue for using language in efforts of early detection.

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Conflict of Interest

The authors declare no conflicts of interest.

Informed Consent

All participants provided informed consent.

Data availability

Anonymized data supporting this study’s findings is available upon request.

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