# EEG based biomarkers in pediatric neuropsychiatry: ADHD – autism (ASD)

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# Disclosure

- This presenter has no financial involvement with pharmaceutical industry or manufacturers of equipment.
- The research is financially supported by Østfold Hospital Trust, Norway
- Professional collaboration with
  - The Norwegian University of Science and Technology (NTNU), Norway
  - Gillberg Neuropsychiatry Centre (GNC) Gothenburg, Sweden

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  - ADHD and ASD
- Criteria for clinically useful biomarkers
- Methods based on EEG, Event Related Potentials (ERPs) and neuropsychological tests
- The biomarker *profile* approach
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- Clinical cases

# ADHD – basic; DSM 5

- Symptoms observed before 12 years.
- Statistically deviant and impairing symptoms of inattention, hyperactivity/impulsivity
- At least 6 of 9 symptoms of inattention, and 6 of 9 symptoms of hyperactivity/impulsivity
- (Inattentive subtype;"ADD")
- Seen for at least 6 months and in different settings (school, home)
- Leading to impairment in home, school, social
- Symptoms not better explained by another diagnosis +++


FEYENOORD
ROTTERDAM

# ASD: Autism Spectrum Disorders

- DSM -5 diagnostic guidelines; two criteria domains:
  - Social interaction domain (including language and social communication deficits)
  - Repetitive or restrictive behaviors
  - A spectrum disorder requiring specifiers
    - Intelligence level
    - Language
    - ++++

# I claim that:

- Neuropsychiatry:
  - In the future the present behavior based diagnostic criteria have to be supplemented by more objective measurements, closer to brain function
- ADHD and ASD:
  - The credibility of these diagnoses will increase if objective criteria are included.
  - Subgroups of ADHD and ASD based on QEEG, ERPs and neuropsychological tests are potentially useful as guidelines for treatment.

# Prevalence of pediatric ADHD in Norwegian counties

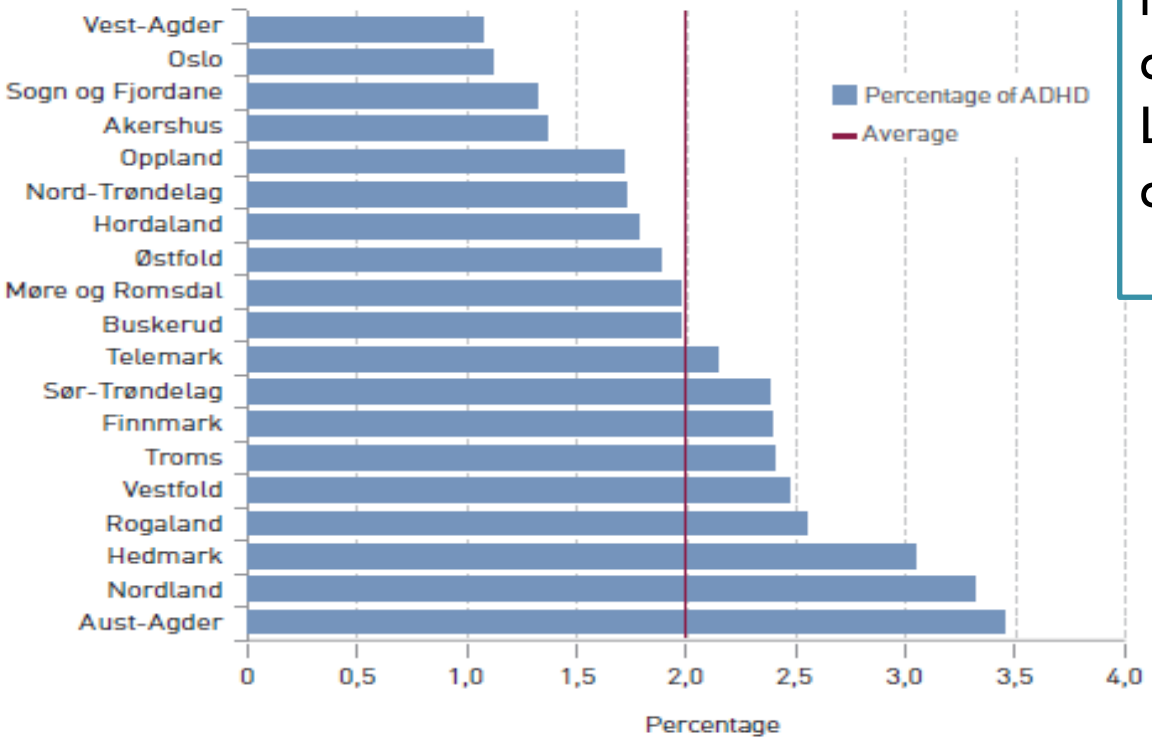



**Figure 2** *Prevalence of ADHD by county in 2008–11 in children aged 6–12 (ADHD registered as a main or other condition once or more during the period)*

From 1.6% to 3.4% in two neighbor counties:
Lack of objective criteria?

# ADHD and ASF: Some challenges

- Genetic/neurobiological causes are claimed, but criteria are based only on observed behavior
  - Too much subjectivity
- Different underlying mechanisms leading to similar symptoms (ex: inattention, hyperactivity)
- Data from interviews, rating scales, developmental history often primarily relying on one source (usually the mother)
- Improved criteria for implementing medication treatment in children are asked for
- Can ADHD/ASD be differentiated from child abuse and PTSD by the use of objective, brain based methods?

# Biomarker – neuromarker - endophenotype

- A ***biomarker*** is: "a *characteristic* that is objectively measured and evaluated as an *indicator* of normal biological or pathogenic processes, or pharmacologic response to a therapeutic intervention. Biomarkers can provide an objective basis for diagnosis, treatment selection, and outcome measures" (Wright, Hall, Matthews, & Brayne, 2009, p. 344).

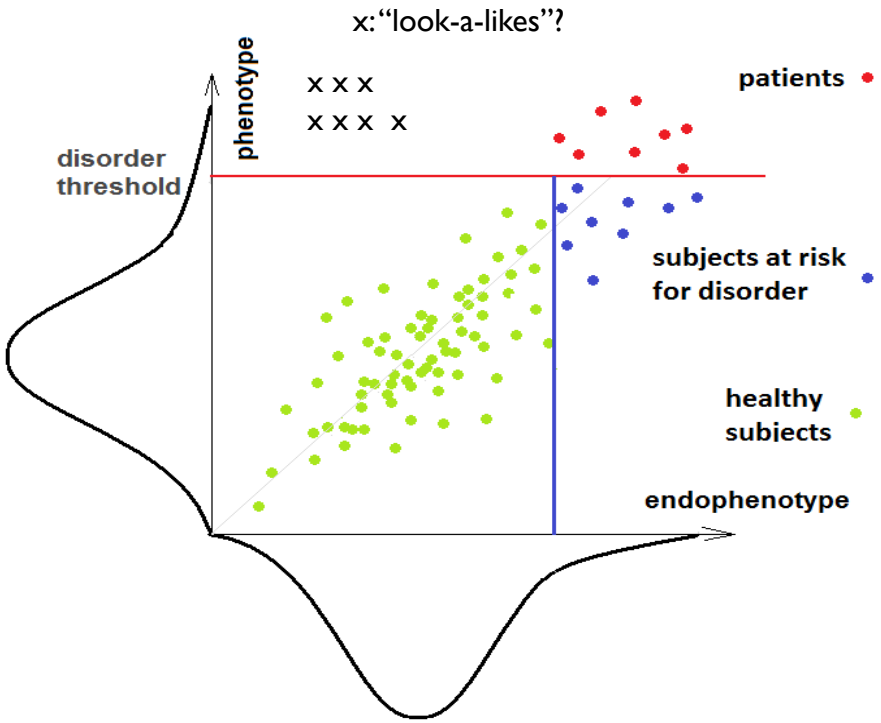
- In psychiatry, the concept of biological marker has been specified as an ***endophenotype***, often called an intermediate phenotype. The concept of endophenotype is more closely associated with genetics than the concept of biomarker is.

# Endophenotypes: Criteria

1. The endophenotype is associated with illness in the population.
2. The endophenotype is heritable.
3. The endophenotype is primarily state-independent (manifests in an individual whether or not illness is active).
4. Within families, endophenotype and illness co-segregate.
5. The endophenotype found among affected family members is found in unaffected family members at a higher rate than in the general population.

# Biomarkers for clinical use

- Test-retest reliability.
- Exploring how well the biological marker discriminates between a diagnostic category and healthy controls,
- -and between diagnoses with overlapping symptoms. A deviation from normality that is equally common in disorders that need to be differentiated (e.g. ADHD and learning disabilities) may not be clinically useful.
- It would be naïve to believe that a single biological parameter can be specific for a single diagnostic category. It is more likely that the tested parameter identifies a certain subgroup covered by several diagnostic categories (e.g. inattention).



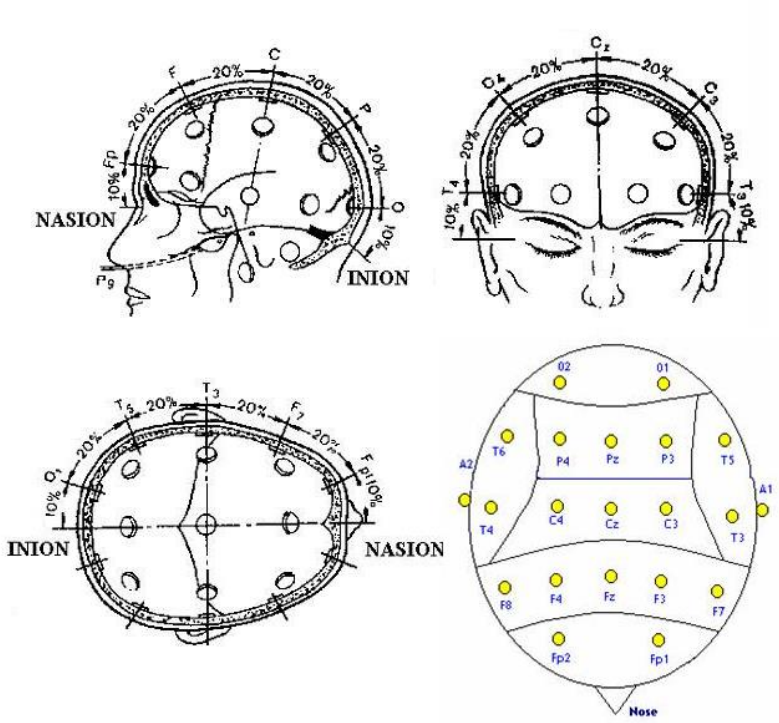

# Diagnoses and biomarkers

**Y-axis**: A "disorder scale". Red line: Diagnostic threshold.
**X-axis**: A "biomarker scale". Left side of blue line; deviant score.

Four groups:
Green: Healthy Red: Disordered Blue: At risk X: "Look-a-likes"?

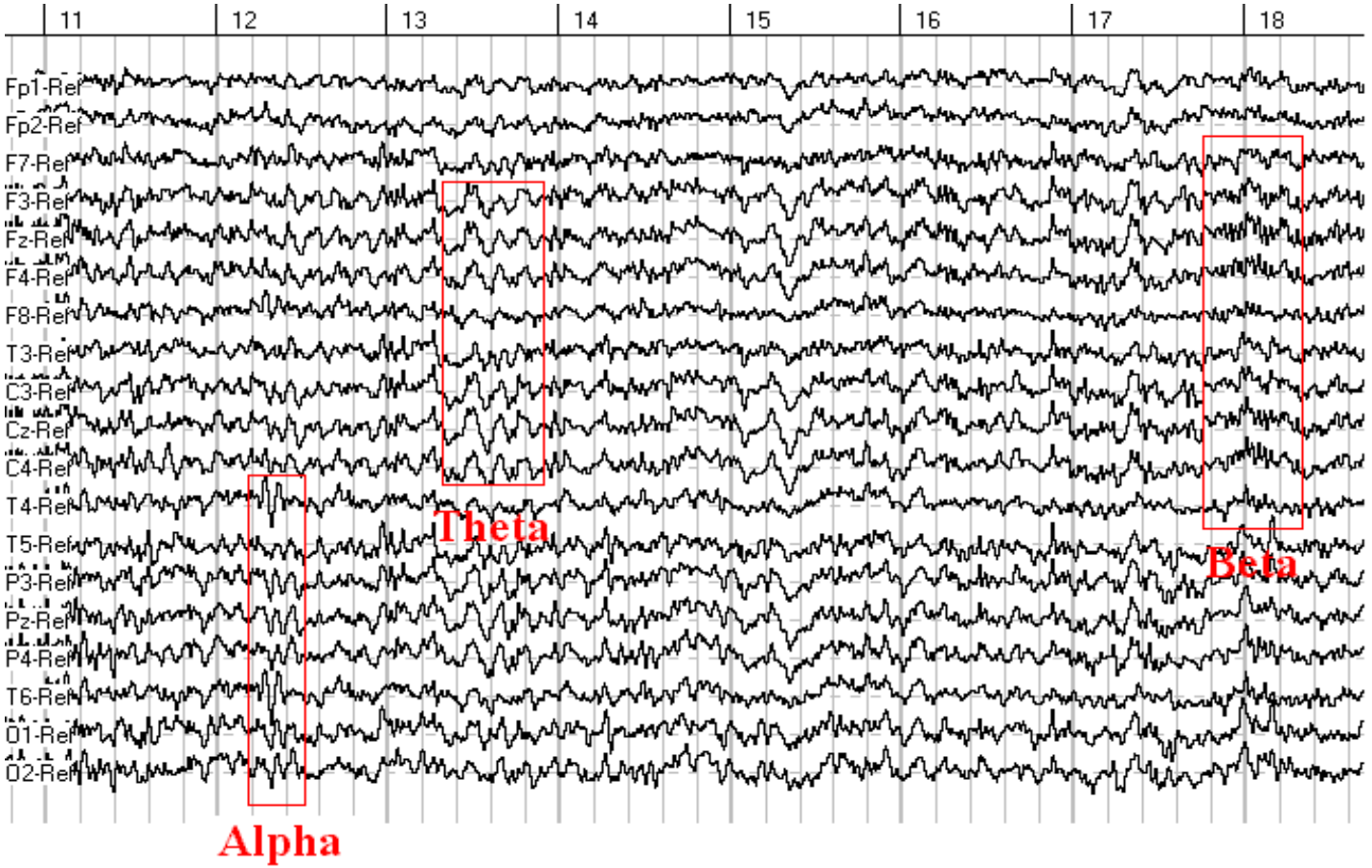
EEG:
Registration of electrical activity from large groups of brain cells firing simultaneously

# 10 – 20 system: How electrodes are placed



# EEG registration

# Seven sec. EEG from 19 sites. Examples of theta, alpha and beta highlighted

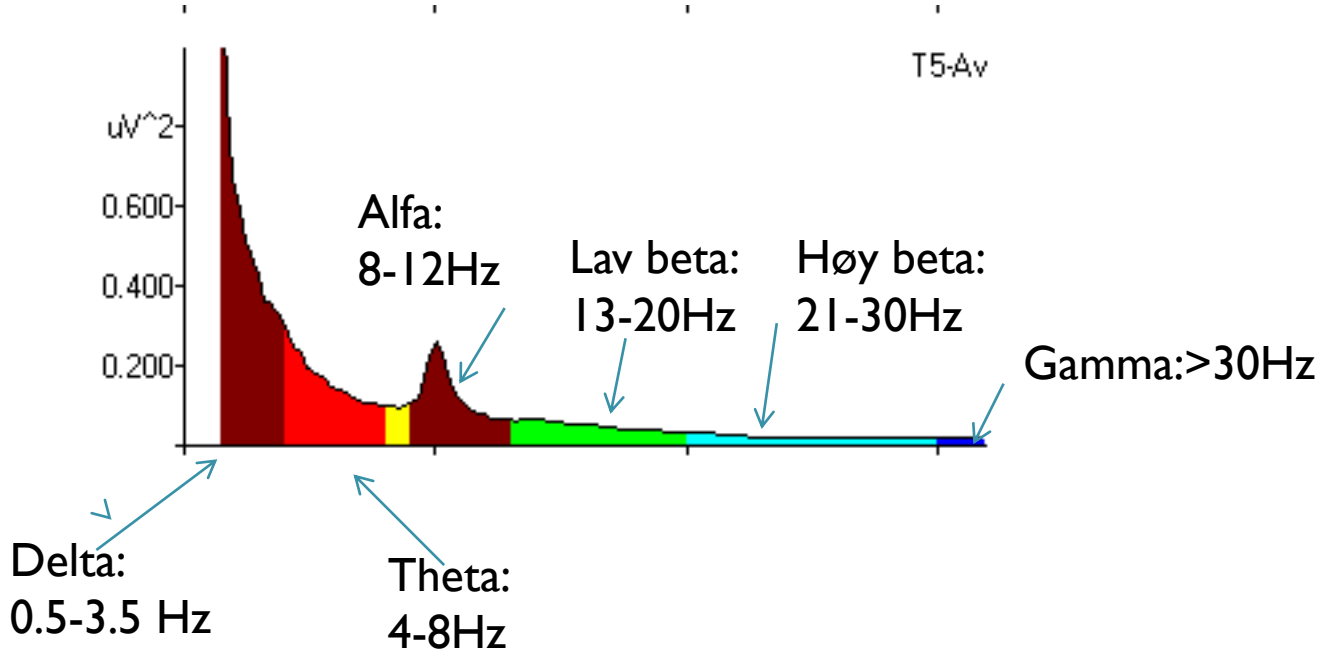


# Quantitative EEG (QEEG), Fourier analysis and EEG spectra

- QEEG:
  - Electronical processing of raw-EEG
- Fourier analysis:
  - Calculating mean power, (microvolt), in different frequency bands in a specified time interval
  - = EEG spectra
  - Often compared with norms

# EEG spectra

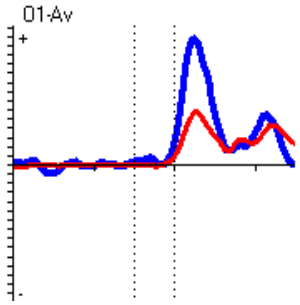
- X-axis: frequency (Hz)
- Y-axis: power(microvolt)




Fp1-AvW
Fp2-AvW
Significant deviations
F7-AvW
F3-AvW
Fz-AvW
F4-AvW
F8-AvW
T3-AvW
C3-AvW
Cz-AvW
C4-AvW
T4-AvW
T5-AvW
P3-AvW
Pz-AvW
P4-AvW
T6-AvW
O1-AvW
O2-AvW
10
20
Hz

# Event Related Potentials: ERPs

- Sensory and cognitive activity ("events") create small deflections in EEG.
- By repeating the events a large number of times with a fixed time interval(ex: 3 sec), background EEG can be cancelled out, and the event related deflection stands out as an ERP component




ERP component P1 in patient M (blue line) compared with norm (red line).

(Significance level: p=0.0001).
(Functional meaning: sensitivity? Anxiety? (BA 31)

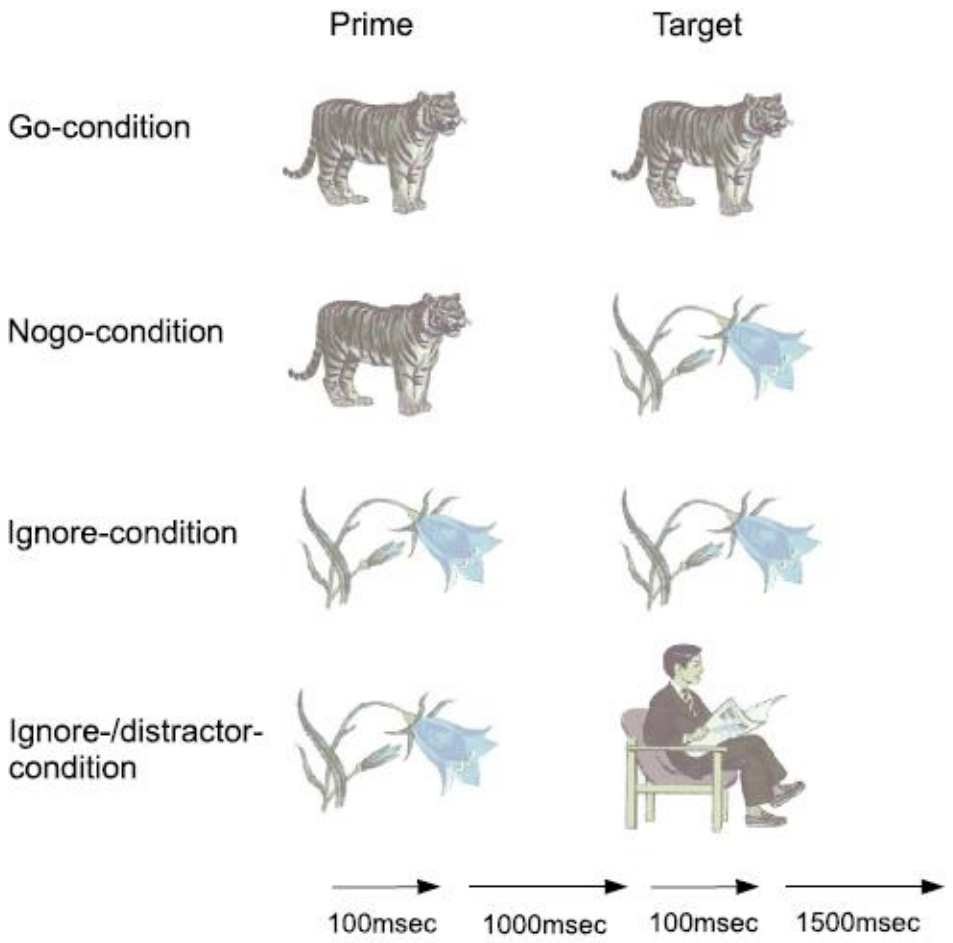
# Visual Continuous Performance Test: VCPT

Conditions of the VCPT:

Animal followed by animal: press button.

Animal followed by plant: do not press button.

Plant followed by plant, and plant followed by human (+ sound): ignore.



# VCPT: Visual Continuous Performance Test

- 20 min. cued go/no-go task while EEG og ERPs are registered
  - Behavioral measures:
    - Number of omissions: measure of attention
    - Number of commission : impulsivity
    - Reaction time (RT): processing speed
    - RT-variability: measure of attention

# What are we looking for?

- What happens, compared with norms:
  - When visual stimuli hit occipital areas?
  - When visual stimuli are identified as targets ("animals" in our paradigm)?
  - When picture 1 was an animal and you prepare for a go-response (press button)?
  - When picture 2 is an animal (Go-condition)?
  - When picture 2 is not the expected animal ("No-go")?
  - When unexpected sounds appear ("Novelty")?

# EEG based biomarkers for ADHD

- Hypotheses based on published research and clinical experience:
  - Excess theta in EEG spectra, high theta/beta ratio
    - Under activation of CNS.
  - Reduced amplitude of ERP component P3No-go
    - Allocation of attentional recourses / inhibition
  - Reduced amplitude of ERP component CNV
    - Preparation of response
  - Reduced amplitude of ERP component "Cue P3"
    - Identification of "target"
  - Increased omissions and RT variability

# EEG based biomarkers for ASD/Asperger's

- Few studies, less experience:
  - Research literature and studies under review (ALH)
    - ASD not different from controls:
      - VCPT: Omissions, commissions, RT, RT variability
      - ERPs probably indexing cognitive control: CNV, P3 no-go
    - ASD seem to be different from controls:
      - Some sensory and perceptual ERP components
      - Hypothesis: Novelty ERP component: Often too strong or too weak in ASD

# Supplementary biomarkers in pediatric neuropsychiatry:

*Measures from electroencephalography (EEG), Event Related Potentials (ERPs) and neuropsychological tests*

Multisite study with a focus on ADHD and ASD

Four groups:

ADHD – ASD – ADHD+ASD - controls

**Highlights**:

•Diagnosing neuropsychiatric disorders like ADHD and Asperger's syndrome/high functioning autism (HFA) is often difficult and controversial partly because criteria based on objective measures are missing.

•Internationally there is an increasing focus on the need for clinically useful biomarkers.

•EEG based biomarkers are excellent candidates as they are non-invasive, can be applied to children, and are affordable.

•This is a multi-site study, building on our ten years of experience, and published research aiming at finding profiles of biomarkers for ADHD and HFA.

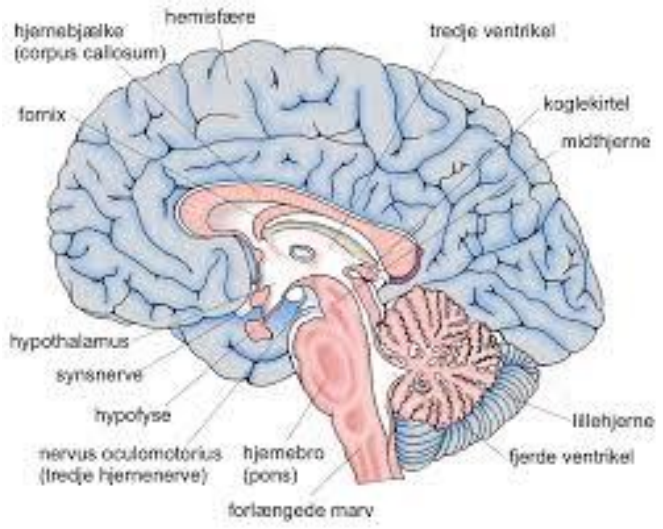
# Aim of the study

- Reduce diagnostic disagreement by applying objective measures with evidence based prediction estimates
- Less time consuming diagnostic processes
- Treatment options:
  - The examination provides hypotheses about cognitive and emotional strengths and difficulties

# Challenges

The brain did not read DSM before deciding how to organize.

DSM does not reflect brain function




ADHD and ASD have overlapping symptoms

A single ERP biomarker may reflect (important aspects of) inhibition, working memory etc., not a specific diagnosis

A *profile* of biomarkers, or a scale combining biomarkers of interest may capture diagnoses like ADHD and ASD

# Our vision

Based on a test lasting one hour plus one hour of scoring/editing, in three years we can tell the probability of an ADHD or ASD diagnosis being correct

Daniel – 17 years