Applying Natural Language Processing and Machine Learning techniques to aid in the diagnosis of Mild Cognitive Impairment and Early Dementia - A Systematic Review

A Preprint

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Abstract

This is the paper's abstract . . .

1 Introduction

Dementia has been identified as one of those fast growing difficulties facing the world. A recent report suggests that in 2015 there were 46 million people with a diagnosis of dementia and that number is expected to hit 131.5 million by 2050 [1]. The report also states that the worldwide cost of dementia in 2018 is estimated to be in the region of one trillion US dollars.

A lot of work has gone into trying to find ways of improving the early diagnosis of Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI) with research focused on two areas - identifying biological markers and analyzing the cognitive decline of those who are suspected to have the disease [2]. As described above, the numbers of those suffering from AD and MCI are going to increase as the population ages [1] and thus it is important that we utilize technology wherever possible to aid clinicians in the detection of MCI and AD. At the present time diagnosis is typically conducted at memory clinics by trained clinicians [3]. I theorize that we may be able to enable an earlier diagnosis of those with MCI and AD using samples of spontaneous speech, natural language processing (NLP) and machine learning (ML).

There is a large body of research that looks at the decline in language in those with MCI and AD [2, 3]. However there is conflicting evidence in these studies about which declining language factors are associated of MCI and AD [2, 3]. Research therefore should look at these features in more detail and a clarification of this currently disorganised picture should go some way to helping researchers further understand the disease and it's progression. Another area of focus for research of this nature is the process of collecting appropriate language samples. Whilst collecting samples of language is comparatively unintrusive, researchers recognise that these samples require a rich sample of language that potentially cannot be generated by tasks such as the picture description task. Therefore, it would be useful to explore whether spontaneous discourse such a semi-structured interview, has the ability to put pressure on both the cognitive and linguistic systems in the same way as traditional cognitive tests such that it might be able to distinguish between healthy controls, those with MCI and those with AD. There is some evidence to support this. Berisha et al [4], has shown through a longitudinal language analysis of spontaneous speech that there are marked differences in this process between those who would go on to have a diagnosis of AD and a healthy control.

The question to be addressed in this systematic review is how has the field of machine learning and natural language processing addresses language deterioration in the diagnosis of Mild Cognitive Impairment and Early Alzheimer's Disease. The potential impact of this research in this area is immense. Research has shown that early diagnosis of people with AD or MCI improves sufferers quality of life and can, in some cases, slow the progress of the disease however the absence of a single test and the complexity of AD can create significant delays in diagnosis. Early diagnosis can increase the number of research opportunities for understanding the early stages of dementia and how the disease progresses so that more research can be conducted which may, in the future, lead to new treatments and other interventions.

The remainder of this article is organized as follows. Section 2 gives an account of the process of this Systematic Review. Our results are described in Section 3. We discuss the results and implications in Section 4. Finally, Section 5 gives the conclusions.

2 Methodology

A systematic literature review (SLR) describes a process which aims to identify, evaluate and interpret the research and literature in a given area. They are designed to provide a complete and exhaustive summary of the current evidence relevant to an identified research question. SLR's conduct a thorough search of all literature following a pre-defined protocol that specifies focused research questions, identifies criteria for the selection of studies and assessment of their quality, and forms to execute the data extraction and synthesis of results.

Common motivations for conducting an SLR are:

1. to summary all the evidence about a topic.
2. find gaps in the research.
3. to provide a ground for a fundament to new research.
4. and to examine how the current research supports a hypothesis.

Performing an SLR comprises the following steps:

1. identify the need for performing the SLR.
2. formulate research questions.
3. execute a comprehensive search and selection of primary studies.
4. assess the quality and extract data from the studies.
5. interpret the results.
6. report the SLR.

The main research question this SLR aims to address is: "How has the field of machine learning and natural language processing addressed language deterioration in the diagnosis of Mild Cognitive Impairment and Early Alzheimer's Disease?". This main question can be decomposed further into four research questions:

- RQ1: Which NLP and ML techniques are being used in dementia research?
- RQ2: What features / data characteristics of text (variables, determinants and indicators) that are considered when applying the ML techniques (n-grams, PoS Tagging etc)?
- RQ3: What are the goals of the studies that employ NLP / ML techniques for prognosis of dementia?
- RQ4: Do the studies focus on time as factor?

The present paper builds upon these questions and additionally presents the results of the other two additional research questions. Further, the key terms related to comorbidities were included in the search string to ensure that relevant studies about ML or MS for the prognosis of a disease, where dementia is considered a comorbidity to that disease would also be retrieved from the database searches, even when the term dementia was not mentioned in the paper's title or abstract.

2.1 Search strategy

To address the research questions, a search string was defined using the PICO approach, which decomposes the main question into four parts:

1. Population - Studies that present research on mild cognitive impairment and dementia. Mild Cognitive Impairment and Dementia keywords were selected from the Systematized Nomenclature of Medicine–Clinical Terms (SNOMED-CT).
2. Intervention - Intervention: ML or MS techniques. The ML keywords were selected from the branch "Machine Learning Approaches" of the "2012 ACM Computing Classification System". The MS keywords were selected by A2.
3. Comparison
4. Outcome - Outcome: Prognosis on dementia and comorbidies. The prognosis keywords were provided by A4.

The automated searches were performed in the Pubmed, Web of Science, Scopus and IEEE databases. Table 1 shows the search string used for the Pubmed automated search, but note that this search string was adapted to each of the other databases' search context.

(dementia OR MCI OR Mild Cognitive Impairment OR Alzheimer's OR Mild Neurocognitive Disorder OR AD) AND TOPIC: (machine learning OR Data Mining OR Decision Support System OR NLP OR Natural Language Processing) AND TOPIC: (prognosis OR prognostic estimate OR predictor OR prediction OR model OR patterns OR diagnosis OR diagnostic OR forecasting OR projection OR Deep Language Model OR Deep Neural Network) AND TOPIC: (classification OR regression OR kernel OR support vector machines OR Gaussian Process OR Bayesian Network OR Factor Analysis OR Deep Learning OR Neural Networks OR Maximum Likelihood OR Principal Component Analysis OR Markov OR Linear Model OR Mixture Model OR Perceptron Algorithm OR Logical Learning OR relational learning OR Supervised Learning OR Unsupervised Learning OR clustering OR Decision Tree) AND TOPIC: (Language OR Cognitive OR Speech OR Conversation OR Connected Speech OR Picture Description OR Discourse Analysis OR Verbal Fluency)
Searched - 4th April 2019 - Generated 1257 Articles

Table 1: Search Terms for Web of Science database

Scopus	Web of Science	PubMed	IEEE Xplore
1002	991	376	230

Table 2: Totals from each database

This yielded 25 studies for review, 43 papers were reviewed.

2.2 Study selection

A total of 1490 unique papers were identified through the searches conducted above. Each paper was initially reviewed by just the title and the abstract. This yielded a total of 67 potential papers. Papers were then evaluated by the JA based on the inclusion and exclusion criteria defined previously (see Table 6). Where JA could not reach a decision, PS and GV were consulted and majority vote on inclusion was conducted.

After these evaluations, 37 papers were selected. Then a one-iteration backward snowballing process was carried out looking for possible additional studies. There were 1199 newly identified studies were assessed analogously as the previous ones, resulting in 41 new selected papers. Throughout the whole selection process, PS and GV acted as additional assessors in the case where there was uncertainty about whether a paper should be included.

In total, 78 papers were selected to be fully read and assessed regarding its eligibility. The ones that successfully passed the filtering criteria described earlier had their relevant data extracted. In order to minimize the chance of selecting studies with bias evidence, a quality assessment questionnaire was used. This questionnaire was adapted from Kitchenham's guidelines and can be found in the SLR protocol. If the grading attributed to a paper fell below 8 points (out of a total of 12), it would be rejected for quality reasons. The 8-point threshold was decided in the research group discussions involving all the authors. In this phase, a paper could also be rejected due to inclusion and exclusion criteria because the selection process adopted an inclusive approach. This means that during the reading of the titles and abstracts, in the case where the information provided was incomplete or too general it was selected to be fully read in the posterior phase. A common example is the case when the data analysis technique specified in the abstract was merely "classification", so it was not possible to know if any machine learning occurred.

As in the study selection, a quality assessment evaluation round was performed beforehand to ensure consistency in the evaluations. A1, A2 and A5 participated in this task. In total, 37 studies composed the final set of included primary studies and had their relevant data extracted, 7 papers were rejected due quality reasons, and 34 papers were rejected due to failing the inclusion and exclusion criteria. One reason for the high number of the latter was the decision to exclude the papers that used solely statistical methods as data analysis tech- niques to build the prognostic models. The selected studies were also assessed for the risk of cumulative evidence bias. This was done by checking, in the case of the same research group with different studies in the final set of included primary studies, if it was justified having both studies (i.e different samples).

A search of the literature was conducted using ProQuest (PsychArticles), SCOPUS, Web of Science. The following results were found (Table 1). All papers were then reviewed for relevance by reading the abstract and full text where appropriate and a shortlist was compiled. An additional search through references of shortlisted papers was also conducted and any papers who upon further review appeared relevant were added to the shortlist. Papers were included where researchers used machine learning to classify participants as MCI, AD or Healthy using language. We excluded any papers that focused on other forms of dementia or cognitive impairment, as well as any papers in which the language being analysed was not English.

2.3 Data collection

For the data collection, a base extraction form was defined in the protocol, but later in the study it was evolved based on the research group discussions. Table 3 lists and defines the collected variables.

Inclusion Criteria	Exclusion Criteria
Be a primary study in English; AND address research on dementia and comorbidities; AND address at least one ML or MS technique; AND address a prognosis related to dementia and comorbidities; AND use cognition or language decline as a factor for analysis.	Be a secondary or tertiary study; OR be written in another language other than English; OR do not address a research on dementia and comorbidities; OR do not address at least one ML or MS technique; OR do not address a prognosis related to dementia and comorbidities.

Table 3: Inclusion and Exclusion Criteria

Variable	Definition
Conditions Studied	For which dementia disorder is the study deriving a prognosis.
Database used in the study	Name and origin of the data source used to derive the prognosis of the studied dementia.
Dataset Categories	Classes in which the data units were divided into.
Follow-up period	Period of time, which the data units were followed.
Techniques used	Natural Language techniques AND/OR ML techniques that were used to build the diagnostic models.
Features generated	NLP generated features used in building the diagnostic models.
Aim of the Study	The goal of the built diagnostic models.

In addition to these variables other basic data about the studies was collected, these were: title, authors, journal/source, year and type of publication. No summary measures were used. Summary tables were used for the synthesis of results and no additional analyses were carried out

3 Results

3.1 Machine Learning methods

Intro - Addresses Research Question 1

Machine Learning technique used	Paper Number
Logistic Regression	Orimaye
Support Vector Machines	Orimaye
Linear Discriminant Analysis	Orimaye
Decision Trees	Orimaye

3.2 Traditional Machine Learning methods

3.2.1 Logistic Regression

3.2.2 Support Vector Machines

3.2.3 Linear Discriminant Analysis

3.2.4 Decision Trees

Curry, Singer and Habash - Alz (66.7 - Pres, 66.7 - Recall) and Control (67.9 - Pres, 67.9 Recall)

3.2.5 Naive Bayes

Curry, Singer and Habash - Alz(80.8 - Pres, 0.75 - Recall) and Control (79.3 - Pres, 82.1 Recall) - In the naive bayes classifier, they identified that pauses, go-ahead, fillers and incomplete words as the most significant features.

3.3 Deep Learning methods

3.3.1 Deep language space neural network for classifying mild cognitive impairment and Alzheimer-type dementia - Orimaye, Wong and Wong (2018)

In this paper, Orimaye et al use deep-deep neural networks language models (D2NNLM) to learn linguistic changes that distinguish the language of patients with MCI and AD-type dementia from the healthy controls using higher order n-grams. An ordinary DNNLM uses lower order n-gram N-dimensional sparse vectors as descrete feature representations to train the neural network with multiple hidden layers.

3.4 Features of Language

Intro - Addresses Research Question 2

Asgari, Kaye and Dodge (2017) [**?**] used another form of word frequency measurement. Using recordings of unstructured conversations (with standardized preselected topics across subjects) between interviewers and interviewees they grouped spoken words using Linguistic Inquiry and Word Count (LIWC) which is a technique used to categorize words into features such as negative and positive words [**?**]. They were able to successfully used machine learning algorithms to distinguish between these two groups with an accuracy of 84%.

3.4.1 Measures of Semantic Complexity

Intro!

Type token ratio (TTR) is the ratio obtained by dividing the types (The total number of different words) by the tokens (the total number of words in an utterance).

$$TTR = numberOfUniqueWords/totalNumberOfWords. \tag{1}$$

Brunet's Index (W) differentiates itself for TTR, as it is not impacted by the length of the text itself. Brunet's Index is defined by the following equation:

$$W = N^{V(-0.165)} \tag{2}$$

where N is the total length of the utterance being measured and V is equal to the total vocabulary being used by the subject. Brunet's Index usually has a score of between 10 and 20, with high numbers indicating a more rich vocabulary compared to low numbers.

Honore's Statistic is based on the idea that vocabulary richness is implied when a speaker uses a greater amount of unique words. This is indicated by the following equation:

$$R = (100 \log N)/(1 - V1/V) \tag{3}$$

where v1 is equal to the number of unique words, V is the total vocabulary used and N is the total number of words in the utterance being measured.

Guinn, Singer and Habash [5], they found in their corpus that there was no significant difference between interviewers and those with dementia when applying these measures. However, when they compared these results with a control dataset, they did find a significant difference in Honore's statistic. They explained this interesting results by suggesting that the interviewer used was trying to match (intentionally or unintentionally) the lexical richness of the person they were interviewing. In comparing healthy older adults with those suffering from dementia, they found that there was an increase in lexical diversity which is contrary to other research. They did note that conversations involving those with dementia contained roughly 50% less speech than those with controls, and that TTR in particular is not a suitable measure because it is more sensitive to length. They also note that Brunet's Index and Honore's Statistic are better statistics that control for the total length of the conversation and controls had statistically greater lexical diversity on those measures.

3.5 Quantity - Total number of words

Several studies report that adults with moderate AD produce fewer words than controls on picture description, however other studies found no differences in total words among groups of controls and patients with MCI or AD. Murray and Nicholas et al investigated normal controls, patients with AD and older adults with depression and found no group differences in total words. In contrast, Lira 2014 found that controls produced more total words than patients with AD but found no difference between mild and moderate groups.

3.6 Syntax and Morphology (Language Form)

Syntax can be defined as the rules that govern how words can be combined to form sentences, whilst Morphology is the system that governs the structure of words and the construction of word forms. Multiple studies of language decline in dementia included at least one measure of syntax or syntactic complexity. Common constructs included words per clause, grammatical form (measures of an appropriate use of syntactic conjections, tenses, conditionals, subordinate clauses and passive constructions), measures of phrase length and proportions of words in sentences. Some researchers have explored the use of formulaic language in those with dementia, the theory being that well practiced phrases are less effortful and therefore place low load on the cognitive abilities of those with AD. The general hypothesis motivating these studies is that either working memory limitations or semantic memory limitations in AD affect one's ability to use complex constructions.

3.7 N-grams and skip-grams

One of the first features discussed as a potential predictor of MCI or AD is the n-gram. An n-gram is a contiguous sequence of n items from a given sample of text or speech. The items can be phonemes, syllables, letters, words or base pairs according to the application. For example, given the sequence of words "to be or not to be", this extract is said to contain six 1-gram sequences (to, be, or, not, to, be), five 2-gram sequences (to be, be or, or not, not to, to be), four 3-gram sequences(to be or, be or not, or not to, not to be) and so on. This is useful as, given a large portion of text or speech, we can predict the probability of a word being close by to a given word. A number of researchers have used n-grams as features. One of the first attempts to use machine learning and natural language techniques to look was conducted by Thomas [**?**] who was able to successfully demonstrate the ability of machine learning algorithms to analyse n-grams as well as other features to outperform a naive rule-based classifier which always selects the modal class. Orimaye et al (2017) [**?**] investigated the use of machine learning algorithms to detect differences primarily in n-gram use to distinguish between those with a diagnosis of AD and healthy controls. Their main finding supported n-grams as the most significant predictor. One of the criticisms is the use of picture description tasks and n-grams. Because the language generated by this task is content specific the n-grams generated are only specific to the task given and cannot be generalised.

Skip-grams are a variant of n-grams in which word tokens are skipped intermittently while creating n-grams. For example, take the sentence 'I am going to London', there are four conventional bigrams: 'I am', 'am going', 'going to', and 'to London' - using skip-grams, we might skip a word to create additional bigrams such as: 'I going' and 'going London'. Orimaye defined k-skip-n-grams as a set of n-gram tokens with the following equation, where n is the specified n-gram (e.g. 2 for a bigram and 3 for a trigram), m is the number of tokens in a given sentence, k is the number of word skip between n-grams given that k < m and a = {1,..., m-n}

One problem with this approach is existing research currently uses language generated from picture description tasks. Given the nature of these tasks, the language generated is relatively constrained in comparison to language generated spontaneously.

$$T_{n-gram} = W_a, ..., W_{a+n-k}, ..., W_{a+n}, ..., W_{m-n}, ..., W_{(m-n)+n-k}, ..., W_m \quad (4)$$

Thus for the sentence 'I am going to London', 1-skip-2-grams will give {I going, am to, going London} and 1-skip-3-grams will give {I going to, I am to, am to London, am going London}

3.8 Mean length of utterance (MLU)

Murray found that MLU was not a distinguishing factor among health adults, adults with depression and adults with AD. Ripich et al found a decrease in MLU in adults with severe AD over time, and this was supported by findings of Le et al in their studies of authors [**?**]

3.9 Proportion of verbs to nouns plus verbs

Kave and Levy used a verb index to capture syntactic complexity and found that adults with AD expressed the same amount of verbs to nouns plus verbs as adult controls.

3.10 Syntactic Complexity - Composite measures of MLU, syntactic errors and verbs

Ahmed et al, and Ahmed, Haigh et al found differences in syntactic complexity between adults with MCI and controls, and between MCI and moderate AD stages. The differences in syntactic complexity were not significant when individual measures were tested, but were apparent using a composite score consisting of MLU, words in sentences, syntactic errors, nouns with determiners, and verbs with inflections.

Lu's Syntactic Complexity Analyser Ygnve measure

3.11 Semantic features

. We compute semantic similarity using the average and minimum cosine distance between each pair of one-hot embeddings of utterances, and the cosine cutoff (i.e., the number of pairs of utterances whose the cosine distance is below a certain threshold). We compute word specificity and ambiguity based on tree depth and the number of senses in WordNet [54]. We also extract multiple WordNet measures of similarity: Resnik [68], Jiang-Coranth [69], Lin [47], Leacock-Chodorow [70], and Wu-Palmer [71].

3.12 Syntactic features

Guinn, Singer and Habash [5] found that syntactic features such as Noun rate, verb rate, adjective rate and pronoun rate were not significantly different between interviewers and those with dementia in their dataset, although they did note that there was a slightly higher but non significant use of pronouns.

3.13 Pragmatic features.

We train a general 100-topic latent Dirichlet allocation (LDA) model [72] on the Wikipedia corpus for generalizability. LDA is a generative statistical model used to determine unlabeled topics in a document. For each transcript, we extract the probabilities of each LDA topic. Next, we extract features related to rhetorical structure theory (RST), which is a classic framework for discourse parsing in which partitions of text are arranged in a tree structure by pragmatic relations such as Elaboration or Contrast [73].

3.13.1 Go-ahead Utterances

Go-ahead utterances are defined as short one or two syllable responses that do not contribute to the conversation beyond a minimal response. The function of these go-ahead utterances can be to validate what the other person is saying, or to agree / disagree with what is being said. Another function can be that they wish speaker is indicating that they have nothing futher to add to the conversation and a signal to the other speaker to continue with what they are saying. In Curry, Singer and Habash's research, they found that in comparing interviewers and those with dementia, that interviewers used significantly fewer go-ahead utterances. In comparing controls and those with dementia, they found that there was a relative lack of go-ahead utterances in the controls which implies that controls had a lot more contributions to make in their conversations than those with dementia.

3.14 Formulaic Language

Fraser, Meltzer and Rudzicz (2015) [**?**] looked at connected speech using the DementiaBank corpus. They found that there were four factors which informed the classification of participants as either healthy or AD. These four factors were semantic impairment, acoustic abnormality, syntactic impairment and information impairment and were based on existing measures of semantic and syntactic complexity. Zimmerer (2016) [**?**] looked at whether language was more formulaic in those suffering from AD. He proposed that those who suffer from AD rely on formulatic sentences, for example 'Noun-Verb-Noun', and this is done to reduce language complexity. He noticed a significant difference in the use of formulaic sentences between AD and Healthy Controls.

3.15 Number of syllables and Characters

3.16 Number of fillers

3.17 Readability

Flesch reading score, Flesch-kincaid grade level

3.18 Polarity

3.19 Frequency

Mean values of frequency, age of acquisition, imageability, familiarity, arousal, dominance and valence based on lexical norms

3.20 Dysfluencies

Curry, Singer and Habash noted that in comparing controls and those with Dementia, that those with Dementia had a significantly higher number of pauses per word and a much higher incidence of words that were truncated in mid-speech. In comparing interviewers with those with dementia, they also showed other signs of difficulties with fluency with higher rates of incomplete words, filler words and repeated words.

3.21 What are the goals of the studies that employ ML or MS techniques for prognosis of dementia and comorbidities?

4 Discussion and conclusions

4.1 Discussion of the current evidence

4.2 Methodological Issues

4.3 Limitations

4.4 The future of the field

5 Conclusions

We worked hard, and achieved very little.

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A Article Table

Paper Number	Paper Title	Authors
1	A Comparison of Syntax, Semantics, and Pragmatics in Spoken Language among Residents with Alzheimer's Disease in Managed-Care Facilities	Authors
2	A Comparison of Syntax, Semantics, and Pragmatics in Spoken Language among Residents with Alzheimer's Disease in Managed-Care Facilities	Authors
3	A Comparison of Syntax, Semantics, and Pragmatics in Spoken Language among Residents with Alzheimer's Disease in Managed-Care Facilities	Authors
4	A Comparison of Syntax, Semantics, and Pragmatics in Spoken Language among Residents with Alzheimer's Disease in Managed-Care Facilities	Authors
5	A Comparison of Syntax, Semantics, and Pragmatics in Spoken Language among Residents with Alzheimer's Disease in Managed-Care Facilities	Authors
6	A Comparison of Syntax, Semantics, and Pragmatics in Spoken Language among Residents with Alzheimer's Disease in Managed-Care Facilities	Authors
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12	A Comparison of Syntax, Semantics, and Pragmatics in Spoken Language among Residents with Alzheimer's Disease in Managed-Care Facilities	Authors
13	A Comparison of Syntax, Semantics, and Pragmatics in Spoken Language among Residents with Alzheimer's Disease in Managed-Care Facilities	Authors
14	A Comparison of Syntax, Semantics, and Pragmatics in Spoken Language among Residents with Alzheimer's Disease in Managed-Care Facilities	Authors
15	A Comparison of Syntax, Semantics, and Pragmatics in Spoken Language among Residents with Alzheimer's Disease in Managed-Care Facilities	Authors
16	A Comparison of Syntax, Semantics, and	Authors