# Deep neural network heatmaps capture Alzheimer's disease patterns reported in a large meta-analysis of neuroimaging studies: Supplementary Material

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## 1 Dice overlaps for the synthetic data

The following Figures report the Dice overlaps between the hippocampus regions altered in the synthetic data sets and the brain regions captured by the activation patterns of the best SVMs and the heatmap values of the best CNN and ModelE classifiers, for the single-subject data set (Figure 1), and the whole-cohort data set (Figure 4). The heatmaps corresponding to the best overlaps are shown in Figure 2 (for the single-subject data) and 5 (for the whole-cohort data). Unsmoothed heatmaps thresholded at 5% are shown in the following Figures (Figure 3 for single-subject, Figure 6 for whole-cohort).

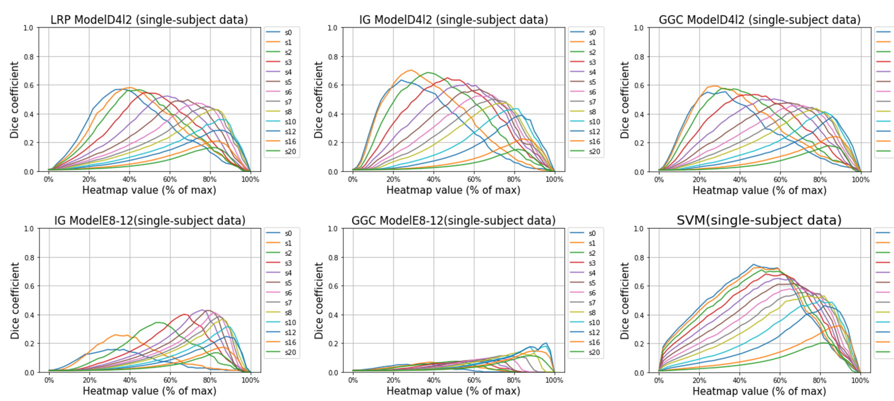


Figure 1: Dice overlap, for the single-subject simulated data, between all the smoothed heatmaps and the hippocampus map for ModelD4l2, ModelE8-12 and the best linear SVM. s0 corresponds to the heatmaps before smoothing, s1 corresponds to the heatmaps after 1 mm FWHM Gaussian smoothing, and similarly for other smoothing FWHM.

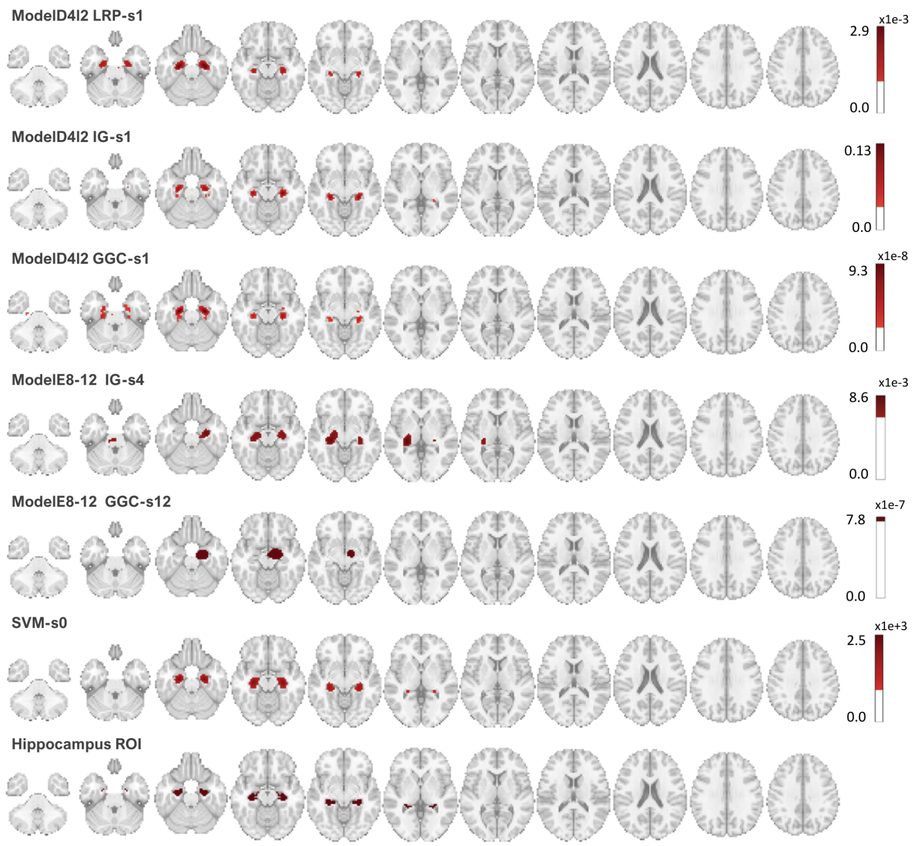


Figure 2: Heatmaps derived for the single-subject simulated data and corresponding to the best Dice overlap with the hippocampus region where the synthetic effect has been introduced, for ModelD4l2, ModelE8-12 and the best linear SVM.

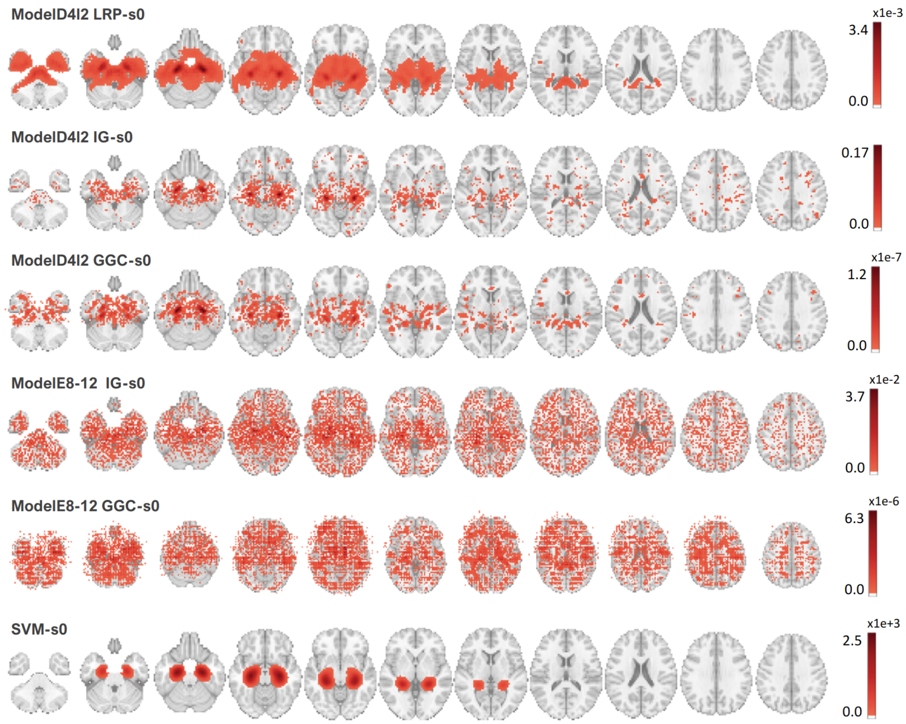


Figure 3: Heatmaps derived for the single-subject simulated data, without smoothing, and thresholded at 5% of their maximum value.

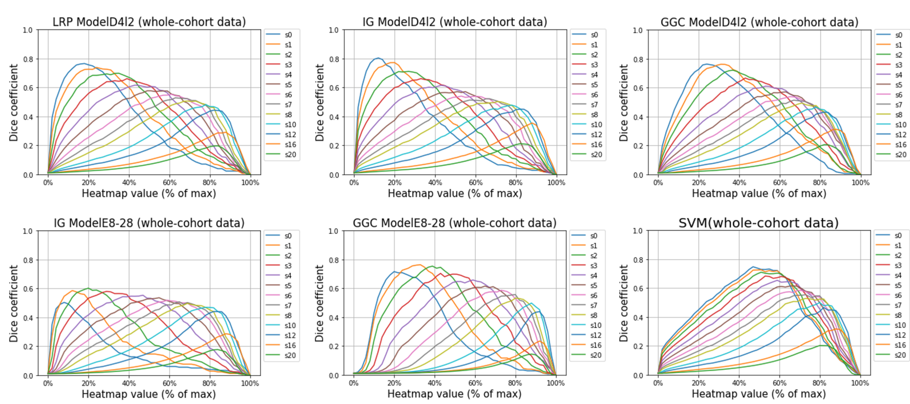


Figure 4: Dice overlap, for the whole-cohort simulated data, between all the smoothed heatmaps and the hippocampus map for ModelD4l2, ModelE8-28 and the best linear SVM. s0 corresponds to the heatmaps before smoothing, s1 corresponds to the heatmaps after 1 mm FWHM Gaussian smoothing, and similarly for other smoothing FWHM.

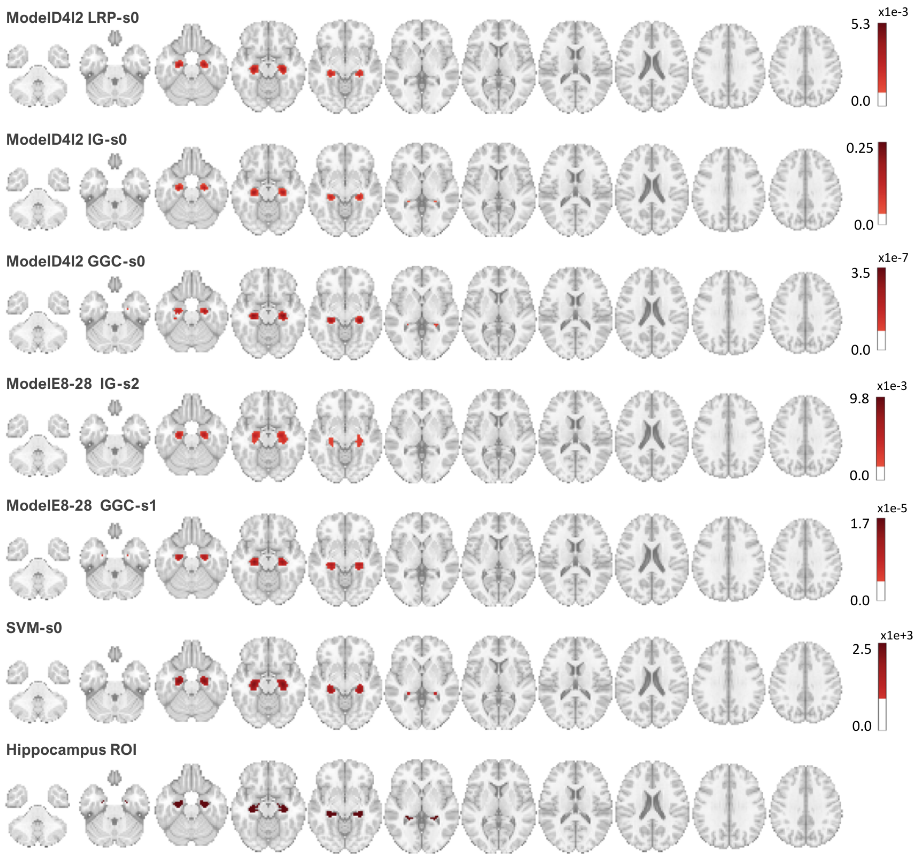


Figure 5: Heatmaps derived for the whole-cohort simulated data and corresponding to the best Dice overlap with the hippocampus region where the synthetic effect has been introduced, for ModelD4l2, ModelE8-28 and the best linear SVM.

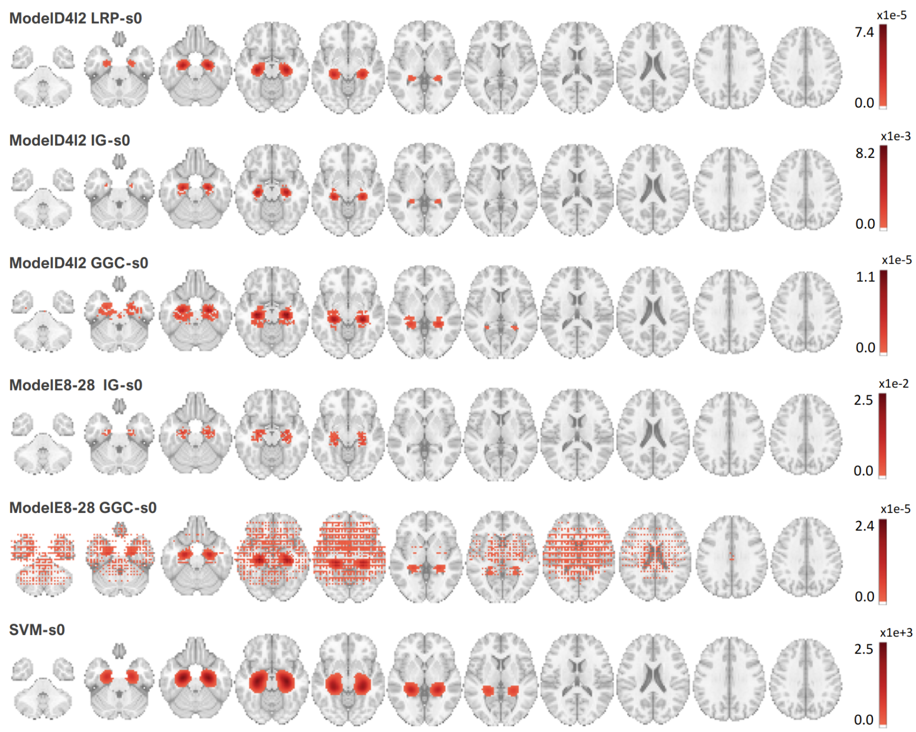


Figure 6: Heatmaps derived for the whole-cohort simulated data, without smoothing, and thresholded at 5% of their maximum value.

## 2 VBM studies included in the meta-analysis

The voxel-based morphometry studies combined in our meta-analysis are reported in Table 1.

| **Article** | **Experiment** | $n$ | **Data source** |
|---|---|---|---|
| Barbeau E et al., 2008[1] | MCI < CN | 28 | Universit´e de Toulouse |
| Baron JC et al., 2001[2] | AD < CN | 19 | University of Caen |
| Baxter LC et al., 2006[3] | AD < CN | 15 | Sun Health Research Institute |
| Bell-McGinty S et al., 2005[4] | MCI < CN | 37 | University of Pittsburgh |
| Berlingeri M et al., 2008[5] | AD < CN | 21 | University of Milano-Bicocca |
| Bozzali M et al., 2012[6] | AD < CN | 31 | IRCCS Fondazione Santa Lucia |
| Bozzali M et al., 2006[7] | Conv < CN | 14 | IRCCS Fondazione Santa Lucia |
| Bozzali M et al., 2006[7] | Non < CN | 8 | IRCCS Fondazione Santa Lucia |
| Brambati et al., 2009[8] | AD < CN | 10 | McGill Center for Studies in Aging |
| Brambati et al., 2009[8] | MCI < CN | 11 | McGill Center for Studies in Aging |
| Brambati et al., 2009[8] | MCI < CN | 14 | McGill Center for Studies in Aging |
| Brenneis C et al., 2004[9] | AD < CN | 10 | General Hospital of Linz |
| Brys M et al., 2009[10] | Conv < CN | 8 | New York University School of Medicine, Center for Brain Health |
| Canu E et al., 2012[11] | EOAD < CN | 18 | IRCCS Centro San Giovanni di Dio Fatebenefratelli |
| Canu E et al., 2012[11] | LOAD < CN | 24 | IRCCS Centro San Giovanni di Dio Fatebenefratelli |

| | | | |
|---|---|---|---|
| Caroli A et al., 2007[12] | Conv < CN | 9 | IRCCS San Giovanni di Dio-FBF |
| Caroli A et al., 2007[12] | Non < CN | 14 | IRCCS San Giovanni di Dio-FBF |
| Chen et al., 2011[13] | AD < CN | 15 | Pennsylvania's Alzheimer's Disease Center |
| Chetelat G et al., 2002[14] | AD < CN | 16 | University of Caen |
| Chetelat G et al., 2002[14] | MCI < CN | 22 | University of Caen |
| Colloby SJ et al., 2014[15] | AD < CN | 47 | Newcastle University |
| Defrancesco M et al., 2014[16] | Conv < CN | 13 | University Clinic of Innsbruck |
| Derflinger S et al., 2011[17] | AD < CN | 35 | Technische Universitat Munchen, Munich, Germany |
| Derflinger S et al., 2011[17] | MCI < CN | 24 | Technische Universitat Munchen, Munich, Germany |
| Dos Santos V et al., 2011[18] | AD < CN | 34 | Heidelberg University |
| Dos Santos V et al., 2011[18] | MCI < CN | 60 | Heidelberg University |
| Farrow TFD et al., 2007[19] | AD < CN | 7 | North Sheffield Research |
| Feldmann A et al., 2008[20] | AD < CN | 6 | local |
| Ford AH et al., 2014[21] | MCI < CN | 65 | Perth Perception Study |
| Gee J et al., 2003[22] | AD < CN | 12 | University of Pennsylvania Department of Neurology |
| Gold BT et al., 2010[23] | MCI < CN | 12 | University of Kentucky |
| Guo X et al., 2010[24] | AD < CN | 13 | Xuanwu Hospital |
| Hamalainen A et al., 2007[25] | MCI < CN | 43 | University of Kuopio |
| Hamalainen A et al., 2007[25] | MCI < CN | 13 | University of Kuopio |

| | | | |
|---|---|---|---|
| Hamalainen A et al., 2007[25] | AD < CN | 15 | University of Kuopio |
| Han Y et al., 2012[26] | MCI < CN | 17 | West China Hospital |
| Hirao K et al., 2006[27] | AD < CN | 61 | National Center Hospital for Mental, Nervous and Muscular Disorders, National Center of Neurology and Psychiatry, Tokyo, Japan |
| Honea RA et al., 2009[28] | AD < CN | 60 | University of Kansas Brain Aging Project |
| Hong YJ et al., 2015[29] | MCI < CN | 29 | Catholic University of Korea |
| Hornberger et al., 2011[30] | AD < CN | 15 | FRONTIER database |
| Huang CW et al., 2017[31] | AD < CN | 50 | Chang Gung Memorial Hospital |
| Ibrahim I et al., 2009[32] | AD < CN | 21 | local |
| Imabayashi E et al., 2013[33] | AD < CN | 5 | Japanese Alzheimer's Disease Neuroimaging Initiative |
| Kim S et al., 2011[34] | AD < CN | 10 | Chung-Ang University Hospita |
| Kim S et al., 2011[34] | AD < CN | 20 | Chung-Ang University Hospita |
| Kim S et al., 2011[34] | AD < CN | 31 | Chung-Ang University Hospita |
| Lagarde J et al., 2015[35] | AD < CN | 14 | Salpetriere Hospital |
| Mazere J et al., 2008[36] | AD < CN | 8 | University Hospital of Bordeaux |
| Miettinen PS et al., 2011[37] | AD < CN | 16 | University of Eastern Finland |
| Miettinen PS et al., 2011[37] | MCI < CN | 18 | University of Eastern Finland |
| Migliaccio R et al., 2009[38] | EOAD < CN | 16 | University of California San Francisco |

| | | | |
|---|---|---|---|
| Mitolo et al., 2013[39] | MCI < CN | 20 | University of Padua, Padua |
| Mok et al., 2012[40] | AD < CN | 14 | Shin Kong Wu Ho-Su Memorial Hospita |
| Mok et al., 2012[40] | AD < CN | 10 | Shin Kong Wu Ho-Su Memorial Hospita |
| Pa et al., 2009[41] | MCI < CN | 32 | University of California San Francisco |
| Pa et al., 2009[41] | MCI < CN | 26 | University of California San Francisco |
| Pennanen C et al., 2005[42] | MCI < CN | 51 | Kuopio University Hospital |
| Polat et al., 2012[43] | AD < CN | 31 | local |
| Raji CA et al., 2009[44] | AD < CN | 33 | CHS |
| Rami L et al., 2009[45] | AD < CN | 31 | local |
| Rami L et al., 2009[45] | MCI < CN | 14 | local |
| Remy F et al., 2005[46] | AD < CN | 8 | local |
| Samuraki M et al., 2007[47] | AD < CN | 39 | Kanazawa University Hospital |
| Saykin AJ et al., 2006[48] | MCI < CN | 40 | Dartmouth Medical School |
| Schmidt-Wilcke T et al., 2009[49] | MCI < CN | 18 | local |
| Shiino A et al., 2006[50] | AD < CN | 40 | Shiga University of Medical Science |
| Shiino A et al., 2006[50] | MCI < CN | 20 | Shiga University of Medical Science |
| Trivedi MA et al., 2006[51] | MCI < CN | 15 | University of Wisconsin |
| Wang P et al., 2019[52] | MCI < CN | 17 | local |
| Waragai M et al., 2009[53] | AD < CN | 15 | Tohoku University |
| Whitwell JL et al., 2011[54] | AD < CN | 14 | Mayo Clinic |
| Whitwell JL et al., 2011[54] | AD < CN | 14 | Mayo Clinic |

| | | | |
|---|---|---|---|
| Xie S et al., 2006[55] | AD < CN | 13 | Peeking University First Hospital |
| Yi D et al., 2015[56] | MCI+ < CN | 10 | Seoul National University |
| Yi D et al., 2015[56] | MCI- < CN | 10 | Seoul National University |
| Zahn R et al., 2005[57] | AD < CN | 10 | University of Freiburg |
| Zhao Z et al., 2014[58] | aMCI < CN | 20 | Xuanwu Hospital |

Table 1: List of publications included in the meta-analysis. AD: Alzheimer's disease, MCI: Mild cognitive impairment, Conv: MCI converters, Non: MCI non-converters, EOAD: Early-onset Alzheimer's disease, LOAD: Late-onset Alzheimer's disease, MCI+: MCI with high cerebral amyloid-beta protein (A$\beta$) deposition, MCI-: MCI with no or little cerebral amyloid-beta protein (A$\beta$) deposition. $n$ indicates the number of participants involved in each study.

# 3 ADNI CNN training

For AD classification, ModelB44 achieved the best accuracy and ModelD obtained the lowest performance. Figure 7 shows the evolution of training and validation losses for ModelB44 and ModelD44. For ModelB44, both training loss and validation loss decreased over time and the training stopped before overfitting. ModelD44, on the opposite, failed to learn: training loss and validation losses remained almost the same. This issue could come from the large size of the ModelD. Model sizes reported in Table 2 indeed indicate that ModelD contains the largest number of trainable parameters.

| $c$ | ModelA | ModelB | ModelC | ModelD |
|---|---|---|---|---|
| 24 | 239186 | 186290 | 342362 | 526658 |
| 28 | 313066 | 229402 | 441390 | 691234 |
| 32 | 396674 | 275970 | 552418 | 877762 |
| 36 | 490010 | 325994 | 675446 | 1086242 |
| 40 | 593074 | 379474 | 810474 | 1316674 |
| 44 | 705866 | 436410 | 957502 | 1569058 |
| 48 | 828386 | 496802 | 1116530 | 1843394 |
| 52 | 960634 | 560650 | 1287558 | 2139682 |

Table 2: Number of trainable parameters for ModelA, ModelB, ModelC and ModelD ($c$ indicates the number of channels)

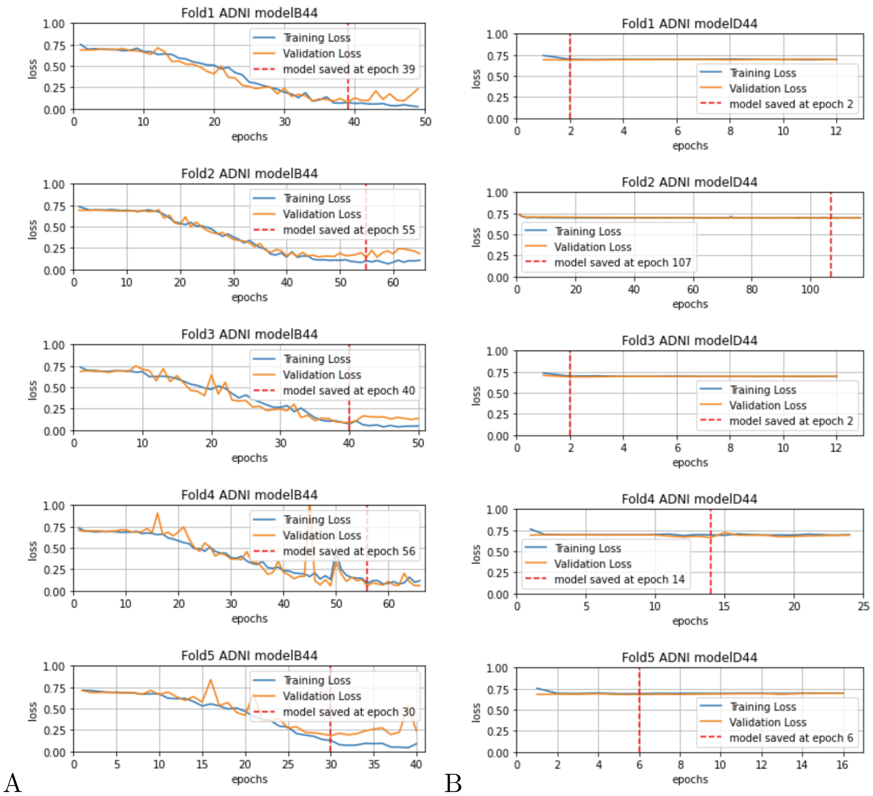


Figure 7: Evolution of training and validation losses for ModelB44 (A) and ModelD44 (B), for each fold of the 5-fold cross-validation conducted on the clinical data.

| $c$ | ME28 | ME24 | ME22 | ME20 | ME18 | ME16 | ME10 | ME8 |
|---|---|---|---|---|---|---|---|---|
| 8 | 48362 | 41386 | 37898 | 34410 | 30922 | 27434 | 16970 | 13402 |
| 10 | 74552 | 63672 | 58232 | 52792 | 47352 | 41912 | 25592 | 20032 |
| 12 | 106382 | 90734 | 82910 | 75086 | 67262 | 59438 | 35966 | 27974 |
| 14 | 143852 | 122572 | 111932 | 101292 | 90652 | 80012 | 48092 | 37228 |
| 16 | 186962 | 159186 | 145298 | 131410 | 117522 | 103634 | 61970 | 47794 |
| 20 | 290102 | 246742 | 225062 | 203382 | 181702 | 160022 | 94982 | 72862 |
| 24 | 415802 | 353402 | 322202 | 291002 | 259802 | 228602 | 135002 | 103178 |
| 28 | 564062 | 479166 | 436718 | 394270 | 351822 | 309374 | 182030 | 138742 |

Table 3: Number of parameters for all the ModelE architectures tested, for all numbers of channels $c$ and all the numbers of layers. ME28 refers to ModelE with 28 layers.

# 4 ADNI Dice overlaps

Figure 8 reports all the Dice overlaps measured between the smoothed heatmaps derived for the ModelB44 and ModelE18-20 and the meta-analysis ALE map. ModelB44 achieved the best 5-fold cross-validation of 87.24% across all tested 3D CNN models. ModelE18-20 achieved the best 5-fold cross-validation of 81.08% across all tested ModelE models.

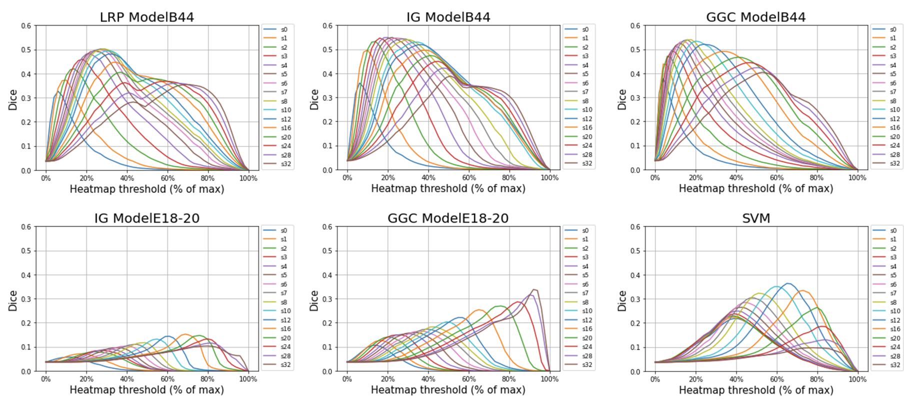


Figure 8: Dice overlap between all the smoothed heatmaps and the meta-analysis map. s0 corresponds to the heatmaps before smoothing, s1 corresponds to the heatmaps after 1 mm FWHM Gaussian smoothing, and similarly for other smoothing FWHM.

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