A Deep Learning Framework for the Prediction of Conversion to Alzheimer Disease

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Introduction

The Alzheimer Disease

- The Alzheimer Disease is the most common form of senile brain disorder
- It is not reversible
- Its neuropathology can be be detected **several years before** clinical manifestation

- Starts with light deterioration of cognitive reserve (Mild-Cognitive-Impairment, **MCI**)
  - Worsens into a more severe form of dementia (AD)

- AD diagnosis is carried out relying on several clinical data
  - Imaging, neuropsychological scores etc…

Clinical needs
and state-of-the-art

- Disease diagnosis and monitoring
  - Discriminate those patients that develop AD from those who manifest a stable MCI condition
- Importance of **data integration**
  - AD has a variegated nature
  - Computational analysis of heterogeneous sources of data might have a decisive impact on the ability to *early identify those subjects with a higher probability of conversion to AD*
- So far, most of the papers focus on the classification of AD, HC, and MCI using imaging data
  - There are **few** relevant papers that combine the necessity of predicting the conversion to MCI or AD **in time** using different sources of data, as we propose in this work.

Materials and Methods

The ADNI Dataset

- ADNI public dataset
  - on-going project
  - At present: **2380** subjects and **15754** time-points
- Each subject has been screened for a variable number of time-points, depending on the ADNI phase he or she had been enrolled in
- The ADNI data-set was analyzed so as to quantifying the amount and the typology of data that could be used for the purposes of our research

The analysis of ADNI

- Starting point: the *ADNI Merge* file
  - It contains a sum-up of almost all the information avaiable in ADNI.
  - It contains 85 variables and a total of 15754 time-points
  - Subjects are identified with their RID (Roster ID)

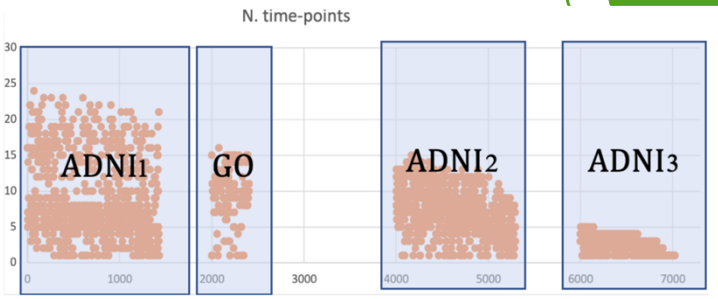


Fig. 1. Distribution of RIDs and the number of time-points per RID in each ADNI phase.

- The data-set is characterized by a high degree of variability in the information it contains
  - **This variability needed to be handled for the purposes of our analysis**
    - Clinical support of the Fondazione Santa Lucia (Rome, Italy)
      - Giovanni Giulietti, Laura Serra, Marco Bozzali

The analysis of ADNI

- The analyses proposed in this study are rare in literature, and we believe it was **fundamental** to share these results.

- For each subject in ADNI Merge it is possible to obtain several details
  - The diagnosis that is made during the first visit (*baseline visit*) and the diagnosis carried out during the following monitoring visits
  - During the baseline visit subjects are categorized as Controls (CN), AD (Alzheimer), LMCI and EMCI (Late Mild Cognitive Impairment and Early Mild Cognitive Impairment), and SMC (Significant Memory Concern)
    - During the monitoring visits subject are classified as CN, AD or MCI (loosing the distinction between LMCI and EMCI).

Table 1. Time-points and labels at baseline.

	Number of time-points
Total time-points	15754
Time-points classified at baseline as SMC	1246 (8%)
Time-points classified at baseline as LMCI	5158 (33%)
Time-points classified at baseline as EMCI	2881 (18%)
Time-points classified at baseline as AD	1713 (11%)
Time-points classified at baseline as CN	4728 (30%)

Data-set creation
and selection criteria

- Our choices have been driven by the numeracy of the ADNI data, that does not allow at this stage to extend the analysis to other phases of the pathology such as the SMC, or the LMCI and EMCI, but our approach does not exclude such extension in the future.

- The goal of the presented Deep Learning framework is to:
  1) Integrate different sources of data such as imaging data, clinical data, neuropsychological tests' scores, and the temporal information related to the last medical evaluation of the subject
  2) Estimate the probability of conversion from MCI to AD or from a stable clinical profile to MCI in a period of time that varies from 6 months to 18 months

Data-set creation

- We are interested in those subject that happen to have **more than one** time-point, and that present a **switch** of the diagnosis in time
  - What do we mean with *conversion of the diagnosis*?

Table 2. Example of a subject that is diagnosed as MCI after 18 months.

Visit (months from baseline)	Diagnose
0 (baseline)	CN
06	CN
12	CN
18	MCI

- 253 single-time-points were not considered
- Those time-points for which no diagnosis is given were not considered
- Each time-point has been further labelled

Table 3. Example of a subject that is diagnosed as MCI after 18 months.

Visit (months from baseline)	Diagnose	Switch
0 (baseline)	CN	CN-CN
06	CN	CN-MCI
12	MCI	MCI-MCI
18	MCI	last time-point

Data-set creation

- It was further noticed that 151 time-points showed **reversion**
  - This might be due to errors in the data-set or to the difficulty in detecting MCI, as the majority of reversions is a MCI-CN reversion

Table 4. Example of a subject with a reversion in the diagnosis

Visit (months from baseline)	Diagnose	Reversion
0 (baseline)	CN	CN-CN
06	CN	CN-MCI
12	MCI	CN-CN
18	MCI	last time-point

- Here you can see the numerosity of the time-points for each switch, those that belong to the control group, MCI group or AD group, and those that revert the diagnosis
  - The size of the classes of interest (i.e. those time-points that show a switch in the diagnosis), is not so consistent

	CN	**MCI**	**AD**
CN	2822	109	4
MCI	121	3531	370
AD	1	29	1567

Data for the Deep Learning framework

	CN	MCI	AD
CN	-	686	200
MCI	-	-	1440
AD	-	-	-

- We expanded the size of classes by considering not only the time-point that precede the switch of the diagnosis, but also all the previous time-points and labelling them by adding, for each time-point, the distance from the conversion

- We are interested in giving as input to the network **a time reference along with clinical data**, we focused on computing the distribution of the time-points of each switch in time.

- In order to compute the interval of time (*months*) between different points, we based on the *EXAMDATE* parameter, and not on the *VISCODE* variable present in ADNI Merge
  - The ADNI documentation highlights that the EXAMDATE is more reliable. The VISCODE was used to match the time-point in ADNI Merge with the corresponding images

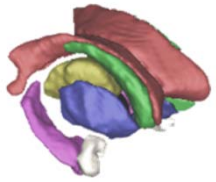
Data for the Deep Learning framework

Switch (m)	CN-MCI	MCI-AD	CN-AD
< 12	100	460	2
12-24	120	359	12
24-36	407	588	141
36-100	55	14	28

→ **533** subjects

2329 time-points

- The majority of switches is condensed within 36 months
- The Deep Learning architecture will be trained to predict the conversion in 12, 24, 36 months from CN to MCI and from MCI to AD.
- Several **architectures** will be tested:
  1) Pure tabular network with the variables present in ADNI Merge
  2) Pure tabular network with variables extracted with *VOLBRAIN package*
  3) Tabular network + images



Analisys of the images

- T1-3D images were selected as images of interest
  - MPRAGE and SPGR sequences

- DICOM images were downloaded and converted to NIfTI with the *dicom2niix* package

- Compressed NIfTI files are given to VOLBRAIN for processing
  - Volbrain generates a report with several volumetric parameters related to the 3D analysis
  - 900 variables added to the ADNI Merge Variables

		T1-3D	DTI	fMRI	FLAIR
sc	ADNI Screening	6370	44	26	31
bl	ADNI Baseline	1098	0	0	0
m06	ADNI1/GO Month 6	5354	43	4	20
m12	ADNI1/GO Month 12	4227	0	0	1
m18	ADNI1/GO Month 18	1888	0	0	0
m24	ADNI1/GO Month 24	2226	0	0	1
m30	ADNI1/GO Month 30	0	0	0	0
m36	ADNI1/GO Month 36	1484	0	0	1
m42	ADNI1/GO Month 42	0	0	0	0
m48	ADNI1/GO Month 48	544	0	3	4
uns1	Unscheduled	0	0	0	0
nv	ADNI2 No Visit Defined	0	0	0	0
scmri	ADNIGO Screening MRI	130	49	5	29
m03	ADNIGO Month 3 MRI	0	0	0	0
m54	ADNIGO Month 54	0	0	0	0
m60	ADNIGO Month 60	78	0	0	0
m66	ADNIGO Month 66	0	0	0	0
m72	ADNIGO Month 72	0	0	0	0
m78	ADNIGO Month 78	0	0	0	0
v01	ADNI2 Screening-New Pt	0	0	0	0
v02	ADNI2 Screening MRI-New P	847	345	43	191
v03	ADNI2 Baseline-New Pt	334	0	0	0
v04	ADNI2 Month 3 MRI-New Pt	0	0	0	0
v05	ADNI2 Month 6-New Pt	547	223	25	126
v06	ADNI2 Initial Visit-Cont Pt	335	44	6	24
v11	ADNI2 Year 1 Visit	788	277	27	144
v21	ADNI2 Year 2 Visit	652	175	17	94
v31	ADNI2 Year 3 Visit	128	37	5	17
v41	ADNI2 Year 4 Visit	184	70	6	32
v51	ADNI2 Year 5 Visit	24	0	0	4
nv	ADNI2 No Visit Defined	0	0	0	0
tau	ADNI2 Tau-only visit	0	0	0	0
init	ADNI3 Initial Visit-Cont Pt	93	41	24	28
y1	ADNI3 Year 1 Visit	44	28	22	23
y2	ADNI3 Year 2 Visit	25	9	8	10
y3	ADNI3 Year 3 Visit	0	0	0	0
y4	ADNI3 Year 4 Visit	0	0	0	0
y5	ADNI3 Year 5 Visit	0	0	0	0

The Deep Learning framework

- We propose a Deep Learning framework that integrates different sources of data, with the aim of estimating a probability index of conversion from CN to MCI and from MCI to AD in time

- The Deep Learning framework is now under construction and the first results will be available soon

- The Deep Learning framework will be also tested with real clinical data provided by the Fondazione Santa Lucia and we will discuss along with clinicians to ensure the best performances and making the best adjustments
  - The aim: creating a tool that can be used during the real clinical practice, identifying reliable bio-markers for monitoring the Alzheimer disease

Conclusion

- This task has a particular importance from a clinical point of view, as no bio marker exists for the prediction of the conversion from a stable clinical profile to a MCI profile, nor for the prediction of the conversion from the MCI profile to the AD profile.

- Furthermore, an extensive analysis has been performed on ADNI and its main results were presented in this paper: literature lacks of such analysis, and we believed it was relevant to share its main points, as well as devote the right amount of time to such analysis.

- The Deep Learning framework construction relies on the analysis that has been conducted

Thank you for your attention