Brain connectivity correlates of the impact of a digital intervention for individuals with subjective cognitive decline on depression and IL-18

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Supplementary Information

1 Supplementary Information

1.1 Self-reported questionnaires

Quality of Life (SF-36)

The 36-Item Short Form Survey (SF-36) is a set of generic, coherent, and easily administered quality-of-life measures [1]. These measures rely upon patient self-reporting and are now widely utilized by researchers, managed care organizations and by Medicare for routine monitoring and assessment of care outcomes in adult patients. The questionnaire evaluates physical functioning; bodily pain; role limitations due to physical health problems; role limitations due to personal or emotional health; general mental health; social functioning; energy/fatigue; and general health perception. Each scale generates a score from 0 to 100, with a high score indicating better health and less body pain. Administration time: 8-10 minutes.

Psychology state questionnaires

PSS-10 (Perceived Stress Scale): A 10-item screening questionnaire originally developed by Cohen et al. (1983) widely used to assess stress levels in young people and adults aged 12 and above. It evaluates the degree to which an individual has perceived life as unpredictable, uncontrollable and overloading over the previous month [2]. Administration time: 5-10 minutes.

MHC-SF (Mental Health Continuum Short Form): The MHC-SF is a scale measuring emotional wellbeing. Each of the 14 items on the MHC-SF can be scored between 0 and 5, which means that the total score on the scale can range from 0 to 70 points. Higher scores indicate a higher level of emotional wellbeing [3]. Administration time: 5-10 minutes.

CES-D (Center for Epidemiologic Studies Depression Scale): a commonly used 20 items self-rating scale designed to measure depressive symptomatology (interpersonal relations, positive affect, depressed affect, and somatic activity) in clinical and non- clinical settings [4]. Administration time: ~ 5 minutes.

GAD-7 (General Anxiety Disorder-7): a self-report screening tool for generalized anxiety symptoms in the primary care setting The scale consists of 7 questions, and is sensitive to treatment-related changes in adults with generalized anxiety disorder [5]. Administration time: ~2 minutes.

2 Supplementary Tables

Table S1: Baseline characteristics

N	17
Age	57.2±1.5
Gender (M)	8 (47.1)
Years of education	16.1±1.7
Marital status	
Married/Live with a partner	13 (76.5)
Divorced	4 (23.5)
Number of children	3.1±0.9
PSS-10 (Perceived Stress Scale)	15.1±4.5
MoCA (Montreal Cognitive Assessment)	27.6±1.9
BMI (Kg/m2)	25.7±2.5

Mean ± SD (%)

Table S2: ROI-ROI connectivity within and between network's regions

Hemisphere	Region*	Region ID	Hemisphere	Region*	Region ID	T(16)	ES**	pUNC	pFDR
L	31a	122	L	d23ab	126	-6.51	-1.58	0.0000	**0.0095**
L	31a	122	R	d23ab	306	-6.13	-1.49	0.0000	**0.0096**
R	PFm	295	L	a32pr	142	-5.32	-1.29	0.0001	**0.0304**
L	31a	122	L	31pv	124	-4.82	-1.17	0.0002	**0.0498**
R	p32	326	R	31pd	303	-4.89	-1.19	0.0002	**0.0498**
L	31a	122	R	PGs	300	-4.61	-1.12	0.0003	0.0600
L	31a	122	L	PGs	120	-4.47	-1.08	0.0004	0.0600
L	31a	122	R	PGi	298	-4.42	-1.07	0.0004	0.0600
L	RSC	132	R	d23ab	306	-4.51	-1.09	0.0004	0.0600
R	p32	326	R	31pv	304	-4.39	-1.06	0.0005	0.0600
L	31a	122	L	31pd	123	-4.26	-1.03	0.0006	0.0724
R	p32	326	L	PGi	118	-4.21	-1.02	0.0007	0.0729
R	p32	326	R	d23ab	306	-4.14	-1.00	0.0008	0.0779
R	p32	326	L	31pd	123	-4.06	-0.98	0.0009	0.0866
L	31a	122	L	v23ab	133	-3.96	-0.96	0.0011	0.0902
L	RSC	132	L	31pd	123	-3.95	-0.96	0.0011	0.0902
L	a24	140	L	PGi	118	-3.95	-0.96	0.0012	0.0902
L	10r	134	L	d23ab	126	-3.89	-0.94	0.0013	0.0964
R	p32	326	L	PFm	115	-3.78	-0.92	0.0016	0.1151
L	31a	122	R	v23ab	313	-3.62	-0.88	0.0023	0.1337
L	31a	122	L	PGi	118	-3.59	-0.87	0.0024	0.1337
L	RSC	132	R	TPOJ3	280	-3.67	-0.89	0.0021	0.1337
L	RSC	132	L	PGi	118	-3.56	-0.86	0.0026	0.1337
L	10r	134	L	31pd	123	-3.63	-0.88	0.0022	0.1337
R	POS2	310	L	31a	122	-3.61	-0.88	0.0023	0.1337
R	p32	326	R	PGi	298	-3.56	-0.86	0.0026	0.1337
L	31a	122	L	PFm	115	-3.54	-0.86	0.0027	0.1345
L	RSC	132	L	31pv	124	-3.50	-0.85	0.0030	0.1398
L	PFm	115	L	a32pr	142	-3.47	-0.84	0.0032	0.1412
L	31a	122	R	31pv	304	-3.42	-0.83	0.0035	0.1412
R	RSC	312	R	TPOJ3	280	-3.44	-0.83	0.0034	0.1412
R	RSC	312	L	31a	122	-3.43	-0.83	0.0035	0.1412
R	p32	326	L	31a	122	-3.44	-0.83	0.0033	0.1412
L	RSC	132	R	31pd	303	-3.37	-0.82	0.0039	0.1523
L	RSC	132	R	POS2	310	-3.31	-0.80	0.0044	0.1602
L	RSC	132	R	31pv	304	-3.23	-0.78	0.0052	0.1602
L	a24	140	L	31pd	123	-3.25	-0.79	0.0050	0.1602
R	PGi	298	L	a32pr	142	-3.29	-0.80	0.0046	0.1602
R	a24	320	R	RSC	312	-3.27	-0.79	0.0048	0.1602
R	p32	326	L	RSC	132	-3.26	-0.79	0.0049	0.1602
R	p32	326	R	PGs	300	-3.25	-0.79	0.0050	0.1602
R	p32	326	R	RSC	312	-3.24	-0.79	0.0051	0.1602
L	a32pr	142	R	p32pr	327	3.22	0.78	0.0053	0.1606
L	POS2	130	R	POS2	310	-3.19	-0.77	0.0057	0.1687
R	TPOJ3	280	R	FOP5	253	3.18	0.77	0.0059	0.1687
L	p32	146	L	d23ab	126	-3.13	-0.76	0.0064	0.1818
R	TPOJ3	280	L	FOP5	73	3.10	0.75	0.0069	0.1896

L	31a	122	R	31pd	303	-3.07	-0.74	0.0073	0.1978
R	31pd	303	R	FOP5	253	3.05	0.74	0.0077	0.2031
L	10r	134	L	PGi	118	-3.04	-0.74	0.0078	0.2039
L	31a	122	R	IP1	292	-3.03	-0.73	0.0080	0.2043
L	31a	122	R	MI	255	3.01	0.73	0.0082	0.2043
L	31a	122	R	FOP4	252	3.01	0.73	0.0083	0.2043
L	POS2	130	R	d23ab	306	-3.00	-0.73	0.0085	0.2046
L	10r	134	R	d23ab	306	-2.95	-0.72	0.0094	0.2074
R	PFm	295	R	a32pr	322	-2.96	-0.72	0.0092	0.2074
R	31a	302	R	AVI	249	2.93	0.71	0.0099	0.2074
R	31a	302	R	MI	255	2.98	0.72	0.0088	0.2074
R	a24	320	R	d23ab	306	-2.93	-0.71	0.0099	0.2074

* Glasser atlas [6], ** Cohen's d effect size, L, left, R, right, UNC, uncorrected, FDR, false discovery rate,

Table S3: DMN and SN cortical regions of the HCPex atlas

HCPex Code*	Hemisphere	Region	Region ID	Region Name
Default Mode Network (DMN)				
HCPex_2mm.100	L	TPOJ3	100	Area_TemporoParietoOccipital_Junction_3
HCPex_2mm.112	L	IP1	112	Area_IntraParietal_1
HCPex_2mm.115	L	PFm	115	Area_PFm_Complex
HCPex_2mm.118	L	PGi	118	Area_PGi
HCPex_2mm.120	L	PGs	120	Area_PGs
HCPex_2mm.122	L	31a	122	Area_31a
HCPex_2mm.123	L	31pd	123	Area_31pd
HCPex_2mm.124	L	31pv	124	Area_31p_ventral
HCPex_2mm.126	L	d23ab	126	Area_dorsal_23_a + b
HCPex_2mm.129	L	POS1	129	Parieto-Occipital_Sulcus_Area_1
HCPex_2mm.130	L	POS2	130	Parieto-Occipital_Sulcus_Area_2
HCPex_2mm.132	L	RSC	132	RetroSplenial_Complex
HCPex_2mm.133	L	v23ab	133	Area_ventral_23_a + b
HCPex_2mm.134	L	10r	134	Area_10r
HCPex_2mm.140	L	a24	140	Area_a24
HCPex_2mm.146	L	p32	146	Area_p32
HCPex_2mm.149	L	s32	149	Area_s32
HCPex_2mm.280	R	TPOJ3	280	Area_TemporoParietoOccipital_Junction_3
HCPex_2mm.292	R	IP1	292	Area_IntraParietal_1
HCPex_2mm.295	R	PFm	295	Area_PFm_Complex
HCPex_2mm.298	R	PGi	298	Area_PGi
HCPex_2mm.300	R	PGs	300	Area_PGs
HCPex_2mm.302	R	31a	302	Area_31a
HCPex_2mm.303	R	31pd	303	Area_31pd
HCPex_2mm.304	R	31pv	304	Area_31p_ventral
HCPex_2mm.306	R	d23ab	306	Area_dorsal_23_a + b
HCPex_2mm.309	R	POS1	309	Parieto-Occipital_Sulcus_Area_1
HCPex_2mm.310	R	POS2	310	Parieto-Occipital_Sulcus_Area_2
HCPex_2mm.312	R	RSC	312	RetroSplenial_Complex
HCPex_2mm.313	R	v23ab	313	Area_ventral_23_a + b
HCPex_2mm.314	R	10r	314	Area_10r
HCPex_2mm.320	R	a24	320	Area_a24
HCPex_2mm.326	R	p32	326	Area_p32
HCPex_2mm.329	R	s32	329	Area_s32
Salience Network (SN)				
HCPex_2mm.40	L	SCEF	40	Supplementary_and_Cingulate_Eye_Field
HCPex_2mm.69	L	AVI	69	Anterior_Ventral_Insular_Area
HCPex_2mm.72	L	FOP4	72	Frontal_Opercular_Area_4
HCPex_2mm.73	L	FOP5	73	Area_Frontal_Opercular_5
HCPex_2mm.75	L	MI	75	Middle_Insular_Area
HCPex_2mm.141	L	a24pr	141	Anterior_24_prime
HCPex_2mm.142	L	a32pr	142	Area_anterior_32_prime
HCPex_2mm.147	L	p32pr	147	Area_p32_prime
HCPex_2mm.168	L	46	168	Area_46
HCPex_2mm.220	R	SCEF	220	Supplementary_and_Cingulate_Eye_Field
HCPex_2mm.249	R	AVI	249	Anterior_Ventral_Insular_Area

HCPex_2mm.252	R	FOP4	252	Frontal_Opercular_Area_4
HCPex_2mm.253	R	FOP5	253	Area_Frontal_Opercular_5
HCPex_2mm.255	R	MI	255	Middle_Insular_Area
HCPex_2mm.321	R	a24pr	321	Anterior_24_prime
HCPex_2mm.322	R	a32pr	322	Area_anterior_32_prime
HCPex_2mm.327	R	p32pr	327	Area_p32_prime
HCPex_2mm.348	R	46	348	Area_46

* **Glasser** atlas [6], L, left, R, right,

3 Supplementary Figures

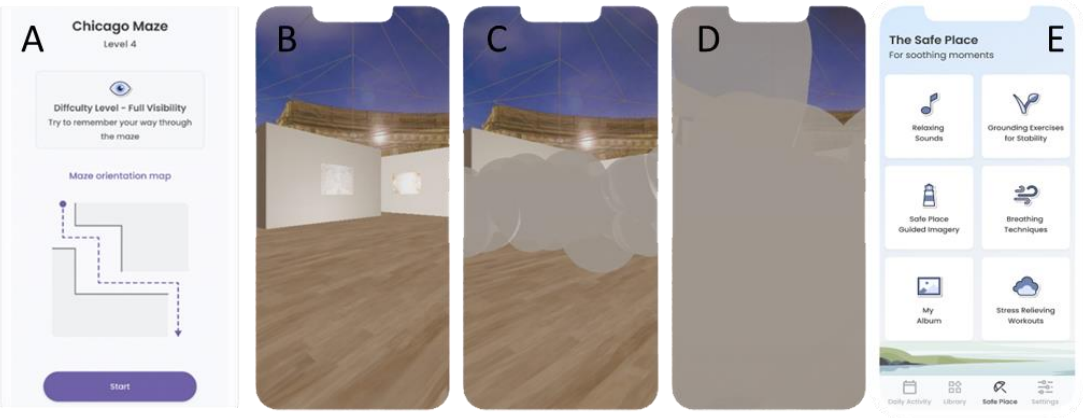

Fig. S1. Remepy APP comprehensive training mobile application. A top view map of HW maze used. The app utilizes a special version of the HW maze which includes both an allocentric view that was introduced visually (A), and a digital 3D egocentric navigation view with visual and auditory input (B). This way subjects were encouraged to integrate both map-based allocentric navigation and egocentric navigation; 50% random screening masked – reducing half of the visual cues and encouraging subjects to integrate visual cues with the auditory cue (C); blindfolded navigation in which no visual cues were available and the subject was further instructed to use blindfolding (D); psychological interventions - video and audio aimed at chronic stress reduction, CBT, etc. (E).

4 References

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