S1. MRI acquisition protocol and image analysis supplementary information

The MRI acquisition protocol used in this study consisted of a sagittal localizer image which was acquired by means of an automated shimming procedure. Then, two imaging modes were applied: a three-dimensional Fourier-transform spoiled gradient recalled sequence (coronal acquisition slice thickness: 1.5-mm; in-plane resolution: 0.78125mm x 0.78125mm flip angle: 45°; repetition time: 35 milliseconds; echo time: 5 milliseconds; field of view: 18 cm; matrix: 256 x 256; 124 slices) and a double-echo (proton density and T2-weighted) spin-echo sequence (3-mm axial slices; repetition time: 3000 milliseconds; echo times: 36 and 162 milliseconds; field of view: 18 cm; matrix: 256 x 256, interleaved acquisition; 68 slices). Normative MRI data in the multi-center NBD study funded by the NIH were also acquired with a 1.5 Tesla system at all sites[1] using a similar acquisition protocol that has been previously described[1-2].

Linux Workstations were used for quantitative image processing. First, the T1 images were linearly registered[3] to an age-matched normal infant Talairach space template[4]. The brain was then automatically extracted for each subject using the Brain Extraction Tool[5]. Subsequently, cerebral and cerebellar tissue classification was performed using INSECT (Intensity-Normalized Stereotaxic Environment for Classification of Tissues), in order to obtain volumes of the cortical grey matter and white matter[6]. This automatic algorithm used for tissue classification labels each voxel as belonging to one of the two tissue classes based on its MRI signal. Manual outlining of the deep grey matter nuclei (basal ganglia and thalamus) of the age specific template were non-linearly warped into the subject space to delineate these structures on each subject's MRI[7]. Finally, the cerebellum was manually outlined and extracted using the Display software, an in-house visualization tool[8]. Manual corrections were made when necessary using the Display software for each step of image processing.

The first step of the cerebral parcellation consisted of dividing the cerebrum into right and left hemispheres. Subsequently, three reference points were manually positioned on the i) anterior commissure, ii) posterior commissure and iii) genu of the corpus callosum. Four planes were then traced: first an axial plane through the anterior commissure and posterior commissure line and then three coronal planes using the three reference points. Discrete volumetric measures for eight anatomical regions in each hemisphere were then obtained: dorsolateral prefrontal, orbitofrontal, premotor, subgenual, sensorimotor, midtemporal, parieto-occipital and inferior occipital (Figure 2 in the main document). Finally, volumetric data (cc) were computed for all eight regions of the cerebrum and their tissue types. Inter-rater reliability for this cerebral parcellation scheme was previously described using voxel assignment agreement, which was averaged to 80.2%[9]. In the current study, the same operator (M.B.) performed all parcellations and was rigorously trained to identify the correct anatomical

landmarks, in order to ensure consistency in our volume measurements. Parcellation was performed a second time on five different scans. Although the operator was blinded to case versus control assignment, it was difficult to ensure 100% blinding given that some of the cerebellar malformations were marked and clearly visible to the naked eye.

References

1. Almli CR, Rivkin MJ, McKinstryc RC, Group BDC. The NIH MRI study of normal brain development (Objective-2): Newborns, infants, toddlers, and preschoolers. NeuroImage. 2007;35:308-325.

2. Evans AC, Brain Development Cooperative Group. The NIH MRI study of normal brain development. NeuroImage. 2006;30:184-202.

3. Collins DL, Neelin P, Peters TM, Evans AC. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. Journal of Computer Assisted Tomography. 1994;18(2):192-205.

4. Fonov VS, Evans AC, McKinstry RC, Almli CR, Collins DL. Unbiased nonlinear average age-appropriate brain templates from birth to adulthood. NeuroImage. 2009;47:S101-S102.

5. Smith SM. Fast robust automated brain extraction. Human Brain Mapping. 2002;17(3):143-55.

6. Zijdenbos A, Forghani R, Evans A. Automatic quantification of MS lesions in 3D MRI brain data sets: Validation of INSECT. Proceedings of the First International Conference on Medical Image Computing and Computer-Assisted Intervention. Cambridge, MA: Springer-Verlag Berlin Heidelberg; 1998:439-448

7. Collins DL, Evans AC. ANIMAL: Validation and Applications of Non-Linear Registration-Based Segmentation. International Journal of Pattern Recognition and Artificial Intelligence. 1997;11:1271-94.

8. MacDonald D. MNI-Display: Program for Display and Segmentation of Surfaces and Volumes. [Technical report] 2003 [updated January 20]; Available from: www.bic.mni.mcgill.ca/~stever/Software/RelNotes/Display.ps

9. Caviness J, Makris N, Meyer JW, Kennedy DN. MRI-based parcellation of human neocortex: an anatomically specified method with estimate of reliability. Journal of Cognitive Neuroscience. 1996;8:566-88.