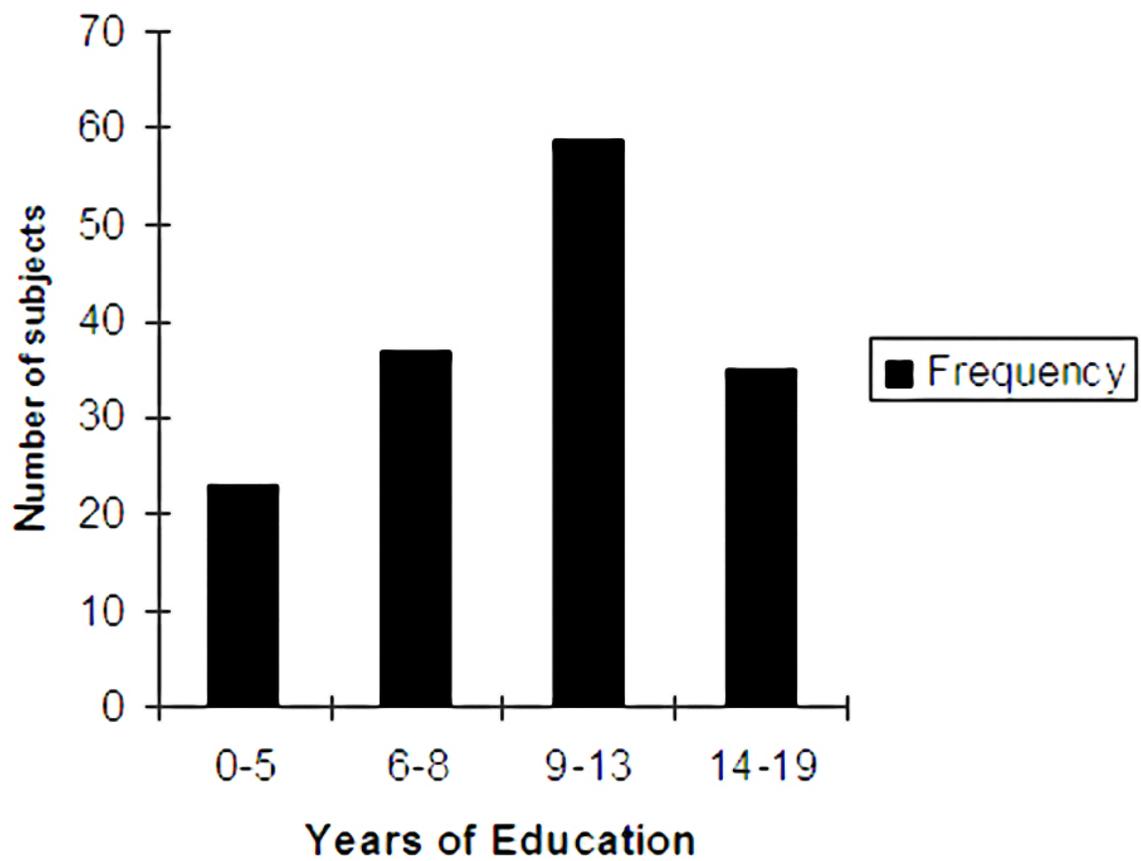


## **Details on Inclusion and Exclusion criteria of aMCI patients and Controls:**

Patients: The project included outpatients newly referred for cognitive complaints to a center dedicated to the evaluation of cognitive disorders. All referrals were considered, including self- or relative-referral, referral from general practitioner, and from first-level neurologic or geriatric clinics. Cognitive complaints mainly included memory complaints but they could also include difficulties in other cognitive domains, such as attention and orientation. Exclusion criteria were dementia; any somatic, metabolic (e.g., vitamin deficiency; endocrine untreated disorders; kidney, liver, or heart failure), psychiatric, or neurological disorder that may cause cognitive impairment, i.e., cerebrovascular accidents; neurodegenerative diseases, such as Parkinson disease; severe head trauma; brain tumor; history of alcohol abuse; severe depression. Patients with major depression, delusions, or hallucinations were excluded. Structural neuroimaging (mainly MR imaging) was available; CT was performed when MR imaging was unfeasible because of contraindications or patient intolerance.

Controls: Mild and well-controlled medical conditions, such as hypertension and diabetes, and a mild depressive trait were not considered as exclusion criteria. Only subjects not taking neuropsychotropic drugs or drugs known to interfere with cerebral metabolism were accepted in the control group.

The proportion of patients and controls was roughly comparable among centers in order to balance for the impact of different scanners. Subject information and scans uploaded by each center were as follows: Brescia (51 amnesic MCI patients and 20 controls); Genoa (52 amnesic MCI patients and 26 controls); Munich (46 amnesic MCI patients and 16 controls); Amsterdam (32 amnesic MCI patients and 18 controls); Marseille (5 amnesic MCI patients and 10 controls).



**SUPPLEMENTAL FIGURE 1:** Frequency distribution of main classes of years of education in the whole group of 154 subjects (median 11.5, mean  $11 \pm 4.2$ , range 2-19 years).

**SUPPLEMENTAL TABLE 1: Overview on Participating Centers and Equipment**

EADC Center	Scanner Type (manufacturer)	Spatial Resolution		Axial field of view (mm)
		In-plane FWHM	Slice thickness	
Amsterdam	ECAT EXACT HR+ (1)	7.00	2.50	155
Brescia	Discovery ST (2)	5.99	2.34	157
Marseille	Discovery ST (2)	6.20	3.27	157
Genoa	Biograph Hi-rez (1)	5.80	3.75	162
Munich	ECAT EXACT HR+ (1)	7.00	2.46	155

Note. Manufacturers: (1) Siemens/CTI, (2) General Electric.

**SUPPLEMENTAL TABLE 2. Results of the FDG brain PET comparison between LE pAD patients and LE CTR, and between HE pAD patients and HE CTR.**

Analysis	Cluster Level			Peak Level					
	Cluster Extent	Corrected <i>P</i> Value	Cortical Region	Maximum <i>z</i> Score	Talairach Coordinates		Cortical Region	BA	
LE-CTR>LE-pAD	2211	0.0001	L-Parietal	5.16	0	-49	34	Precuneus	31
			R-Parietal	4.5	6	-70	39	Precuneus	7
HE-CTR >HE-pAD	11247	0.0001	L-Limbic	4	-8	-57	20	Posterior Cingulate Gyrus	23
			L-Parietal	5.95	-8	-73	55	Precuneus	7
			L-Limbic	5.05	-10	-43	39	Posterior Cingulate Gyrus	31
			L-Parietal	5.04	-42	-74	44	Precuneus	19
			L-Temporal	5.02	-63	-54	1	Middle Temporal Gyrus	21
			L-Parietal	4.98	-44	-68	49	Inferior Parietal Lobule	7
			R-Parietal	4.89	50	-47	28	Inferior Parietal Lobule	40
			L-Parietal	4.83	-12	-47	34	Precuneus	31
			L-Temporal	4.69	-65	-44	10	Superior Temporal Gyrus	22
			R-Temporal	4.56	57	-30	-10	Middle Temporal Gyrus	21
			L-Temporal	4.53	-61	-53	23	Supramarginal Gyrus	40
			R-Temporal	4.53	44	-65	24	Middle Temporal Gyrus	39
			L-Temporal	4.41	-67	-28	-5	Middle Temporal Gyrus	21
			R-Occipital	4.24	30	-75	24	Precuneus	31
			R-Parietal	4.19	10	-64	47	Precuneus	7
			L-Occipital	4.12	-40	-87	10	Middle Occipital Gyrus	18
			L-Occipital	4.09	-38	-87	17	Middle Occipital Gyrus	19
L-Parietal	4.08	-61	-53	34	Supramarginal Gyrus	40			
R-Parietal	3.94	30	-50	47	Superior Parietal Lobule	7			
R-Occipital	3.91	8	-94	27	Cuneus	19			
R-Temporal	3.84	44	-62	7	Middle Temporal Gyrus	37			
L-Occipital	3.83	-26	-92	30	Cuneus	19			
L-Parietal	3.83	-57	-38	50	Inferior Parietal Lobule	40			
L-Limbic	3.73	-18	-58	16	Posterior Cingulate Gyrus	30			
L-Occipital	3.73	-30	-92	25	Superior Occipital Gyrus	19			

*P* < 0.05, corrected for multiple comparisons with the False Discovery Rate (FDR) option at both peak and cluster level were accepted as statistically significant. In the “cluster level,” section on the left, for each cluster found to be statistically significant, the number of voxels, the corrected *P* value and the cortical region where the cluster is found are reported. In the “peak level” section on the right, for each significant cluster, the peak coordinates and *z* score, the corresponding cortical region, and Brodmann area (BA) are reported. LE, Low Education; HE, High Education; pAD, Prodromal Alzheimer Disease; CTR, Controls; L, left; R, right.

**SUPPLEMENTAL TABLE 3. Results of interregional correlation analysis of VROI-compensation in LE and HE CTR**

Analysis	Cluster Level				Peak Level				
	Cluster Extent	Corrected <i>P</i> Value	Cortical Region	Maximum <i>z</i> Score	Talairach Coordinates		Cortical Region	BA	
LE-CTR	6840	0.03	L-Cerebellum	4.28	-16	-51	-18	Culmen	
			R-Cerebellum	4.1	4	-53	-18	Culmen	
			R-Occipital	4.03	16	-72	5	Lingual Gyrus	18
			R-Occipital	3.95	14	-73	22	Cuneus	18
			R-Parietal	3.9	24	-59	25	Precuneus	7
			R-Occipital	3.89	18	-87	17	Middle Occipital Gyrus	18
	5703	0.045	R-Frontal	4.3	22	28	-18	Middle Frontal Gyrus	11
			R-Frontal	3.71	30	30	-15	Inferior Frontal Gyrus	47
			R-Midbrain	3.66	-4	-22	-14	Red Nucleus	
			R-Frontal	3.61	18	17	-11	Subcallosal Gyrus	47
			R-Frontal	3.58	52	28	6	Inferior Frontal Gyrus	45
			L-Medulla	3.57	4	-37	-40		
			R-Frontal	3.56	50	29	2	Inferior Frontal Gyrus	45
			R-Frontal	3.53	42	49	16	Middle Frontal Gyrus	46
			R-Frontal	3.46	46	41	4	Inferior Frontal Gyrus	46
			R-Limbic	3.41	28	-6	-35	Uncus	20
			R-Limbic	3.4	8	34	-12	Anterior Cingulate	32
			R-Limbic	3.4	24	-6	-32	Uncus	36
			R-Frontal	3.4	4	60	-11	Medial Frontal Gyrus	11
			R-Limbic	3.37	20	1	-27	Uncus	28
			R-Frontal	3.33	63	0	31	Precentral Gyrus	6
			R-Sub-lobar	3.32	34	6	2	Clastrum	
			R-Sub-lobar	3.29	18	-12	2	Thalamus	
R-Frontal	3.27	40	11	25	Middle Frontal Gyrus	9			
HE-CTR	6011	0.009	R-Frontal	4.25	22	28	-18	Middle Frontal Gyrus	1
			R-Frontal	4.24	30	30	-15	Inferior Frontal Gyrus	47
			L-Midbrain	4.17	-4	-22	-14	Red Nucleus	
			L-Cerebellum	4.13	-16	-51	-18	Culmen	

		R-Cerebellum	3.99	4	-53	-18	Culmen	
		R-Occipital	3.89	16	-72	5	Lingual Gyrus	18
		R-Temporal	3.89	52	-42	-20	Fusiform Gyrus	20
		R-Temporal	3.87	57	-45	-13	Inferior Temporal Gyrus	20
		L-Sub-lobar	3.83	-20	13	-11	Lentiform Nucleus	
		L-Frontal	4.2	-24	34	-15	Middle Frontal Gyrus	11
4011	0.013	L-Frontal	3.83	-36	9	24	Inferior Frontal Gyrus	9
		L-Frontal	3.57	-18	-28	59	Precentral Gyrus	4
		L-Parietal	3.51	-44	-23	36	Postcentral Gyrus	2
		R-Frontal	3.52	18	-26	55	Sub-Gyral	4
		R-Frontal	3.54	14	-11	61	Medial Frontal Gyrus	6
		R-Frontal	3.46	32	-11	45	Middle Frontal Gyrus	6
		R-Occipital	3.46	40	-83	6	Middle Occipital Gyrus	19
		R-Occipital	3.46	30	-90	-2	Middle Occipital Gyrus	18
		R-Cerebellum	3.46	26	-39	-33	Cerebellar Tonsil	
		R-Frontal	3.43	22	31	35	Middle Frontal Gyrus	8
		R-Parietal	3.42	63	-41	32	Supramarginal Gyrus	40
		R-Parietal	3.41	61	-37	46	Inferior Parietal Lobule	40
		R-Temporal	3.41	55	-61	27	Superior Temporal Gyrus	39
		L-Cerebellum	3.4	-14	-81	-3	Pyramis	
		R-Cerebellum	3.4	22	-81	-30	Pyramis	
		R-Occipital	3.4	-42	-68	2	Middle Occipital Gyrus	37
		L-Parietal	3.14	-20	-54	49	Precuneus	7
2270	0.045	L-Cerebellum	3.14	-16	-45	-40	Cerebellar Tonsil	
		R-Parietal	3.14	59	-49	37	Inferior Parietal Lobule	40
		L-Limbic	3.14	-28	-15	-20	Hippocampus	
		L-Cerebellum	3.12	-28	-81	-31	Pyramis	
		L-Cerebellum	3.11	-26	-83	-30	Tuber	
		R-Parietal	3.1	32	-68	31	Precuneus	19

Uncorrected  $P < 0.001$  at voxel level and  $P < 0.05$ , corrected for multiple comparisons at cluster level, were accepted as statistically significant. In the 'cluster level,' section on the left, for each cluster found to be statistically significant, the number of voxels, the corrected  $P$  value and the cortical region where the cluster is found are reported. In the 'peak level' section on the right, for each significant cluster, the peak coordinates and  $z$  score, the corresponding cortical region, and Brodmann area (BA) are reported. LE, Low Education; HE, High Education; CTR, Controls; L, left; R, right.