

# The functional coding variant Asn107Ile of the neuropeptide S receptor gene (NPSR1) is associated with schizophrenia and modulates verbal memory and the acoustic startle response

## Background

The novel **neuropeptide S** demonstrates **anxiolytic-like** and stress-reducing effects in rodent models [1].

NPS **blocks the potentiation of fear** typically observed when the acoustic startle response is enhanced by conditioned shock [2].

NPS **improves memory retention** but not acquisition pointing to a specific effect on memory consolidation [3].

NPS blocks NMDA-antagonist induced prepulse inhibition (PPI) deficits suggesting an **antipsychotic effect** of NPS [4].

A **functional coding variant** within the neuropeptide S receptor gene (NPSR1) leads to an amino acid exchange (Asn107Ile, rs324981) with a **gain-of-function** in the Ile107 variant encoded by the T-allele [5].

In **humans**, the T-allele of this Asn107Ile variant was associated with panic disorder in two independent samples [6,7].

**Aim of the study: Exploring the role of NPSR1 in schizophrenia.**

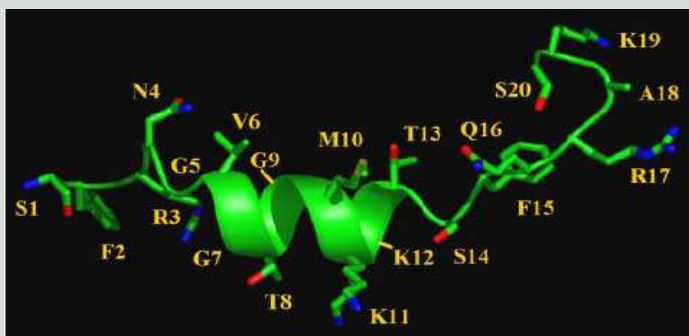


Figure 1: Putative structural conformation of NPS in the context of receptor binding, showing an-helix in the region determined to contain a nascent helix in the unbound, solubilised peptide. Adopted from [8].

## Methods

### Sample

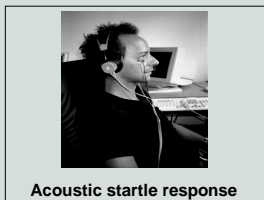
The NPSR1 encoding variant Asn107Ile (rs324981) was genotyped in a case-control sample including 778 schizophrenia patients and 713 healthy control subjects.

### Memory functions

In a subset of 199 schizophrenia patients and 204 healthy control subjects, verbal memory was assessed using the Rey Auditory Verbal learning test (AVLT).

### Acoustic startle response

Amplitude of acoustic startle response and prepulse inhibition (PPI) were measured in a subset of 69 schizophrenia patients.



## References

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- [9] Lennertz, L. et al. The functional coding variant Asn107Ile of the neuropeptide S receptor gene (NPSR1) is associated with schizophrenia and modulates verbal memory and acoustic startle. In preparation.

## Acknowledgements

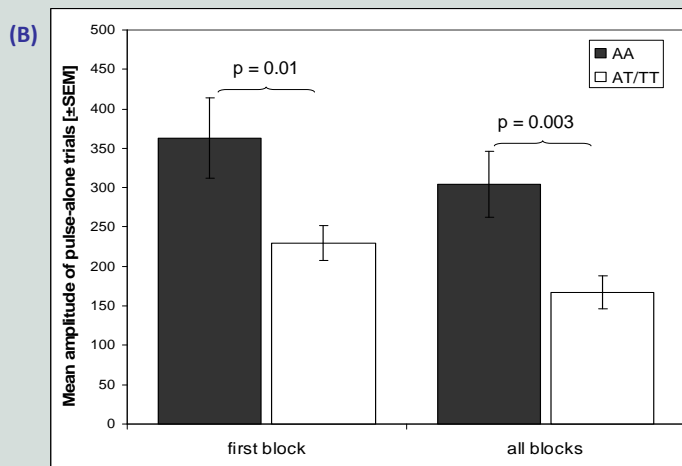
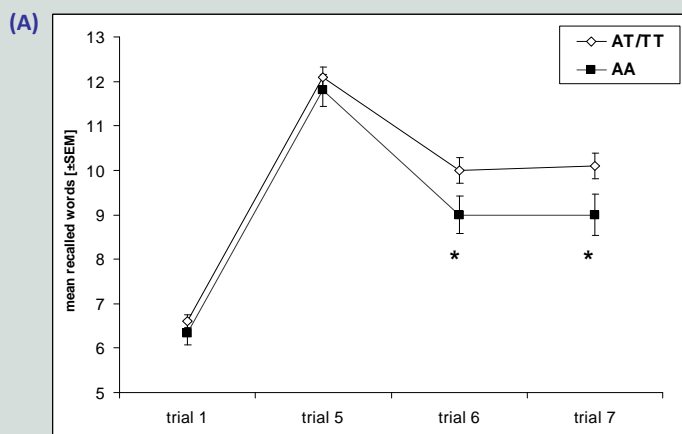
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## Results

NPSR1	Schizophrenia cases N = 778	Healthy controls N = 713	Odds ratio [95% CI]
Genotypes			
AA	243 (31.2%)	190 (26.6%)	1.25 [0.99-1.56]
AT	388 (49.9%)	359 (50.4%)	0.98 [0.80-1.20]
TT	147 (18.9%)	164 (23.0%)	0.78 [0.61-1.00]
Alleles			
A	874 (56.2%)	739 (51.8%)	1.19 [1.03-1.38]
T	682 (43.8%)	687 (48.2%)	0.84 [0.73-0.97]

Armitage trend test: global  $p = 0.01685$

### Functional characteristics of the low-functioning risk-variant Asn107



(A) Schizophrenia patients carrying the AA genotype show impaired memory consolidation compared to carriers of the risk-buffering T-allele (\* $p < 0.05$ ).

(B) Increased acoustic startle amplitudes but unaffected PPI was found in schizophrenia patients carrying the AA genotype.

## Discussion

The low-functioning NPSR1 Asn107 variant was significantly associated with schizophrenia leading to a probably less active NPS system.

The genetically driven less active NPS system may contribute to impaired memory consolidation and changed acoustic startle response commonly found in schizophrenia patients.

We suggest that NPS may attenuate schizophrenia symptoms and thus constitutes a highly promising antipsychotic drug target [4,9].