NORMENT
Norsk senter for forskning
på mentale lidelser

An emotional rollercoaster?

- An update of affective lability in bipolar disorder

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STIFTELSEN KGJ

Affective lability in bipolar disorder

- What is affective lability?
- Could affective lability be an endophenotype to bipolar disorder?
- Could we use the polygenic risk score approach?
- Current study (preliminary findings)

What is affective lability?

What is affective lability?

- Many terms used to describe the concept:
  - Mood instability, affective and emotional dysregulation and mood swings, affective instability etc.

Definition:

"*Rapid oscillations of intense affect, with a difficulty in regulating these oscillations or their behavioural consequences*"

(Marwaha et al., 2014)

Affective lability scales

- Self-report measure of changeable affect, originally 54 items (Harvey et al., 1989)
  - Tendency to shift between baseline mood into anger, depression, hypomania and anxiety; as well as their tendency to oscillate between the same
- 18-items short version (Oliver & Simons, 2004)
  - Three subscales; Anxiety/Depression, Depression/Elation, and Anger

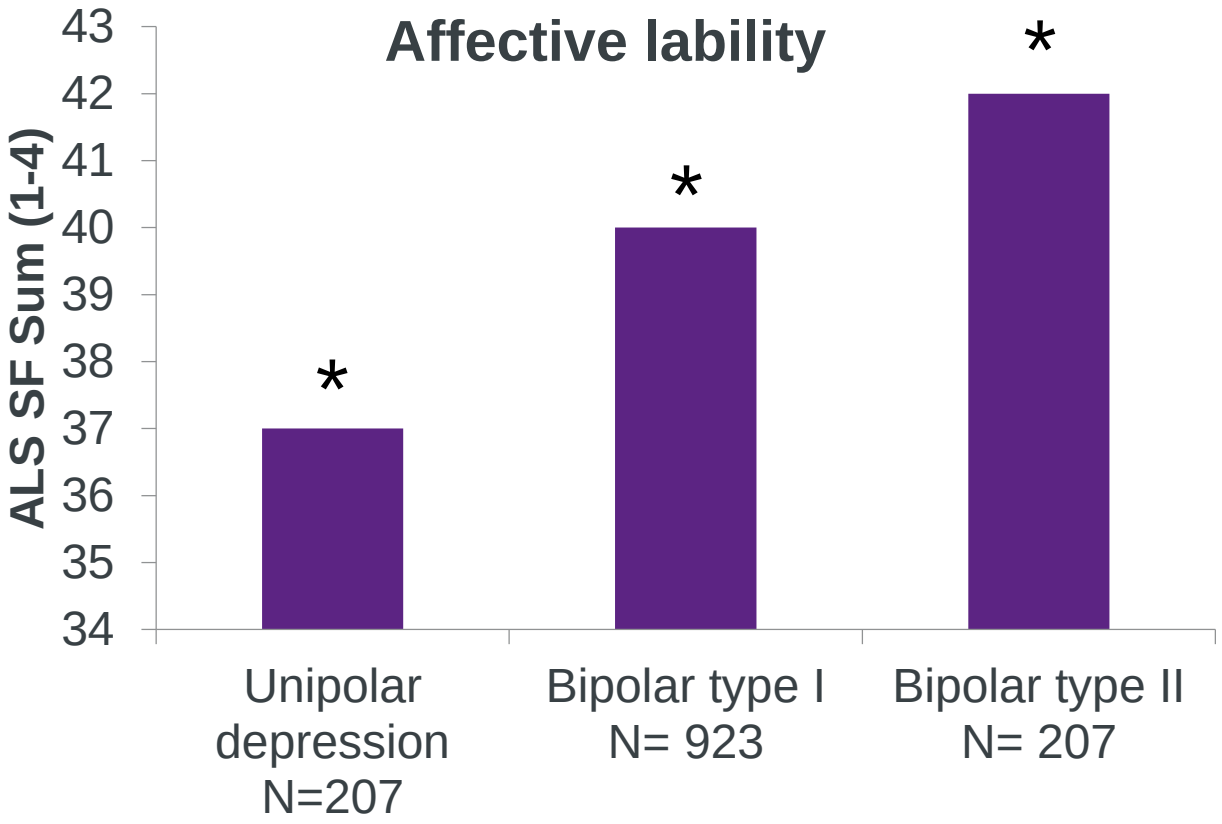
Affective lability scales

- Subjective experiences (Anxiety-depression subscale)
  - (“One minute I can be feeling OK and then I feel tense, jittery, and nervous”)
- Physiological perceptions (Anger subscale)
  - (“There are times when I’m so mad that my heart is pounding and then shortly afterwards I feel quite relaxed”)
- Behaviors (depression/elation subscale)
  - (“I shift back and forth between being very unproductive and being just as productive as everyone else”)

Affective lability in a clinical setting

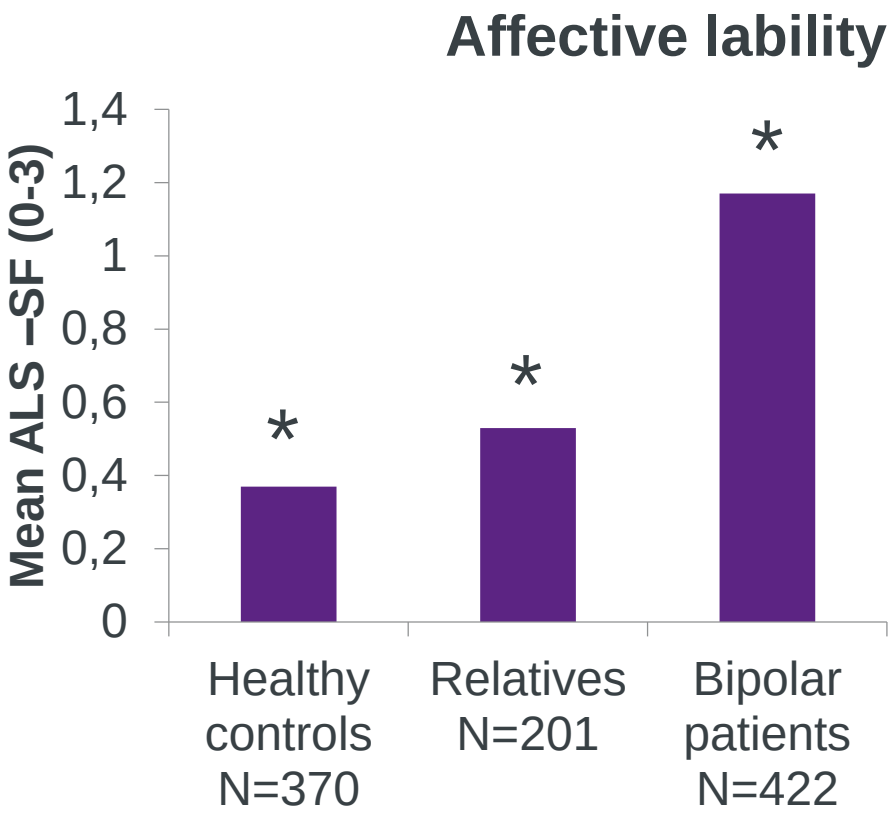
- Common in a clinical setting in;
  - Borderline personality disorder (BPD) (Silvers et al., 2016)
  - Bipolar disorder (BD) (Henry et al, 2008; Aminoff et al., 2012)
  - ADHD (Richard-Lepouriel et al., 2016, Weibel et al, 2017)
  - PTSD (Dutton et al., 2016)
  - Alcohol & nicotine abuse (Simons et al., 2005, Dvorak et al ., 2008)

Affective lability in the clinical setting



Marwaha et al 2016

Affective lability in the clinical setting



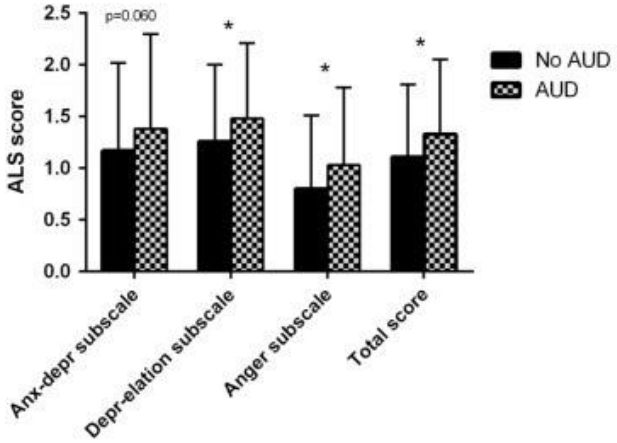
Aas et al, 2015

Affective lability in the clinical setting

- ALS subscales:
  - Anxiety/depression/anger BPD > BD
  - Depression/elation BD > BPD (Reich et al., 2012)
- ALS= BD > ADHD
- AIM= ADHD > BD (Richard-Lepouriel et al., 2016)

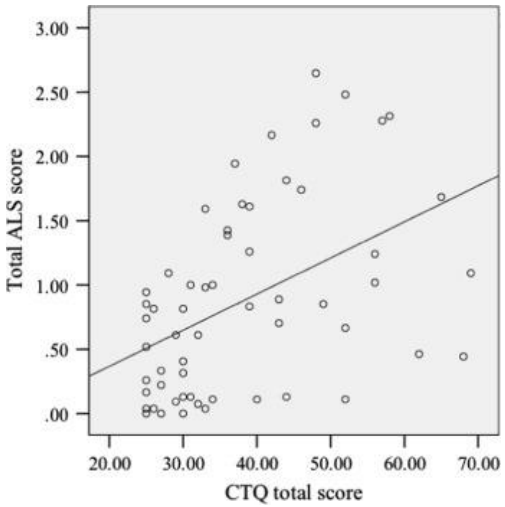
Who in the BD population has affective lability?

Alcohol use disorders



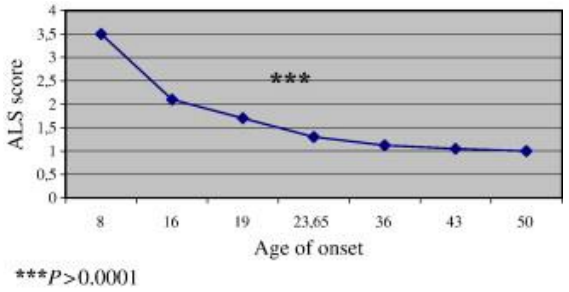
Lagerberg et al., 2017

Childhood trauma



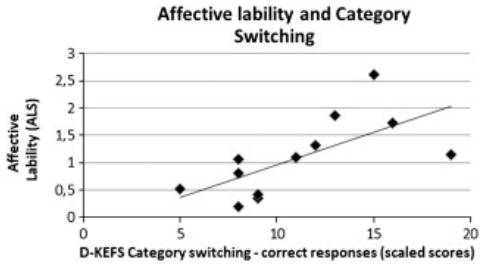
Aas et al., 2014

Age at onset



Henry et al., 2008

Cognition



Aminoff et al., 2012

Could affective lability be a endophenotype to BD?

A little bit about genetics of BD

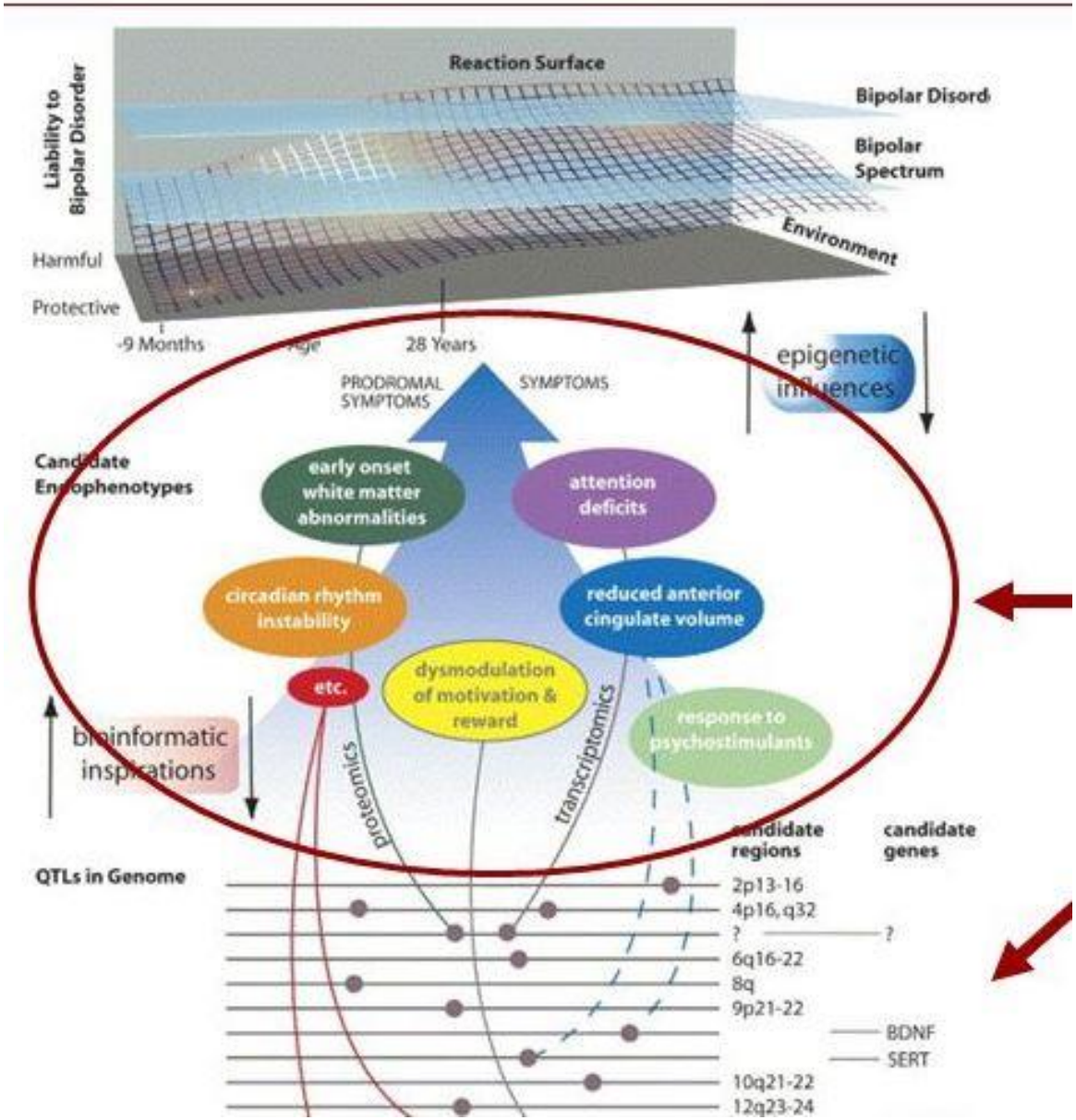
- Distinction between "genotype“ (genetic aspect) and "phenotype“ (observable characteristics)
- The phenotype (depression and mania) described already in ancient Greece.
- Runs in families
- Genetically and clinically heterogeneous
- Psychiatry lacks validating diagnostic tests such as those available for many physical illnesses
- The definition of BD phenotype is by now based solely on clinical features

Endophenotype

- Complex etiology. Simpler units, biologically closer to the genes themselves - Endophenotypes

- Measurable components unseen by the unaided eye along the pathway between disease and genotype
    a) Heritable
    b) Associated with illness
    c) Independent of state
    d) Family members that do not meet diagnostic criteria present it to a higher extent than the general population
    e) Reproducible measurements

(Gottesman & Gould, 2003; Glahn et al., 2014)



«Toward contructing an endophenotype strategy for bipolar disorders» (Hasler et al., 2006)

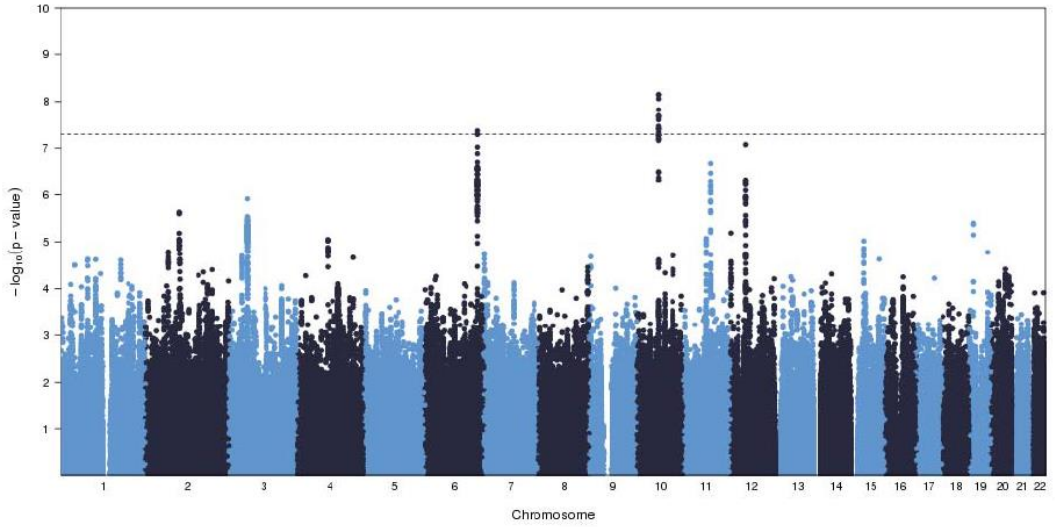
Affective lability in bipolar disorder

a) Heritable? (moderate heritability for depressive lability in healthy twin males) (Coccaro, Ong, Seroczynski, & Bergeman, 2012)
b) Associated with illness (Henry et al., 2012)
c) Independent of state (Henry et al., 2008; Aminoff et al., 2012)
d) Family members that do not meet diagnostic criteria present it to a higher extent than the general population (Aas et al., 2014; Birmaher et al., 2013, Hafeman et al., 2016).
e) Reproducible measurements (Aas et al., 2014)

Could we use the polygenic risk score approach?

Polygenic risk

- Individually significant markers GWAS (Genome wide association) studies explain limited portion of the heritability of complex traits
- A larger proportion of phenotypic variation can be explained by the ensemble of markers not reaching significance
- Polygenic contribution = many alleles each with small effect
- Polygenic risk score (PRS)



PGC; Sklar et al., 2011

What is a polygenic risk score?

- Cumulative risk load from the whole genome
- Aquired from independent ’discovery’ case-control sample
- Polygenic risk score assigned to each individual in a ’replication’ sample
- To predict case-control status or endophenotypic characteristics

How do we obtain a PRS?

- Psychiatric Genomics Consortium (except TOP-data)
  - GWAS Meta-analysis
  - Risk allele effect sizes for all SNP
  - SNPs pruned to select representatives with lowest p-values
  - Summing up effect sizes of the selected SNPs, multiplied by the number of risk alleles carried by each individual
  - Select GWAS p-value cutoff explaining most variance

Pros and cons with PRS (Kendler 2016)

Pro:

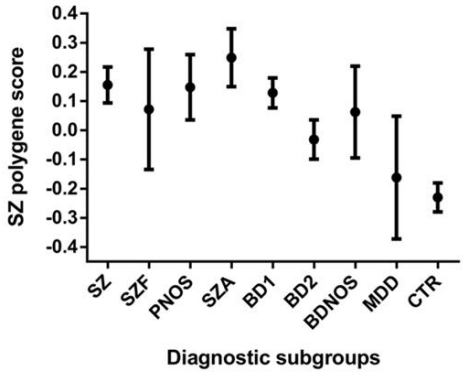
- you only need DNA (and a good training set).
- You do not need twins or adoptees.
- You do not need to interview relatives.

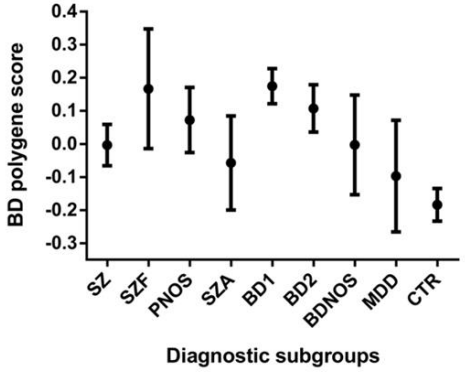
Con:

- PRS reflects the variation captured by the common SNPs used for the GWAS. It may not reflect rare variants.
- PRS is *an aggregate measure of risk,* and does not point to specific variants or any underlying biology

Stories told using the PRS-approach

- Associations have been found between BD PRS and mania in patients with SCZ (Ruderfer et al 2013)
- Support for the psychosis continuum model in a sample with BD spectrum disorders, SCZ spectrum disorders and CTR (Tesli, 2014).

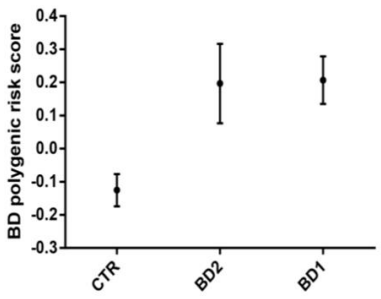


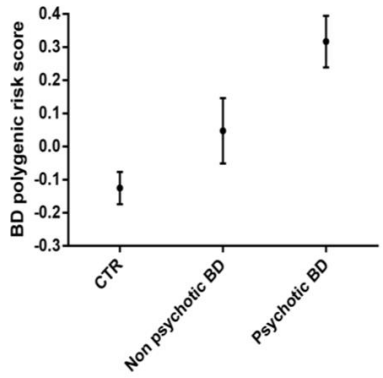


Stories told using the PRS-approach

- SCZ PRS - a trend towards higher SCZ PRS in BD patients with a history of psychosis, *p* = 0.092 (Hamshere et al., 2011)

- BD PRS – a trend towards higher BD PRS in BD-patients with a history of psychosis, *p*=0.079 (Aminoff et al., 2015)





Current study (preliminary findings)

Sample

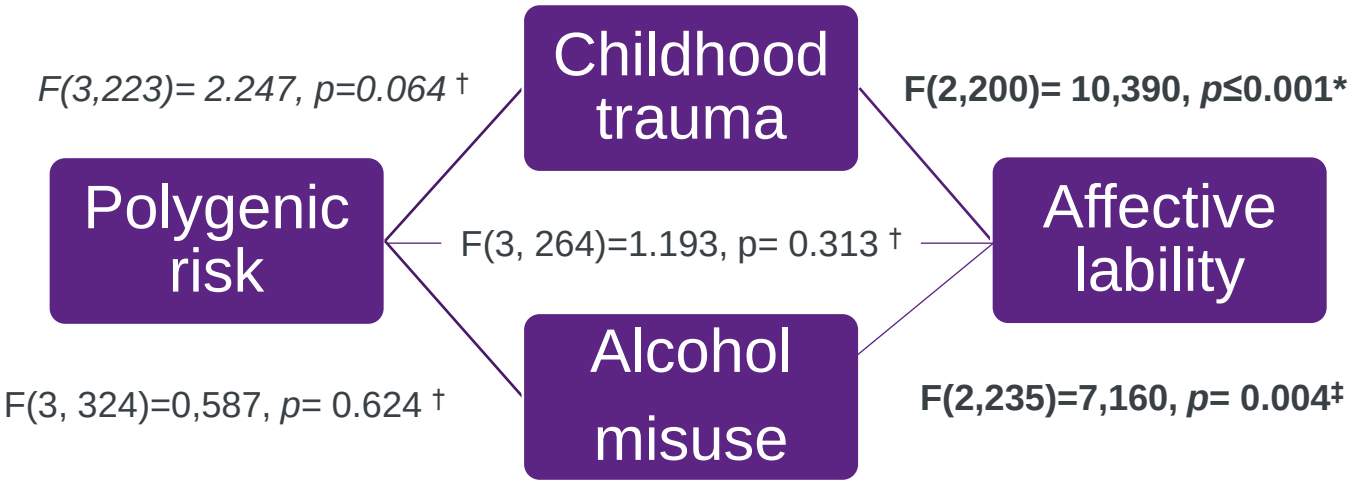
Paris

- N= 264 patients with BD with ALS and PRS
- Mean age (SD): 43±12

Oslo

- N=110 CTR, 41 patients with BD with ALS and PRS
- Mean age (SD): 33±10

Preliminary findings (French sample)



† Adjusted for 2 PCA
* Adjusted for AAO
‡ Adjusted for gender

Conclusion

- Affective lability may not be an endophenotype to BD
  - Affective lability seems primarily associated with environmental factors
  - Some results in favor for the vulnerability stress model

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