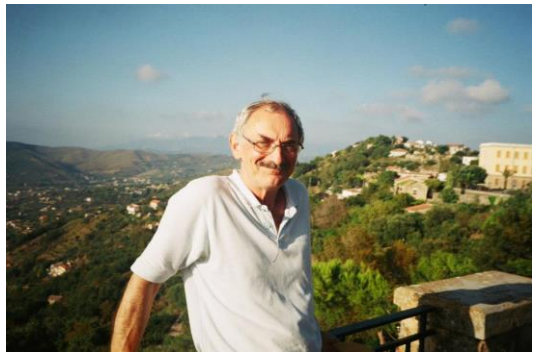
ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

PER TRADITIONES AD FUTURUM

The electrophysiology and genetics of visual backward masking



Micah Murray
(Kanizsa figures)

Olaf Blanke
(Full body illusion)

THE ROYAL SOCIETY

VolkswagenStiftung

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ÉCOLE POLYTECHNIQUE
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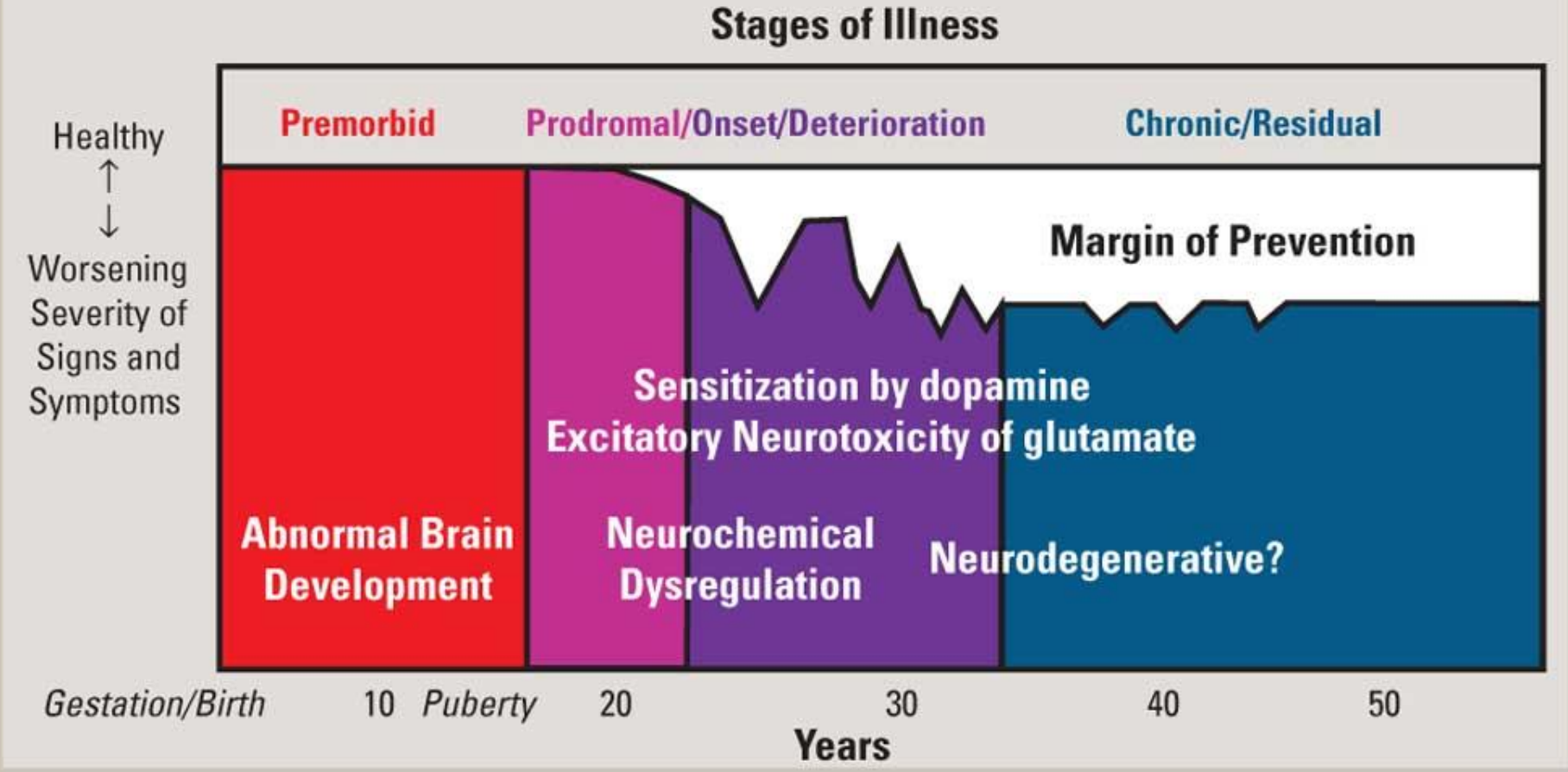
synapsy
bringing together brain research and psychiatry
National Center of Competence in Research

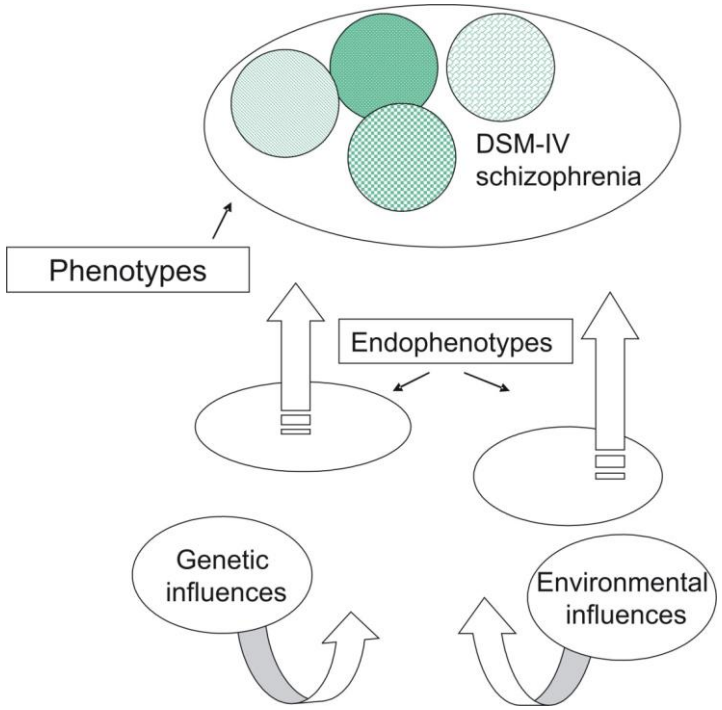
Agricultural University of Georgia

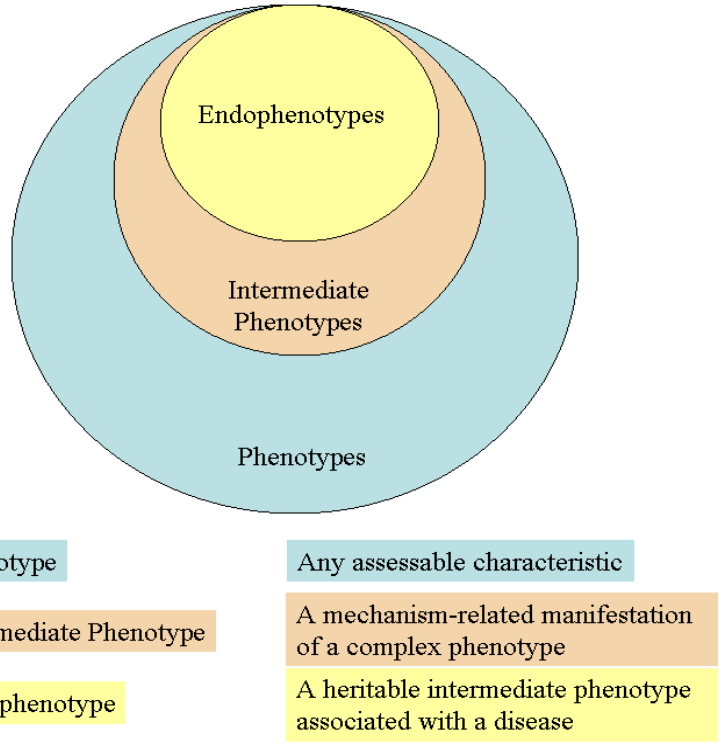
SLIDE 1

Natural History of Schizophrenia[1]



Endophenotype concept





intermediate between gene (genotype) and overt signs and symptoms of the disorder (phenotype)

“internal” marker, (e.g. biochemical, physiological, -neuroanatomical, neuropsychological, perceptual, cognitive)

Heinrichs, 2004

Marker's Criteria to be defined as an endophenotype

1. An endophenotype is associated with the illness

2. An endophenotype is state-independent

3. An endophenotype of the illness is heritable and found at a higher rate in non-affected family members

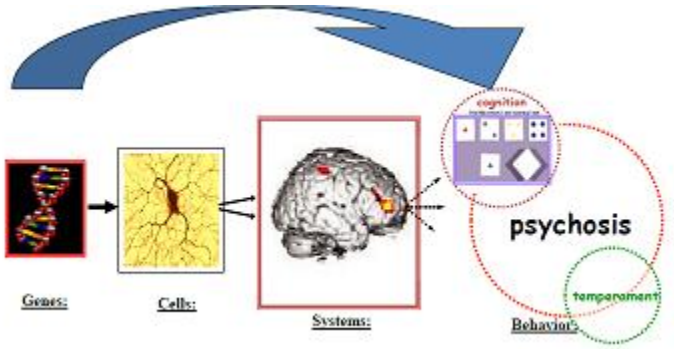
4. An endophenotype and the illness co-segregate

5. Reflect a neurobiological mechanism

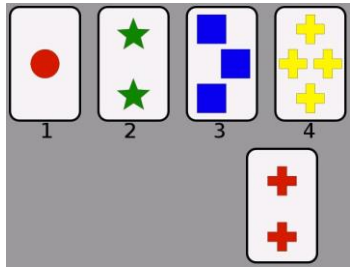
Gottesman & Gould 2003
Turetsky et al., 2007

COGS - Consortium on the Genetics of Endophenotypes in Schizophrenia

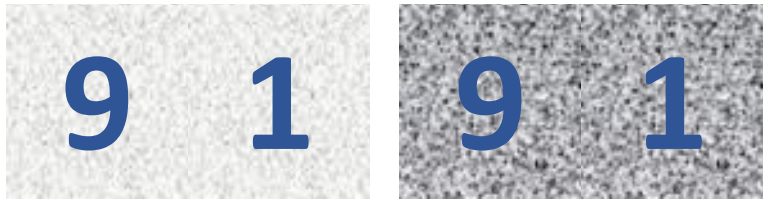
Gur, et al. Schizophr Bull., 2007



- (WCST) Wisconsin Card Sorting Test

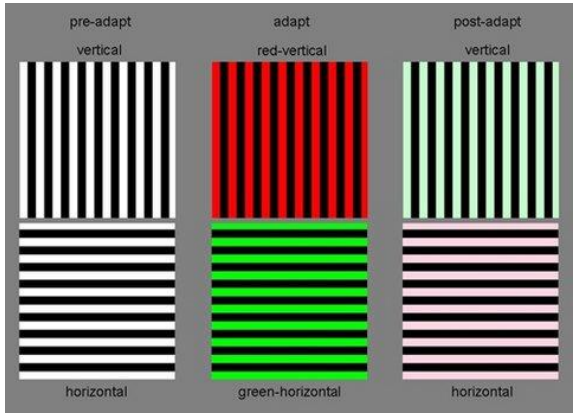


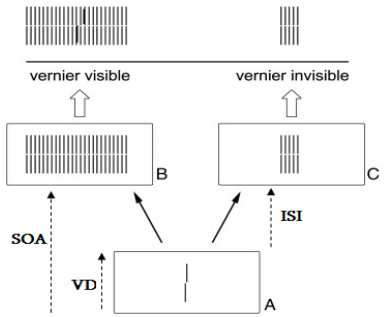
- (CPT)

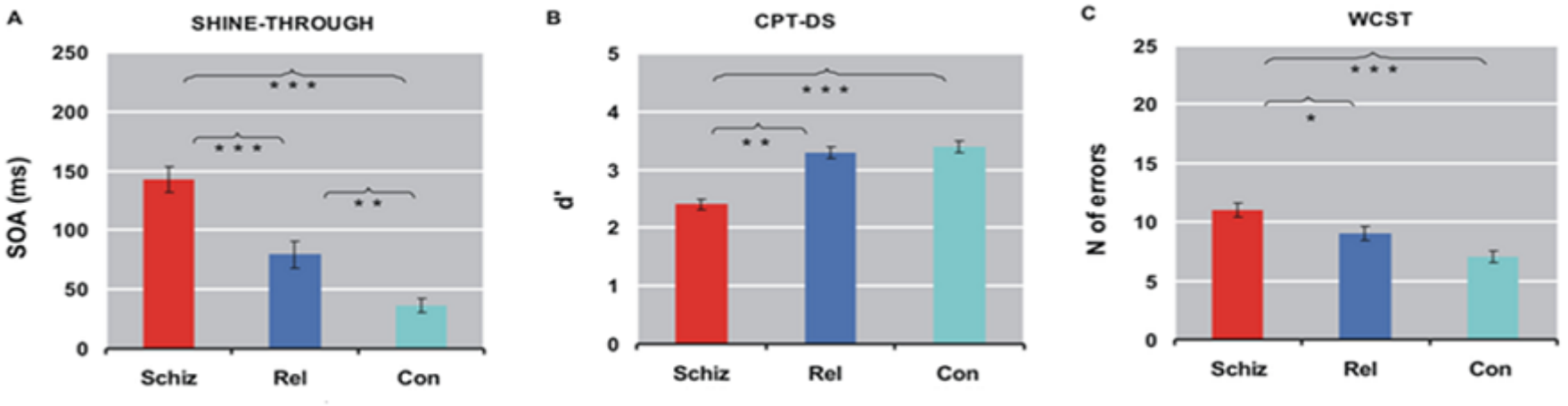


- FAR – (The Facial Affect Recognition)

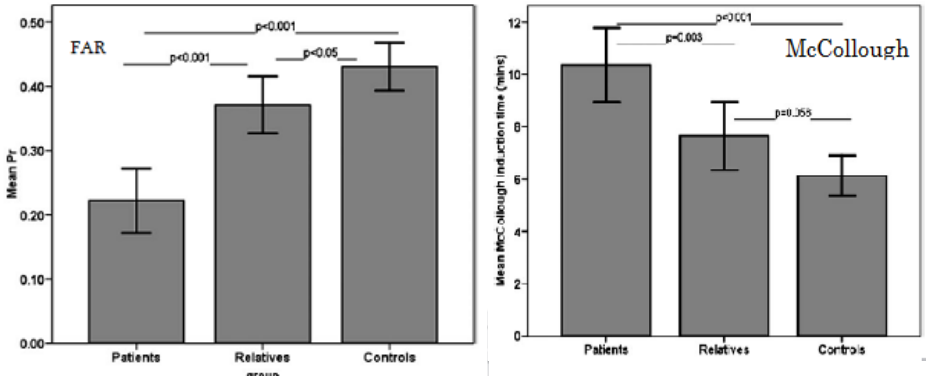
- McCollough Effect







Chkonia et al., Clin Exp Neuropsychol. 2010

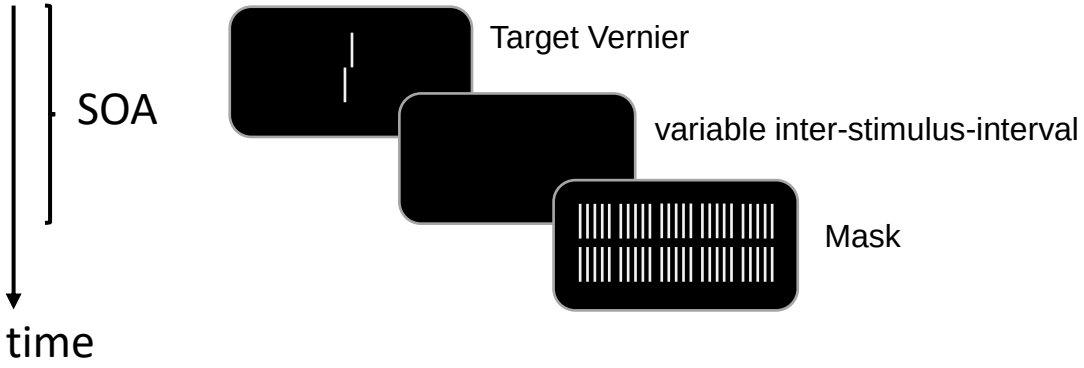


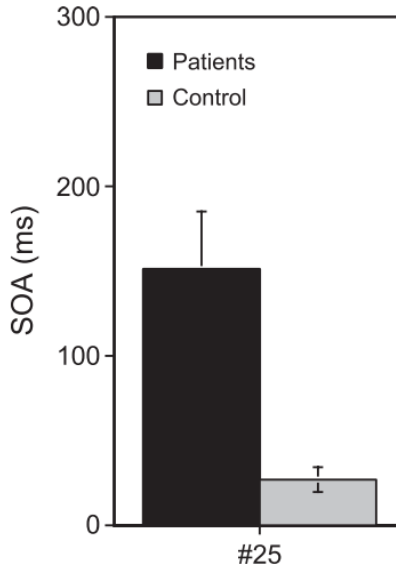
Surguladze, Chkonia et al Schizophr Bull. 2010

Thresholdes for patients are dramatically elevated compeared with the one of controls. Relatives' perform worse than controls and better than patients.

Visual backward masking: behavioral - recap

Shine-through paradigm





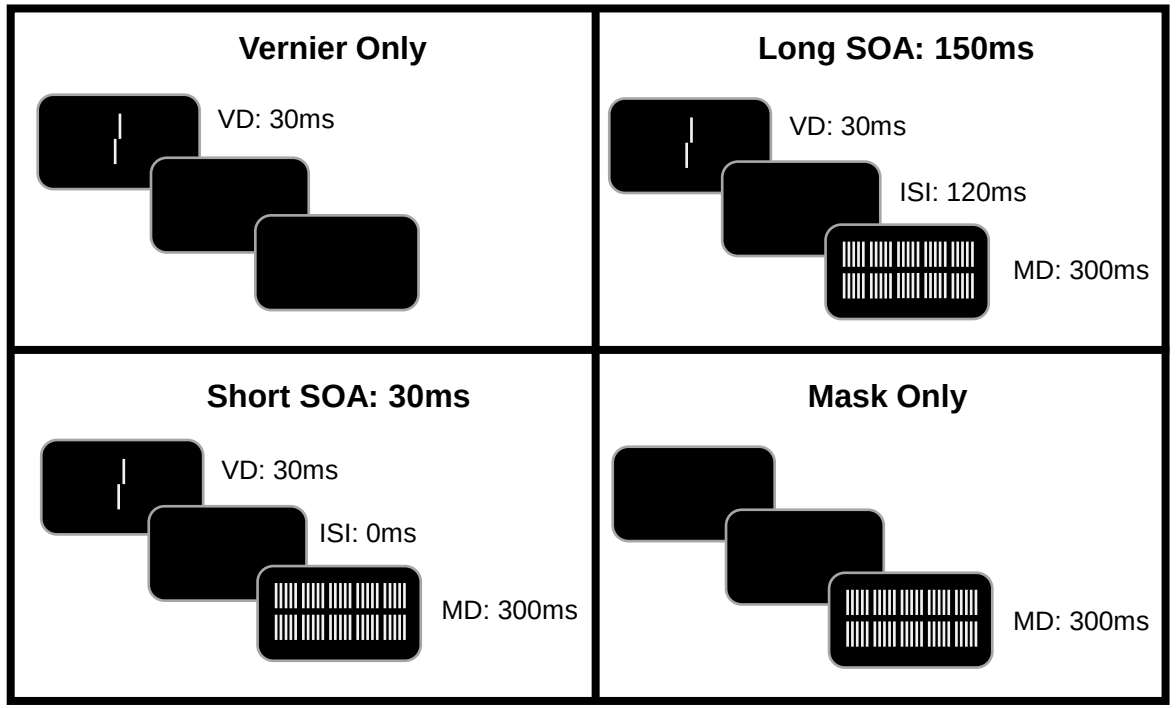
adapted from
Herzog et al., 2004

Deficits also for:

- Siblings of schizophrenia patients (Chkonia et al., 2010)
- Adolescents with psychosis (Holzer et al., 2009)
- Patients with first-episode psychosis (Favrod et al., 2018)
- Students scoring high in schizotypal traits (Cappe et al., 2012)
- Schizoaffective patients (Chkonia et al., 2012)
- Patients with bipolar disorder (Chkonia et al., 2012)

EEG correlates of the shine-through paradigm

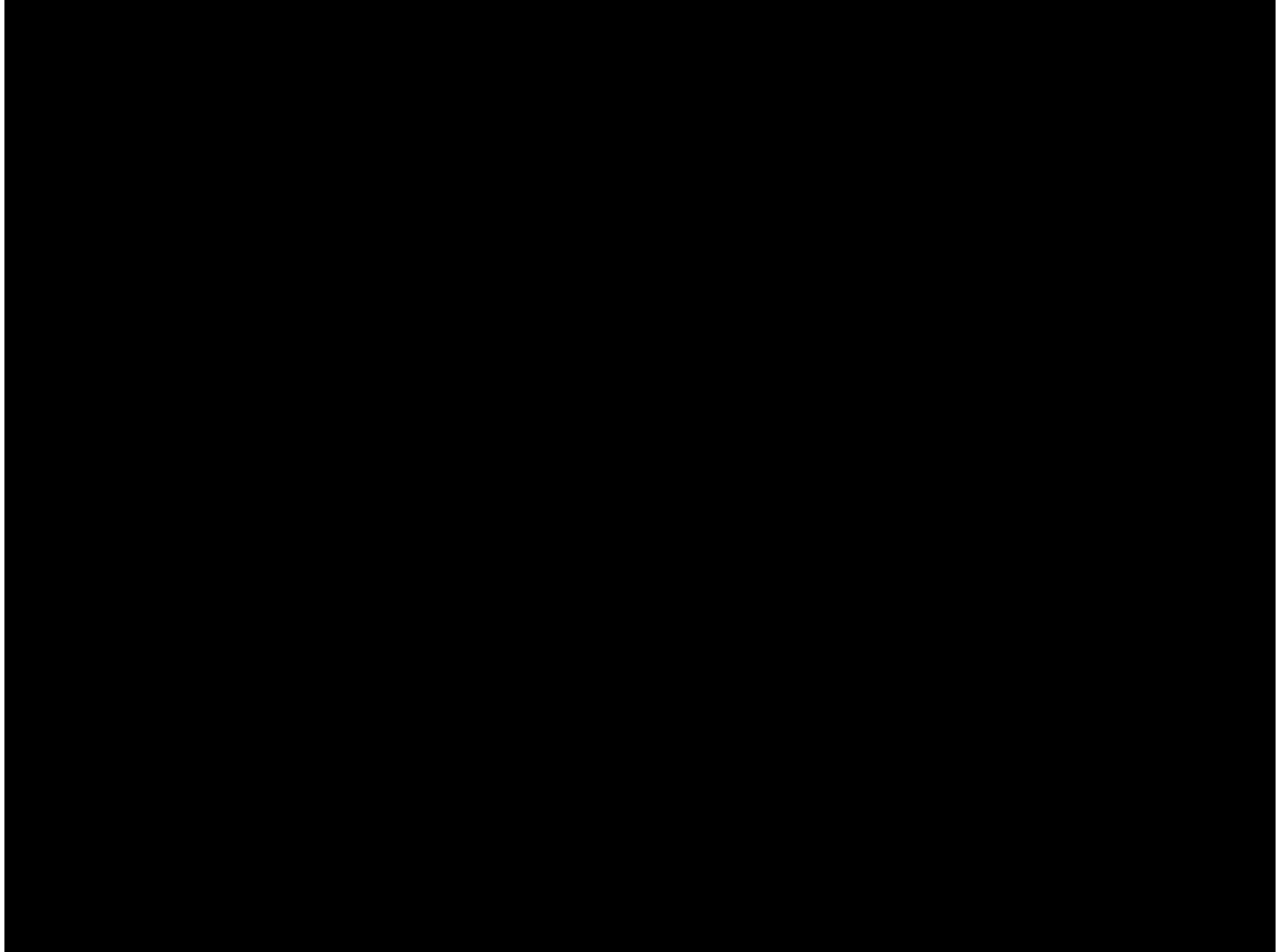
EEG experiment

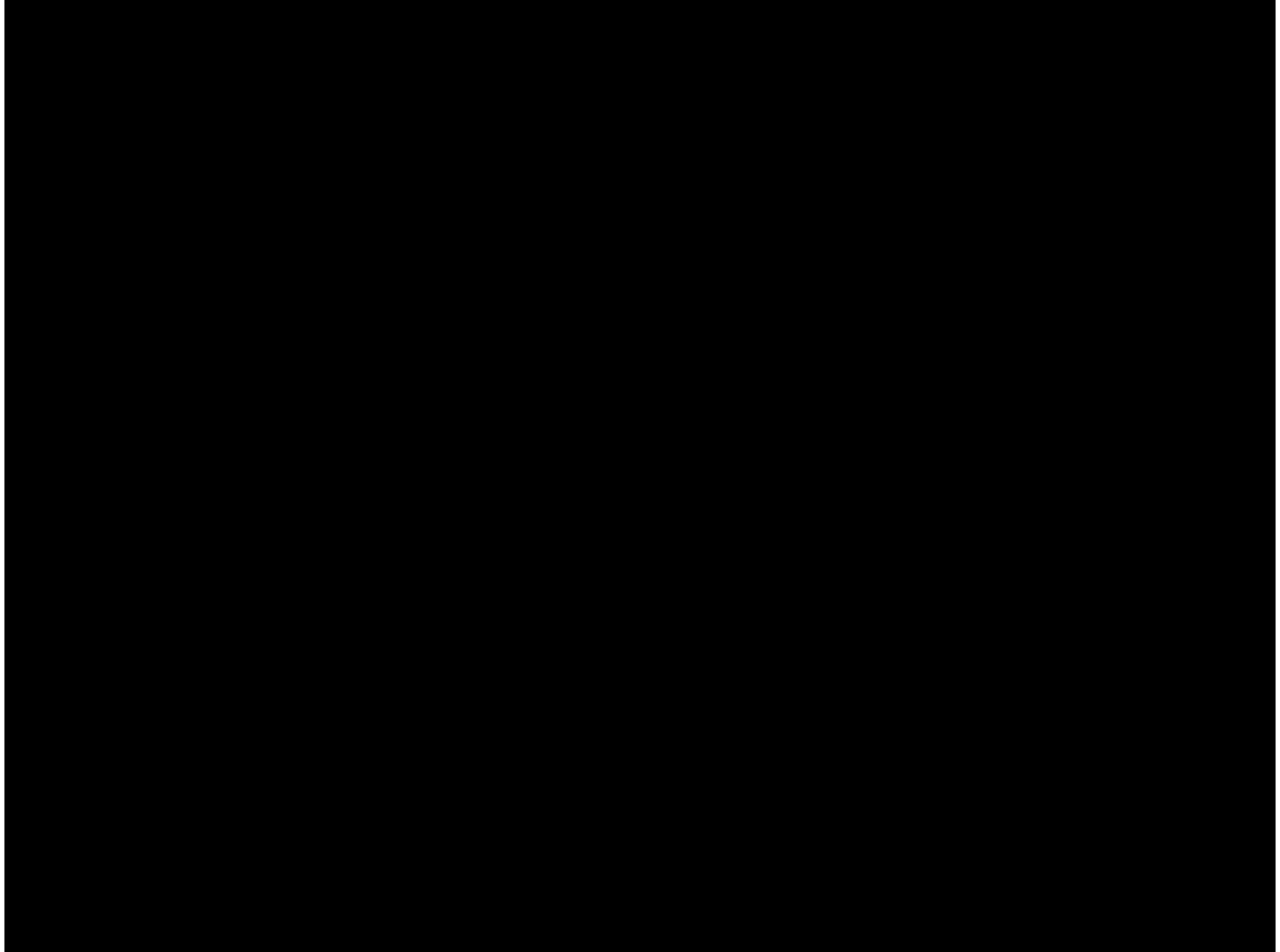


- Constant stimuli
- VD of 30 ms: average VD for schizophrenia patients
- SOA of 150 ms: mean performance level of schizophrenia patients
- SOA of 30 ms: mean performance level of controls
- Mask Only: control condition

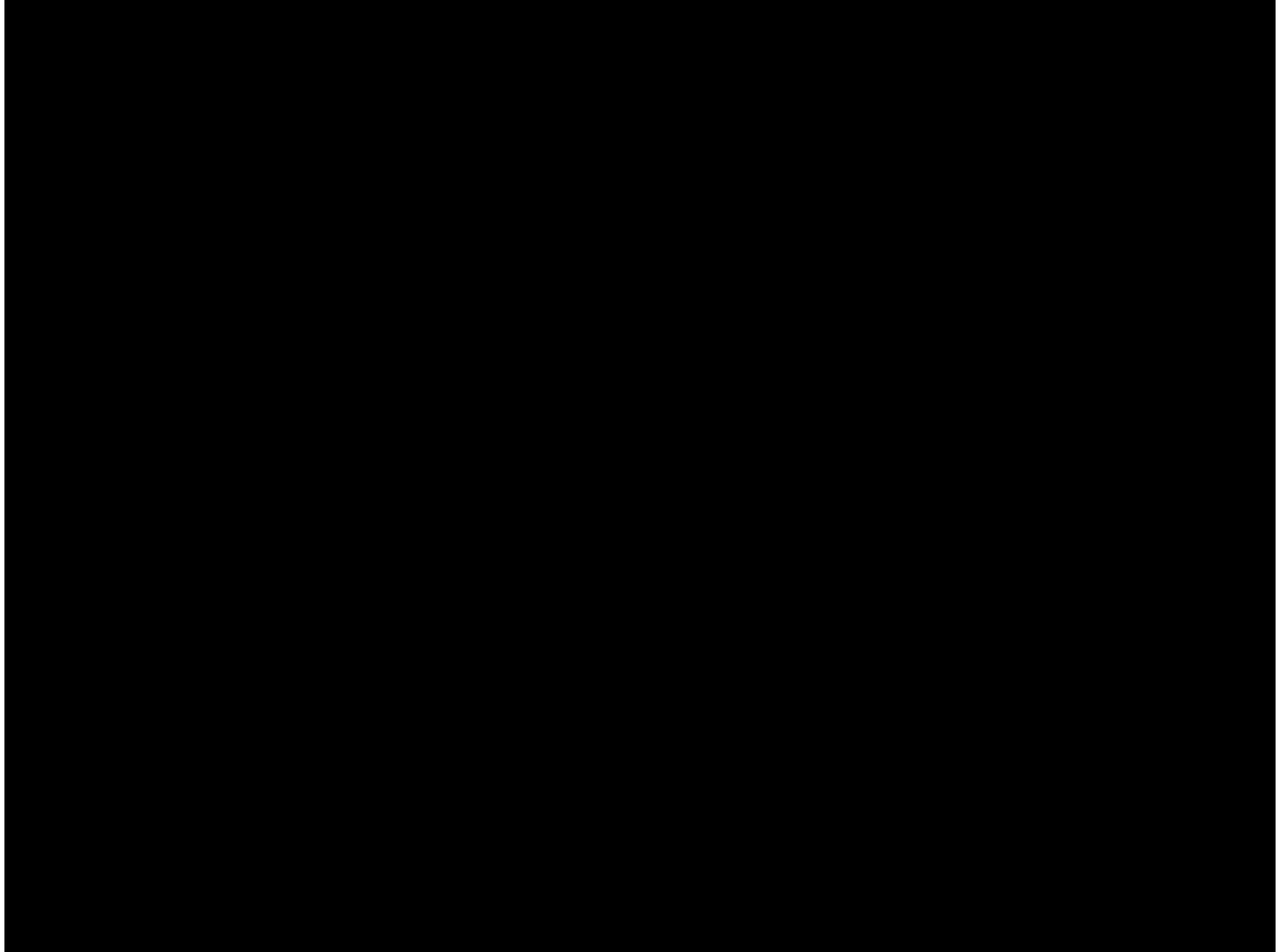
Primary measure: Global field power Standard deviation across all electrodes $GFP(TF) = \sqrt{\frac{\sum_{i=1}^{N}\left(u_i(TF) - \bar{u}(TF)\right)^2}{N}}$

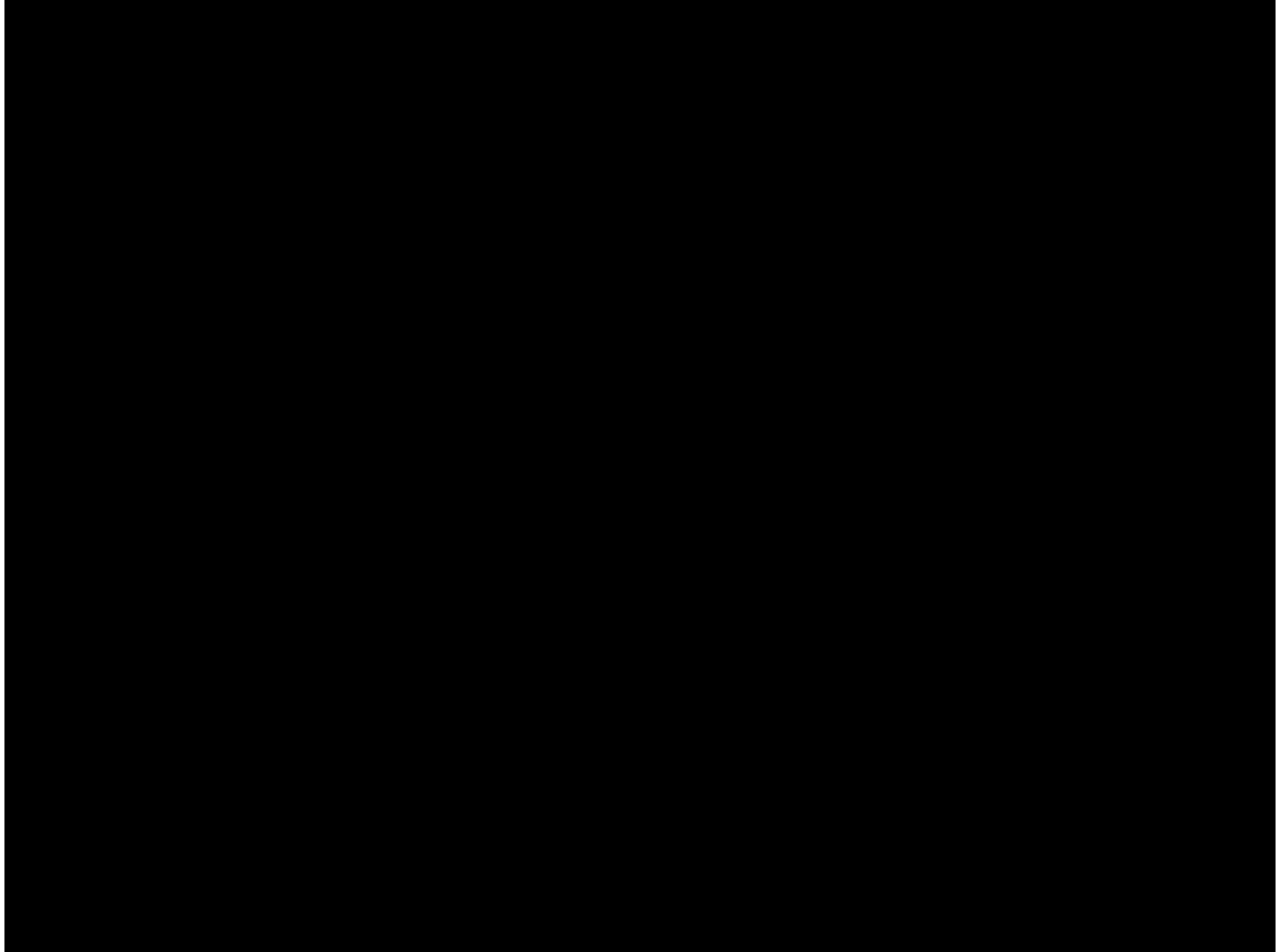
5 grating elements mask



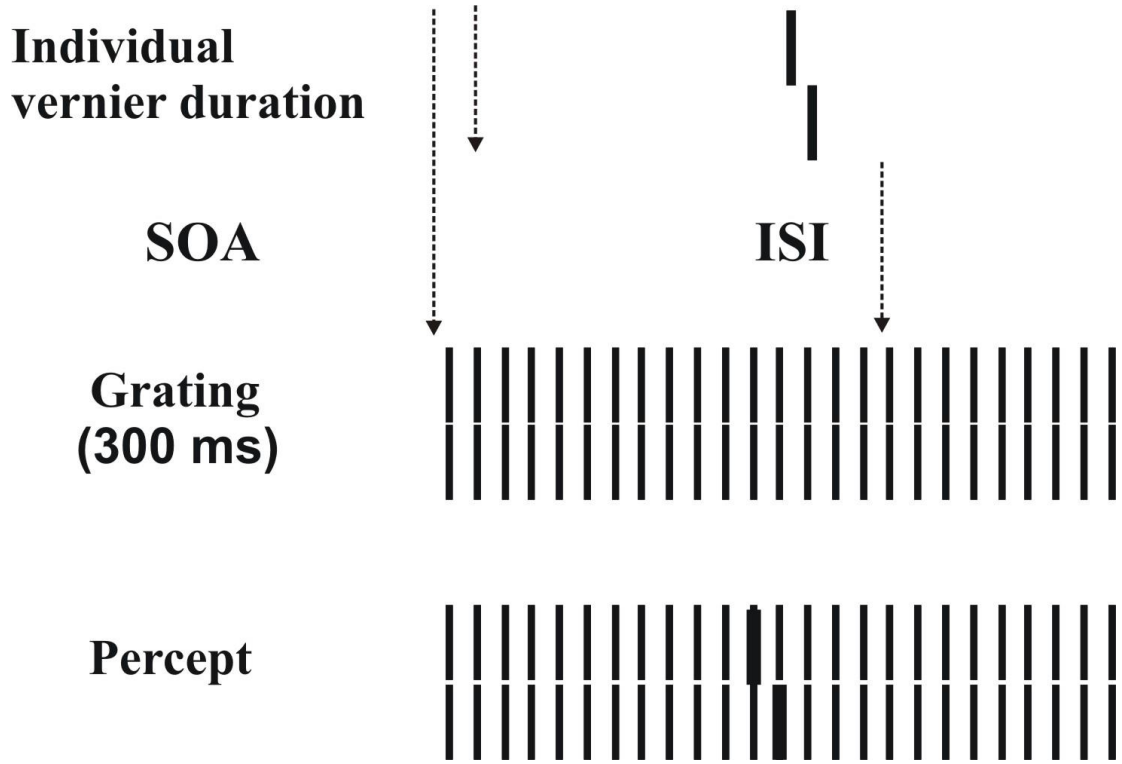


25 grating elements mask

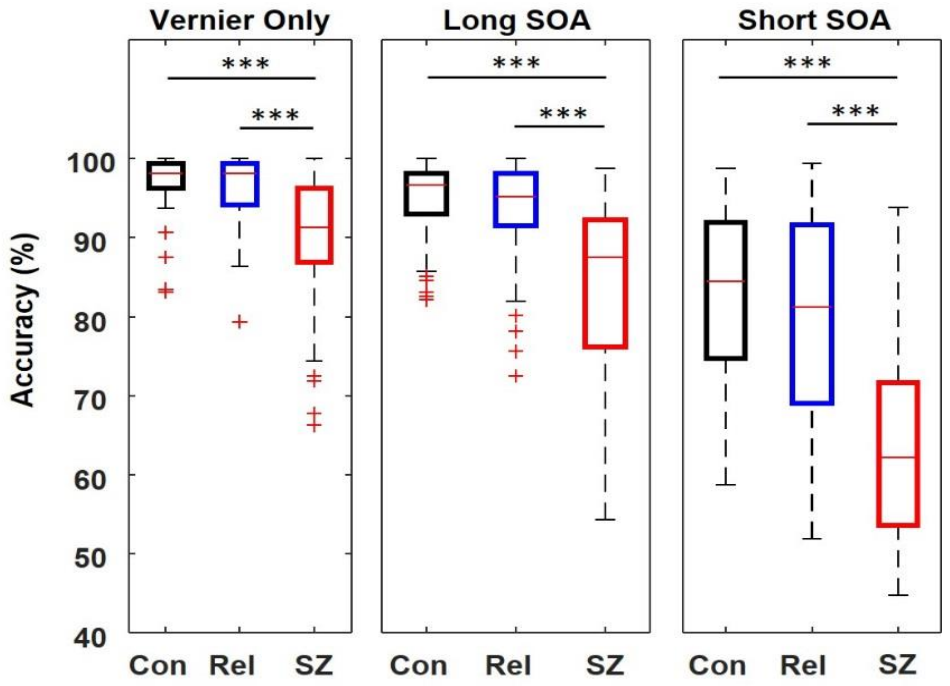




The „shine-through“ effect



EEG task: behavior



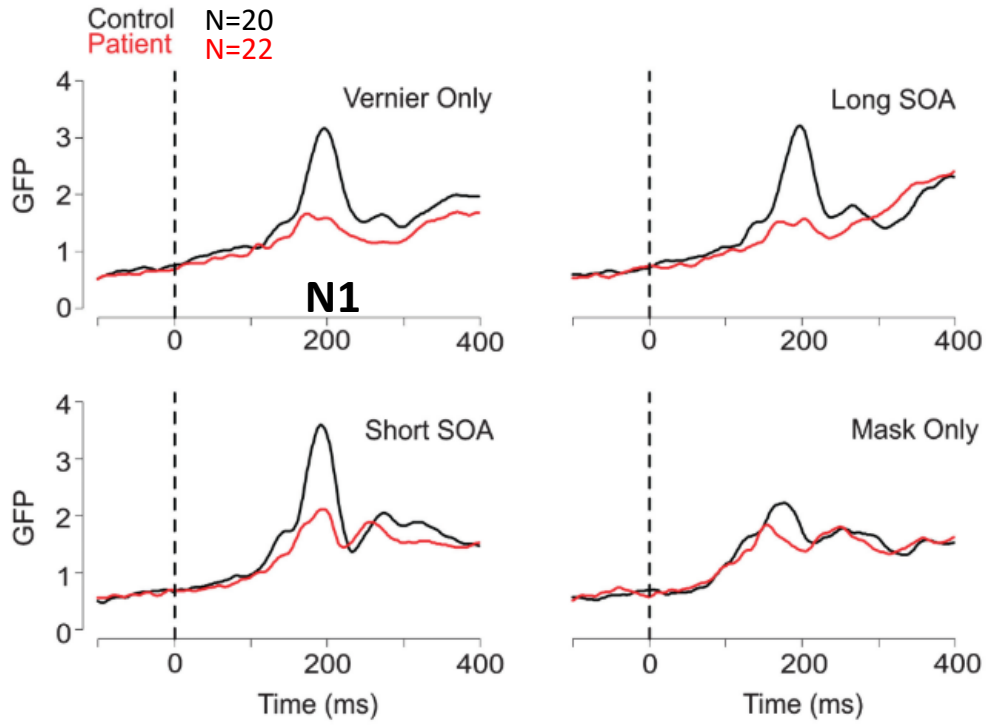
Fixed SOAs

Da Cruz et al.; 2020

EEG correlates of the shine-through paradigm

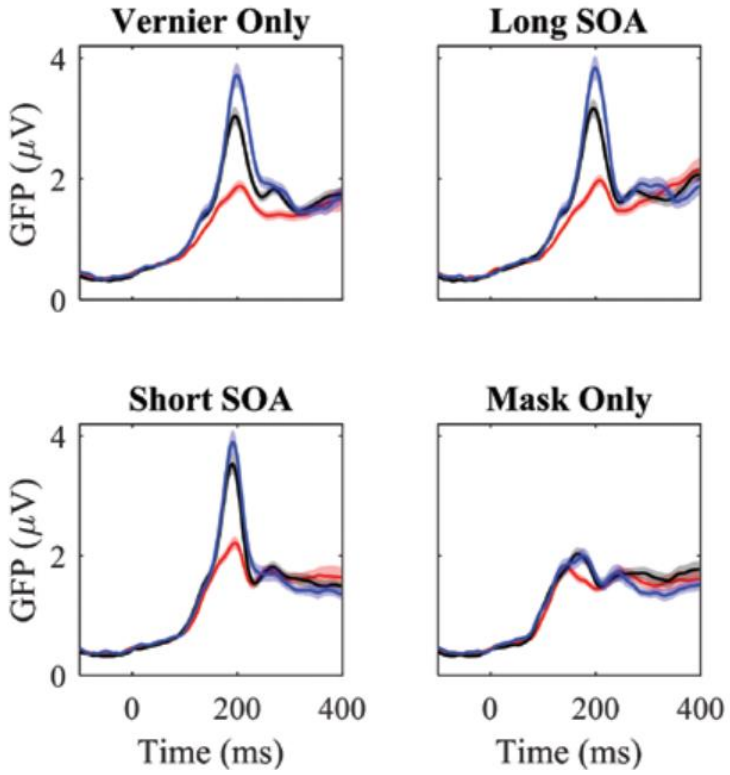
Schizophrenia patients

Plomp et al., 2013



Siblings

Da Cruz et al.; 2020



SZ N = 110
Ctrl N=83
Sib N=60

N1 amplitude: amplification of the target

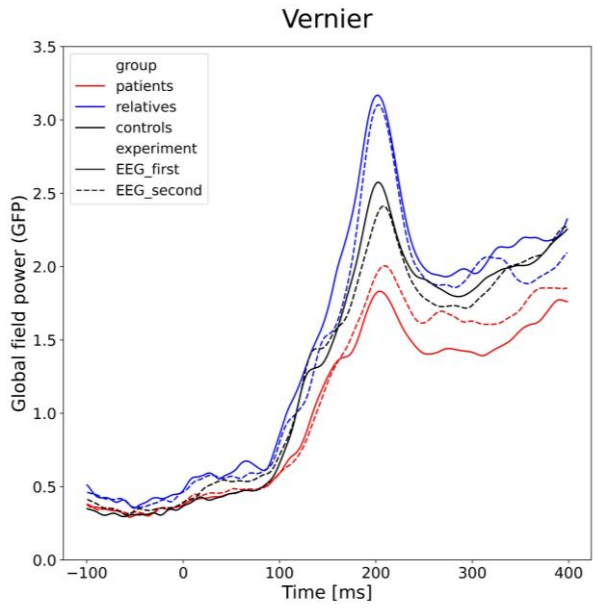
Herzog et al., 2013

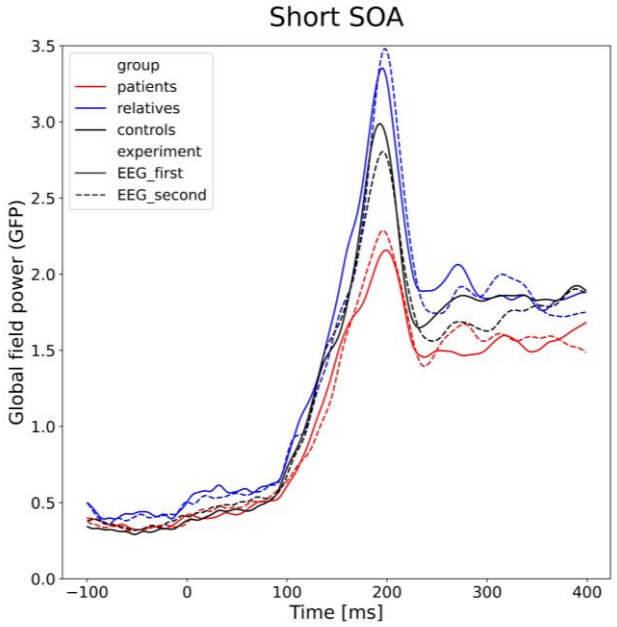
Compensation mechanism

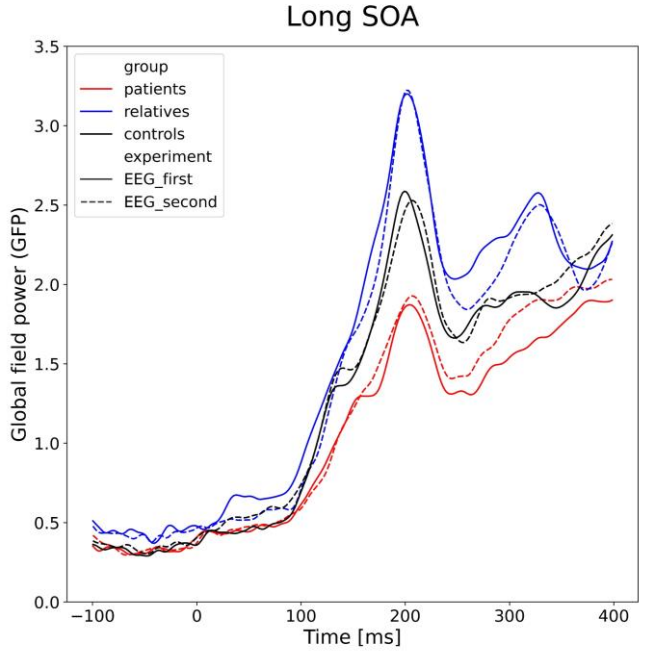
EEG correlates of the shine-through paradigm

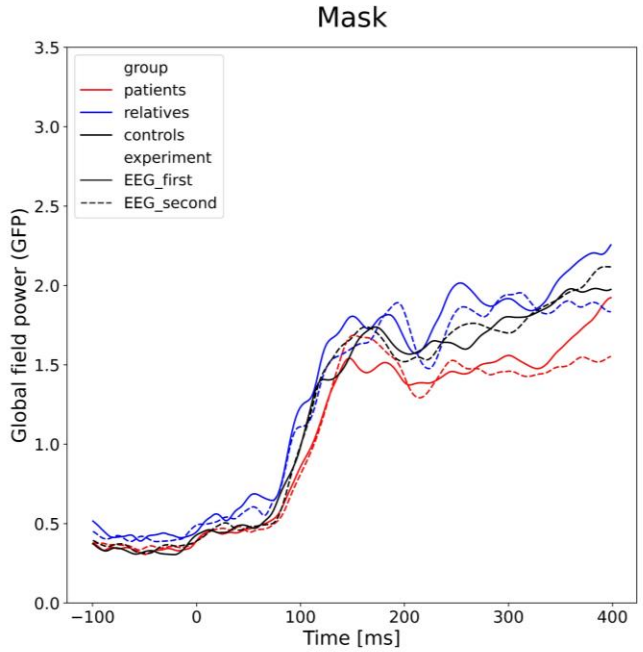
Longitudinal data Analysis ongoing

SZ N = 34	4.88 yrs ± 1.9
Ctrl N=28	5.6 yrs ± 2.17
Sib N=23	4.99 ± 1.48





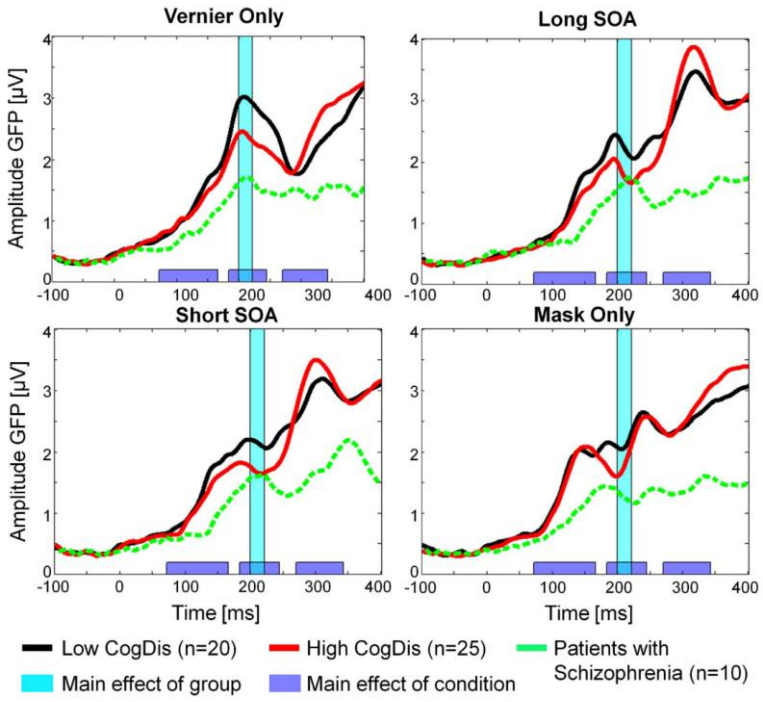




EEG correlates of the shine-through paradigm

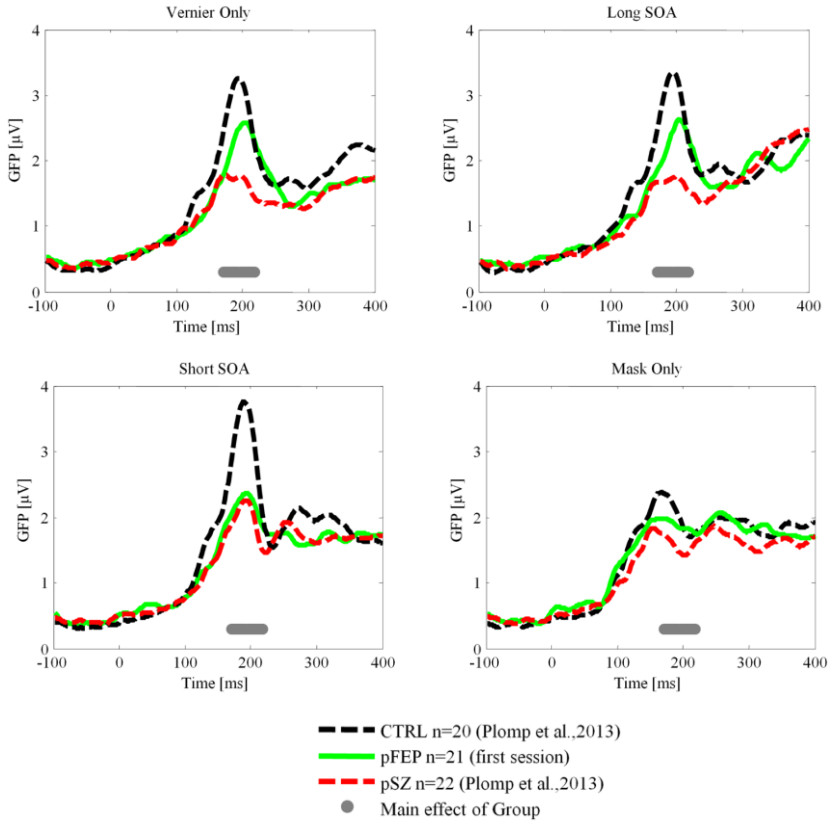
Schizotypy

Favrod et al., 2017



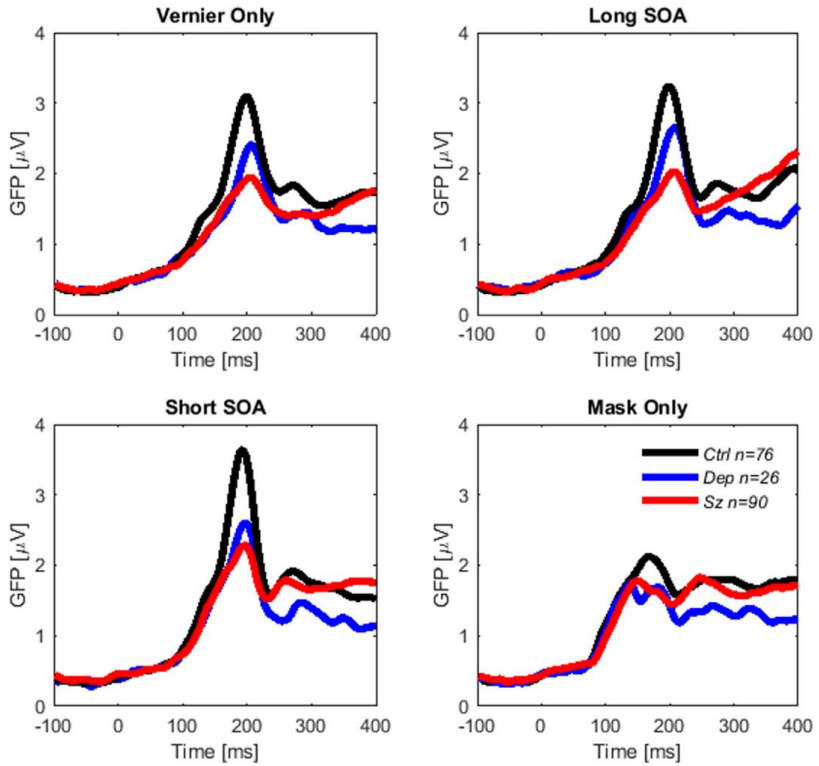
First episode psychosis

Favrod et al., 2018



EEG correlates of the shine-through paradigm

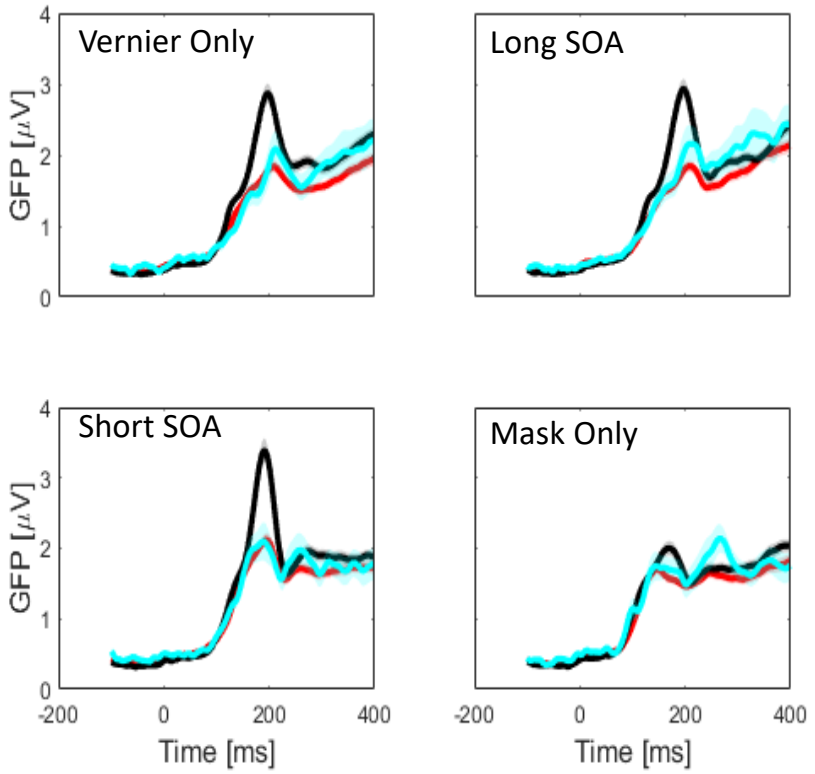
Depression Favrod et al., 2019



Bipolar disorder

Garobbio et al., 2021

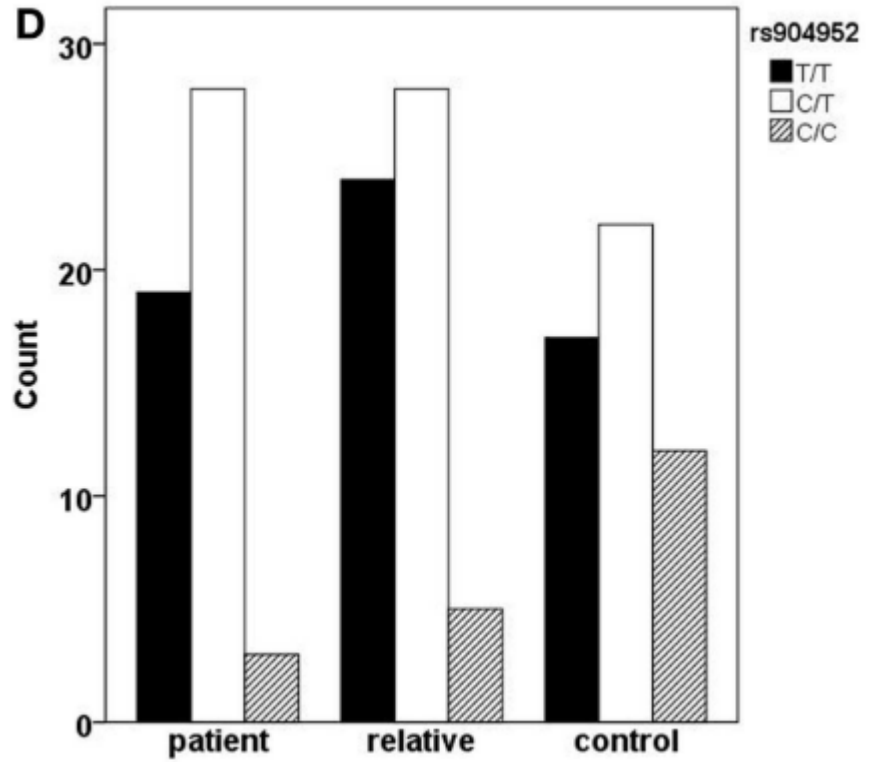
SZ N = 121 Ctrl N=9 BP N=16

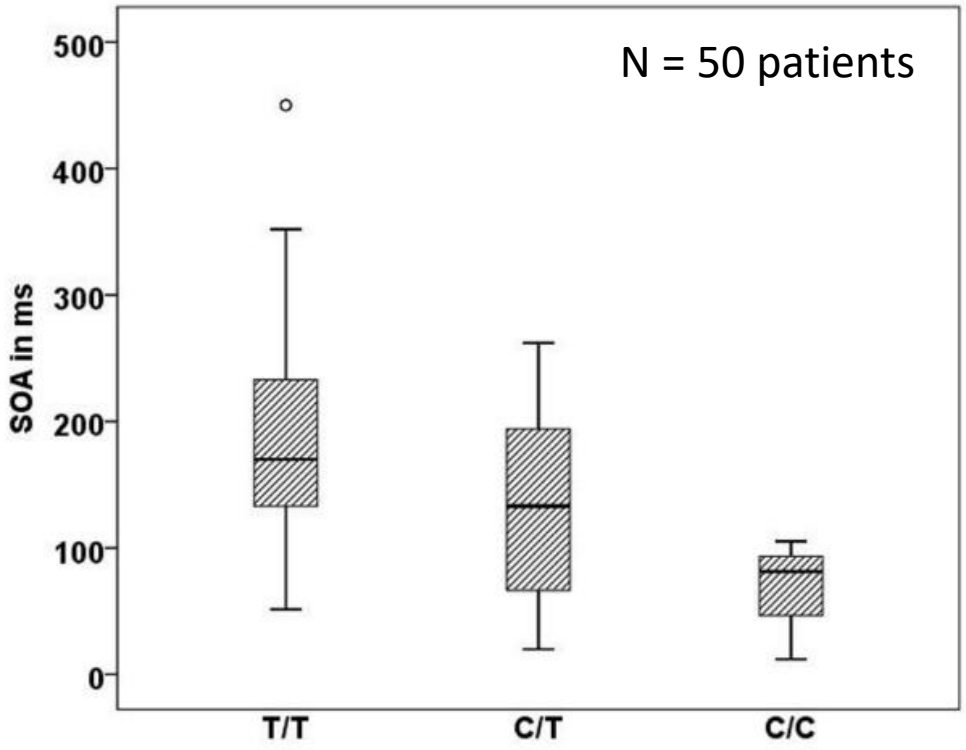


N1 amplitude: amplification of the target

+ how much intrinsic effort was put in the task

Genetics of visual backward masking





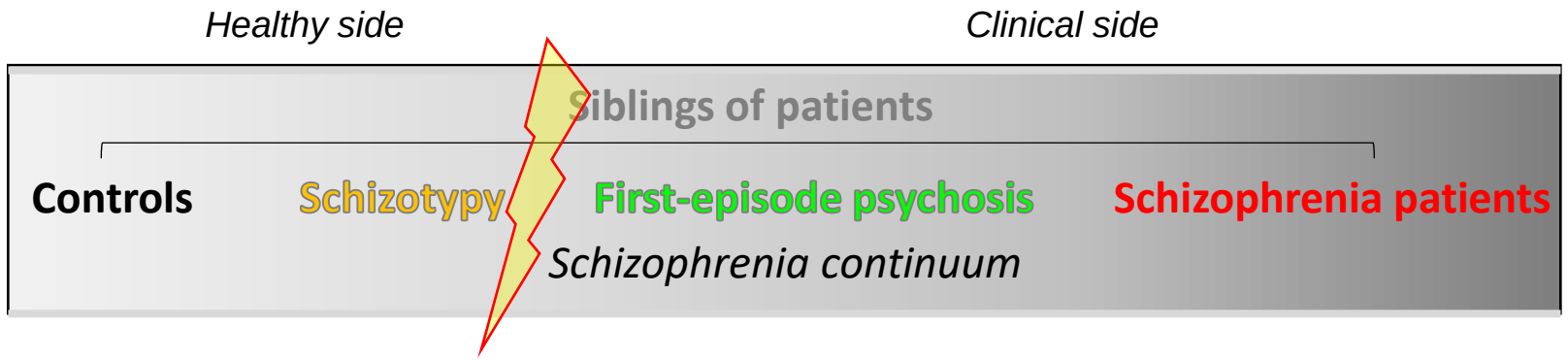
T/T carriers need the longest SOA

Genetics: masking deficits in schizophrenia patients correlate well with a mutation of the cholinergic nicotinic receptor (CHRN α7) Bakanidze et al., 2013

Cholinergic system important to boost weak but important information

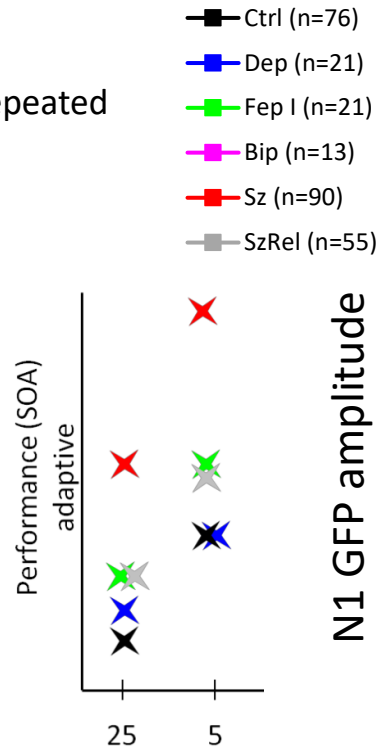
Conclusion and take home message

- Schizophrenia patients have difficulties to enhance faint sensory information (i.e., target enhancement deficit) reflected by the GFP.
- The endophenotype is the adaptive behavioral performance, not the neural correlates.
- The deficits are found along the entire continuum.



Visual backward masking as an edophenotype candidate for schizophrenia: 2004 - 2022

	Behavior	EEG
Controls	1st: Herzog 2004; repeated in most other studies	1st: Plomp et al., 2013; repeated in most other studies
Schizophrenia		
Relatives (Sz)	Chkonia 2010	Da Cruz 2020
First Episode	Favrod 2018	Favrod 2018
Depression	Chkonia 2012	Favrod 2019
Bipolar	Chkonia 2012	Garobbio 2021
Schizotypy	Cappe 2012	Favrod 2017
Adolescents with psychosys	Holzer 2009	
Schizoaffective	Chkonia 2012	
Alcohlism	Chkonia 2012	



Genetics: Bakanidze et al., 2013
Shaqiri et al., submitted

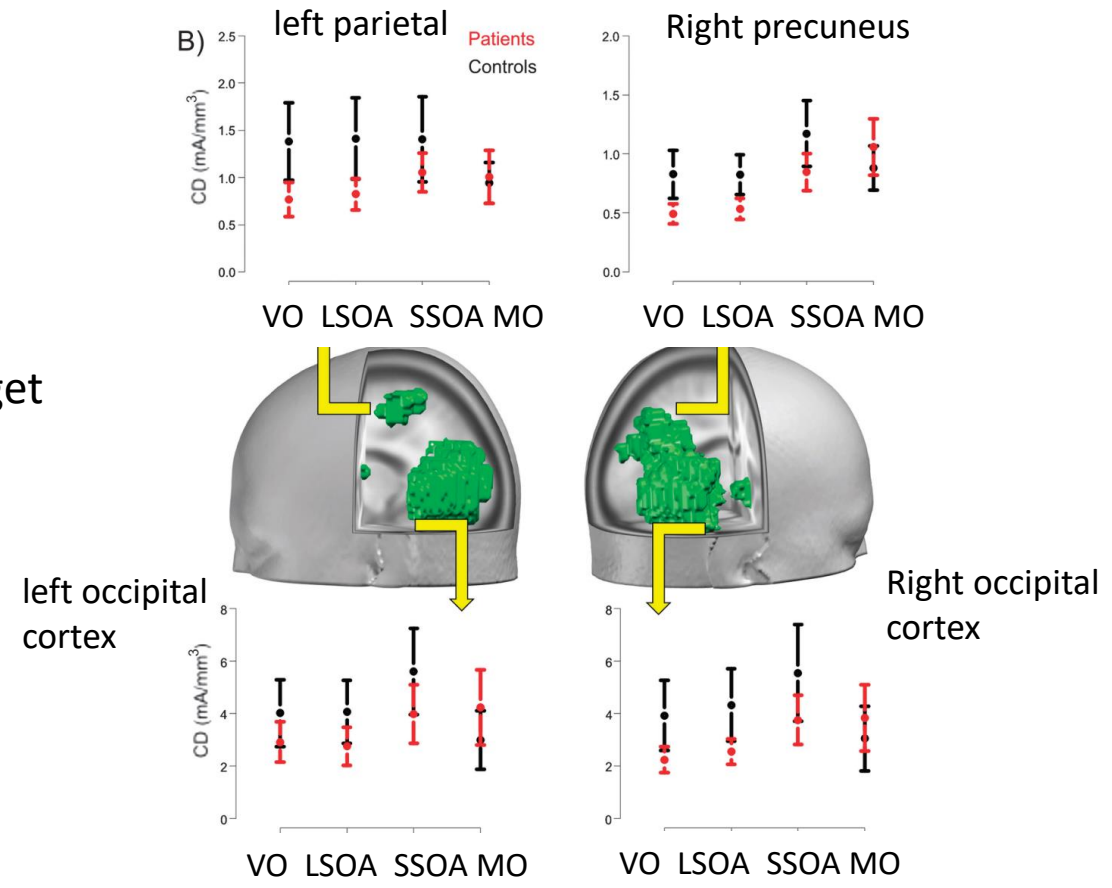
Theory: Herzog 2013: Schizophrenia and visual backward masking: a general deficit of target enhancement
Herzog 2015: Visual masking & schizophrenia

ADDITIONAL SLIDES

EEG task: Source imaging

Differences schizophrenia patients vs. controls, when target present:

- Right precuneus
- Left parietal cortex: dorsal stream
- Left and right lateral occipital cortex (LOC): ventral stream
- Left and right insula: regulates the interaction between selective attention and arousal to keep focused on the target



Plomp et al., 2013
Da Cruz et al.; 2020

APP

Da Cruz et al., 2018

- filtering via a bandpass filter of 1-40 Hz
- removal of line-noise
- re-referencing to the biweight estimate of the average of all electrodes
- removal and 3D spline interpolation of bad electrodes
- removal of bad epochs
- independent component analysis (ICA) to remove artifacts related to eye movements, muscle activity, and bad electrodes
- and removal of epoch artifacts.
- The clean EEG data were then re-referenced to the common average reference.
- We extracted EEG epochs from 100 ms before (baseline) to 400 ms after stimulus onset. The averaged epochs for each participant were baseline corrected.
- On average, 0.5 channels per EEG recording were interpolated. The proportion of rejected trials was about 2% for each EEG recording.

Source Imaging - Visual backward masking

Da Cruz.; 2020
Siblings

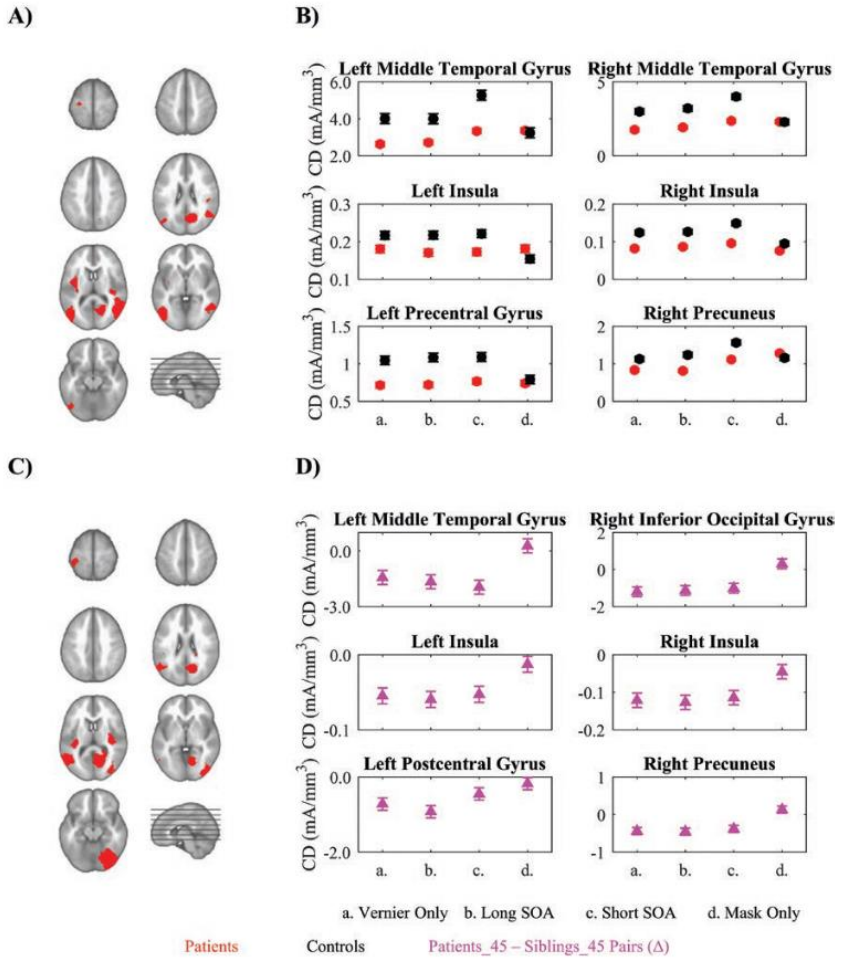
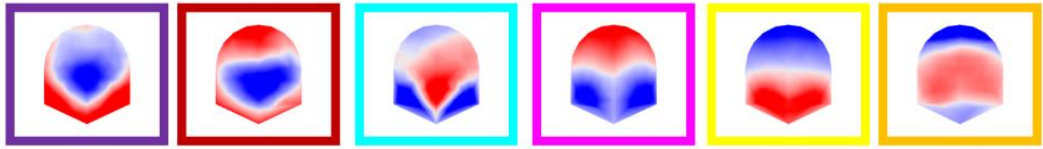


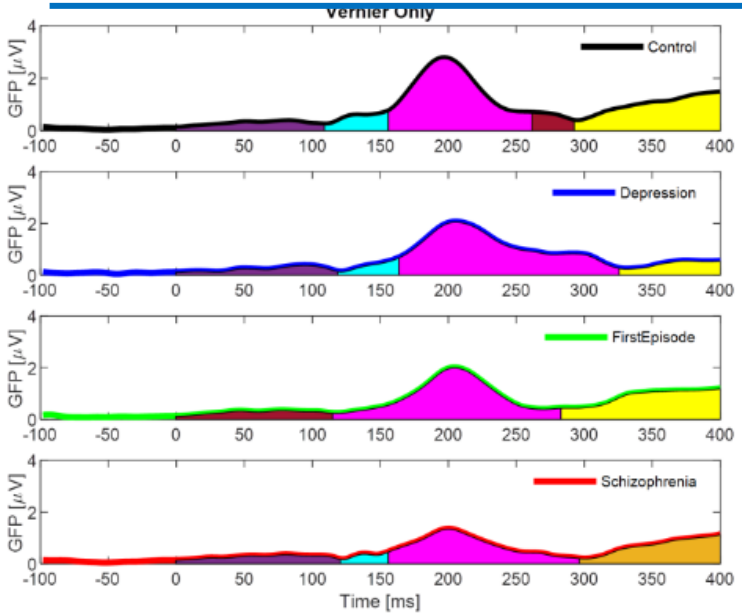
Fig. 3. Source imaging results. (A) Clusters exhibiting significant Group ×Condition interaction effects for patients vs controls are indicated in red. (B) Average current density (CD) at the center of mass (CoM) for the 6 clusters, indicating the direction of the interaction effects. (C) Clusters exhibiting significant Condition effects for patients_45 vs siblings_45. (D) Patients_45 vs siblings_45 difference score at the CoM for the 6 clusters, indicating the direction of the differences. In general, group differences were larger in target conditions compared to the Mask Only condition. Error bars indicate SEM. (Colored figure is available online.)

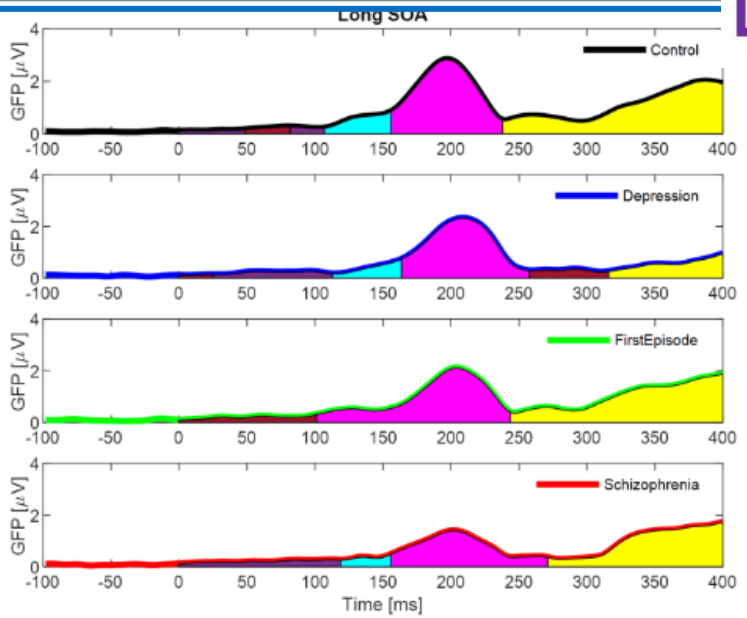
For patients vs controls, clusters were located bi-laterally in the middle temporal gyrus and insula, as well as in the left precentral gyrus and the right precuneus. For patients_45 vs siblings_45, clusters were located in the left middle temporal gyrus, right inferior occipital gyrus, right/left insula, left postcentral gyrus, and right precuneus

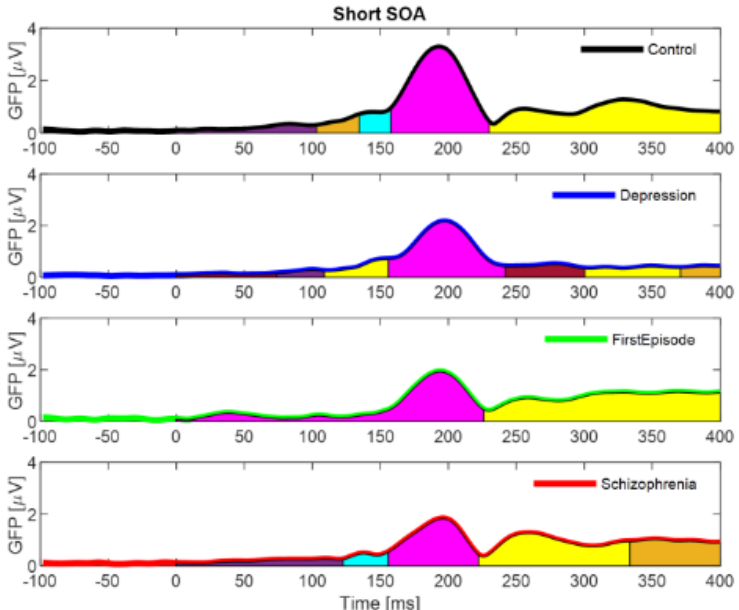
It has been proposed that the right insula regulates the interaction between selective attention and arousal to keep focused on the target. Too little activity of the right insula, as in patients, may lead to an impairment in collecting evidence for decision making. Too much activity of the right insula, as in siblings, might indicate that participants need to engage more to achieve a good performance in this challenging task.

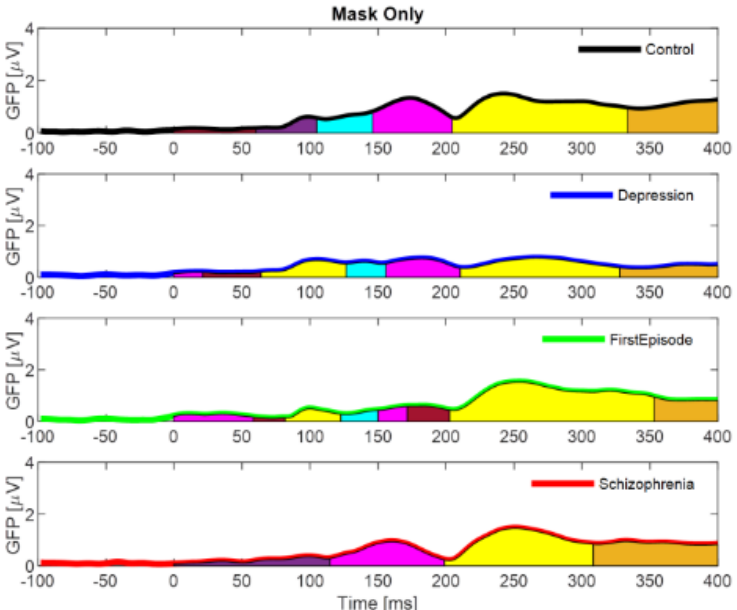
ERPs VBM segmented into microstates



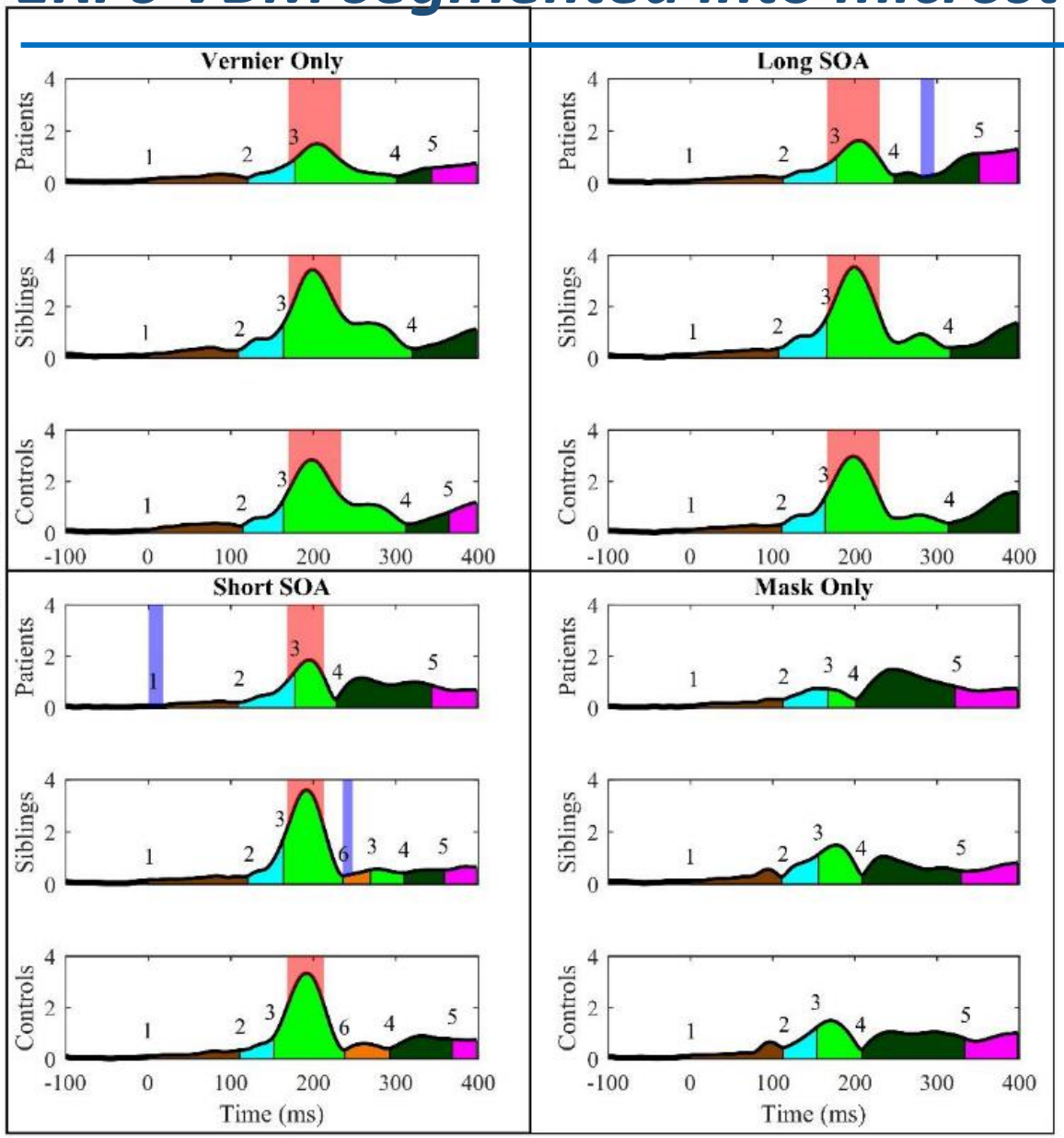


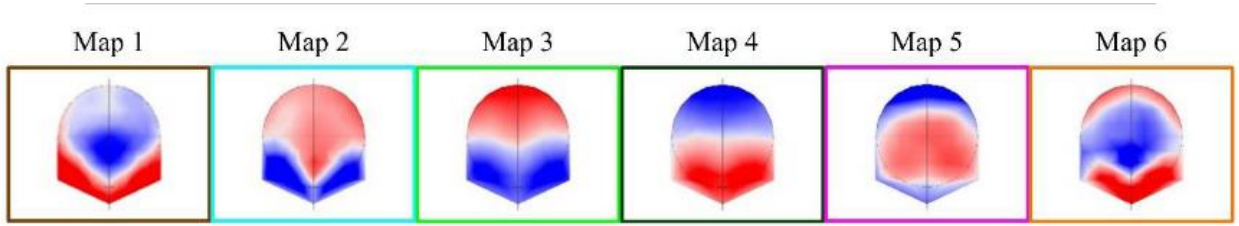






ERPs VBM segmented into microstates

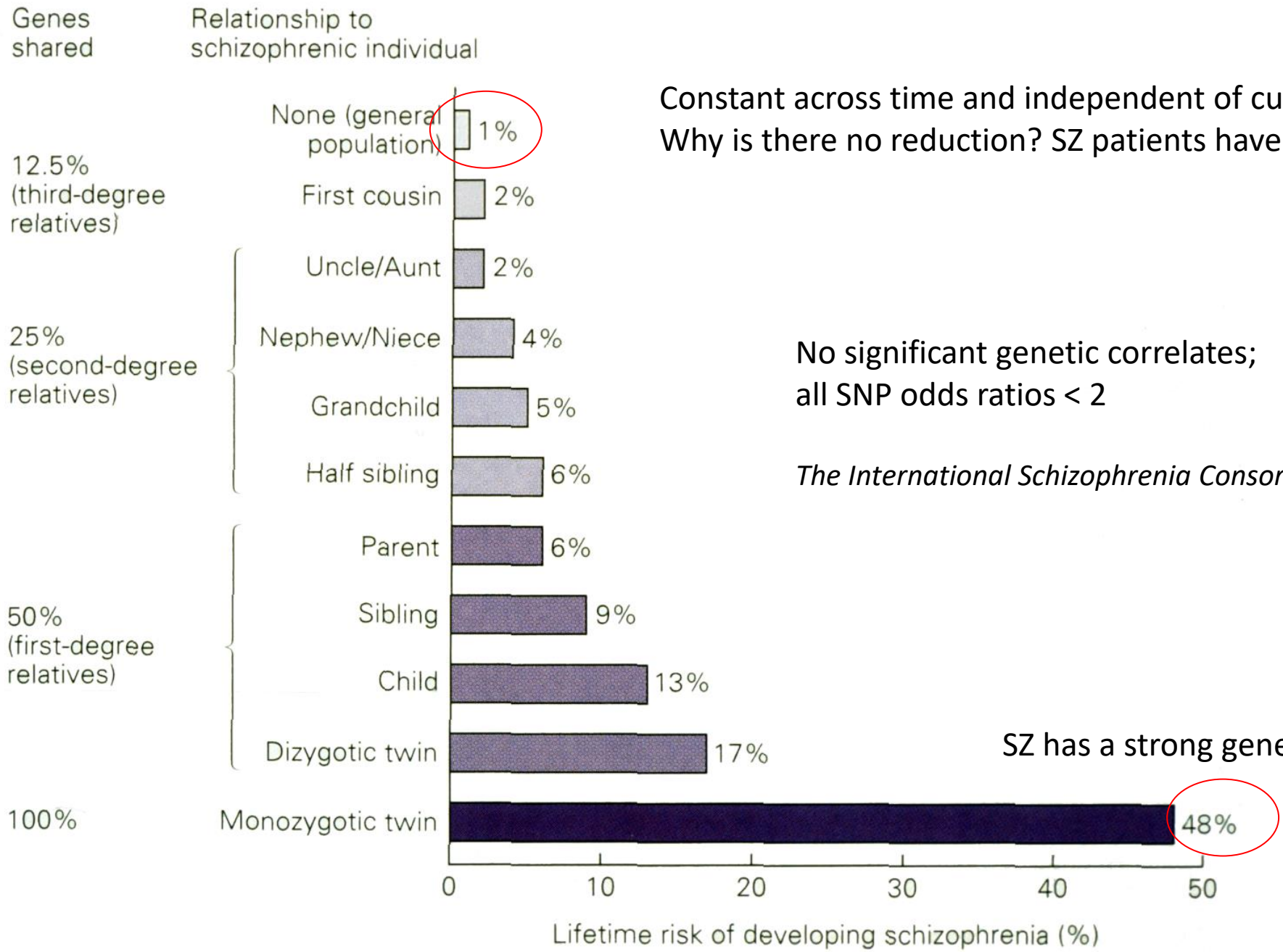




P100, P300 of VBM

P1, which appears at 100 ms, is thought to reflect the physical properties of the stimulus and sensory processes (Luck et al., 2000). The masking paradigm does not elicit a strong P1. For this reason, it was not investigated further.

Second, the P3 or P300, which appears around 300 ms, reflects cognitive processes such as working memory (Polich and Kok, 1995; Polich, 2007). Here, this component appears in the schizotypy study. It is possible that because the task is very challenging (5-element mask with short SOAs), participants need to allocate another resource (i.e., P300) to retrieve the information related to the vernier in their immediate memory.



Constant across time and independent of culture: 1% SZ
Why is there no reduction? SZ patients have less offsprings

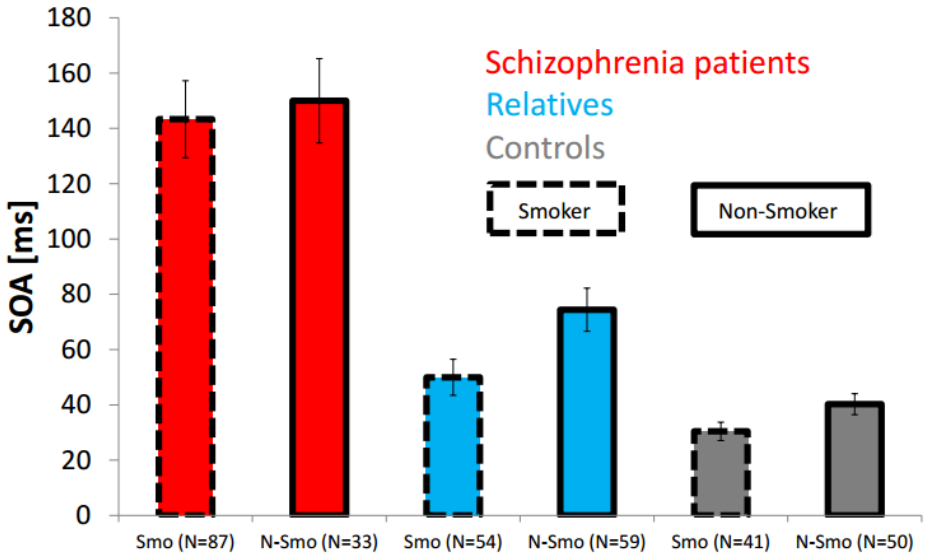
No significant genetic correlates;
all SNP odds ratios < 2

The International Schizophrenia Consortium, Nature, 2010

SZ has a strong genetic component

Genetics of visual backward masking

Nicotine consumption



Adapted from Shaqiri et al., 2015

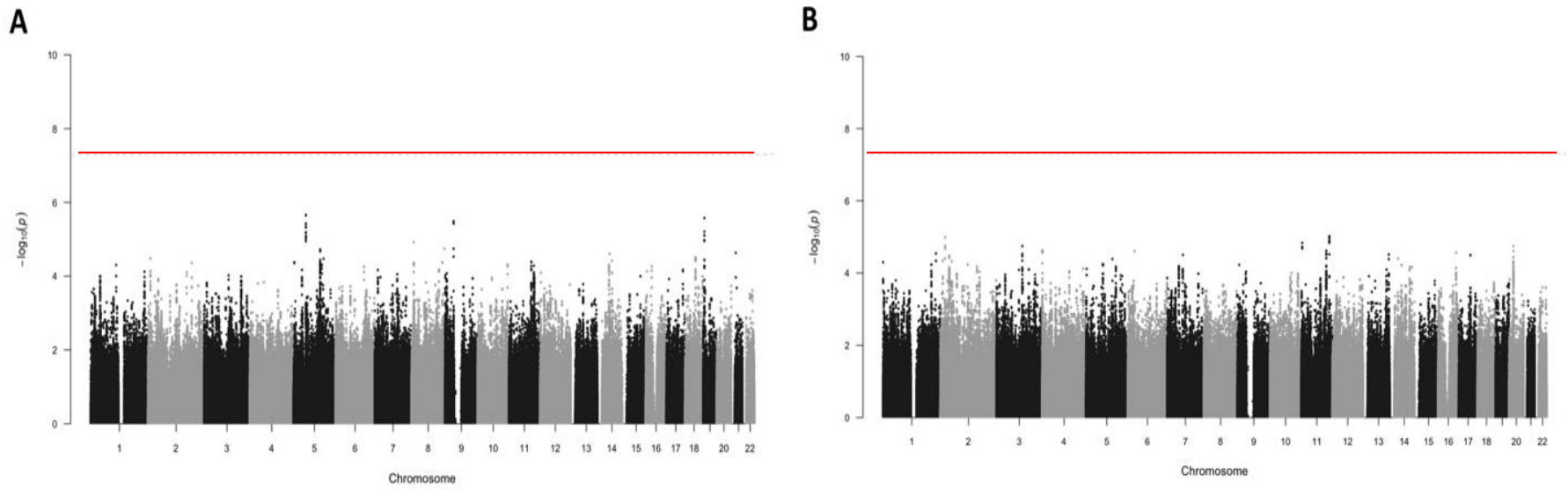
Cholinergic system important to boost weak but important information

Genetics of visual backward masking: GWAS

Genome wide association study with VBM as a covariate on:

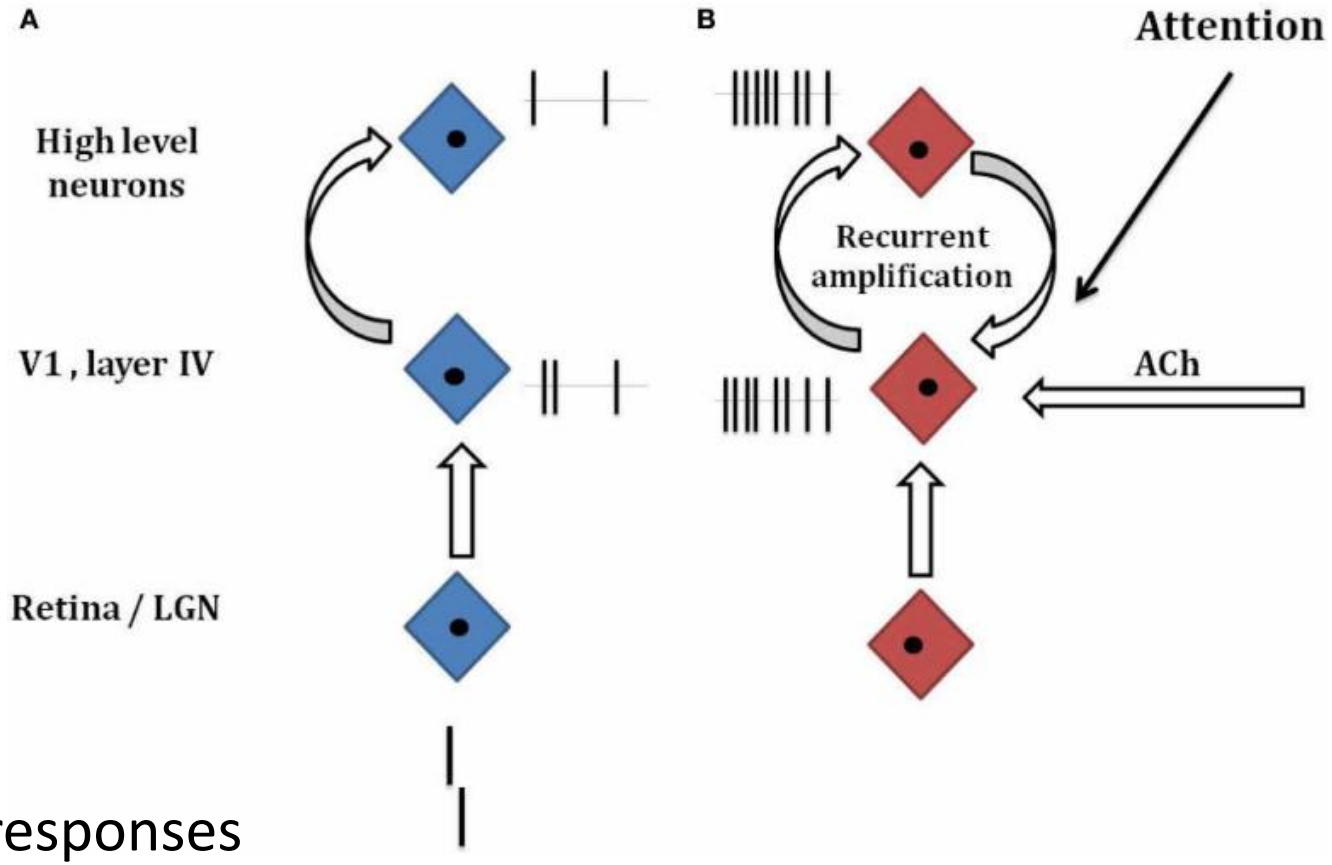
Schizophrenia patients: N=214
Relatives of patients: N=113
Controls: N=148

- No significant SNP or genes, but sample size is small (rs904952 did not pass quality controls)
- PRS scores correlated with the performance on the VBM task



Shaqiri et al., submitted

Target enhancement hypothesis



Herzog et al., 2013;
Herzog et al., 2015

- A) only weak neural responses
- B) recurent processing, attention, neuromodulation: weak response of the Vernier is amplified
- N1 amplitudes: amplification of the target
- N1 amplitudes lower in patients: process of target enhancement is dysfunctional

Conclusion and take home message

- Schizophrenia patients have difficulties to enhance faint sensory information (i.e., target enhancement deficit) reflected by the GFP.
- The endophenotype is the adaptive behavioral performance, not the neural correlates.
- The deficits are found along the entire continuum.
- Deficits are shared to some extent between disorders, reflecting the complex genetics of psychiatric diseases.

PSYCHIATRIC GENOMICS

Analysis of shared heritability in common disorders of the brain

The Brainstorm Consortium†

2018