

Childhood Motor Coordination and Adult Schizophrenia Spectrum Disorders

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Objective: The authors examined whether motor coordination difficulties assessed in childhood predict later adult schizophrenia spectrum outcomes.

Method: A standardized childhood neurological examination was administered to a sample of 265 Danish children in 1972, when participants were 10–13 years old. Adult diagnostic information was available for 244 members of the sample. Participants fell into three groups: children whose mothers or fathers had a psychiatric hospital diagnosis of schizophrenia (N=94); children who had at least one parent with a psychiatric record of hospitalization for a nonpsychotic disorder (N=84); and children with no parental records of psychiatric hospitalization (N=66). Psychiatric outcomes of

the offspring were assessed through psychiatric interviews in 1992 when participants were 31–33 years of age, as well as through a scan of national psychiatric registers completed in May 2007.

Results: Children who later developed a schizophrenia spectrum disorder (N=32) displayed significantly higher scores on a scale of coordination deficits compared with those who did not develop a mental illness in this category (N=133).

Conclusions: Results from this study provide further support for the neurodevelopmental hypothesis of schizophrenia and underscore the potential role of cerebellar and/or basal ganglia abnormalities in the etiology and pathophysiology of schizophrenia.

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A substantial amount of research has documented minor neurological abnormalities in people with schizophrenia. Neurological soft signs are frequently cited abnormalities that have been defined as “nonlocalizing neurological abnormalities that cannot be related to impairment of a specific brain region or are not believed to be part of a well-defined neurological syndrome” (1, p. 959). Soft signs commonly observed in adults with schizophrenia include motor incoordination, motor sequencing impairment, sensory integrative dysfunction, and eye movement abnormalities (2–7). Since neurological soft signs are common not only among people with schizophrenia but also among their first-degree relatives, it has been proposed that these signs reflect a genetically transmitted biological marker of risk for the disorder (4, 8–11).

Additionally, a widely cited meta-analysis examining neurocognitive deficits in schizophrenia relative to comparison subjects reported neuromotor abnormalities as the second-largest effect of 22 assessed domains (12). The majority of studies revealing neuromotor dysfunction in schizophrenia are based on examination of individuals with full-blown schizophrenia in adulthood. Studying patients already diagnosed with schizophrenia makes it impossible to determine whether dysfunction precedes schizophrenia or is a byproduct of disease onset or treatment. Although a few studies have uncovered a link between motor abnormalities and schizophrenia among

neuroleptic-naïve individuals (13) and in individuals experiencing their first episode of psychosis (14), studies examining individuals before illness onset provide the most direct evidence for preexisting neurological dysfunction preceding psychosis (8, 10, 15–18).

Motor incoordination stands out as perhaps the most frequently reported category of soft signs in schizophrenia patients as well as in those at risk for the disease (19). Motor coordination deficits have frequently been cited as significant discriminators of the schizophrenia neurodevelopmental diathesis (20, 21) and have been referred to as “the most common childhood neuromotor deviation” (11, p. 68). Similarly, the authors of a comprehensive review of prospective high-risk projects stated that “motor uncoordination was the most common finding differentiating high-risk children from controls in many high-risk studies” (21, p. 251).

However, relatively few prospective studies (8, 15) have specifically examined whether childhood coordination deficits predict the development of schizophrenia spectrum disorders in adulthood. In published prospective studies of neuromotor functioning, the number of individuals who developed a schizophrenia spectrum disorder was exceedingly small. Additionally, the measures of neuromotor deviations have varied and have not always been standardized. Some studies employed composite examination ratings, combining not only multiple motor find-

TABLE 1. Primary Diagnosis by Age, Sex, and Genetic Risk Status in 244 Participants From the Copenhagen Perinatal Cohort^a

Diagnostic Status	Age		Sex (N)		Genetic Risk (N)			Total
	Mean	SD	Male	Female	High Risk	Other Risk	Low Risk	
Schizophrenia spectrum disorders								
Schizophrenia	11.5	0.77	10	8	15	2	1	18
Any psychosis or delusional disorder	11.7	0.83	5	3	4	3	1	8
Schizotypal personality disorder	11.6	0.57	0	4	1	3	0	4
Paranoid personality disorder	11.3	0.61	0	2	2	0	0	2
Total schizophrenia spectrum disorders	11.6	0.73	15	17	22	8	2	32
Other disorders								
Nonpsychotic mood or anxiety disorder	11.7	0.63	12	15	12	11	4	27
Nonpsychotic alcohol/drug abuse	11.9	0.63	23	11	9	17	8	34
Non-spectrum personality disorders	11.6	0.83	6	12	7	6	5	18
Total other disorders	11.8	0.68	41	38	28	34	17	79
No mental illness	11.7	0.64	64	69	44	42	47	133

^a This follow-up sample comprised three groups: children with a parent with a psychiatric hospital diagnosis of schizophrenia (N=94); children with a parent with a record of hospitalization for a nonpsychotic psychiatric disorder (N=84); comparison subjects drawn from the original cohort with no parental records of psychiatric hospitalization (N=66).

ings but also cognitive factors (18). Unfortunately, summing disparate types of examination data into total scores makes it difficult to extract information with neurological localizing significance.

The aim of this study was to investigate motor coordination at ages 10–13 years, as assessed through a thorough neurological examination, and the risk of subsequently developing schizophrenia spectrum disorders. In light of the existing literature, we tested the hypothesis that motor coordination deficits in childhood predict schizophrenia spectrum disorders in adulthood, relative to either a nonpsychotic mental illness or no diagnosis in adulthood.

Method

Participants

Participants were drawn from the Copenhagen Perinatal Cohort, which comprised 9,125 individuals born between September 1, 1959, and December 31, 1961, at Rigshospitalet, in Copenhagen, Denmark (22). To identify high-risk children and comparison subjects, in 1961 the lifetime record of parental psychiatric admissions was checked through the Danish psychiatric record for the parents of the birth cohort. In 1972, 265 children 10–13 years old from this cohort were intensively examined at Psykologisk Institut, Kommunehospitalet (23).

In 1992, when the offspring were 31–33 years of age, their psychiatric status was ascertained. A psychiatrist administered the Structured Clinical Interview for DSM-III-R (24) and the psychosis section of the Present State Examination (25). In addition, Danish psychiatric hospital records for the participants were examined. A detailed coding scheme was used to yield DSM-III-R diagnoses. An additional attempt to ascertain diagnostic status was made through scanning of the Danish Psychiatric Central Registry between 1994 and 2007. Previous research suggests that scanning national registers is a valid method for obtaining psychiatric diagnoses (26). As a function of this process, we identified six additional participants who met ICD-10 criteria for schizophrenia, schizotypy, paranoid psychosis, or delusional disorder and 10 who met criteria for a nonpsychotic disorder. By May 2007, 32 participants were identified who met criteria for a disorder within the schizophrenia spectrum. The use of different diagnostic systems was inevitable given the longitudinal nature of the present study. A number of recent studies use different diagnostic systems interchangeably for the spectrum (27), and research suggests high diagnostic agreement across diagnostic systems for the

spectrum (28) as well as comparable prevalence estimates for the spectrum between diagnostic systems (29). Given these findings, we do not anticipate significant inconsistencies between diagnostic systems used in this study.

On the basis of the interviews and/or hospital records, we obtained adult diagnostic outcomes for 244 of the 265 participants (follow-up rate, 92%). The follow-up rate did not significantly differ by risk status (94/102 high-risk participants; 84/89 other-risk participants; 66/74 low-risk participants). The follow-up sample comprised three groups: children whose mother or father had a psychiatric hospital diagnosis of schizophrenia (N=94); children with a parent with a psychiatric record of hospitalization for a nonpsychotic disorder (N=84); comparison subjects drawn from the original cohort with no parental records of psychiatric hospitalization (N=66). In the original design of the study, an effort was made to match the comparison subjects to the high-risk subjects on the basis of gender, social class, and parents' age (all participants were Caucasian). Although the majority of participants did not change risk status over time, some did so as a result of lifetime parental psychiatric hospitalization records ascertained through scanning of the Danish Psychiatric Central Registry in 2007. Given a shift in the original matching protocol, to assess whether groups were still equivalent based on demographic information, groups were compared on the above-mentioned demographic characteristics. No significant differences between risk groups were found. (Further consideration of this issue is taken into account in a subsequent statistical analysis.) Diagnostic outcome and risk status information are presented in Table 1.

Participants received a complete description of the study and provided written informed consent. All procedures were in accordance with the ethical standards set forth with the committee on human experimentation of the Psykologisk Institut, Kommunehospitalet, and with the Helsinki Declaration of 1975.

The 1972 Neurological Examination

All 265 children were examined between ages 10 and 13 at the Psykologisk Institut in Copenhagen by an experienced child neurologist (N.M.) who was blind to information about the parents' psychiatric status. A detailed description of the 1972 neurological examination has been provided elsewhere (20). In brief, the examination consisted partly of subtests drawn from traditional adult neurological examinations, from subtests known from pediatric neurological examination procedures, and from motor performance tests described in the literature at the time (30). We have previously reported results of tests of minor physical anomalies, ocular alignment, and laterality from the comprehensive battery used in the current study (22, 31, 32). For this study, we were particularly interested in measures of coordina-

TABLE 2. Multinomial Logistic Regression Predicting Adult Diagnostic Outcome in a Study of Childhood Motor Coordination and Adult Schizophrenia

Group and Predictor	Wald χ^2	df	B	Odds Ratio	95% CI
Predictor: coordination only					
Other psychopathology group vs. schizophrenia spectrum group	3.85*	1	−0.06	0.95	0.90–1.00
No mental illness group vs. schizophrenia spectrum group	10.95**	1	−0.09	0.91	0.86–0.96
Predictors: genetic risk and coordination					
Other psychopathology group vs. schizophrenia spectrum group					
Genetic risk	8.75***	1	−1.34	0.26	0.11–0.64
Coordination	2.88*	1	−0.05	0.95	0.90–1.00
No mental illness group vs. schizophrenia spectrum group					
Genetic risk	10.64**	1	−1.41	0.25	0.11–0.57
Coordination	8.82**	1	−0.09	0.92	0.87–0.97

* $p < 0.10$; ** $p < 0.05$; *** $p < 0.01$.

tion, an area with known associations with schizophrenia. A total of 13 coordination tasks were administered in the 1972 assessment. These tasks roughly covered the same areas of motor coordination functioning as described in the review by Boks et al. (3) and are consistent with major neurological batteries (33, 34). Four of these were excluded because of zero variance (left and right finger to nose and left and right heel to knee). The remaining nine tests were considered as measures of coordination: left diadochokinesia, right diadochokinesia, left finger opposition test, right finger opposition test, left speeded finger opposition test, right speeded finger opposition test, right index finger and right foot tap, right and left index finger and right foot tap, and right hand-left hand opens-closes.

Statistical Analyses

The coordination variables were generally scored on a continuum from normal to abnormal. The metric for certain tests varied, so we created a "coordination scale" by individually standardizing and summing the nine coordination measures; higher scores indicate poorer performance. To address rare instances of missing data (13 missing data points from a total of 2,385 possible), within-group mean substitution was employed. The distributional properties of the resulting coordination scale were such that they appeared not likely to violate assumptions of normality in analyses (skewness=1.20, SE=0.16; kurtosis=0.94, SE=0.31), and the internal consistency of the scale was high ($\alpha=0.89$).

The primary analysis was a multinomial logistic regression performed to assess the ability of genetic risk and childhood coordination to predict adult diagnostic outcome. The dependent variable was diagnostic outcome (schizophrenia spectrum disorder, other mental disorder, no mental illness), with genetic risk and coordination serving as independent variables (predictors). To increase power for the primary analysis, genetic risk status was dichotomized into high-risk and non-high-risk. The potential interaction between genetic risk and coordination was also assessed. Participants shifted groups from the original case-control design, and therefore analyses were performed controlling for variables for which the original groups were matched (parental age, marital status, social class, and sex).

Results

Our primary hypothesis was that the coordination scale assessed in childhood would predict those who would later develop schizophrenia spectrum disorders and those who would not. The average coordination scale score was highest for the spectrum disorders group (mean=3.37, SD=8.0), followed by the other psychopathology group (mean=0.38, SD=6.40) and the no mental illness group (mean=−1.03, SD=6.03). Given the importance of genetic

risk factors for developing schizophrenia spectrum disorders, as well as the role of genetic risk in the design of the project, risk status was considered an independent variable in addition to coordination in predicting outcome. As there were only two individuals in the low-risk group who developed a spectrum disorder, the low-risk and other-risk groups were combined. A multinomial logistic regression was conducted to test the ability of genetic risk and the childhood coordination scale to predict adult diagnostic outcome. The overall model was significant ($\chi^2=23.21$, df=4, $p < 0.001$) and yielded a Nagelkerke pseudo $R^2=0.11$. Both the coordination scale and genetic risk status emerged as significant predictors (Table 2). (We also ran the multinomial logistic regression considering all three levels of genetic risk, which yielded similar findings.) We also assessed a possible interaction between coordination and genetic risk and found no significant difference between the model with and without the interaction terms. We were also interested in whether coordination deficits were mediated by genetic risk. No evidence to support a mediational effect was found. To assess for mediation, given that the odds ratio in logistic regression is a measure of effect size (35), we obtained the estimates for the mediation effects by subtracting the coefficients associated with coordination when the logistic model contained both coordination and genetic risk as predictors in the equation, from the coefficient of the model when coordination was the only predictor in the logistic model. Then we obtained the odds ratios of the coefficients of mediation effects by taking the exponent. For both spectrum disorders compared to no mental illness and spectrum disorders compared to other psychopathology, the odds ratios were close to 1, indicating almost no effect size (spectrum versus no mental illness, mediation effects odds ratio=0.99; spectrum versus other psychopathology, mediation effects odds ratio=0.99).

The project was originally designed as a case-control individually matched study of children with a parent with schizophrenia, a parent with a nonpsychotic disorder, and parents with no history of mental illness. Some participants, however, shifted risk groups as parental diagnostic status changed over time (i.e., some parents developed a mental illness after the birth of their child and after the ini-

TABLE 3. Coordination Item Score by Diagnostic Outcome in a Study of Childhood Motor Coordination and Adult Schizophrenia

Test	Schizophrenia Spectrum Group						Other Psychopathology Group					
	Normal		Suggestive		Definitive		Normal		Suggestive		Definitive	
	N	%	N	%	N	%	N	%	N	%	N	%
Diadochokinesia (right) ^a	15	50	13	43	2	7	54	69	21	27	3	4
Diadochokinesia (left) ^a	7	23	13	43	10	33	32	41	28	36	18	23
Finger opposition (right)	19	59	7	22	6	19	48	61	25	32	6	8
Finger opposition (left)	17	53	9	28	6	19	45	57	26	33	8	10
Right index finger and right foot tap	23	72	6	19	3	9	62	79	14	18	3	4
Right and left index finger and right foot tap ^a	13	41	6	19	13	41	42	53	16	20	21	27
Right hand-left hand opens-closes ^a	14	44	16	50	2	6	47	60	29	37	2	3

^a Schizophrenia spectrum and no mental illness groups significantly different ($p < 0.05$).

TABLE 4. Left and Right Speeded Finger Opposition Test Speed (in Seconds) by Outcome Group

Side	Schizophrenia Spectrum Group (N=32)		Other Psychopathology Group (N=79)		No Mental Illness Group (N=133)	
	Mean	SD	Mean	SD	Mean	SD
Left ^{a,b}	17.0	5.6	14.8	4.0	13.8	3.7
Right ^b	16.3	5.5	14.4	3.6	14.3	4.3

^a Schizophrenia spectrum and other psychopathology groups significantly different ($p < 0.05$).

^b Schizophrenia spectrum and no mental illness groups significantly different ($p < 0.05$).

tial risk groups were established). As a result, we conducted a second multinomial logistic regression controlling for variables for which the original groups were matched (sex, maternal age, paternal age, social status, and marital status). None of the controlling variables were significant, and the results for risk and coordination remained consistent with our original analysis.

Individual Coordination Scale Items

To provide a comprehensive view of our findings, Table 3 summarizes how each outcome group scored in terms of categories in which the individual coordination scale items were scored ("normal," "suggestive," and "definitive"). The odds ratios of having a normal versus non-normal score between the spectrum disorders and no mental illness groups are also presented. Table 4 displays results for the two continuously scored coordination variables, left and right speeded finger opposition test.

Discussion

Coordination Scale

Results from this study suggest childhood differences in coordination between those who do and do not develop a schizophrenia spectrum disorder in adulthood. Coordination deficits appeared specific to the spectrum group, as participants who eventually developed a schizophrenia spectrum disorder exhibited significantly poorer premorbid coordination scores compared to those who did not develop a mental illness, and nearly significantly ($p = 0.08$) poorer premorbid coordination than those who developed a nonpsychotic mental illness in adulthood. These results were found while incorporating genetic risk, and they held when controlling for demographic variables. Our primary analyses involved a coordination scale consisting of several individual tests of coordination. The aggregate scale provided increased statistical power to de-

tect differences relative to a single item and yielded an effect size in the high range (Cohen's $d = 0.62$) when comparing the spectrum disorders group to the no mental illness group.

The finding of elevated coordination deficits among those who eventually developed schizophrenia spectrum disorders is consistent with the overall findings in this research domain as well as with the few existing prospective studies. As in the reports of the Israeli High-Risk Survey (36), the Swedish High-Risk Survey (9), and the New York High-Risk Project (10), motor abnormalities detected in infancy and/or childhood were associated with an increased risk of subsequent schizophrenia spectrum disorders. Findings from this current study diverge, however, from a landmark study by Walker et al. (17) in that the differences in motor functioning observed among infants in their study group were not observable beyond age 2. Substantial methodological differences may account for this inconsistency. Walker et al. rated motor function on the basis of the coding of spontaneous behaviors visible on home movies. In contrast, assessment of infant and child coordination in our study involved formal, highly structured, hands-on examinations performed by a pediatric neurologist. We believe that this approach is more likely to detect neurological soft signs.

This study included several other methodological advantages over previous studies, including an assessment of coordination blind to risk group and eventual diagnostic outcome; an analysis of a composite scale as well as of individual items; a familial psychiatric risk comparison group; and a relatively high number of individuals with a schizophrenia spectrum disorder at follow-up through middle age (ages 46–48). The unique methodological advantages we incorporated in this long-term longitudinal prospective study, along with previous studies documenting movement abnormalities beyond infancy (6, 15), to-

No Mental Illness Group						Comparison of Spectrum Disorders and No Mental Illness Groups	
Normal		Suggestive		Definitive			
N	%	N	%	N	%	Odds Ratio	95% CI
99	76	27	21	4	3	3.7	1.6–8.4
56	43	60	46	14	11	2.5	1.0–6.2
92	69	30	23	11	8	1.5	0.7–3.4
90	68	33	25	10	8	1.8	0.8–4.0
111	84	18	14	4	3	2.0	0.8–4.8
69	52	41	31	23	17	2.5	1.1–5.5
84	63	48	36	1	1	2.2	1.0–4.8

gether increase confidence in the conclusion that coordination deficits frequently antedate the diagnosis of schizophrenia spectrum disorders, perhaps by as much as two decades, and are detectable at a variety of developmental stages.

The results of this study clearly suggest direct effects between outcome and coordination and between outcome and genetic risk. The analyses did not support an interaction between genetic risk and coordination or a model whereby coordination deficits are mediated by genetic risk. Although it is important not to overinterpret null findings (especially in light of our imperfect measure of genetic risk), these findings suggest that coordination predicts over and above, and is independent of, genetic risk for schizophrenia. Possible neural and environmental explanations as to how coordination deficits might relay to adult schizophrenia outcome are described below.

Possible Mechanisms

Multiple motor systems, including the corticospinal/pyramidal, supplemental motor, basal ganglionic/extrapyramidal, and cerebellar systems, and their associated networks likely contribute to motor task performance in our coordination battery (37, 38). That being said, motor incoordination is classically attributed to dysfunction of the cerebellum and/or basal ganglia. This neurological understanding, originally derived from clinical-pathological correlations, has been confirmed by functional MRI studies and other strategies (see, for example, references 5, 7, 39, 40). Therefore, we consider it likely that dysfunctions in the cerebellum, basal ganglia, or both play a role in the observed coordination deficits in those who developed a schizophrenia spectrum disorder.

Rather than abnormalities in specific brain structures such as the cerebellum or the basal ganglia, several authors argue that disruptions of specific pathways (fronto-cerebellar dysfunction, striatal pathology) are responsible for neuromotor dysfunction in schizophrenia (19, 41). For example, Mittal et al. (40) suggest that, similar to minor physical anomalies, movement dysfunction potentially reflects subcortical brain dysfunction resulting from prenatal insults. This conclusion appears compatible with our own results, documenting coordination deficits well before symptom onset. Thus, it seems reasonable that both positions are true. That is, individuals with schizo-

phrenia may exhibit both intrinsic dysfunction and neuroanatomical atypicality of the cerebellum and/or basal ganglia and disruption of the patterns of connectivity through which the cerebellum and perhaps the basal ganglia exert modifying effects on motor output. Regardless of the precise mechanisms and timing, the findings from this study implicate neural substrate involvement (structural, pathways, or both) in schizophrenia, early in the course of illness, prior to the emergence of psychotic symptoms.

Given the likely role of the cerebellum and other related circuits in coordination deficits, our findings might be viewed in the context of Andreasen and colleagues' unitary model of "dysmetria" (42). Andreasen et al. suggest that dysfunction in the cerebellum and cortico-cerebellar-thalamo-cortical circuits might be a unifying explanation for diverse motor, cognitive, and psychiatric symptoms of the illness. Recent studies suggest that cerebellar dysfunction might underlie some of the core features of the disease (e.g., cognitive abnormalities) (43), and our findings provide further evidence that such cerebellar dysfunction precedes illness onset. Andreasen et al. suggest that the presence of coordination deficits indicates underlying abnormalities in basic cognitive processes (e.g., perception, associations) that could lead to misinterpretation of external and internal stimuli. Misinterpretation might account for schizophrenia symptoms, ultimately taking the form of psychotic processes (e.g., hallucinations, delusions, thought disorder, and negative symptoms).

Previous studies from this project have reported other neurodevelopmental markers and precursors to schizophrenia spectrum disorders that provide additional information about regions of possible disruption as well as timing of possible insults (e.g., increased minor physical anomalies, ocular disalignment, and atypical laterality) (22, 31, 32). These findings, together with those from this study, support the presence of dysfunction of the cortico-cerebellar-thalamo-cortical circuit and perhaps other neural networks and processes (e.g., hemispheric asymmetry) early in life (possibly originating in the first and second trimesters of gestation), well before the onset of more downstream hallmark symptoms (i.e., delusions and hallucinations). However, additional studies are needed to pinpoint the specific regions or pathways, as well as the timing of disruption and developmental processes, that

are responsible for the diverse symptomatic manifestations of schizophrenia, using more advanced techniques over time (43).

From a diathesis-stress perspective (emphasizing environmental stress), research suggests that poor coordination is associated with a number of social, academic, and emotional consequences (44). Additionally, there is evidence to support detrimental effects of coordination abnormalities over time (45). Beyond the neurodevelopmental implications of our findings discussed above, it is reasonable to speculate that poor coordination in childhood engenders at least some taxing psychosocial encounters that may contribute to stress within a diathesis-stress framework. It is also reasonable to speculate that these stressful events further exacerbate preexisting coordination deficits as well as neurological vulnerabilities, resulting in a self-sustaining, iterative, and perhaps progressively detrimental process between coordination and stress.

This study suffers from some notable limitations. Despite a relatively large number of individuals who developed a schizophrenia spectrum disorder, the total number of people in this group limited the statistical power for some analyses. This is particularly true of the number of individuals who developed a spectrum disorder who were not in the high-risk group, and it might also have contributed to the finding of only a trend-level difference between the schizophrenia spectrum disorders group and other psychopathology group. Another concern, shared by all research on high-risk groups, is the issue of generalizability to those individuals who develop a spectrum disorder but who do not have a parent with schizophrenia. It is likely, however, that genetic influences play a role in most cases of schizophrenia, even if the parents fail to manifest the disorder phenotypically (46). Finally, only one neurologist performed the neurological examinations, preventing an evaluation of interrater reliability. The neurologist was, however, highly trained and was functioning under strict research procedures and conditions.

Despite these limitations, given the strengths and uniqueness of this study, the findings advance the understanding of the development of schizophrenia in several ways. Detecting coordination deficits prospectively adds considerable support to the notion that coordination dysfunction precedes schizophrenia and may be a meaningful expression of an underlying biomarker. Applying what is known about the mechanisms of coordination deficits to the etiology of schizophrenia offers possible clues to how early neural deficits mediate the development of the disorder.

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