Genetic interaction between neuronal nitric oxide synthase and serotonin transporter on prepulse inhibition in humans

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Introduction

- **Sensorimotor gating** is an automatic inhibitory process to filter out irrelevant stimuli. A proper gating function is important for goal-directed behavior. A deficit in gating is considered to play a role in psychopathology, particularly in disorganization and thought disorder.
- A standard measure of sensorimotor gating is the **prepulse inhibition** of the acoustic startle reflex (PPI). Numerous studies validated PPI as an important endophenotype and translational biomarker of psychiatric disorders.
- **Neuronal nitric oxide synthase** (nNOS or NOS1) is an enzyme mediating the production of nitric oxide (NO), implicated in several psychiatric conditions. We have recently found that NOS1 Ex1f-VNTR, a common variation in exon 1, was associated with PPI in humans (Rovný et al., 2018). Beside other effects, nNOS binds with the serotonin transporter and decreases its presence in cell membrane (Chanrion et al., 2007).
- Genetic variability of the **serotonin transporter-linked promoter region** (5-HTTLPR-VNTR) has been linked with several psychiatric disorders. Research indicates that that this polymorphism is also associated with inhibitory processing (e.g., Landrø et al., 2015).
- The current study investigated whether the NOS1 Ex1f-VNTR and 5-HTTLPR-VNTR jointly affect PPI.

Methods

- **Subjects:** 256 healthy volunteers, 159 men, age: 18–40 years (mean: 23.8, SD: 3.8 years), 68 smokers.
- **DNA samples** were collected by buccal swabs.
- **Auditory stimulation:** pulses: white noise, 105 dB, 40 ms; prepulses: white noise, 75 dB, 20 ms; prepulse-pulse intervals: 30, 60, 120 ms; intertrial interval: 10-20 s.
- **Eyeblink startle response assessment:** Electromyogram (EMG) of the orbicularis oculi muscles was recorded using surface electrodes. Startle response magnitude was defined as the maximal EMG value in the time interval 20-150 ms following the pulse onset.
- **PPI** was calculated as *(1 - mPP/mPA) × 100 %*, where *mPP* and *mPA* denote mean startle response in prepulse-pulse and pulse alone trials, respectively.
- Sex, smoking status and baseline startle reactivity were included as covariates.

Results

- When analyzed separately, only NOS1 Ex1f-VNTR, but not 5-HTTLPR-VNTR, was significantly associated with PPI (Fig. 1A).
- A joined analysis revealed a statistically significant interaction ($p<.05$) between NOS1 Ex1f-VNTR and 5-HTTLPR-VNTR on PPI (Fig. 1B).

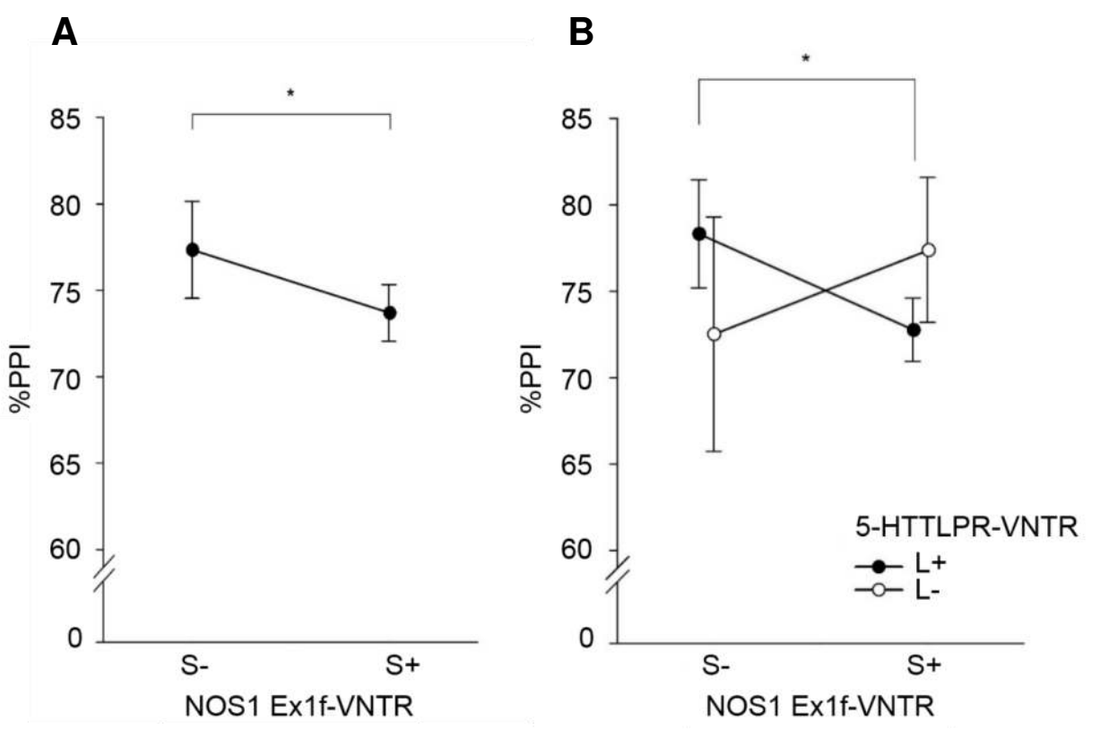

Figure 1. (A) *PPI as a function of NOS1 Ex1f-VNTR genotype.* ***(B)*** *PPI as a function of the combined genotype of NOS1 Ex1f-VNTR and 5-HTTLPR-VNTR.*

*S+/S-: presence/absence of the short allele of NOS 1 Ex1f-VNTR. L+/L-: presence/absence of the long allele of 5-HTTLPR-VNTR. Group sizes: S-/L- 11, S-/L+ 52, S+/L- 29 and S+/L+ 152. Plotted are means for prepulse-pulse interval of 120 ms and their 95% confidence intervals. * p<.05*

Conclusions

- Our data indicate that the genetic determinants of the nitrergic and the serotonergic neurotransmission play a role in sensorimotor gating.
- These associations may be relevant for the pathogenesis of mental disorders.

References

Chanrion et al. (2007), Proc Natl Acad Sci USA, 104: 8119–24.
Landrø et al. (2015), Neurosci Lett, 584: 109–112.
Rovný et al. (2018), Nitric Oxide, 80: 32–36.

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