Possible Basal Ganglia Pathology in Children With Complex Symptoms

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Background: Clinical observation of children presenting with a myriad of motor, behavioral, emotional, and sensorial symptoms who do not respond to treatment led to the hypothesis that these children may constitute a unique population, perhaps even a new clinical entity. The literature on child and adolescent psychopathology does not specifically address the phenomenological, diagnostic, and etiological factors that make these children unique. For this reason, a preliminary study was conducted to identify additional symptoms and features that make these children different.

Method: Data were collected in 2001 on 7 children with complex symptomatology using the Behavior Assessment System for Children, the Anxiety Disorders Interview Schedule for DSM-IV, and a neurological illnesses and symptoms questionnaire designed by the authors.

Results: On average, these children met full DSM-IV criteria for 1 to 5 diagnoses. The most prevalent diagnoses were attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, oppositional defiant disorder, and pervasive developmental disorder. These children also exhibited a high incidence of sensory hyperarousal, aggressiveness, hypersexuality, and neuroethological behaviors. Almost all of the children also had indications of a history of bacterial or viral infection.

Conclusion: The specific symptoms identified and the biological factors found in many of the children seem to suggest basal ganglia involvement.

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Basal ganglia have previously been thought to be responsible solely for motor activity and regulation. However, more recently, modern conceptualization and the current literature suggest that the basal ganglia may be related to a wider, more complex array of behaviors. This new relationship is postulated to occur both within the basal ganglia and via cerebral-neural interconnections with neighboring structures.[1] Thus, many diverse motor, behavioral, emotional, and sensorial symptoms have been linked to basal ganglia pathology.

The basal ganglia are a cluster of nuclei arranged in the telencephalic structure. These nuclei constitute an anatomical-biochemical system comprising the caudate nucleus, putamen, globus pallidus, substantia nigra, and subthalamus. These structures are surrounded by a multitude of neural connections operating closely with the thalamus, subthalamic nucleus (diencephalon), substantia nigra (zona reticularis, zona compacta), frontal lobes, amygdala, and the olfactory region.[2,3] These neural connections are modifiable[4] and may participate in a neurodevelopmental model of obsessive-compulsive disorder (OCD).[5] Three major neurotransmitters, dopamine, serotonin, and γ-aminobutyric acid (GABA), seem to control basal ganglia input/output messages.[6–8]

Phylogenetically, the basal ganglia are the oldest brain structure. In birds, fish, and amphibious animals, where the cerebral cortex is poorly developed, the basal ganglia encompasses practically the entire brain and performs most essential functions, with limited participation of the olfactory brain. The basal ganglia therefore regulate many animal behaviors and have been implicated in animal displacement behaviors in humans.[9] Such animal displacement behaviors, including grooming behavior, compulsive sniffing, prolonged staring, and compulsive grunting, have been observed in psychiatrically ill children.[10]

One important basal ganglia function is the inhibition of muscle tone throughout the body. The caudate nucleus and putamen (the striate body) initiate and regulate gross intentional movements. The globus pallidus provides background muscle tone for intended movements by preparing the position of the body. The basal ganglia transmit impulses through the substantia nigra, by way of the thalamus, to the cerebral cortex, and finally to

downward pathways in the spinal cord. Overall, the connections of the basal ganglia to the rest of the brain allow it to integrate motor activity.[2] Finally, the loss of motor inhibition permits the presence of involuntary movements and stereotypes. Therefore, a range of hyperactive to akinetic motor behavior may be observed in processes affecting basal ganglia pathology.

Several recent articles show motor and emotional symptoms associated with basal ganglia pathology in adults and children alike.[10,11,12] These symptoms are often expressed as OCD,[13] attention-deficit/hyperactivity disorder (ADHD),[14] Gilles de la Tourette's disorder,[15,16] extrapyramidal disorders,[17–19] disruptive behavior disorders, and oppositional defiant disorder (ODD).[20] These disorders may result from a combination of faulty neurobehavioral developments found at different stages of growth, affecting the basal ganglia as a pivotal factor.

The clinical observation of multiple symptoms in some children, many of which seem related to basal ganglia pathology, led the researchers to investigate whether the symptoms in these children represent a new manifestation of basal ganglia pathology, not yet defined. The similarity of some of their symptoms to displacement behaviors in animals (e.g., sniffing, prolonged staring, smelling, and grooming), the complexity of their symptoms, and the difficulty encountered in treating these children made them seem different from other children. Consequently, in this preliminary article, we further investigated basal ganglia involvement in symptom expression.

METHOD

Participants

Seven children from the patient population of Bio-Behavioral Institute (Great Neck, N.Y.) were included in the study. Six (86%) of the children were male. Six (86%) of the children were white and 1 was half white and half Asian. The children ranged from 7 to 16 years of age, with a mean age of 10.5 years. The children were all enrolled in school, with grades ranging from 2nd to 11th grade. Six of the children were in special education programs. Five of the children lived with both parents, while 2 lived with only their mothers but had regular contact with their fathers. Six of the children had only 1 sibling, while 1 child had 3 siblings. Four of the children (57%) were adopted. This study was approved by the internal institutional review board of Bio-Behavioral Institute.

Sample Selection

Initially, clinicians at the Bio-Behavioral Institute referred children to the study who presented with multiple symptoms and represented significant treatment challenges. The study was explained to the children and their parents and informed consent was obtained from the children's parents. From these children, the current sample was derived using several selection criteria. First, in order to include children with only severe symptoms, a t score of 70 or higher was required on the Behavioral Symptoms Index of the Behavior Assessment System for Children (BASC) Parent Rating Scale,[21] indicating a clinically significant overall level of maladaptive behavior. Second, 2 of the 3 other composite scores had to be at least in the "at risk" range, indicating maladaptive behavior in more than one area. Therefore, all of the children in the sample were rated by their parents as having severe difficulties in multiple areas of functioning, as represented by externalizing, internalizing, and/or adaptive behavior problems. All children also had to exhibit these problems in multiple domains and settings including school, home, and/or social domains.

The third selection criterion was the inclusion of children who had not responded to both previous psychiatric and psychological treatment interventions and therefore were initially thought to be treatment refractory. Treatment resistance was operationalized by at least 3 or more medication trials that did not result in successful management of the children's symptoms, as well as at least 1 trial of psychological treatment. Simply put, these children represented the most difficult and complex cases at the Institute during the time of the study (2001).

Measures

Behavior Assessment System for Children. The BASC is a comprehensive behavioral assessment tool that assesses a child's current behavior using multiple methodologies and informers. The BASC interview schedule is a semistructured interview that targets comprehensive biodata information. The BASC also contains several paper-and-pencil questionnaires that assess multiple behavioral domains. The BASC Parent Rating Scale is available in child and adolescent forms consisting of 138 and 126 items, respectively. Parents rate statements on a 4-point Likert scale from Never to Almost Always. The Parent Rating Scale generates 12 behavioral scales and 4 composite scales including externalizing, internalizing, adaptive scales, and an overall Behavioral Symptom Index. t Scores of 60–69 indicate "at-risk" behavior, while t scores of 70 and above indicate clinically significant behavior.

Anxiety Disorders Interview Schedule for DSM-IV. The Anxiety Disorders Interview Schedule for DSM-IV (ADIS)[22] is a semistructured interview that is organized diagnostically according to DSM-IV classifications. The ADIS includes modules for assessing all DSM-IV anxiety disorders, as well as mood and externalizing disorders, and also includes screening sections for other disorders found in childhood and adolescence. The ADIS consists of a Parent and Child version.

Neurological Illnesses and Symptoms Questionnaire. The Neurological Illnesses and Symptoms Questionnaire is a paper-and-pencil questionnaire devised by the authors

Table 1. DSM-IV Disorders in 7 Children With Complex Symptomatology[a]

Subject	ADHD	OCD	ODD	PDD	Anxiety Disorders	Mood Disorders	Tourette's Disorder	Total (Cl + SCl)
1	SCl	SCl	SCl				Cl	4
2	Cl	Cl	Cl	Cl	Cl	SCl		6
3	Cl	SCl	Cl		Cl			4
4	Cl	SCl	Cl		Cl	Cl		5
5	Cl	SCl	SCl		Cl	Cl		5
6	Cl	Cl		Cl	SCl	SCl		5
7	SCl	Cl		Cl	SCl		Cl	5
Total (Cl/SCl)	5/2	3/4	3/2	3/0	4/2	2/2	2/0	

[a]Cl indicates that the subject meets DSM-IV criteria for the diagnosis; SCl indicates that the subject exhibits some functionally impairing symptoms but does not meet full diagnostic criteria.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, Cl = clinical, OCD = obsessive, OCD = obsessive-compulsive disorder, ODD = oppositional defiant disorder, PDD = pervasive developmental disorder, SCl = subclinical.

to assess the presence of several specific neurological and infectious diseases as well as several behaviors that are not usually assessed for in typical psychological or psychiatric evaluations. Parents were asked whether their child was ever diagnosed with certain illnesses or conditions and whether they observed certain behavioral symptoms on a regular basis. Parents were also asked whether their child displayed hypersensitivity of any of the 5 senses. Parents were then interviewed about their responses to this questionnaire to gain a fuller description of the symptoms. (See Appendix 1 for questionnaire.)

Procedure

In-depth information about each child was collected using a combination of multiple methodologies including semistructured interviews with both a psychiatrist and a psychologist and multiple paper-and-pencil questionnaires. Demographic data were collected along with comprehensive information about the children's current and past psychiatric symptoms and medical history, as well as psychosocial information. Information was obtained from parents, pediatricians, and hospital records when available.

Extensive background information was collected on each child. Each child's parents met with a psychiatrist who completed the BASC history form with them in order to gain a complete developmental and medical history in a semistructured manner. Parents also completed the Neurological Illnesses and Symptoms questionnaire, as well as the BASC Parent Rating Scale. The children also completed the BASC self-report questionnaire appropriate to their age category. Lastly, the ADIS was administered by a trained psychologist to both the parents and the children.

RESULTS

Due to the small sample size of the study, statistical analyses were not computed. However, the investigators observed a high degree of comorbid symptomatology, neuroethological behaviors, sensorial hypersensitivity, and neurologic/infectious history that was clinically significant. These descriptive findings suggest possible important clinical implications.

The first observation was that these children displayed multiple symptomatology including both emotional and motor disturbances, as assessed by the ADIS. Overall, these children exhibited multiple symptoms from at least 4 different diagnostic categories. (Table 1). Externalizing symptoms were most prevalent, with all 7 children exhibiting some degree of attention deficit, and 5 of the children meeting diagnostic criteria for ADHD. All 7 children also exhibited symptoms of OCD, with 3 meeting diagnostic criteria for the disorder. Three of the children met criteria for ODD, with 2 others exhibiting subclinical symptoms. Three of the children met diagnostic criteria for pervasive developmental disorder (PDD), and 2 children were diagnosed with Tourette's disorder. Four of the children met diagnostic criteria for an anxiety disorder (either generalized anxiety disorder, social phobia, specific phobia, or separation anxiety), while 2 exhibited subclinical anxiety symptoms. Four children also exhibited mood symptoms, with 2 meeting diagnostic criteria for dysthymia and 2 displaying subclinical symptoms. Another frequent general symptom that was reported was a high degree of impulsive aggression and anger. Six of the children exhibited some level of explosive uncontrollable anger, including frequent rage attacks and outbursts of physical aggressiveness such as punching, kicking, and throwing of objects. All of the children therefore exhibited some sort of emotional disturbance as characterized by anger, anxiety, or dysthymia, while at the same time exhibiting motor disturbances such as hyperactivity, impulsivity, compulsions, and/or tics.

In addition to the unusually high incidence of these disorders and the high level of comorbidity, the ages at onset for these children were very young as well. All 7 children began to display some symptoms by the age of 4 years. By the age of 6, all of the children had met full diagnostic criteria for at least 1 disorder, with most exhibiting more than 1 disorder (see Table 1).

A second finding was that these children exhibited an array of neuroethological symptoms such as stereotypical

Table 2. Neuroethological Behaviors in 7 Children With Complex Symptomatology

Subject	Nose Picking	Skin Picking	Hair Pulling	Sniffing	Hoarding	Motor Tics	Verbal Tics	Staring	Sex[a]	Anger	Encopresis
1				✓		✓	✓		✓	✓	
2	✓	✓					✓	✓	✓	✓	
3	✓			✓	✓			✓	✓	✓	
4										✓	
5	✓				✓	✓				✓	✓
6						✓			✓		
7		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

[a]Inappropriate sexual behavior.

grooming and regressive behaviors (Table 2). Four (57%) of the children engaged in grooming behaviors including nose picking; skin, scab, and scalp picking; and hair pulling. Regressive behaviors were also reported in 4 children (57%). These behaviors included making sniffing and grunting noises, compulsive sucking and chewing on clothing and other objects, sniffing their own body parts such as their fingers and hands, or sniffing other people's body parts such as their heads and genital areas. Two of the children were encopretic, and 1 was enuretic. Hoarding behavior was reported in 3 (43%) of the children. Four (57%) of the children had involuntary motor tics. An additional neuroethological symptom was the routine staring at objects or body parts (43%).

The third finding was inappropriate sexual behavior, which was reported in 5 (71%) of the 7 children. Abnormal and inappropriate sexual behaviors included compulsive masturbation, preoccupation with sexual material, excessive use of sexually explicit language, repetitive exposing of their genitals, sexual drawings, and repetitive attempts to touch the genitals or anus of others.

A fourth finding of interest was the extremely high incidence of sensorial sensitivity or hyperarousal. Six (86%) of the 7 children had hypersensitivity of at least 1 of the 5 senses. Of the 6 children with reported hypersensitivity, 2 had hypersensitivity of 4 senses, 2 had hypersensitivity of 3 senses, and 2 had hypersensitivy of only 1 sense. All 6 children with hyperarousal were hypersensitive to sound. This included being highly attuned to soft noises such as whispers, becoming distressed at repetitive sounds, or having difficulty tolerating loud sounds or noisy areas. When in the presence of such noises, these children typically attempted to avoid the sounds by either leaving the situation, placing their hands over their ears, or becoming irritable. Three children were hypersensitive to light in that they avoided looking directly at lights and avoided bright lights. Three children were hypersensitive to touch, with particular sensitivity to and avoidance of textures such as stickiness. Two children were hypersensitive to smell, and 2 to taste, with the hypersensitivity often manifesting as fussiness in eating and food-related behaviors.

Lastly, there was an unusually high incidence of neurologic or infectious disease history among this sample. All but 1 of the children had some history of neurologic or infectious symptoms. While none of the children had a documented history of clinical encephalitis, 2 children reported incidences of extremely high fever over 104°F (40°C) as an infant or toddler that could be interpreted as subclinical encephalitis. Five (71%) of the 7 children had a history of severe repeated streptococci. One of these children also had a history of meningitis and atrophy of the brain, as assessed by a computed tomography scan. Another child had a history of seizures, high fevers, and heterotropia, which resulted in an abnormal magnetic resonance imaging (MRI) and electroencephalogram findings. Only 1 child reported no significant medical history. Thus, overall, 6 (86%) of 7 children had some indicator in their medical history of possible neurologic difficulties or infectious disease.

DISCUSSION

The results describe a group of children exhibiting multiple complex emotional, motor, behavioral, and neuroethological symptoms, along with hypersexuality and sensorial hyperarousal. These findings may be linked to the high incidence of neurologic or infectious disease history found within this population.

Complex behaviors have been postulated to be a result of nervous system development, acquisition of behaviors, and adaptation of these behaviors to the environment.[23] Our patients manifested complex symptoms representing 5 major disorders (ADHD, OCD, ODD, PDD, and Tourette's disorder) with accompanying excessive behavioral, motoric, and sensorial activity. The children presented with a cluster of complex behaviors including anxiety with increased attention (hypervigilance), aggressiveness, neuroethological compulsive behavior, stereotypy, hypersexuality, and sensorial hyperarousal. These behaviors may be a result of a maladaptive integration and expansion of behavior beyond acceptable limits[23] as well as an awakening of dormant symptomatology,[24] all combined in a grafted neurodevelopmental model like the one proposed for OCD.[4] Furthermore, this process may have its roots in basal ganglia pathology.

The presence of both anxiety and stereotypy may be explained in terms of an attention framework during wakefulness[25] in which anxiety is a representation of motor agitation and increased attention (hypervigilance) and in which stereotypy is conceptualized as a triggered increase in motor activity. The reappearance of stereotypy in anxious children, and even in adults, may produce feedback of pleasure, as described for self-stimulatory behavior,[26] a theory that raised controversy.[27] Aggressive behavior was also highly concomitant with this cluster of symptoms. This finding corroborates previous reports[20] in which disruptive behavior disorders are highly comorbid with ADHD and ODD. Furthermore, aggressiveness complicates therapeutic outcome due to this comorbidity.

Neuroethological compulsive behavior has been characterized by grooming, staring, and sniffing and is a reemergence of rhythmical behavior developed during infancy[28] and is associated with an ethological perspective.[29] In addition, these patterns express a maturational process, as children develop a cephalo-caudal motor control[30] similar to the one observed in Tourette's disorder. However, in our patient population, neuroethological compulsive behavior may represent a release phenomenon that is a return to more primitive or less integrated levels of neurologic function.[31]

Deviant sexuality characterized by sexual verbalization, masturbation, and genital touching, along with excessive aggressiveness, is similar to behaviors found in groups of patients diagnosed with encephalitis.[32] Because our sample presented a possible history of infections, deviant sexuality may be considered of anamnestic importance.

The degree of sensorial hyperarousal in our patients was clinically significant considering the small sample size. Sensorial changes have been reported in OCD with Tourette's disorder,[33] consistent with bodily and mental sensations (usually tactile, musculoskeletal/visceral, or both). A relation between hypervigilance and hyperarousal may explain increased sensorial awareness as a protective mechanism.

How can we isolate specific conditions presented in such an intermingled manner? As research expands its scope due to technological advances, it becomes more difficult to isolate factors with special and definite functions of a given disorder to the exclusion of others. This statement may explain the merging of symptoms related to several conditions participating in the nosology of our patients.

Several questions arise as a result of our findings and the aforementioned theories. Why do movements that are normal during certain neurodevelopmental stages return as pathological symptoms? As pointed out long ago, the timing, smoothness, and integration at one age foretell behavior at a later age.[34] Movements and emotions are adaptive behaviors constituting part of the communication process during the growing stage. The return of these behaviors expressed as symptoms indicates neurodevelopmental regression in our patients. Overall, neurobehavioral growth undergoes 5 field differentiations: adaptive behavior, gross motor behavior, fine motor behavior, language behavior, and personal behavior. This network moves gradually toward maturity, following 8 key ages from week 4 to 36 months. During this time period, any noxa affecting usual progression of development will alter, temporarily or chronically, normal growth. In our patients, the presence of complex behavior is manifested by an expansion of the behaviors[23] as a reactive mechanism to help the patient avoid the damage caused by the disorder.

We propose that these symptoms express a return of functions normally no longer required. Of note, basal ganglia functions in lower mammalian and avian categories, such as hoarding, grooming, washing, plucking, biting, and phototropism, do not disappear and remain part of their daily activities. In humans, some of these activities may become part of the basal ganglia pathology, manifesting a return to primitive functioning and establishing inappropriate mechanisms of defense and survival. Parkinson's disease, the choreas, tics, hemiballismus, Gilles de la Tourette's disorder, and the catatonias[15,17,19,35] represent well-documented emotional pathology manifested in the sensory and motor system.

The inhibitory function served by the basal ganglia may be suppressed by infectious noxa, which causes exacerbation or reemergence of excitatory behavior. Thus, extinguished or stunted neurologic development may reappear in the form of hyperexcitatory behaviors such as hyperactivity, inattention, anxiety, aggression, tics, hypersexuality, and sensorial hyperarousal. These symptoms are similar to the clinical symptoms of encephalitis, whether as a consequence of an acute or subclinical phase, as described in the literature of the 1920s.[36,37] More recently, cases of pediatric autoimmune neuropsychiatric disorders associated with streptococcus have similarly traced the origin of certain cases of OCD and Tourette's symptoms to infectious origin.[38]

Limitations

While we have reported several cases with a possible infectious noxa etiology affecting behavioral, motoric, and sensorial activity, the lack of corroborative etiological evidence represents a major caveat to reach conclusions. Are these symptoms truly the outcome of an infectious noxa located in the basal ganglia region? Further research should investigate the existence of a conclusive infectious entity as well as documentation of basal ganglia involvement or deterioration by such means as MRI, positron emission tomography, electromyogram, etc. Furthermore, it is unclear whether basal ganglia pathology alone is responsible for the observed symptoms

within our sample. Other structures such as the cerebellum, which also plays a role in motor activity and psychopathology,[39] may be involved due to the neural interconnectivity within the brain. Thus, future research should also focus on the role of other structures.

Another major caveat of the study is the pilot nature of the data. Larger sample sizes and parametric statistics are needed to further test these hypotheses.

Clinical Implications

On the basis of the current findings, one may hypothesize that these children may represent a unique manifestation of a constellation of psychiatric symptoms. The complexity of their symptom presentation raises the question of whether these children have multiple comorbid diagnoses or are exhibiting a yet unidentified distinct overarching diagnosis that subsumes the current diagnostic nomenclature. Further research is needed to assess the existence of such an overarching diagnosis.

The current findings also suggest clinical implication with regard to assessment and prognosis. In cases that present with complex symptomatology, assessments should be expanded to include a detailed medical history with specific attention to infectious symptoms known to have neurologic or behavioral implications such as streptococcus. Additionally, symptoms such as hypersexuality and sensorial hypersensitivity, while not a specific diagnostic criterion in any one disorder, should be assessed. Existence of these factors may be indicative of basal ganglia pathology and may inform about treatment prognosis and open up a new avenue of research.

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Appendix 1. Neurological Illnesses and Symptoms Questionnaire

Please check off all emotional/psychological issues your child either exhibits currently or has exhibited in the past.
Please provide details on the lines below.

- ❑ Has staring rituals
- ❑ Stares at lights
- ❑ Makes grunting noise
- ❑ Has sudden anger attacks
- ❑ Avoids sweet/salty foods
- ❑ Has enuresis (bed wetting)
- ❑ Has blinking tics
- ❑ Has encopresis (defecation retention)
- ❑ Picks nose excessively
- ❑ Sniffs fingers/hands
- ❑ Is bothered by sticky substances
- ❑ Has involuntary movements (tics)
- ❑ Hoards possessions
- ❑ Hypersensitivity to touch
- ❑ Hypersensitivity to light
- ❑ Engages in self-injurious behaviors (cutting arms/legs, etc.)
- ❑ Other Please explain in further details on the lines below.
- ❑ Stares at others' heads
- ❑ Makes sniffing noises
- ❑ Displays inappropriate sexual behaviors
- ❑ Has excessive concern with symmetry
- ❑ Avoids foods due to texture
- ❑ Makes snorting noises
- ❑ Touches others' heads
- ❑ Masturbates compulsively
- ❑ Hair pulling
- ❑ Picks skin/scabs/scalp
- ❑ Needs to tap/touch or rub things
- ❑ Makes inappropriate sexual comments
- ❑ Hypersensitivity to smell
- ❑ Hypersensitivity to taste
- ❑ Hypersensitivity to sound

_____

_____

_____

Please check off any medical conditions that your child has been diagnosed with in the past. Please provide details on the lines below.

Encephalitis	❑ Yes	❑ No	Age? _____	
Meningitis	❑ Yes	❑ No	Age? _____	
Streptococci	❑ Yes	❑ No	Age? _____	
Seizures	❑ Yes	❑ No	Age? _____	
Brain trauma	❑ Yes	❑ No	Age? _____	
Brain atrophy	❑ Yes	❑ No	Age? _____	
Brain tumors	❑ Yes	❑ No	Age? _____	
Vascular hemorrhages	❑ Yes	❑ No	Age? _____	
Rheumatic fever	❑ Yes	❑ No	Age? _____	
Chorea	❑ Yes	❑ No	Age? _____	
Motor tics	❑ Yes	❑ No	Age? _____	
Verbal tics	❑ Yes	❑ No	Age? _____	
Heterotopia	❑ Yes	❑ No	Age? _____	
Demylination	❑ Yes	❑ No	Age? _____	
Myoclonus	❑ Yes	❑ No	Age? _____	
Hemiballismus	❑ Yes	❑ No	Age? _____	
Abnormal EEG	❑ Yes	❑ No	❑ Never had an EEG	Age? _____
Abnormal MRI	❑ Yes	❑ No	❑ Never had an MRI	Age? _____

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