– Supplementary Materials –

Visual working memory encoding in schizophrenia and first-degree relatives: Neurofunctional abnormalities and impaired consolidation

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Supplementary Methods

Image Acquisition, Quality Control and Data Preprocessing

MRI data were obtained using a Siemens Magnetom Trio scanner with a 3 Tesla field strength at the Brain Imaging Center, Goethe University Frankfurt, Germany. Functional T_2* weighted images were scanned with a gradient echo EPI pulse sequence (30 slices, TR = 2000 ms, TE = 30, FA= 90°, FOV = 192 × 192 mm, matrix = 64 × 64, voxel size: 3 × 3 × 3 mm, gap 0.6 mm). Images were scanned in transversal orientation in descending order and co-planar with the anterior-commissure – posterior-commissure. We acquired 456 whole brain volumes in 2 runs during one scanning session. In addition, a T_1 weighted 3D volume was acquired for co-registration of the functional data using a magnetization prepared rapid gradient echo pulse sequence (MPRAGE; 160 sagital slices, TR = 2250 ms, TE = 2.6; FA= 9°, FOV = 256 × 256 mm, voxel size: 1 × 1 × 1 mm).

Functional and anatomical MRI data were processed and analyzed with the BrainVoyager QX software package (v2.8.4; Brain Innovation, Maastricht, The Netherlands). The first two volumes of each functional run were discarded to allow for T_1-equilibration. We preformed the following functional preprocessing steps in the given order: Slice scan timing correction (interpolation: cubic spline); 3D head motion correction (interpolation: trilinear / sinc; intra-session alignment to last volume of second scanning run); linear trend removal and temporal high-pass filtering (GLM-Fourier of 2 sines/cosines).

Quality control encompassed the inspection of all raw data to detect potential scanner artifacts and severe neuroanatomical abnormalities and the evaluation of head motion after 3D motion correction. Datasets with head motion that exceeded 3 mm in each direction were discarded. Subjects whose behavioral performance indicated that they had severe problems in handling the working memory task (i.e. many misses/response accuracy below 50%) were also excluded. After quality control 9 subjects were removed from the analyses due to severe neuroanatomical abnormalities (1 SCZ/1 REL), minor neuroanatomical anomalies that caused

MRI signal loss (1 SCZ/1 CON), increased head motion (2 SCZ / 1 REL) and substantially reduced response accuracy (2 SCZ).

In the high-resolution 3D anatomical images we segregated the brain from the head tissue and corrected the images for intensity inhomogeneity applying an automated BrainVoyager QX approach that uses image intensity peaks to optimize within-tissue homogeneity and white and grey matter separation. The resulting data set was used for co-registration with the preprocessed functional images (automated 12 parameters full affine transformation with manual quality control and realignment if necessary) and transformation into Talairach coordinate space.

Visual Working Memory Task

Please note that the term Stimulus onset asynchrony (SOA) traditionally refers to the time between stimulus 1 onset and stimulus 2 onset. Here, we use the term to describe the time interval between stimulus 1 offset (sample array) and stimulus 2 onset (mask), i.e. the interval where only a fixation cross is shown. In traditional terms our SOA conditions would be 500 ms, 800 ms and 1200 ms.

Table S1. Brain activation differences between groups in the SOA conditions of the working memory task during the encoding phase.

Anatomical region	R/L	BA	Talairch coordinates			Cluster Size (voxels/mm³)	$t_{(142)}$
			x	y	z		
			SOA 100				
SCZ < CON							
Thalamus	R	*	3	-16	13	306	3.7604
Cuneus	L	23	0	-73	10	695	3.7781
Caudate	L	*	-3	2	7	510	5.4431
REL < CON							
Fusiform Gyrus	R	37	45	-58	-11	768	3.8477
Superior Frontal Gyrus	R	10	18	49	19	446	3.6962
Culmen	R	*	9	-55	-15	747	3.8726
			SOA 400				
SCZ < CON							
Cingulate Gyrus	R	31	6	-46	43	355	3.4959
	L	24	0	-1	25	300	3.9394
Cuneus	L	18	-3	-76	7	441	3.3935
Precuneus	L	7	-9	-62	46	289	4.0060
REL < CON							
Middle Frontal Gyrus	L	6	-21	-10	58	408	3.8260
REL > CON							
Superior Frontal Gyrus	R	9	18	50	34	252	3.5405
			SOA 800				
SCZ < CON							
Superior Temporal Gyrus	R	22	54	-49	10	330	3.8164
Postcentral Gyrus	R	4	24	-25	49	456	4.4804
Caudate	R	*	18	2	22	665	3.7177
	L	*	-15	11	19	303	3.8287
Paracentral Lobule	R	6	6	-25	49	546	4.2374
Cingulate Gyrus	L	6	-12	-4	49	298	3.4027
SCZ > CON							
Anterior Cingulate	L	24	-3	32	-2	356	3.5903
REL > CON							
Inferior Frontal Gyrus	R	9	39	5	31	855	4.1110

Note: R/L = Right/Left; BA = Brodmann area; * = no Brodmann area; P < 0.05, corrected using cluster thresholding approach with initial single-voxel threshold of P < 0.01 (uncorrected); Talairach coordinates, anatomical regions and Brodmann areas refer to peak voxel of cluster. SCZ = schizophrenia patients; REL = first-degree relatives of persons with schizophrenia; CON = healthy control subjects.

Post-hoc Region-of-Interest Analysis: Correlation with Behavioral Performance

In order to examine the potential relationship between neural activation in specific brain regions of interest and behavioral performance, we conducted a post-hoc Region-of-Interest (ROI) analysis with the four brain areas in which we observed aberrant neural activation in REL during encoding (MFG, MeFG, PrCG, Insula) and performed a subsequent correlation analysis. We conducted a (multi-subject) random effects ROI-GLM analysis ($P < 0.05$, FDR corrected) and obtained beta values for the encoding phase predictor (contrast: encoding>baseline) in the above named brain regions. For each group the correlation of individual beta values and response accuracy in visual working memory task was analyzed using the Pearson product-moment correlation coefficient. Correlation coefficients were compared between groups using Fisher Z-transformation and subsequent single sided Z-tests.

Table S2. Correlations between brain activation in selected Regions-of-Interest during the encoding phase and behavioral performance in the visual working memory task

Anatomical region (ROI)	Response Accuracy			Probability		
	SCZ (*r*)	REL (*r*)	CON (*r*)	SCZ *vs.* CON (*p*)	REL *vs.* CON (*p*)	SCZ *vs.* REL (*p*)
Middle Frontal Gyrus (MFG)	0.127	0.235	0.198	0.404	0.451	0.361
Medial Frontal Gyrus (MeFG)	0.233	0.234	0.108	0.334	0.339	0.499
Precentral Gyrus (PrCG)	0.143	-0.061	0.123	0.473	0.278	0.256
Insula (IN)	-0.047	-0.071	0.170	0.234	0.219	0.469

Note: ROI = Region-of-Interest; SCZ = schizophrenia patients; REL = first-degree relatives of persons with schizophrenia; CON = healthy control subjects. Left side of the table shows correlation matrix, right side shows group differences in correlation coefficients.