



# Neuropeptide Y (NPY) gene: Impact on emotional processing and treatment response in anxious depression

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## Abstract

Neuropeptide Y (NPY) has been found to play a role in the pathomechanism of both anxiety and depression. Thus, NPY is a promising candidate in the investigation of the clinical phenotype of “anxious depression”. Five NPY gene variants were investigated for an influence on antidepressant treatment response in a sample of 256 patients with depression. Additionally, NPY gene impact on amygdala activation during facial emotion processing was analyzed in a subsample of 35 depressed patients. Particularly in anxious depression, the less active NPY rs16147 –399C allele conferred slow response after 2 weeks and failure to achieve remission after four weeks of treatment. The rs16147 C allele was further associated with stronger bilateral amygdala activation in response to threatening faces in an allele-dose fashion. The present results point towards a possible influence of functional NPY gene variation on antidepressant treatment response in anxious depression, potentially conveyed by altered emotional processing.

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## 1. Introduction

Depression and anxiety disorders occur with a high degree of comorbidity conferring increased overall morbidity, poorer acute and long-term outcome as well as increased suicide

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risk (Lydiard and Brawman-Mintzer, 1998). The clinical phenotype of anxious depression has been suggested to possibly constitute a diagnostic entity of its own requiring specific diagnostic and therapeutic attention (Silverstone and von Studnitz, 2003). Indeed, accumulating evidence points to anxious features of depression complicating the course of antidepressant treatment (e.g. Bagby et al., 2002; Fava et al., 2008; see Nelson, 2008). In a recent analysis, we observed significantly decreased response rates after four (26.3% vs 54.2%,  $p=0.0005$ ) and six (65.3% vs 78.1%,  $p=0.014$ ) weeks of treatment for anxious depression as defined by a HAM-D anxiety/somatization factor score  $\geq 7$  in 340 Caucasian in patients with a DSM-IV major depressive episode (MDE), particularly in the subsample of major depression (MDD) ( $N=256$ ) (Domschke et al., in press).

Neuropeptide Y (NPY) (MIM \*162640) is widely expressed in the central nervous system including the amygdala (Marcos et al., 1999) and has repeatedly been suggested to play a pivotal role in the pathophysiology of anxiety and depression as well as the mediation of treatment response in both disorders (see Heilig, 2004; Obuchowicz et al., 2004), which renders NPY a promising candidate in the investigation of the clinical phenotype of anxious depression.

NPY as well as NPY Y1 receptor knock-out mice and rats treated with NPY Y1 receptor antagonists exhibit significantly higher anxiety levels as compared to wild-type animals (Bannon et al., 2000; Karl et al., 2005; Wahlestedt et al., 1993). Conversely, in a wide range of animal models anxiolytic-like effects of NPY have been observed (Broqua et al., 1995; Heilig et al., 1989, 1993; Karlsson et al., 2005; Sajdyk et al., 1999; Sorensen et al., 2004; Tovote et al., 2004). In animal models of depression, suppressed central NPY levels have been reported (Caberlotto et al., 1998, 1999), while antidepressant treatment led to an up-regulation of central NPY synthesis (Husum et al., 2000; Mathé et al., 2007; Stenfors et al., 1989; Stenfors et al., 1994). Accordingly, central NPY administration resulted in antidepressant-like effects (Redrobe et al., 2002; Stogner and Holmes, 2000). In depressed patients as well as in post-mortem tissue of suicide victims, a robust suppression of cerebrospinal fluid (CSF) NPY levels has been found (Heilig et al., 2004; Widdowson et al., 1992; Widerlöv et al., 1988). Long-term treatment with the selective serotonin reuptake inhibitor (SSRI) citalopram led to a significant increase in NPY CSF concentrations (Nikisch et al., 2005). Anti-anxiety as well as anti-stress effects of NPY have been suggested to be in part mediated by the amygdala, particularly the lateral/basolateral complex (e.g. Primeaux et al., 2005; Sajdyk et al., 2002), where NPY and GABA are co-localized (McDonald and Pearson, 1989).

In anxiety and anxiety disorders, particular evidence for a risk locus on chromosome 4q31–34 encompassing the NPY gene (chromosome 4q31.3–32) has been reported (Kaabi et al., 2006). Neuropeptide Y system polymorphisms have been found to be possibly involved in the pathogenesis of panic disorder (Domschke et al., 2008a) and unipolar depression with a significantly elevated frequency of the NPY rs16147 –399C allele in depressed patients (Heilig et al., 2004), while another study failed to detect an influence of NPY gene variation on panic disorder or major depression (Lindberg et al., 2006). NPY rs16147 located in the promoter region of the gene is of particular functional relevance, since

the –399C allele has been shown to alter NPY expression in vitro by accounting for a 30% decrease in mRNA expression (Zhou et al., 2008). Furthermore, a low-NPY-expression diplotype containing the NPY –399C allele was reported to be associated with increased amygdala activity in response to threat-related facial expressions in healthy probands (Zhou et al., 2008).

Thus, given the converging lines of support for a pivotal role of NPY in both anxiety and depression as well as growing evidence for the combined clinical phenotype of anxious depression to be associated with impaired treatment response, in the present study the influence of several NPY gene variants including the functional NPY rs16147 on antidepressant treatment response was investigated in a sample of patients with major depression, particularly the subtype of anxious depression. In order to identify potentially mediating neurobiological mechanisms, we further investigated the impact of NPY gene variants that were significantly associated with poor treatment response in our sample on amygdala activity by means of functional magnetic resonance imaging (fMRI). The amygdala is a core structure in limbic emotion processing circuitries (Davis and Whalen, 2001). Several studies have shown that depression (Phillips et al., 2003) as well as trait anxiety and anxiety disorders (Etkin and Wager, 2007) are associated with increased amygdala responsiveness particularly to negative facial expressions. Consequently, amygdala responsiveness to negative facial cues is regarded having endophenotype character (Hariri et al., 2006; Hasler et al., 2004), a notion which has stimulated several studies in the emerging research field of imaging genetics, including the study by Zhou et al. (2008) as mentioned above. Therefore, we have analyzed NPY rs16147 and rs9785023 impact on amygdala activation during facial emotion processing in a subsample of 35 depressed patients. We hypothesized that the low-expressing variants, particularly rs16147 C alleles, are associated with increased amygdala responsiveness to negative facial expressions.

## 2. Experimental procedures

### 2.1. Sample

A sample of consecutive 268 unrelated patients of Northern European ancestry with current major depression (MDD) (mean age:  $49.7 \pm 15.4$ ;  $f=154$ ,  $m=114$ ) admitted for inpatient treatment was recruited at the Department of Psychiatry, University of Muenster, Germany, between 2004 and 2006. Only MDD patients with an HAM-D admission score  $>10$  and a treatment cycle of at least 6 weeks from baseline were considered leaving a final sample of  $N=256$  patients with MDD (mean age:  $50.4 \pm 14.9$ ;  $f=145$ ,  $m=111$ ) for pharmacogenetic analyses. Patients with Schizoaffective disorders or comorbid Substance Abuse disorders, mental retardation, pregnancy and neurological, neurodegenerative disorders or other clinically unstable medical illnesses impairing psychiatric evaluation were not included in this analysis. In order to minimize the risk of ethnic stratification, Caucasian descent was ascertained by Caucasian background of both parents.

From the overall sample, a subsample of  $N=35$  patients with MDD (mean age:  $37.3 \pm 12.6$ ;  $f=24$ ,  $m=11$ ) with complete rs16147 genotype and fMRI data was drawn for the imaging genetics analysis. Besides the usual MRI contraindications, additional exclusion criteria were any neurological abnormalities, substance abuse, former

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