Epilepsy and psychiatry in children and adolescents
Childhood epilepsy, psychiatry, and “ESSENCE”

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– London, November 2015, Mind The Gap
Childhood epilepsy linked to a wide range of psychiatric disorders/academic failure/”ESSENCE”

- ADHD
- ASD
- IDD/BIF
- Academic difficulties/educational underachievement
- DCD
- Depression
- Anxiety
- EDA
- OCD
- Intermittent explosive disorder?
- Psychosis in small proportion
ESSENCE - Early Symptomatic Syndromes Eliciting Neuropsychiatric/Neurodevelopmental Clinical Examinations
– are predictors of behavioural, psychiatric, physical, and academic problems throughout life

• Syndromes/disorders in the ESSENCE group
  – ADHD (Attention-Deficit/Hyperactivity Disorder Spectrum) with or without ODD/CD (Oppositional Defiant Disorder/Conduct Disorder)
  – ASD (or the “Autisms” incl Asperger Syndrome, around in spite of the DSM-5!)
  – DCD (Developmental Coordination Disorder)
  – TS (Tic Spectrum Disorders including Tourette Syndrome)
  – BD (Bipolar Spectrum Disorder)
  – SLI/LI (“Specific” Language Impairment/Disorder), never specific?
  – IDD/MR (Intellectual Disability or Intellectual Developmental Disorder/Mental Retardation)
  – Selective mutism
  – “Non-accepted” categories such as NVLD (Non-Verbal Learning Disability), Working Memory Disorder, Slow Processing Disorder, EDA (“Pathological Demand Avoidance”)
  – (BIF (Borderline Intellectual Functioning))
  – (BPS (Behavioural Phenotype Syndromes), incl FRAX, TS, PMS, FAS, VAS)
  – (Epilepsy and other “Neurological” Syndromes: Landau-Kleffner Syndrome, CSWS, CP, hydrocephalus, FS+)
  – (Some cases of PANS?)
ESSENCE - where do we find the cases?

- Major symptoms - usually lasting >6 months - from one or more (usually several) of the following domains before age 4-5 years are the markers of ESSENCE (or extremely acute onset)
  - General development (pediatrics, GP)
  - Motor control/Perception-Sensory (OT, pediatrics, GP, neurology)
  - Communication/Language (SLT, CAMHS, pediatrics, neurology)
  - Activity/Impulsivity (pediatrics, CAMHS, )
  - Attention (audiology, ENT, CAMHS, neurology, psychology)
  - Social interaction/Reciprocity (pediatrics, CAMHS, autism centres)
  - Behaviour (CAMHS, pediatrics)
  - Mood swings (CAMHS)
  - Sleep (pediatrics, GP)
  - Feeding (pediatrics, GP, CAMHS)
  - Seizures (A&E, pediatrics, GP, neurology, occasionally CAMHS)

(plus NEWBORN UNITS, CHILD HEALTH VISITING, WELL-BABY-CLINICS, PRE-SCHOOLS, SCHOOLS, AND SOCIAL WORK)

Gillberg 2010
ESSENCE - signal symptom (language)

• **Example: delayed language at 2.5 years**
  – Screen takes no more than 5 minutes
  – About 3-6% of all children screen positive and have “confirmed” language delay at 2.5 years
  – **Screen positive and confirmed language delay at 2.5 years => 70% have “neuropsychiatric/neurodevelopmental” diagnosis (with clinical impairment) at age 7 years (ADHD, ASD, LD, DCD), virtually all have remaining speech-language problems**
  – i.e. all children with “SLI”/LI at 2.5 years need to be followed carefully and vast majority will need services
ESSENCE - another signal (autism)

- **Example: suspected ASD under age 3 years**
  - 28 children followed for several years from under age 3 years with suspected ASD: 75% met criteria for autistic disorder at age 6 years, and remainder had other neuropsychiatric diagnosis (other ASD, ADHD, LD)
    - Gillberg et al 1990
  - 208 children with ASD diagnosis made by clinicians at age 0-4 years: 52% met criteria for autistic disorder at follow-up, 39% met criteria for other ASD, 9% had other neuropsychiatric diagnosis (ADHD, LD) - prevalence of ASD in this age group 0.6%
    - Fernell et al 2009
  - **ASD diagnosis around age 2-4 years highly stable in 90% of cases, virtually no “over-diagnosis”, many Asperger cases missed**
  - **Epilepsy is present in about 8-20% of the young clinically impaired cases of ASD but will eventually develop in 25-50%**
The autisms

- One per cent or a bit more of the general population of children
- Half or more recognized in children under 6 years of age
- Main presenting symptoms: motor-perceptual-sensory, attention (does not seem to listen), activity, learning, sleep, social, and language (maybe even in that developmental order), sometimes with epilepsy
- Maybe not very severe “in itself”; maybe only ASD+ (as in ASD+epilepsy, ASD+ADHD, ASD+IDD) very severe?
Autisms or ASD

- ASD is a dyad, not a triad (the dyad of social communication impairment and extreme repetitive behaviours)
- ASD is not one spectrum but many
- High rates of autistic traits in the general population (several per cent), majority not clinically impaired
- DSM-5 has seven symptoms in two domains
- In the new manual, maybe only autistic disorder and Gillberg’s Asperger syndrome will meet the new criteria, many PDDNOS will possibly “disappear”
Autisms and epilepsies

• 45% of individuals with classic autism have or have had epilepsy by age 45 years, much lower rates, but still considerably raised, in other forms of ASD
• 8-20% have had their first seizure before school age
• 43-78% of individuals with autism have epileptogenic discharge in their EEG during sleep, much of this is midfrontal or right temporal
• Those with LKS and ESES have very high rates of autistic behaviour and ADHD
• Tuberous sclerosis, MR, autism and epilepsy a consistent triad (with ADHD!)
• According to one study children with autism have midtemporal (and midfrontal in most cases) SPECT-verified reduction in cerebral blood flow – both those with and those without epilepsy
ADHD as an example of ESSENCE

- ADHD occurs in 2-8% (5%) of all school age children according to studies performed in more than 20 different countries, probably half recognized/should be recognized <6 years
- Severe variants are at a rate of at least 1.5-3% of the general population or a little under half of all cases meeting diagnostic criteria for the disorder; these are the ones most likely to be recognized in very young children
### ADHD and underrated comorbidities

<table>
<thead>
<tr>
<th>Comorbidity Description</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any significant comorbidity</strong></td>
<td>85-100%</td>
</tr>
<tr>
<td><strong>One comorbidity</strong> (e.g. DCD)</td>
<td>85-100%</td>
</tr>
<tr>
<td><strong>Two comorbidities</strong> (e.g. DCD, ASD)</td>
<td>65-70%</td>
</tr>
<tr>
<td><strong>Three comorbidities</strong> (e.g. ODD, TS, BD)</td>
<td>35-50%</td>
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<tr>
<td><strong>Epilepsy</strong> as a comorbidity</td>
<td>5-7%?</td>
</tr>
<tr>
<td><strong>Febrile seizures</strong> in ADHD</td>
<td>15-25%?</td>
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</tbody>
</table>
Autisms, ADHD and epilepsies: genetic factors

- Neuroligin, neurexin, SHANK-1, -2 and -3 and glutamate genes in ASD (some overlap with ADHD); neurexin linked to autism and epilepsy?
- DRD-3 gene affected in ASD (stereotyped behaviours) and ADHD (and in certain forms of absence epilepsy in rats)
- DRD-4 and DAT-genes affected in children (and DRD-5 in adults) with ADHD
- DRD-5 gene affected in adults with ADHD
- Noradrenaline-and dopamine-related genes in both ASD/ADHD/epilepsy with psychiatric complications from levetiracetam
- SNAP25 affected in children and adults with ADHD, in ASD with hyperactivity (and in mice with epilepsy)
- Melatonin-genes (related to sleep problems?) in ASD and ADHD (and possibly epilepsy)
- SCN1A, 15q13.3, 16p13.11, and 15q11.2 in epilepsy/ASD/ADHD, other “new” genes in autism/epilepsy
- Serotonin receptor genes in ADHD
Autisms and ADHD: environmental risks/associated factors

- Prematurity
- Alcohol
- Thalidomide
- Valproic acid
- TORCH-virus-group
- Environmental toxins
- Vitamin D
  - Coleman and Gillberg 2012, Gillberg 2013, Omoy et al 2015
ASD and ADHD: genetics and epigenetics

• Different synapse and clock genes interact in the “protection against” autism and ADHD. Variant/mutant synapse/synapse scaffolding genes lead to impaired neural networks with poor connectivity – particularly portions of the default mode network? - that underpin ASD symptomatology (and ADHD? and epilepsy in some cases). Variant/mutant clock genes (melatonin) disrupt sleep and circadian/seasonal rhythms and affect ASD and ADHD symptomatology. Vitamin D regulates the function of 300+ neurodevelopmental genes
CSWS and “unspecific epileptiform discharge” in ASD and ADHD

• Clearly linked to psychiatric disorder
• Probably linked to autistic behaviours, possibly ADHD, and other cognitive dysfunctions
• **CSWS disrupts and deactivates the default network**
• 61% of 889 patients with ASD without seizures had epileptiform activity during sleep, most often in the medial temporal lobe, which is part of the default network; half of valproic-acid-treated group had normalized/much improved EEG-findings (n=176)
• 16% of 180 children with ADHD had epileptiform discharges of whom some had had epilepsy in the past and others developed epilepsy over the years
ADHD, the autisms, DCD and antisocial development

• When ADHD is associated with DCD (and no ODD) there is small risk of antisocial development but considerable risk of autistic traits, language problems and academic failure, depression, and anxiety

• ADHD without DCD (usually with ODD) a marker for possible antisocial problems?

• EDA/PDA and its association with epilepsy
Autisms: risk for extreme behaviour

• ASD usually means that there will be an “unusual” life

• A few have such extreme behaviours as to present to other people as “extreme”, “eccentrics”, and “maniacs”, often with evidence of “dangerous tantrums”, occasionally related to epilepsy

• Small number commit heinous crimes (shoot-outs, Molotov cocktails, religious) (However, Asperger’s own cases had no increase in criminal convictions)
  
Behavioural phenotype syndromes

- 0.6-1.3% of general population of children
- All potentially recognizable before age 6 years
- 80% have IDD (but many, e.g. 22q11 and FRAX, quite often no IDD)
- Main presenting symptoms: empathy problems, impulsivity, general development delayed, motor-perceptual-sensory, feeding, physical, stigmata, attention, activity, social, “ASD”, learning, and language, sometimes epilepsy as onset symptom
- Most, but not all have a large minority-majority with epilepsy, and many of these have autism, ADHD and DCD
- In many of these syndromes, the default network is dysfunctional
The Scandinavian perspective: is there one?

- A few centres of excellence around epilepsy in the Nordic countries, almost all specifically linked to epilepsy surgery or to difficult-to-treat-epilepsy
- Oslo, Gothenburg, Stockholm, Helsinki, Copenhagen, and a few small centres
- Helsinki and Oslo now appear to be those with the best developed service, but still no “epidemiological perspective”
- The CNC and the “Child Neuro Area” at Queen Silvia’s Hospital has a broad neuropsychiatric perspective involving pediatricians, neurologists, psychiatrists, psychologists, speech therapists, education specialists, neurophysiologists, and physiotherapists working as a group, but not really “one team”
ESSENCE and epilepsy: conclusions

- Look for ESSENCE “everywhere”, every patient with epilepsy that you see for anything more longlasting than infections etc, think “Could be ESSENCE, other psychiatric problems or academic underachievement, and I need to know”
- Child psychiatrists, paediatricians, health visitors, well-baby staff, pre-school and school teachers and social workers need to be “upgraded”
- ASD, ADHD, TS, bipolar disorder, LD, SLI, DCD, EDA, selective mutism, depression, anxiety etc. overlap throughout life (and often not separable <5 years)
- All children presenting with major and impairing ESSENCE symptoms need to be followed up, most will need some intervention, many will have epilepsy or develop epilepsy with time
- Even though refined diagnosis is needed in all cases, at early stages ESSENCE may be the only “safe” label, and then gradually you can begin to disentangle the web
- There are very effective treatments for many ESSENCE (including meds, cognitive and physical training, not to mention psychoeducation)
ESSENCE: conclusions

- The default network and “decreased connectivity” could be the target network and mechanism for most of the child neuropsychiatric disorders that are also associated with epilepsy.
- There are functional subportions of that network that are probably differentially affected in different behavioural syndromes.
- Maybe in the future, the psychiatric diagnoses will be linked to genetics, epigenetics, networks/connectivity measures, other biological markers, and dimensional behaviour problem “scores” rather than to categorically distinct “syndromes” that are currently the trend, not to say “craze”.
- Even so, categories will remain for a long time to come.
- ESSENCE is NOT a diagnosis in itself.
Services for childhood epilepsy

- No good model implemented for the assessment and long-term medical, psychiatric and educational care in childhood epilepsy
- Child psychiatrists are almost never “part of the team”
- Child psychiatrists are sometimes “called in” (rarely)
- Child psychiatrists may be involved in surgery assessments (pre- and postoperatively)
- Education almost never “on board” in health care programmes
- NO EPIDEMIOLOGICAL THINKING
- The vast majority of all children with epilepsy have psychiatric disorder, cognitive problems or educational underachievement
- vement
- ESSENCE-teams of the ESSENCE