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ESSENCE: Early recognition of autism and related disorders – can it improve outcomes?

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- University of Glasgow and University of Edinburgh, and Yorkhill Hospital (Scotland)
- Institute of Child Health, University College London, and Young Epilepsy (England)
- Diferenças, Lisboa (Portugal)
- Genetic Biobank, Torshavn (Faroe Islands, Denmark)
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ESSENCE (neurodevelopmental/psychiatric disorders)

• ESSENCE - Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations

- ADHD with or without ODD/CD (Oppositional Defiant Disorder/Conduct Disorder) 5-7%
 - SLI (Language disorder including antecedents of dyslexia) 5%
 - DCD (Developmental Coordination Disorder) 5%
 - IDD (Intellectual Disability/Intellectual Developmental Disorder) 2%
 - ASD (Autism Spectrum Disorder) with or without regression 1.2% (20% regression)
 - TD/TS/OCD (Tic disorders/Tourette syndrome/OCD) 1%
 - RAD (Reactive Attachment Disorder/Disinhibited Social Engagement Disorder) 0.5-1.5%
 - (BIF (Borderline Intellectual Functioning) 10%)
 - (BPS (Behavioural Phenotype Syndromes, including FAS and VAS) 2%)
 - (EP/NEUROMUSC (Epilepsy syndromes and other neurological/neuromuscular disorders (HC, CP, Sturge-Weber, Duchenne, myotonic dystrophy, neurometabolic): Landau-Kleffner Syndrome, CSWS, FS+, FS? 0.6%)
 - (PANS (Pediatric Acute-onset Neuropsychiatric Syndrome)? 0.1%)
- Predictors of *academic failure*, other school adjustment problems, social exclusion, *substance use*, psychiatric disorder, eating disorders including obesity, accidents *empathy problems*, antisocial lifestyle and *criminality* later in life, persistent autistic features “only”, early death through accidents, criminality, substance abuse and physical health problems



What are the “symptoms” of ESSENCE?

- **Major childhood onset** symptoms either **lasting more than 6 months** or of extremely **abrupt onset** from one or more of the following domains are the markers of developmental disorder/ESSENCE; the **symptoms lead to concern** and **“specialist” consultation**
 - General development – delayed mental development
 - Motor coordination – delayed gross or fine motor development
 - Perception/Sensory – hyper- or hyposensitive to sensory stimuli
 - Communication/Language – delayed speech, few or no gestures
 - Activity/Impulsivity – too active or too passive
 - Attention – inattention, not listening, “not hearing”, distracted
 - Social interaction/Reciprocity – little interest in (most) adults, children, play
 - Behaviour including stereotypic, insistence on sameness, tics, and OCD
 - Mood swings/emotional dysregulation – inability to control temper
 - Sleep – disrupted sleep-wake cycle, sleep onset problems, night waking problems
 - Feeding – food fads, selective or consistent food refusal
- Gillberg 2010, revised Gillberg 2013, Hatakenaka et al 2016, Mina et al 2017



ASD: The Autisms

- *The autisms* are a group of multifactorially determined conditions, that **ALWAYS coexist with other developmental/neurological problems in cases with early impairment (SLI, DCD, ADHD, IDD, tics, “OCD”, epilepsy, other medical disorders), and there are almost as many causes as there are cases.** Cases with no comorbidity at all are not recognized or impairing early in life, or may be acknowledged as “loners”, “nerds”, “weirdos”, “geniuses”. **The prevalence of the phenotype is not increasing!** Synapse and clock genes play a major role in cases with impairment, but environmental factors (prematurity, fetal drug and toxin exposure, infections, trauma, vitamin D deficiency?) contribute to or are associated with the clinical presentation in many cases and can themselves cause autism in some instances. Abnormalities/variations of default network and decreased connectivity (?) almost universal finding. Impaired social facial perception in large subgroup, related to specific brain areas. Arousal and sleep problems important in subgroup. **No sharp boundary between ASD and autistic traits or between autistic traits and “normality”.** **You do not grow out of it, but impairment may increase or decrease and is usually, at least partly, an “effect” of comorbidities.** **No good evidence that base rate of autism symptoms has increased in the population, but diagnosis has gone through the roof (heavily overdiagnosed in some parts of the world), fewer and fewer symptoms required for diagnosis**

– Iacoboni 2006, Buckner and Vincent 2007, Bourgeron 2007, Monk et al 2009, Gillberg 2010, Dinnstein et al 2010, Coleman and Gillberg 2012, Lundström et al 2012, Leblond et al 2012, Delorme et al 2013, Kocovska et al 2013, Zürcher et al 2013, Lundström and Gillberg 2014, Toro et al 2014, Lundström et al 2015; Posserud et al 2016, Arvidsson et al 2017



ADHD

- ***The ADHDs*** are a group of multifactorially determined conditions, that almost **ALWAYS coexist with other developmental problems in cases with early impairment (SLI, DCD, ASD, IDD, tics, “OCD”, epilepsy, other medical disorders), and there are probably almost as many causes as there are cases.** Cases with no comorbidity at all are usually not recognized or impairing early in life, or may be acknowledged as “hyper”, “early walkers”, “never listening”, “emotionally labile”. ***The prevalence of the phenotype is not increasing!*** Dopamine and glutamate genes possibly play a major role in cases with impairment, but environmental factors (prematurity, asphyxia, fetal drug and toxin exposure, infections, trauma, vitamin D deficiency?) contribute to or are associated with the clinical presentation in many cases and can themselves cause ADHD in some instances. Abnormalities/variations of default network, reward system and brain volume (slightly reduced) in certain areas almost universal finding. Arousal and sleep problems important in large subgroup. Real-life executive dysfunction almost universal (not necessarily “validated” on tests). Inattention (and possibly impulsivity) core features of all with poor outcome, hyperactivity not. ***No sharp boundary between ADHD and “ADHD features” or such features and “normality”. You do not grow out of it, but impairment may increase or decrease and is often, at least partly, an “effect” of comorbidities. 20-80% of adults with SUD, GAD, psychosis, bipolar disorder, personality disorder or criminality have ADHD or met criteria for ADHD when younger. Highly treatable at all ages***

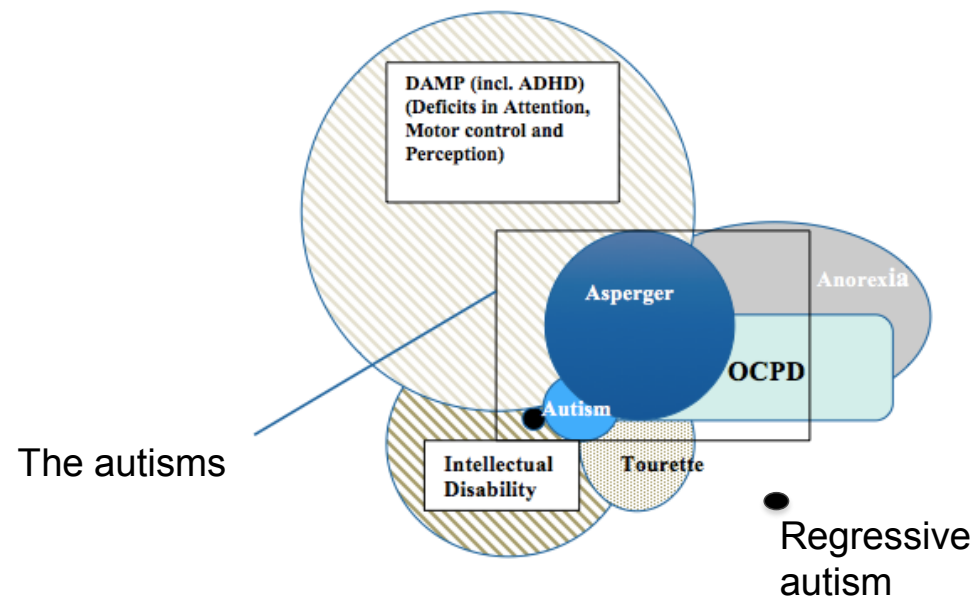
– Gillberg 2013



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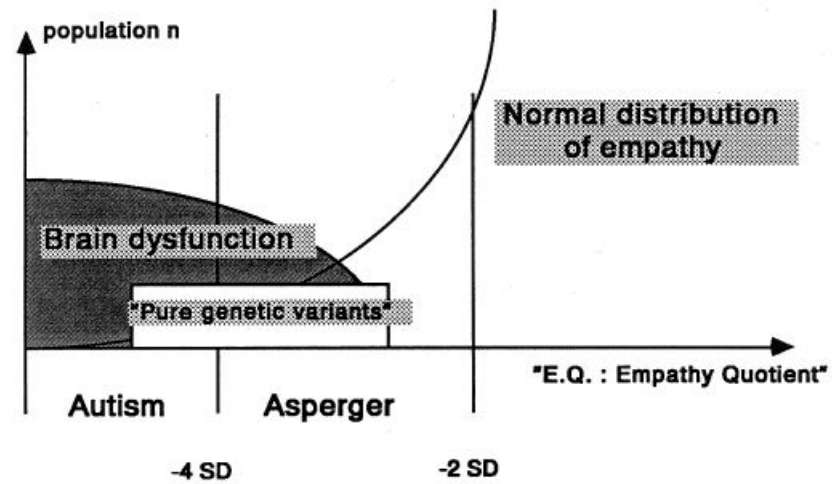




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Early symptoms of ASD (<5 years)

- **Motor** control problems first year of life (“serious” face, relatively little smiling (but social smile can be elicited), strange movements from back to front, compartmentalised motor development, limpness, partial hypotonia) 50-100%
- Sensory-**perceptual** abnormalities/unusual preferences in 90-100%
- **Behaviour** problems (including insistence on sameness) in 90-100%
- **Repetitive** movements in 80-100%
- **Language** problems/pragmatic problems/strange voice in 90-100%
- **No/little reaction to own name 30-100%**
- **No or limited initiation of joint attention (=> major social interaction problems), no pointing to attract attention 80-100%**
- **Hyperactivity** and impulsivity (often extreme) in 40-50%
- Hypoactivity in 10-25%
- **Sleep** problems in 40%
- Food fads and other **feeding** problems in 50%
- **Delayed** general development in 20%
- Major **mood** swings in 10%
- **One or several of the above could be presenting complaint**
 - Coleman and Gillberg 2012, Allely et al 2013, Höglund-Carlsson et al 2013, Barnevik-Olsson et al 2013, 2014, Hatakenaka et al 2016, Höglund-Carlsson et al 2016



How many people are affected by ESSENCE?

- **At least 10% of school age children** are or have been affected by “neuropsychiatric/neurodevelopmental disorders” (**ESSENCE**) (12% of boys, 8% of girls) - including ADHD, ASD, TS, CD, DCD, IDD – half this group “discovered” by age 6 years; **many more than half this group will have persistent problems in adult life**
- **Overlap/”Comorbidity”/Co-existence is the rule**; almost never “one problem only”
- When looking back: **vast majority had symptoms <5 years**
- **Girls usually are not recognized until adolescence/adult age (and usually as non-ESSENCE)**
- **Half or (many?) more of all “chronic” adult psychiatric patients have had ESSENCE?**

Gillberg 1983, Nylander et al 2009, Gillberg 2010, Kopp et al 2010, Gillberg 2013

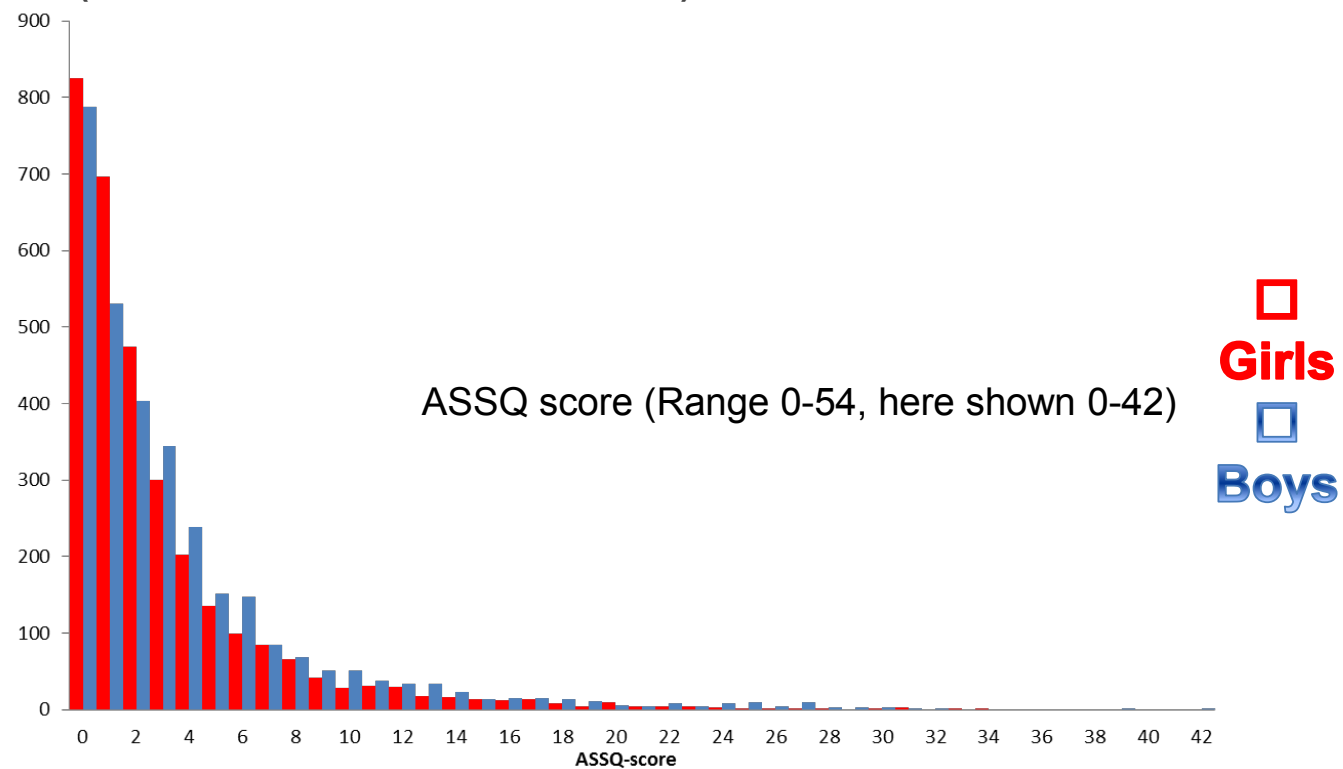


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PARENT REPORTS ON AUTISM SYMPTOMS (ASSQ) IN 6200 CHILDREN AGED 7-9 YEARS DATA FROM (LARGE GENERAL POPULATION) BERGEN CHILD STUDY





Autism

- **Once (Kanner 1943, Rutter 1994), autism was considered a discrete disorder – the best and most clearly delineated in child psychiatry, also the most severe**
- **Gillberg (1983) found autistic traits to be very common in ADHD with DCD and found ASD in 0.7% of 7-year-olds in the mid 1970s**
- **Wing and Gillberg in the 1980s proposed a continuum/spectrum of autism**
- **Coleman and Gillberg proposed several different autism spectra (later “many different varieties of autisms”) in the 1980s**
- **Gillberg (1991 and 1992) proposed that autism was on a spectrum with normally distributed empathy skills and that some variants even of the “disorder” could be considered mild, others moderate, yet others severe**
- **Gillberg (2010) proposed that autism is “hundreds of spectra” and a subgroup of ESSENCE**
- **Some (=marked) scorn because of this proposition**
- **Gillberg proposed Autism Plus as a clinically meaningful category (2013)**
- **Regressive autism something completely different? – neuroinflammation?**
 - Kanner 1943, Gillberg 1983, Coleman and Gillberg 1985, Wing 1979, Gillberg 1983, Gillberg 1992, Rutter 1994, Gillberg 2010, Coleman and Gillberg 2012, Gillberg and Fernell 2014, Gillberg et al 2017



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Autism

- **L v Beethoven**
- **A Bruckner**
- **B Bartok**
- **E Satie**
- **HC Andersen**
- **S Kierkegaard**
- **A Conan Doyle**
- **I Kant**
- **L Wittgenstein**
- **A Einstein**
- **A Robbe-Grillet**
- **W Kandinskij**
- **P Klee**
- **E Hopper**
- **G Garbo**
- **A Warhol**
- **D Springfield**
- **S Kubrick**
- **S Boyle**
- **“ALL THE LONELY PEOPLE – WHERE DO THEY ALL COME FROM”**
 - Gillberg 1992, Baron-Cohen 2003, Fitzgerald 2005, Wing 2011



From preschool to school and into adult life: what predicts what in autism?

- In virtually all studies of the outcome of autism, **language** disorder/problems/delay and low **IQ** predict poor outcome
- **Medical disorders**, including **epilepsy**, predict poor outcome
- **ADHD/EF** dysfunction in ASD predicts poor outcome
- Persistent NVLD in ASD predicts poor outcome
- Intervention may or may not predict the very long-term outcome, the jury is out, but we know it helps to do something (diagnosis + info) in the early years as regards intermediate-term outcomes; can early diagnosis prevent schizophrenia?
- *But autism preschool or school “load” in itself does not predict long-term outcome, maybe later persistence does, adolescent load does though*
- *SO IT IS AUTISM PLUS THAT MATTERS IN EARLY LIFE*
- *REGRESSIVE AUTISM ALWAYS MATTERS – neuroinflammation?*

– Gillberg and Steffenburg 1987, Billstedt et al 2007, Cededrlund et al 2008, Fernell et al 2011, Eriksson et al 2013, Hagberg et al 2013, Helles et al 2014, 2016, Gillberg et al 2016, Thompson et al 2017



Girls and women

- **IT IS LIKELY THAT ADOLESCENT AND ADULT FEMALES (AND SOME MALES) WHO HAVE HAD ASD AND/OR OTHER ESSENCE ALL THEIR LIVES ARE OFTEN MISDIAGNOSED AS SUFFERING FROM (ONLY):**

DEPRESSION (OFTEN IN ASD OR DCD, SOMETIMES IN ADHD)

EATING DISORDER (ASD COMMON IN AN, ADHD IN BULIMIA AND OBESITY)

ANXIETY (CATASTROPHIC CONFUSION IN ASD, GAD IN ADHD)

BORDERLINE/OTHER PERSONALITY DISORDER/SELF-HARM

OPPOSITIONAL DEFIANT BEHAVIOURS

NOT SO FEW REFERRED TO SOCIAL SERVICES

– Kopp et al 2010, Gillberg et al 2017



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Girls and women may have a different ASD/ESSENCE phenotype or different associated “symptoms” or “traits” or “personality styles”

- Females are biologically less aggressive, less violent, less insistent on sameness as compared with males
- Females are also not as obviously motorically active as males
- Females generally show more social interest and are more talkative than men
- **HOWEVER INDIVIDUAL VARIATION IS ENORMOUS, AND ALL THE DIFFERENCES OUTLINED ARE AT A GROUP LEVEL**



Schizophrenia and autism: some Swedish studies

- 30-year-olds with schizophrenia have a prior history of (usually undiagnosed) autism/Asperger syndrome in about half the cases (even higher among those with paranoid disorders)
- 30-year-olds with an early diagnosis of autism/Asperger syndrome do not meet criteria (and have never met criteria for schizophrenia)
- Both schizophrenia and autism are at about 1% prevalence rates in the population
- So how can early diagnosed autism not lead to schizophrenia in about half the cases when half of all cases with schizophrenia have a background history of autism?
- **Could the answer be that early autism diagnosis means stress reduction throughout adolescence and early adult life, and this protects from the development of schizophrenia?**
 - Lugnegård et al 2011, Unenge Hallerbäck et al 2012, Helles et al 2016



How should we proceed if we suspect ESSENCE?

- **Observation** inside and outside clinic (if at all possible)
- Parent (and teacher) **questionnaires** plus follow-up interview – e.g. FTF (Five To Fifteen) or TTF (Two To Five), ATAC, SDQ, SNAP, ASSQ, most of these can probably be used for adults retrospectively
- **Parent interview** by doctor/psychologist
- **Medical/neurologic/psychiatric examination of child**
- **Hearing, vision, height, weight, head circumference, MPA screen including FASD screen**, genetic discussion, screening for thyroid and metabolic disorders, EEG sometimes (more often than currently), more if needed
- ***Assessment of intellectual functioning/neuropsychological/speech and language strengths and weaknesses***
 - Kadesjö et al 2004, Hansson et al 2005, Coleman and Gillberg 2012, Miniscalco et al 2013, Gillberg 2013, Marinopoulou et al 2016



How should we plan for best intervention in clinics and research ASD PLUS, i.e. Autism with comorbidity (and ESSENCE more generally)?

- We need to recognize **all** the problems as early as possible - **not just “the autism”, “the ADHD”, “the DCD”, “the Tourette syndrome”, “the IDD”, “the SLI”** and **all** interventions **must** be **individually** tailored **THROUGHOUT THE LIFESPAN**
- Parent “training” and education plan perhaps most important of all (“understanding the condition”), but parent ESSENCE problem needs to be taken into account (!)
- ADHD – whether or not combined with ASD, tic disorders, epilepsy or IDD - is **usually** responsive to treatment (meds and computer/cognitive training, possibly small effect of Omega-3)
- DCD is **usually** responsive to focused motor training regardless of comorbidity
- Epilepsy (possibly including “subclinical”), when present, **should** be treated as a top priority in all ESSENCE
- **Schizophrenia might be prevented by stress reduction through early autism diagnosis**
- Sleep disorders **sometimes** responsive to melatonin or dose adjustment of other meds
- Violent behaviours/SIB **can** be responsive to low-dose neuroleptics or mood stabilizers
- Do **not** treat tics per se unless extreme
- Do **not** treat autism per se with meds (Bumetanide? Oxytocin?)
- **Psychoeducation, communication enhancement, ESSENCE-friendly environment (“understanding the condition”), school and work place “adjustment”, and behavioural approaches - sometimes only possible with medication - first and foremost throughout life**



ASD and ESSENCE preliminary conclusions

- ***ESSENCE (not autism per se) is an extreme risk factor*** for adolescent/adult social exclusion, academic failure, other school adjustment problems, problems in the work-place antisocial personality disorder (and depression/anxiety, drug abuse, and criminality) – and for “non-handicapping” autistic traits?
- We still know VERY little about early intervention
- ***The OVERFOCUS on ASD ONLY in young children is possibly a big mistake; but AUTISM PLUS HAS HUGE IMPLICATIONS, SO HAS REGRESSIVE AUTISM and PANS***
- For some ESSENCE we can screen and intervene early
- All advanced societies need to increase/spread knowledge about ESSENCE, including ADHD and IDD, **not just ASD**
- In research following children over time ***all aspects of ESSENCE need to be taken into account – with screeners such as ESSENCE-Q, A-TAC or TTF***



Final conclusions: What we need to think about when setting up clinical and research routines

- **ASD is but one of a group of ESSENCE that overlap genetically, symptomatically and as regards brain dysfunction/variation, environmental factors also play a role, but it is unclear how much of the variance they account for**
- **AUTISM PLUS (i.e. with comorbidity) is a severe disorder, AUTISM ONLY?**
- ASD persists into adult life (as do most other ESSENCE), re-assessments needed
- ADHD is common (c. 5%), ASD is relatively common (c. 1%)
- Other psychiatric disorders/problems/academic failure emerge or become “diagnosable” over time – these are the diagnoses that adult psychiatrists will make
- **Autism *in itself* has *different* outcome, not necessarily poor, current focus on autism *only* in screening, assessment and intervention programs a big mistake**
- **IDD has “poor” outcome, ADHD probably has worse outcome (including obesity, pain syndrome, substance use, MCI?) than ASD “in itself”, SLI may also have partly “poor outcome”**
- **Regressive autism, Landau Kleffner, CSWS,, FASD, and PANS need to better assessed and worked up, better researched as regards neuroinflammation, perhaps even FS+**
- **Girls still usually missed or misdiagnosed**



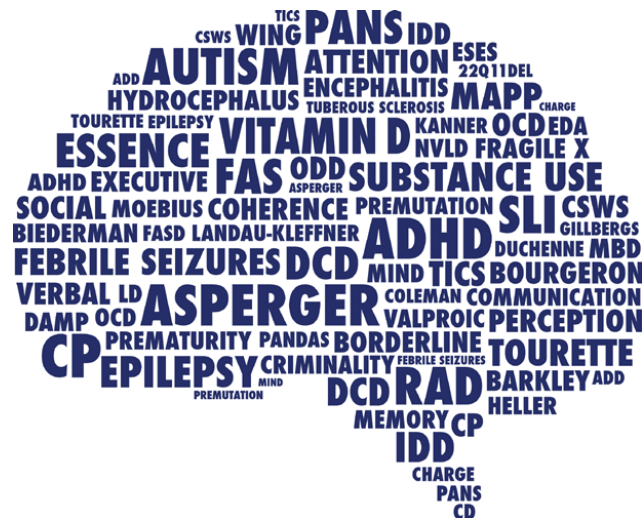
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