Fronto-cerebellar systems are associated with infant motor and adult executive functions in healthy adults but not in schizophrenia

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Delineating longitudinal relationships between early developmental markers, adult cognitive function, and adult brain structure could clarify the pathogenesis of neurodevelopmental disorders such as schizophrenia. We aimed to identify brain structural correlates of infant motor development (IMD) and adult executive function in nonpsychotic adults and to test for abnormal associations between these measures in people with schizophrenia. Representative samples of nonpsychotic adults ($n = 93$) and people with schizophrenia ($n = 49$) were drawn from the Northern Finland 1966 general population birth cohort. IMD was prospectively assessed at age 1 year; executive function testing and MRI were completed at age 33–35 years. We found that earlier motor development in infancy was correlated with superior executive function in nonpsychotic subjects. Earlier motor development was also normally associated with increased gray matter density in adult premotor cortex, striatum, and cerebellum and increased white matter density in frontal and parietal lobes. Adult executive function was normally associated with increased gray matter density in a fronto-cerebellar system that partially overlapped, but was not identical to, the gray matter regions normally associated with IMD. People with schizophrenia had relatively delayed IMD and impaired adult executive function in adulthood. Furthermore, they demonstrated no normative associations between fronto-cerebellar structure, IMD, or executive function. We conclude that frontal cortico-cerebellar systems correlated with adult executive function are anatomically related to systems associated with normal infant motor development. Disruption of this anatomical system may underlie both the early developmental and adult cognitive abnormalities in schizophrenia.

neuroimaging | neurodevelopmental | connectivity | epidemiology | dysmetria

Little is known about how the early development of the human brain predicts its adult structure. Several twin studies have established that adult brain structure is heritable (1, 2), but these designs cannot address questions concerning the timing of genetic effects on neuroanatomical variation in adults. Hypothetically, the responsible genetic differences may be expressed during early brain development with anatomical effects being conserved over the course of childhood and adolescence, albeit conditioned by environmental factors and gene × environment interactions (3).

It would be useful to know more about (dis)continuities between early developmental markers and adult brain structure as a basis for better understanding of the pathogenesis of psychiatric disorders such as schizophrenia, which typically present in young adults but may be predicted, at least in part, by earlier neurodevelopmental aberration. Longitudinal epidemiological studies of schizophrenia show early developmental adversity imparting increased risk of adult psychosis, with the emergence of psychotic symptoms preceded by subtle abnormalities of motor coordination (developmental dysmetria), social function, and cognition in childhood and adolescence (4–6). Typically, cognitive and social malfunction increases during the prodromal period before presentation of the psychotic schizophrenia syndrome, when motor dysfunction indicative of basal ganglia involvement is evident (7).

A parsimonious explanation for such a diverse profile of behavioral and cognitive abnormality is that a single brain system may normally be responsible for both early acquisition of motor skills and aspects of later cognitive function; developmental abnormality of this system is an endophenotype or risk modifier for schizophrenia (8). By this account, adumbrated by Weinberger (9), the long-term natural history of an individual predisposed to schizophrenia represents age-dependent change of function in a persistently abnormal system. Andreasen (10) has argued that the diverse emergent schizophrenia syndrome can be considered to result from a "cognitive dysmetria" characterized by abnormality in cortico-cerebellar-thalamo-cortical circuits that prioritize, process, coordinate, and trigger responses to information.

We investigated a hypothetical model that integrates these seminal longitudinal (9) and crosssectional (10) models by exploiting early developmental and adult neuroimaging and cognitive data acquired on a representative sample of a general population birth cohort. We tested two specific predictions: (*i*) normal variation in infant motor development and adult executive function is correlated with neuroanatomical variation in cortico-cerebellar systems; and (*ii*) normal associations between brain structure, early motor development, and adult executive function evident in nonpsychotic subjects are attenuated in people with schizophrenia.

Results

Infant Motor Development (IMD) and Adult Executive Function. Descriptive statistics on age at learning to stand without support and ages at learning to walk with and without support are summarized in Table 1. IMD was significantly delayed, in terms of each of these variables, in children who would later develop schizophrenia compared with children who would not. The first principal component

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Abbreviations: IMD, infant motor development; PC, principal component; AIM, abstraction, inhibition, and working memory task; BA, Brodmann area; CSF, cerebrospinal fluid.

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Table 1. Descriptive statistics and ANOVA for IMD and adult executive function (AIM) tests

	Nonpsychotic subjects		People with schizophrenia		ANOVA		
Measure	Mean	SD	Mean	SD	*F*	df	*P*
IMD							
Age of standing without support (months)	10.80	1.67	11.69	1.36	10.16	1,141	<0.002
Age of walking with support (months)	9.21	1.51	10.27	1.79	13.58	1,141	<0.001
Age of walking without support (months)	11.93	1.36	12.54	1.14	7.14	1,141	<0.009
IMD PC score	0.22	0.99	−0.41	0.90	13.64	1,141	<0.001
Adult executive function							
Abstraction	24.22	2.77	22.49	3.68	9.34	1,133	<0.003
Abstraction plus working memory	23.60	3.51	20.44	3.35	24.82	1,133	<0.001
AIM PC score	0.25	0.90	−0.50	1.01	18.91	1,133	<0.001

IMD data were available on 49 people with schizophrenia and 93 nonpsychotic subjects for between-group comparisons of infant motor development; adult executive function scores were available on a subset of this sample (45 people with schizophrenia and 89 nonpsychotic subjects).

(PC) accounted for 75% of total variance in these data, so we adopted individual scores on this PC as a summary measure of IMD: the earlier the age of learning to walk/stand, the greater the positive value of an individual's IMD PC score. As expected, there was a significant between-group difference in IMD scores ($F_{1, 141} = 13.64$, $P < 0.001$) that were lower in children who would have schizophrenia as adults.

Descriptive statistics on both subscales of the abstraction, inhibition, and working memory (AIM) task of adult executive function are summarized in Table 1. Performance was significantly impaired both on the abstraction subscale and the abstraction plus working memory subscale in people with schizophrenia compared with nonpsychotic adults. The first PC of these data accounted for 86% of total variance and was adopted as a summary measure of adult

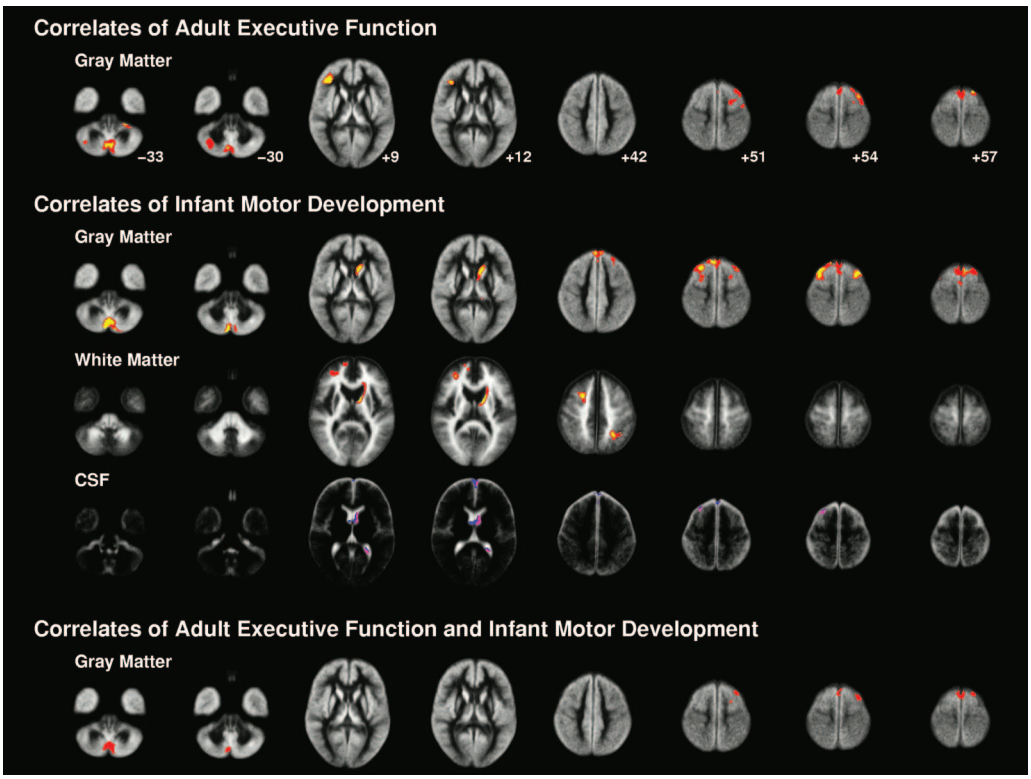

Fig. 1. Maps of neuroanatomical variation normally associated with variation in adult executive function (first row: gray matter only) and IMD (second to fourth rows: gray matter, white matter, and CSF). Voxels colored in yellow/red identify regions of gray or white matter where greater tissue density was associated with better adult executive function and/or earlier motor development; voxels colored blue/purple identify regions of CSF where greater tissue density was associated with later motor development. In the bottom (fifth) row, voxels colored in red identify regions where greater gray matter volume was associated with both higher adult executive function *and* earlier motor development. The left side of each section represents the right side of the brain; *z* coordinates in the standard space of Talairach and Tournoux (1988) are given in millimeters on the right side of each axial section in the top row. Significance testing was by a nonparametric permutation test with cluster-wise $P < 0.003$ such that the expected number of false positive tests per map is less than one.

executive function. There was a significant between-group difference in adult AIM scores ($F_{1,\ 133} = 18.91$, $P < 0.001$) that were reduced in adults with schizophrenia.

IMD scores were positively correlated with adult executive function scores in nonpsychotic volunteers ($r = 0.239$, df = 87, $t = 2.30$, $P < 0.024$), indicating that relatively precocious motor development was significantly associated with better executive function in adulthood and vice versa. There was also a positive correlation between IMD and adult executive function in people with schizophrenia, but this correlation was not significant ($r = 0.164$, df = 43, $t = 1.087$, $P < 0.283$; see also Fig. 3, which is published as supporting information on the PNAS web site).

IMD and Adult Brain Structure in Nonpsychotic Subjects. Using computational morphometry, we found a significant *positive* association between IMD scores and gray matter density in the following three brain regions: (*i*) bilateral and medial premotor cortex (approximate Brodmann area [BA] 6, including the supplementary motor area) and the bilateral rostral prefrontal cortex (BA 8) ($r = 0.37$, df = 91, $t = 3.85$, $P < 0.0003$); (*ii*) left caudate nucleus (head and body) and left thalamus ($r = 0.31$, df = 91, $t = 3.15$, $P < 0.0023$); and (*iii*) medial cerebellum ($r = 0.43$, df = 91, $t = 4.61$, $P < 0.0001$) (Fig. 1). In all these regions, earlier motor development was significantly associated with greater gray matter density. These results were corroborated by parametric tests of association between IMD and gray matter volumes in corresponding regions of a parcellated template image: left supplementary motor area ($r = 0.232$, df = 91, $P = 0.025$) and left superior medial frontal gyrus ($r = 0.225$, df = 91, $P = 0.030$).

In addition, we found a significant positive association between IMD scores and white matter volume in the frontal lobes (right-sided predominantly), the left parietal lobe, and immediately adjacent to the left caudate nucleus and thalamus (Fig. 1). Earlier motor development in infancy was associated with greater white matter density in these regions (Table 2, which is published as supporting information on the PNAS web site). There was also a significant negative association between IMD scores and cerebrospinal fluid (CSF) density in the lateral, 3rd, and 4th ventricles and the superior interhemispheric fissure (Fig. 1). Earlier motor development was associated with reduced CSF density in these regions (Table 2).

IMD and Adult Brain Structure in People with Schizophrenia. Applying the same morphometric methods to data acquired only from people with schizophrenia, we found no regions of significant association between IMD scores and gray matter density. To explore more directly the hypothesis that normal associations between brain structure and early motor development were abnormal in people with schizophrenia, we tested the difference between groups in the strength of association between IMD and gray matter density in the three main regions that showed this association in the nonpsychotic group. However, we found no significant associations between IMD score in the schizophrenic group and gray matter volume in the superior prefrontal region ($r = -0.05$, df = 47, $t = -0.43$, $P < 0.670$), the left caudate and thalamic region ($r = 0.23$, df = 47, $t = 1.65$, $P < 0.106$), or the medial cerebellum ($r = 0.12$, df = 47, $t = 0.84$, $P < 0.405$). We also found no significant association in the schizophrenic group between IMD scores and either white matter or CSF volume in those regions which showed an association with motor development in the nonpsychotic group.

For each of the gray matter, white matter, and CSF regions which were associated with IMD in the nonpsychotic group, we tested formally for a group × IMD interaction: this finding was significant for premotor/prefrontal gray matter and fronto-parietal white matter, in both cases reflecting the absence of the normal association between precocity of early motor development and increased premotor gray (or white) matter density in adults with schizophrenia (Fig. 2 *A* and *B*). See also Table 3, which is published as supporting information on the PNAS web site, for full ANOVA results on all regions.

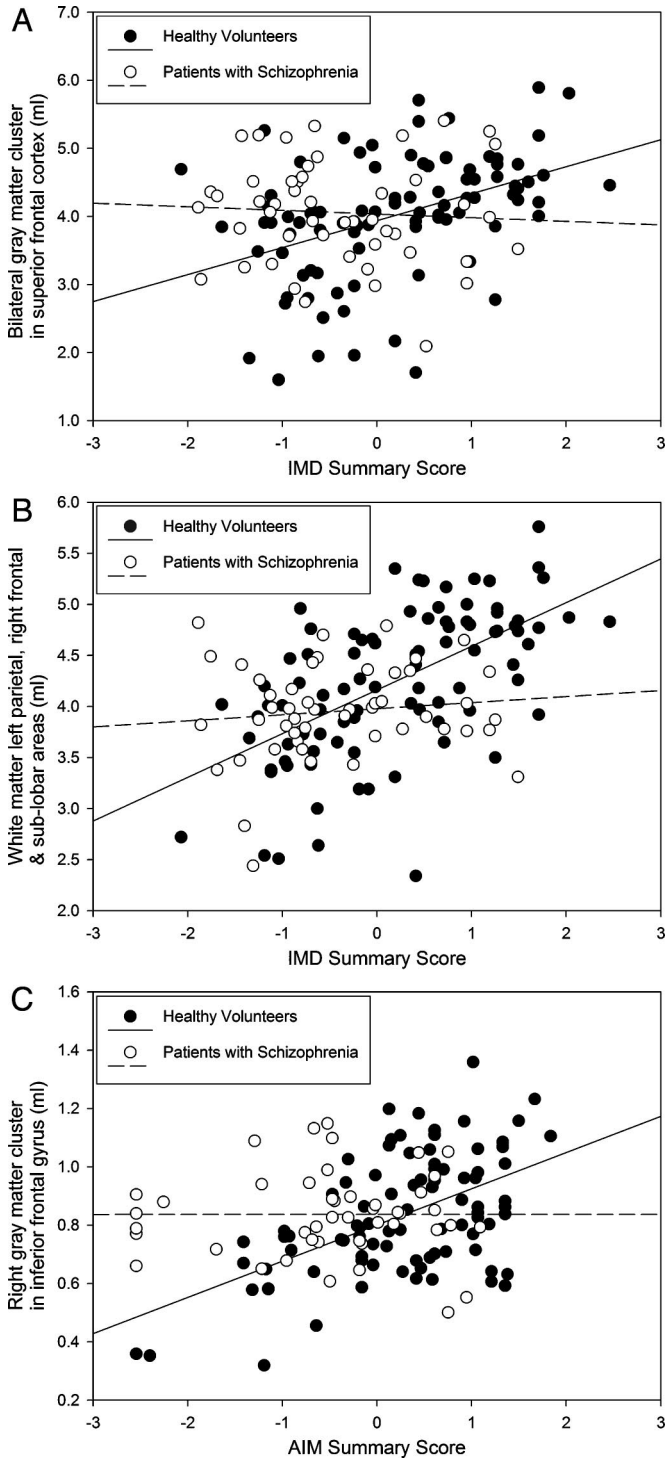

Fig. 2. Associations between IMD or adult executive function and adult brain structure. (*A*) IMD (IMD summary score, *x* axis) predicts gray matter density in bilateral premotor cortex (*y* axis) and (*B*) white matter density in parietal and frontal lobes (*y* axis) and (*C*) adult executive function (AIM summary score, *x* axis) predicts gray matter density in right inferior frontal gyrus (*y* axis) in nonpsychotic subjects (solid line) but not in people with schizophrenia (dashed line).

Executive Function and Adult Gray Matter Volume in Nonpsychotic Subjects. Using computational morphometry, we found a significant positive association between executive function scores and gray

matter density in the following four regions (Fig. 1): (*i*) bilateral medial premotor cortex (BA 6, including the supplementary motor area) and left rostral prefrontal cortex (BA 8) ($r = 0.44$, df = 87, $t = 4.55$, $P < 0.0001$); (*ii*) right inferior and middle frontal gyri (BA 45, 10, and 46) ($r = 0.54$, df = 87, $t = 6.02$, $P < 0.0001$); (*iii*) bilateral medial cerebellum ($r = 0.46$, df = 87, $t = 4.80$, $P < 0.0001$); and (*iv*) right posterolateral cerebellum ($r = 0.42$, df = 87, $t = 4.30$, $P < 0.0001$). In all these regions, better executive performance was associated with increased gray matter density. These results were corroborated by a parametric test of association between AIM score and gray matter volume in a corresponding region of a parcellated template image: the left superior dorsolateral frontal gyrus ($r = 0.223$, df = 91, $P < 0.036$).

Some of the gray matter regions associated with adult executive function were anatomically coincident with regions also associated with IMD (see Fig. 1). More specifically, 50% of the voxels in prefrontal/premotor cortex associated with adult executive function were also associated with IMD; likewise, 48% of the voxels in medial cerebellum associated with executive function were also associated with IMD.

Executive Function and Adult Gray Matter Volume in People with Schizophrenia. Applying the same morphometric methods to data acquired only from people with schizophrenia, we found no regions of significant association between adult executive function scores and gray matter density. To explore more directly the hypothesis that normal associations between brain structure and adult executive function were abnormal in people with schizophrenia, we tested the difference between groups in the strength of association between AIM scores and gray matter density in the four main regions that showed this association in the nonpsychotic group. However, we found no significant associations between AIM score in the schizophrenic group and gray matter volume in superior premotor/prefrontal cortex ($r = 0.20$, df = 43, $t = 1.34$, $P < 0.189$), right inferior frontal gyrus ($r = 0.00$, df = 43, $t = 0.00$, $P < 0.998$), or right posterolateral cerebellum ($r = 0.03$, df = 43, $t = 0.17$, $P < 0.867$). There was a marginally significant association with adult executive function in medial cerebellum ($r = 0.32$, df = 43, $t = 2.18$, $P < 0.035$) (see Table 2).

For each of the gray matter, white matter, and CSF regions which were associated with AIM scores in the nonpsychotic group, we tested formally for a group × AIM interaction: this finding was significant for right inferior frontal gyrus and right posterolateral cerebellum, in both cases reflecting the absence in adults with schizophrenia of the normal association between adult executive function and increased prefrontal or cerebellar gray matter density (Fig. 2*C*; see also Table 4, which is published as supporting information on the PNAS web site, for full ANOVA results on all regions).

Discussion

Normal Continuities between IMD and Adult Brain Structure. We have shown that normal variation in timing of motor developmental milestones in the first year of life is associated with anatomical variation in adult brain motor systems measured by MRI. The earlier the age of learning to stand and walk, the greater were gray matter volumes measured in premotor cortex, caudate nucleus, thalamus, and cerebellum ≈35 years later. This report demonstrates long-term *continuity* between behavioral markers of early postnatal development and adult brain structure in humans.

One explanation of this normative finding is based on the hypothesis that the IMD score reflects (unmeasured) variation in contemporaneous anatomical and functional maturation of motor systems. Thus, children who learned to walk and stand earlier did so because their motor systems matured earlier, presumably reflecting normal variation in genetic, environmental, or other factors acting early in development to favor maturation of integrated motor systems. If we additionally suppose that an initial advantage in constitution of integrated cortico-subcortical motor circuits is somehow sustained, e.g., by the mutually trophic effects of anatomical connectivity between component regions, then we can see how IMD scores could normally be correlated with structural measures of adult motor systems.

The fact that precocious motor development was also associated with increased white matter density in frontal and parietal lobes lends circumstantial support to this mechanistic model based on the sustained, mutually trophic effects of anatomical connectivity between component nodes of motor systems.

Normal Continuities Between Adult Executive Function and Adult Brain Structure. We have also shown that normal variation in adult executive function, measured by the AIM test, was positively correlated with anatomical variation in premotor and prefrontal cortex and in cerebellum. Individuals who performed better on the AIM test tended to have greater gray matter volumes in these regions. There is abundant functional neuroimaging and neuropsychological data implicating prefrontal and premotor cortex in diverse executive functions, and there is increasing evidence also for a role for cerebellum in executive functions (11–13). This association between approximately contemporaneous structural MRI and executive test performance is arguably less novel than the association between adult brain structure and IMD. However, it is notable that some of the regions associated with adult executive test performance, e.g., lateral premotor cortex and medial cerebellum, were also associated with IMD.

The anatomical overlap between systems associated with adult executive function and IMD was incomplete (≈50% in premotor/prefrontal cortex and medial cerebellum). But it might help to explain the behavioral correlation between adult executive function and IMD in nonpsychotic subjects (see also ref. 12). Adult executive test performance apparently depends on anatomical integrity of a set of distributed cortical and cerebellar regions that include some regions also implicated in early development of motor skills (13). An anatomical substrate in common between motor and executive functions might predict that children with relatively delayed motor development should normally grow into adults with relatively poor executive function, particularly because of the putative role of planning and anticipation in the development of coordinated movement in infancy (14, 15). On the other hand, these data suggest that some brain regions, specifically dorsolateral prefrontal cortex, are important for adult executive function but not for IMD. Thus, it seems unlikely that infant motor skills and adult executive function both depend on *exactly* the same frontal-subcortical system. It is arguably more likely that adult executive systems emerge developmentally by integration of additional (prefrontal and lateral cerebellar) regions with a "core" or prototypic, frontal premotor-medial cerebellar circuit that has previously matured in support of early motor skills.

Discontinuities Between IMD, Adult Executive Function, and Adult Brain Structure in Schizophrenia. In the context of these normative results and the explanatory model based upon them, how can we interpret our findings in schizophrenia? Compared with the nonpsychotic subjects, people with schizophrenia had significantly delayed motor development in early childhood (persisting at age 16 years [6]), implying abnormally delayed or deviant maturation of motor systems, presumably due to disadvantageous effects of genetic or other early developmental factors. People with schizophrenia were also distinguished by the absence of normative associations between IMD scores and both premotor cortical gray matter volume and fronto-parietal white matter volumes. This report demonstrates a long-term *discontinuity* between behavioral markers of early development and adult brain structure in a human neurodevelopmental disorder.

Assuming that axonal connectivity is a key neurodevelopmental mechanism underpinning the normative association between IMD

scores and structure of adult motor systems, the lack of long-term association between these measures in people with schizophrenia would imply a developmental failure to establish anatomical connectivity to or from premotor cortex. Furthermore, because premotor cortex is a component of the fronto-cerebellar system that is normally critical for adult executive function (13, 16), early developmental failure to establish premotor connectivity in people with schizophrenia would be consistent with the observed impairment of adult executive test performance.

The general idea that schizophrenia is a delayed consequence of aberrant early brain development is currently orthodox (9, 17). The more specific theory that schizophrenia is associated with impaired early formation of motor systems is supported by evidence from a variety of sources (5, 18–20). Furthermore, a motoric aspect to schizophrenia was included in the earliest descriptions of the disease (21) and is confirmed by the demonstration of extrapyramidal movement disorder in patients at first onset, before taking antipsychotic drugs (7). Likewise, the general idea that schizophrenia is associated with anatomical and functional dysconnectivity of frontal cortex is not new; it originated with the 19th century work of Carl Wernicke and has recently been supported by several distinct but convergent lines of evidence (see refs. 22 and 23 for reviews). The concept of cognitive dysmetria, or abnormalities of cognitive function arising because of abnormal integration of fronto-cerebellar-thalamic circuits in patients with schizophrenia (10, 24–27), is particularly apposite here. The circuits hypothetically implicated by cognitive dysmetria include frontal, striatal, and cerebellar regions, which we show here are abnormally associated with both early motor development and adult executive function in people with schizophrenia.

Methodological and Conceptual Issues. It is an empirical strength that representative samples of both people with schizophrenia and nonpsychotic subjects were drawn from an unselected, general population birth cohort. We systematically ascertained all cases of operationally diagnosed schizophrenia incident in the cohort over the age-range of maximum risk for this disorder and confirmed the lifetime absence of a clinical diagnosis of any psychotic disorder in the nonpsychotic group. These epidemiologically principled aspects of the sample make it more representative than most imaging studies and support generalization of our findings to both the normal population and to the population of patients with schizophrenia. This claim is supported by examination of the limited data available on nonparticipating cohort members: for example, there was no significant difference between participating and nonparticipating subsets of psychotic patients in terms of age at onset of illness (see *Supporting Text*, which is published as supporting information on the PNAS web site, for detail). Sampling from a birth cohort conferred further benefits in terms of developmental assessment. Motor development in the first year of life was measured prospectively, so our estimates of age at learning to walk and stand are unbiased by systematic and random errors of recall over a 30-year period.

Associations between MRI and infant or adult behavioral data were explored by using computational morphometry. This approach to MRI data analysis is increasingly widely used because it allows a comprehensive examination of the whole brain without prior hypothetical constraints; but its results are dependent on accuracy of image registration in standard space. To address this potential concern, we segmented the images in their native space so that the quality of tissue classification could not be biased between groups by differential registration with a prior image of tissue class probabilities. Furthermore, images were registered with a customized template image to minimize registration errors due to different tissue contrast in the template image and sample images. The possibility of artifactual differences arising because of systematic misregistration of data from the patient group was also addressed by corroborating some of our key results at a regional level of anatomical resolution that is likely to be less sensitive to any potential biases introduced by subtle misregistration.

Statistical significance of normative associations between IMD or executive function scores and probabilistic tissue class maps was assessed by using permutation tests on spatially informed voxel-cluster statistics. This nonparametric approach to inference makes few assumptions about the probability distributions of nonclassical test statistics, such as cluster mass, and imparts enhanced statistical power compared with parametric alternatives (28, 29). Inevitably, the smaller size of the patient group will reduce the power to detect significant structure-function associations in people with schizophrenia. However, the data on structure-function associations fully reported in Table 2 indicate that the correlations between brain structure and either IMD or executive function are quite consistently and substantially reduced in the patient group, suggesting that the lack of statistically significant associations in people with schizophrenia cannot easily be accounted for by type 2 error. It is also acknowledged that, in common with most case-control studies of chronic schizophrenia, antipsychotic medication is confounded with diagnostic status (see Table 5, which is published as supporting information on the PNAS web site for details). It is, therefore, conceivable that group differences in structural–behavioral associations could be affected by differential exposure to antipsychotic medication, although this might seem an unlikely explanation for lack of association between adult gray matter structure and motor development scores measured many years before antipsychotic exposure.

Conclusions. Frontal cortico-cerebellar systems that are correlated with adult executive function are anatomically related to systems normally associated with infant motor development. Disruption of this fronto-cortico cerebellar system is a plausible endophenotype that may underlie both developmental and adult cognitive dysmetria in schizophrenia.

Materials and Methods

Birth Cohort. The study sample was drawn from the Northern Finland 1966 Birth Cohort (30). The present study is based on 10,934 individuals living in Finland at the age of 16 years old; for further detail on the birth cohort and sampling procedure see ref. 31 and *Supporting Text*. The Faculty of Medicine Ethics Committee of the University of Oulu approved the current study, for which all participants gave informed, written consent.

Sampling of Nonpsychotic Volunteers. These were randomly selected from cohort members living in the city of Oulu who had no history of psychosis according to the Finnish Hospital Discharge Register. Altogether, 187 nonpsychotic volunteers were invited and 104 (62 men) agreed to participate; IMD, adult executive test scores, and adequate MRI were available on 93 (56 men).

Ascertainment and Sampling of People with Schizophrenia. The Finnish Hospital Discharge Register was used to identify cohort members with schizophrenia incident at age 16 years or older; the diagnosis was then confirmed by chart review applying DSM-III-R criteria. Of 146 people with a history of psychosis, 92 agreed to participate. IMD, adult executive test scores, and MRI were available on 49 (30 male). Most patients (72%) were receiving antipsychotic medication at the time of their participation; for additional details on medication exposure in the patient group see Table 5.

Prospective Assessment of IMD. Age at learning to stand without support and to walk with and without support were recorded during children's visits to welfare centers, supplemented with a special examination at age 1. Missing data on age at learning to walk were imputed as age at time of missing assessment plus one month. The three motor development measures were highly correlated, all

measures loading positively on the first PC. There were no major between-group differences in eigenvector loadings, so data were combined from all participants in a single PCs analysis. The resulting first PC scores were used as summary measures of each subject's IMD.

MRI Data Acquisition. MRI was conducted in 1999–2001 when participants were aged 33–35 years. Structural MRI data were acquired from all participants by using a GE Signa system (General Electric, Milwaukee, WI) operating at 1.5 tesla in Oulu University Hospital, Finland. Dual echo fast spin echo (T2- and proton density-weighted) images of the whole brain were acquired in the coronal plane with slice thickness = 3 mm, repetition time = 4000 ms, and echo time = 24 and 96 ms. MRI data were quality controlled by radiological screening, and the data reported here exclude three scans with poor quality due to subject movement and two scans that showed gross structural lesions (hydrocephalus).

Adult Executive Function Testing. The assessment of executive function was performed on the same day as MRI scanning or, when not possible, within two weeks. The AIM task is a computerized, rule-abstraction/category-learning task that requires subjects to use information to group stimuli in a meaningful way, based on feedback during the test (32). Categorization performance is assessed with and without an explicit working memory component, i.e., all of the objects are presented simultaneously in some trials, whereas in other trials there is a delay of 2.5 seconds between object presentation and response. Immediate and delayed subtest scores were highly correlated over subjects; both measures loaded positively on the first PC. There were no major between-group differences in eigenvector loadings so we combined data from all participants in a single PC analysis and defined the resulting first PC scores as a summary measure of each subject's executive test performance.

MRI Data Analysis. MRI data were segmented and probabilistic maps of gray matter, white matter, and CSF were created for each subject by using BAMM software (http://www-bmu.psychiatry.cam.ac.uk/software) (33, 34). Tissue classification maps were resliced in the axial orientation and coregistered with a customized template image in standard stereotactic space (35) by using an affine transformation and trilinear interpolation implemented in FSL software (http://www.fmrib.ox.ac.uk/fsl) (36). These preprocessing procedures resulted in maps of the density of gray matter, white matter, and CSF at each voxel; density is here defined as the probability that a voxel represents tissue of a particular class, which is also interpretable as the proportional volume of the voxel occupied by a specific tissue class; see *Supporting Text* for preprocessing details.

Associations between IMD (or adult executive function) and adult brain structure were tested primarily by computational morphometry. Voxel-level statistic maps, representing local strength of associations between IMD (or AIM) scores and variation in gray matter, white matter, or CSF maps, were tested for statistical significance by using a nonparametric permutation test of the mass or sum of suprathreshold voxel clusters (29, 37). For whole brain maps, the size of each cluster-wise test was set such that the expected number of false positive tests in each map was <1: for gray and white matter maps, cluster-wise $P < 0.003$. The automated anatomical labeling template image (38) was also used to estimate regional mean gray matter volumes in each of 116 cortical and subcortical structures for each participant, and structure–function associations were secondarily tested at a regional level (see *Supporting Text*).

Gray and white matter and CSF clusters of association with IMD scores, as defined by whole-brain analysis of the nonpsychotic group data, were used as "masks" to estimate volumes of these tissues in the same regions of the patients' data. We then fitted an analysis of covariance model to estimate the main effect of diagnostic group (nonpsychotic subjects versus people with schizophrenia), the effect of IMD PC scores, and the group × IMD interaction on tissue class volumes in the masked regions. The same process was completed independently to assess group differences in the association between adult brain structure and executive function scores.

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1. Thompson PM, Cannon TD, Narr KL, van Erp T, Poutanen VP, Huttunen M, Lonnqvist J, Standertskjold-Nordenstam CG, Kaprio J, Khaledy M, *et al.* (2001) *Nat Neurosci* 4:1253–1258.
2. Wright IC, Sham P, Murray RM, Weinberger DR, Bullmore ET (2002) *NeuroImage* 17:256–271.
3. Johnson MH (2003) *Biol Psychiatry* 54:1312–1316.
4. Jones P, Rodgers B, Murray R, Marmot M (1994) *Lancet* 344:1398–1402.
5. Cannon M, Caspi A, Moffitt TE, Harrington H, Taylor A, Murray RM, Poulton R (2002) *Arch Gen Psychiatry* 59:449–456.
6. Isohanni M, Murray GK, Jokelainen J, Croudace T, Jones PB (2004) *Schizophr Res* 71:213–225.
7. Gervin M, Browne S, Lane A, Clarke M, Waddington JL, Larkin C, O'Callaghan E (1998) *Am J Psychiatry* 155:1202–1206.
8. Gottesman II, Gould TD (2003) *Am J Psychiatry* 160:636–645.
9. Weinberger DR (1987) *Arch Gen Psychiatry* 44:660–669.
10. Andreasen NC, Paradiso S, O'Leary DS (1998) *Schizophr Bull* 24:203–218.
11. Duncan J, Owen AM (2000) *Trends Neurosci* 23:475–483.
12. Murray GK, Veijola J, Moilanen K, Miettunen J, Glahn DC, Cannon TD, Jones PB, Isohanni M (2006) *J Child Psychol Psychiatry* 47:25–29.
13. Diamond A (2000) *Child Dev* 71:44–56.
14. Thelen E (1995) *Am Psychol* 50:79–95.
15. von Hofsten C (2004) *Trends Cogn Sci* 8:266–272.
16. Heyder K, Suchan B, Daum I (2004) *Acta Psychol (Amsterdam)* 115:271–289.
17. Murray RM, Lewis SW (1987) *Br Med J (Clin Res Ed)* 295:681–682.
18. Erlenmeyer-Kimling L, Rock D, Roberts SA, Janal M, Kestenbaum C, Cornblatt B, Adamo UH, Gottesman II (2000) *Am J Psychiatry* 157:1416–1422.
19. Walker EF, Savoie T, Davis D (1994) *Schizophr Bull* 20:441–451.
20. Jones PB, Harvey I, Lewis SW, Toone BK, Van Os J, Williams M, Murray RM (1994) *Psychol Med* 24:995–1011.
21. Kraepelin E (1919) *Manic-Depressive Insanity and Paranoia* (Thoemmes Continuum, Bristol, UK).
22. Bullmore ET, Frangou S, Murray RM (1997) *Schizophr Res* 28:143–156.
23. Jones EG (1997) *Schizophr Bull* 23:483–501.
24. Wiser AK, Andreasen NC, O'Leary DS, Watkins GL, Boles Ponto LL, Hichwa RD (1998) *Neuroreport* 9:1895–1899.
25. Andreasen NC (1999) *Arch Gen Psychiatry* 56:781–787.
26. Andreasen NC, Nopoulos P, O'Leary DS, Miller DD, Wassink T, Flaum M (1999) *Biol Psychiatry* 46:908–920.
27. Andreasen NC, O'Leary DS, Cizadlo T, Arndt S, Rezai K, Ponto LL, Watkins GL, Hichwa RD (1996) *Proc Natl Acad Sci USA* 93:9985–9990.
28. Nichols TE, Holmes AP (2002) *Hum Brain Mapp* 15:1–25.
29. Bullmore ET, Suckling J, Overmeyer S, Rabe-Hesketh S, Taylor E, Brammer MJ (1999) *IEEE Trans Med Imaging* 18:32–42.
30. Rantakallio P (1969) *Acta Paediatr Scand* 193:Suppl 193:1+.
31. Tanskanen P, Veijola JM, Piippo UK, Haapea M, Miettunen JA, Pyhtinen J, Bullmore ET, Jones PB, Isohanni MK (2005) *Schizophr Res* 75:283–294.
32. Glahn DC, Cannon TD, Gur RE, Ragland JD, Gur RC (2000) *Biol Psychiatry* 47:34–42.
33. Brammer MJ, Bullmore ET, Simmons A, Williams SC, Grasby PM, Howard RJ, Woodruff PW, Rabe-Hesketh S (1997) *Magn Reson Imaging* 15:763–770.
34. Suckling J, Sigmundsson T, Greenwood K, Bullmore ET (1999) *Magn Reson Imaging* 17:1065–1076.
35. Talairach J, Tournoux P (1988) Co-planar Stereotaxic Atlas of the Human Brain (Thieme, New York).
36. Jenkinson M, Smith S (2001) *Med Image Anal* 5:143–156.
37. Suckling J, Bullmore E (2004) *Hum Brain Mapp* 22:193–205.
38. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M (2002) *NeuroImage* 15:273–289.