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Abstract: The neuropeptide S (NPS) system contributes to the pathogenesis of anxiety. The more active T allele of the functional rs324981 variant in the neuropeptide S receptor gene (NPSR1) is associated with panic disorder (PD) and distorted cortico-limbic activity during emotion processing in healthy adults and PD patients. This study investigated the influence of NPSR1 genotype on fronto-limbic effective connectivity within the developing brain. Sixty healthy subjects (8-21 years) were examined using an emotional go-nogo task and fMRI. Fronto-limbic connectivity was determined using Dynamic Causal Modeling. In A allele carriers, connectivity between the right middle frontal gyrus (MFG) and the right amygdala was higher in older (≥14 years) than that in younger (=14 years) showed a reduction of fronto-limbic connectivity between the MFG and both the amygdala and the insula. Fronto-limbic connectivity varied between NPSR1 genotypes in the developing brain suggesting a risk-increasing effect of the NPSR1T allele for anxiety-related traits via impaired top-down control of limbic structures emerging during adolescence. Provided robust replication in longitudinal studies, these findings may constitute valuable biomarkers for early targeted prevention of anxiety disorders.