Supporting Information

Supporting information document for "***Central Neurogenetic Signatures of the Visuo-Motor Integration System***" by Bueichekú et al.

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The document contains the following sections:

SI Methods

Visuo-Motor Integration Task Description

A finger-tapping task was used as the experimental task-MRI paradigm. The task consisted of learning a sequence of alternating finger movements. Colored circles assigned one to each finger were used to present the sequence of finger movements (color 1: little finger, color 2: ring finger; color 3: middle finger; and, color 4: index finger). First, the sequence of movements was presented on the screen at 0.67 Hz, followed by a fixation cross that remained for 12.5 seconds, allowing time for the participants to reproduce the sequence. Before each sequence, there was a random jitter (0-500 ms), the task had eight sequences of movements per condition and there were 4000 ms of rest after each sequence. There were two task conditions: 1) ordered sequence of movements, where the participants performed the following movements: 1-2-3-4-1-2-3-4; and, 2) alternating sequence of movements where the participants performed novel sequences. The sequences were performed with the right hand, the left hand and bimanually; the hand condition was counterbalanced across participants. The bimanual performance required symmetrical simultaneous movements. Feedback was not provided during the task performance or after it. For the purpose of the present investigation, only the data related to the ordered sequence of movements and the bimanual performance were used.

Data Acquisition Details

MRI data from Cohort 1 were acquired on a 3.0 T Siemens TIM Trio scanner (Siemens Healthcare, Erlangen, Germany) using an 8-channel head coil. The acquisitions covered the whole brain including the entire cerebellum. Firstly, a high-resolution T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) images were acquired as structural data (repetition time / echo time [TR/TE] =1620 / 3.09 ms, flip angle=15º, 1 mm^3 isotropic voxels, 160 slices). Then, T2-weighted gradient echo echo-planar imaging (EPI) sequences sensitive to blood oxygenation level-dependent (BOLD) contrast (TR/TE = 3000/30ms, flip angle = 90º, 3 mm^3 isotropic voxels, no inter-slice gap, 49 slices) were used to acquire 244 volumes for each task run (right hand run, left hand run, and bimanual run).

Stimuli presentation and response collection was controlled using Cogent (Cogent 2000, UCL, London) and Matlab software (MATLAB R2010a, Natick, Massachusetts: The MathWorks Inc.), which was installed in a fixed workstation (screen-resolution

1080p, refresh rate of 67 Hz). Images were projected onto a screen and then reflected by a mirror system attached to the head coil into the subjects' field of vision and their responses were collected by two 4-key response pads (Current Designs, Inc.), one for each hand.

According to (1), Cohort 2 images were acquired on a 3.0 T Siemens TIM Trio scanner (Siemens Healthcare, Erlangen, Germany) at Harvard University and the Massachusetts General Hospital using a 12-channel phased-array head coil. The acquisitions covered the whole brain including the entire cerebellum. Slices were aligned to the AC-PC plane. Firstly, a high-resolution T1-weighted multi-echo MPRAGE images were acquired as structural data (TR=2.2 ms, TE= 1.5/3.4/5.2/7.0 ms, flip angle = 7º, 1.2 mm^3 isotropic voxels, 144 slices). Then, functional images corresponding to the resting-state scan were acquired using a gradient-echo EPI sequence sensitive to BOLD contrast (TR / TE = 3000 / 30 ms, flip angle = 85º, 3 mm^3 isotropic voxels, 124 volumes). For resting-state scans, participants were instructed to stay awake and still, with their eyes open and blinking normally.

Image Preprocessing

The four initial data time points of the BOLD acquisitions were discarded from the analysis to allow for signal stabilization. As abovementioned, for task activation analysis (from Cohort 1) only the data related to the ordered sequence of movements and the bimanual performance was used, thus, 120 data time points were analyzed. The set of images were preprocessed using Statistical Parametrical Mapping 12 software (SPM12, Wellcome Department of Imaging Neuroscience, London, England; www.fil.ion.ucl.ac.uk/spm/). Standard preprocessing was conducted, which included the following steps: (*i*) the correction of the slice timing differences for interleaved ascending acquisitions (using the middle slice, which was the 49^{th}, as the reference slice); (*ii*) two-pass procedure in realignment (registered to the first image, and then registered to the mean image) to correct for head motion during acquisition, no head motion for any participant's data had more than 2.0 mm of maximum displacement in any direction, or 2.0° of any angular motion; (*iii*) spatial normalization to Montreal Neurological Institute (MNI) space (3 mm^3 isotropic), which was conducted using the mean resliced image as source and the EPI provided by SPM12 as the template; (i*v*) spatial smoothing using an isotropic Gaussian kernel of 6 mm^3 full-width at half-maximum (FWHM).

For functional connectivity analysis, task related functional images from Cohort 1 and resting-state functional images from Cohort 2 were independently preprocessed, but the same procedure was used to obtain low-frequency fluctuations of BOLD signal (**Fig. 3A**). As for the task-activation analysis, for functional connectivity analyses 120 data time points were analyzed, discarding the initial four BOLD volumes. Each set of images was processed using a custom in-house developed preprocessing pipeline. The preprocessing included the following steps: (*i*) slice timing acquisition correction for interleaved ascending acquisitions (using the middle slice as the reference); (*ii*) two pass procedure in realignment (first registration to the first image, then registration to the mean image); (*iii*) intensity normalization; (*iv*) nuisance covariate regression which included signal detrending (lineal and quadratic trends), applying the Friston 24-parameter model as a head motion regression model (signal regression of six parameters from rigid body head motion obtained from realignment step and their temporal derivative, followed by the quadratic conversion of all 12 variables), and applying the component based method CompCorr for the reduction of noise (with 5 parameters for cerebrospinal fluid signal and 5 parameters for white matter signal); (*v*) normalization to the MNI space (3 mm^3 isotropic); (*vi*) band-pass filtering retaining BOLD signal between 0.01 Hz and 0.08 Hz; (*vii*) data demeaning with mean centered to 0; (*viii*) data motion-censoring step (*i.e.*, scrubbing of the time points with excess motion) was performed through interpolation according to (2), with the frame displacement (FD) threshold set to FD > 0.5 mm, none of the participants had excessive head motion; (*ix*) finally, for computational efficiency, the data were down-sampled from 3 mm^3 to 6 mm^3 voxel size.

SI Figures

Figure S1. Bootstrap resampling approach (I). Resampling-based similarity scores histograms of syndromic genes - SCN1A, MAGEL2 and CACNB4 - with genetic expression highly associated with the VMI map (using each gene's median cortical expression for the bootstrap resampling analysis). All relevant neuroimaging-genetic associations remained statistically significant after FDR correction.

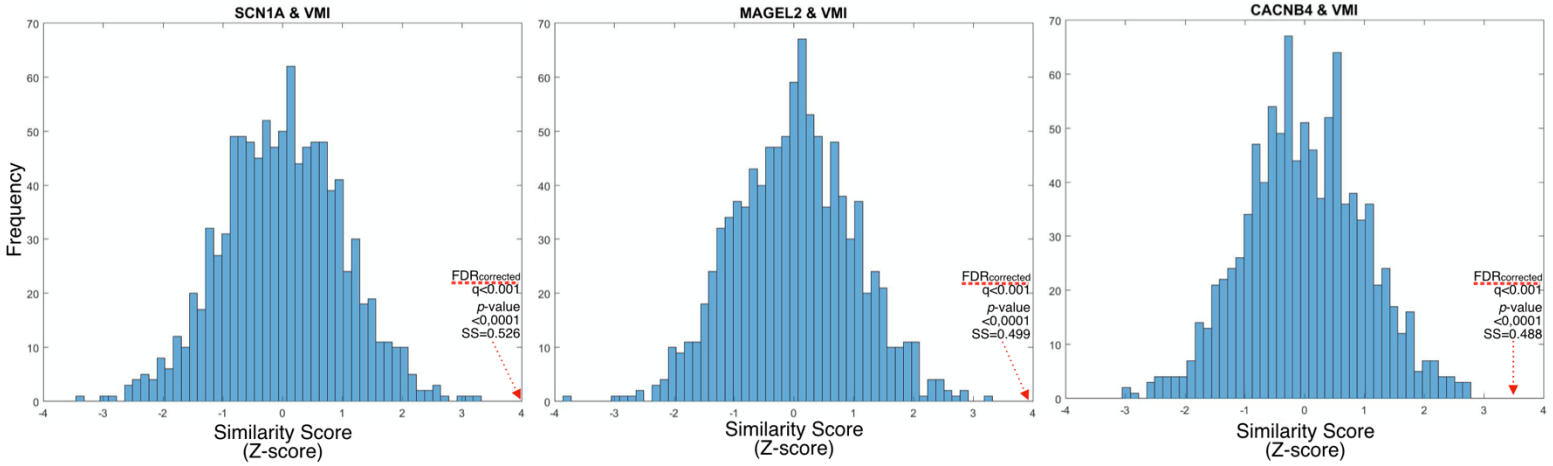


Figure S2. Bootstrap resampling approach (II). Resampling-based similarity scores histograms of syndromic genes - TBR1, SCN1A, MAGEL2 and CACNB4 - with genetic expression highly associated with the VMI map (using random maps for the bootstrap resampling analysis). All relevant neuroimaging-genetic associations remained statistically significant after FDR correction.

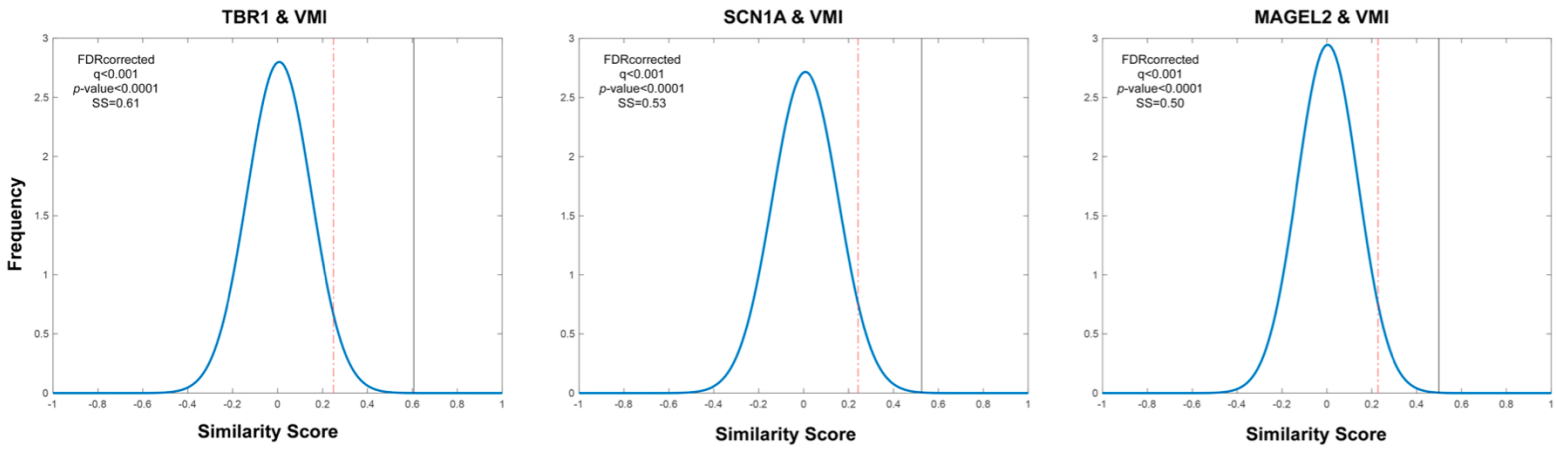
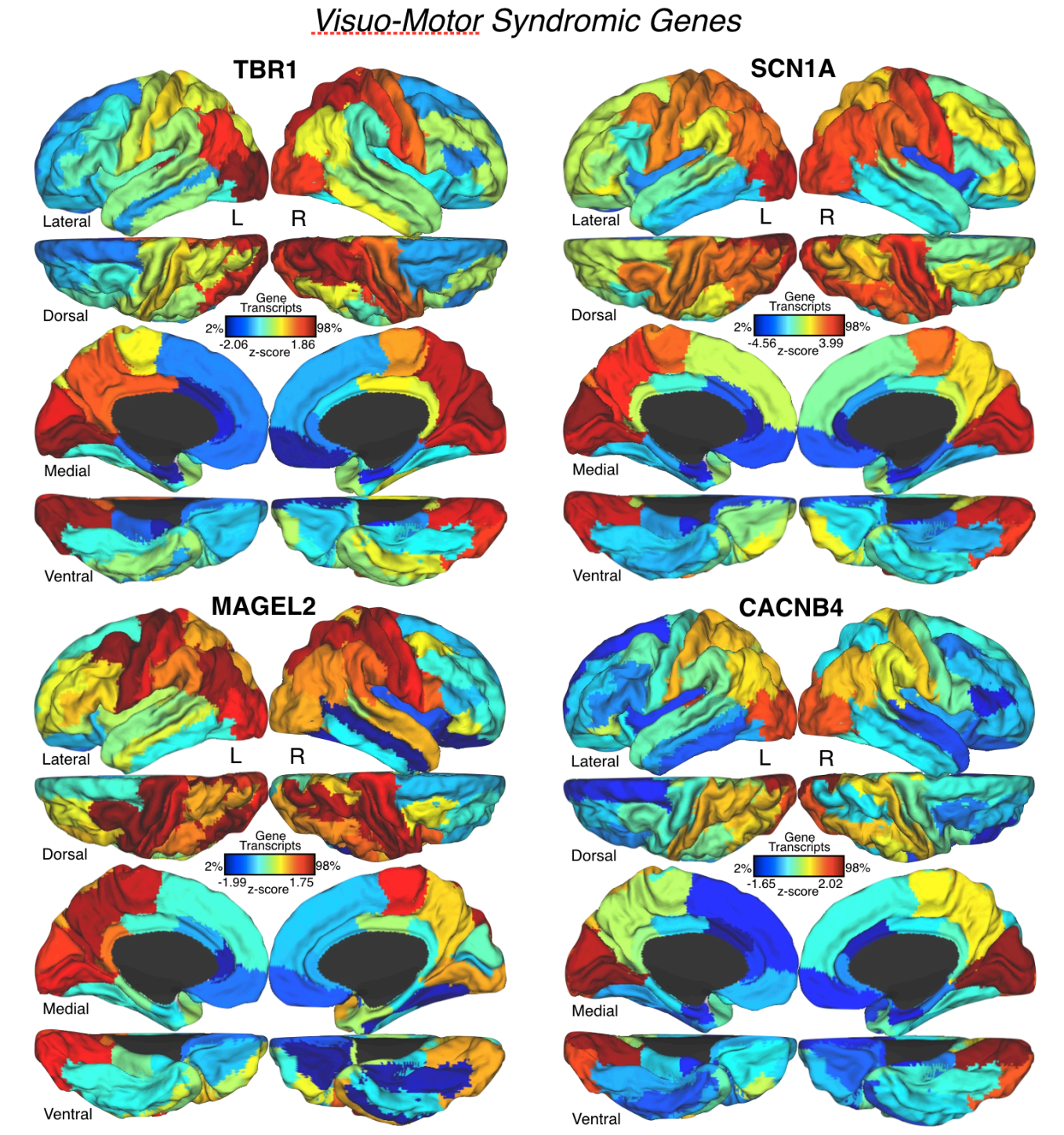


Figure S3. Gene expression levels of VMI-related genes. Cortical topology in the Desikan-Killiany atlas space of gene expression levels of TBR1 (top-left), SCN1A (top-right), MAGEL2 (bottom-left), and CACNB4 (bottom-right). Color scale represents the Allen Human Brain Atlas scores of gene transcripts (minimum = 2% and maximum = 98%).



SI Tables

Table S1. List of genes associated with neurodevelopmental syndromes. The GeneReviews resource was used for searching the chromosomes impaired in each syndrome, along with genes affected within those chromosomes (N=80).

Autism Spectrum Disorder	Dravet Syndrome	Fragile-X Syndrome	Prader-Willi Syndrome	Turner Syndrome	Williams Syndrome
ADNP	CACNA1A	FMR1	ATP10A	SHOX	ABHD11
ANK2	CACNB4		BP3		BAZ1B
ARID1B	POLG		GABRA5		BCL7B
ASH1L	SCN1A		GABRB3		CLDN3
ASXL3	SCN9A		GABRG3		CLDN4
CHD8			GCP5		CLIP2
CUL3			HERC2		DNAJC30
DSCAM			MAGEL2		EIF4H
DYRK1A			MKRN3		ELN
GRIN2B			NDN		FKBP6
KATNAL2			NECDIN		FZD9
KMT2A			NIPA1		GTF2I
KMT5B			NIPA2		GTF2IRD1
MYT1L			NPAP1		LAT2
NAA15			OCA2		LIMK1
POGZ			PAR1		MLXIPL
PTEN			PAR4		NCF1
RELN			PAR5		RFC2
SCN2A			PAR7		TBL2
SETD5			PWRN1		VPS37D
SHANK3			PWS		WBSCR11
SYNGAP1			SNORD115		WBSCR2
TBR1			SNORD116		WBSCR22
TRIP12			SNURF-SNRPN		WBSCR27
			UBE3A		

SI References

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2. M. Jenkinson, P. Bannister, M. Brady, S. Smith, S, Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage.* **17**, 825–841 (2002) https://doi.org/10.1016/s1053-8119(02)91132-8