Inter-cohort validation of SuStaIn model for Alzheimer's disease

Damiano Archetti[a], Alexandra Young[b,c], Neil P Oxtoby[c], Daniel C Alexander[c], Giovanni B Frisoni[d,a], Alberto Redolfi[a]

a: IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy; b: Department of Neuroimaging, Institute of Psychiatry, Psychology and Neuroscience, King's College London

c: Centre for Medical Image Computing, Department of Computer Science, UCL, London, UK; d: University of Geneva, Geneva, Switzerland

Background and Methods

Sustain[1] (Subtype and Stage Inference) is a novel modelling approach of the Event-Based Models family which is capable of detecting different disease subtypes. In this work, we demonstrate the transferability of an AD model built with SuStaIn using baseline data of 1043 subjects from ADNI to a heterogeneous test set composed by 767 subjects form OASIS, Pharma-COG and ViTA cohorts (Tab.1) which mirrors the clinical setting. Subjects from all stages of the disease (CN, MCI, AD) were included in ADNI and the test set, additionally subpopulations of stable MCIs (sMCI) and MCIs that progress to AD (pMCI) were identified to assess the predictive value of the model that was built using volumes of relevant brain areas extracted via Freesurfer v5.3 from T1-3D MRI scans.

		N	Age (years)	Sex (M/F)	Education (years)	APOE4 (carriers/non carriers)
ADNI	CN	335	73.5±5.9	154/181	16.3±2.6	89/246
	MCI	537	72.0±7.2	315/222	16.0±2.8	270/267
	AD	171	73.4±8.2	92/79	15.5±2.7	124/47
	sMCI	271	72.3±7.1	156/115	16.1±2.8	114/157
	pMCI	205	73.1±6.8	121/84	15.8±2.8	131/74
Test Set	CN	440	54±25	164/276	8.4±5.7	9/31
	MCI	283	72.3±7.6	131/152	9.2±5.1	54/91
	AD	44	77.3±7.4	15/29	5.8±5.3	0/2
	sMCI	152	71.2±7.5	71/81	11.5±4.2	38/65
	pMCI	39	69.8±6.4	19/20	11.7±3.9	13/10

***Tab.1**: Population demographics (pMCIs = progressive MCIs; sMCIs = stable MCIs)*

Subtype disease model

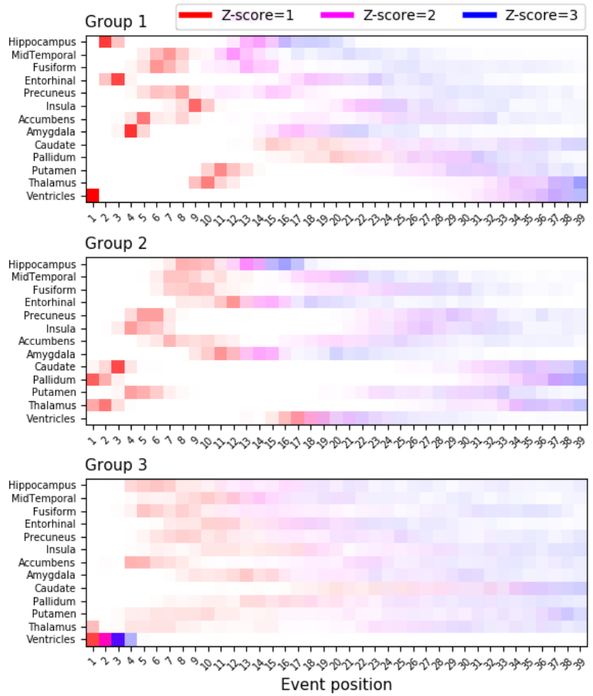

***Fig.1**: Subtype model built on ADNI data*

The disease model built with SuStaIn accounted for three disease subtypes (Fig.1). The first group represents the classic manifestation of AD and most of the subjects were assigned to this subtype (Tab.2). For the second group atrophy starts in pallidum and thalamus, and progresses towards the regions of the middle temporal lobe. In the third group, which is the least populated, ventricles are the first region to show full abnormality (z-score>3), followed by thalamus, putamen and nucleus accumbens.

Subject subtype

		G1	G2	G3
ADNI	CN	96	74	9
	MCI	243	128	22
	AD	126	26	7
	sMCI	111	67	10
	pMCI	116	44	8
Test Set	CN	303	37	9
	MCI	185	49	3
	AD	41	1	1
	sMCI	83	35	4
	pMCI	32	6	0

***Tab.2:**Number of subjects for each subtype in the case of ADNI and test set*

For each diagnostic category, the vast majority of subjects was assigned to the classical AD subtype (Tab.2). In order to assess the temporal consistency of the model, subjects for which a 12-month visit was available were subtyped and only a small fraction of subjects from both ADNi and the test set was assigned to different subtypes (Fig.2).

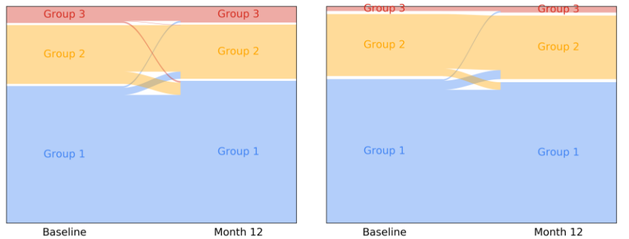

***Fig.2**: 12 month subtype stability for ADNI (left) and test (right) subjects*

Classification performance

Subjects from Group 1 were staged on the respective event sequence to assess the predictive value of the model and its transferability between cohorts. Classification task was performed on pMCIs vs sMCIs and results were similar in both sets (Tab.3), reaching in both cases good sensitivity and low specificity. No significant differences were observed between AUC of ADNI and test set (DeLong test returned p-value=0.94). As proof of the validity of the model, subject staging showed good linear relation with cognitive decline measured by MMSE with R^2=0.74 for ADNI and R^2=0.82 for the test set.

	ADNI	Test Set
Sensitivity	0.81	0.71
Specificity	0.51	0.58
Balanced accuracy	0.66	0.64
AUC	0.67	0.68

***Tab.3**: Classification metrics of sMCIs vs pMCIs from ADNI and test set staged on the Group 1 event sequence*

Conclusion

SuStaIn showed similar classification performance on both ADNI and test set, thus giving proof of concept of the transferability of the model from research to a clinical setting. The model detected one classical subtype (Group1) and 2 less common phenotypes of atrophy (Groups 2 and 3).

[1] Young AL. et al. Uncovering the heterogeneity and temporal complexity of neurodegenerative diseases with Subtype and Stage Inference. Nat Commun 2018;9:4273