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Short Communication

Benefits of a "vulnerability gene"? A study in serotonin transporter knockout mice

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HIGHLIGHTS

- Mice varying in 5-HTT expression were provided with a beneficial experience.
- The beneficial experience reduced anxiety-like behaviour in the open field test.
- This effect was only apparent in mice with reduced 5-HTT expression.
- Thus, susceptibility to beneficial experience seems to depend on 5-HTT genotype.

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ABSTRACT

Over the past years, certain "vulnerability genes" have been identified that play a key role in the development of mood and anxiety disorders. In particular, a low-expressing variant of the human serotonin transporter (5-HTT) gene has been described that renders individuals more susceptible to adverse experience and hence to the development of psychiatric diseases. However, some authors have recently argued that lower 5-HTT expression not only increases vulnerability to adverse experiences, but also enhances susceptibility to beneficial experiences, thus promoting phenotypic plasticity. The aim of the present study was to assess the effects of 5-HTT expression on susceptibility to beneficial experience in a hypothesis-driven experimental approach. Using a well-established rodent model for the human polymorphism, male heterozygous 5-HTT knockout (HET) and 5-HTT wildtype (WT) mice were either provided with the beneficial experience of cohabitation with a female (mating experience) or kept as naïve controls in single-housing conditions. Following the experimental treatment, they were tested for their anxiety-like behaviour and exploratory locomotion in three widely used behavioural tests. Interestingly, while cohabitation reduced anxiety-like behaviour and increased exploratory locomotion in the open field test in HET mice, it did not affect WT mice, pointing to a genotype-dependent susceptibility to the beneficial experience. Thus, our results might support the view of the low expressing version of the 5-HTT gene as a "plasticity" rather than a "vulnerability" variant.

The serotonin transporter (5-HTT) is a key regulator of serotonergic neurotransmission. By removing serotonin from the synaptic cleft, it regulates the strength and duration of the serotonergic response [1]. In humans, a polymorphism in the transcriptional control region of the 5-HTT gene SLC6A4 (5-HTT gene-linked polymorphic region, 5-HTTLPR) is associated with differences in the efficiency of serotonin clearance from the extracellular space. Specifically, a short (s) or a long (l) allele, differing in the number of repetitive elements, are characterized by either low or high transcriptional efficiency and, hence, either low or high serotonin re-uptake activity [1]. The lower expressing s allele has been linked to higher frequencies of anxiety-related traits and affective disorders [1,2]. In a study on gene-by-environment interactions, s-allele carriers were also more likely to suffer from depression—but only if they had experienced recent stressful life events or maltreatment during childhood [3]. As this finding could be replicated for several times (for review see [4]), the s allele of the 5-HTTLPR has often been referred to as "vulnerability gene" or "risk allele" in the scientific literature [5,6].

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However, this view has recently been questioned by Belsky and co-authors [6,7]. Based on a systematic review of studies on the interplay between 5-HTTLPR genotype and environmental factors, they suggest that lower 5-HTT expression might not only increase susceptibility to negative, but also to positive experiences with effects on emotionality in a "for-better-for-worse" manner [6,7]. According to this so-called *differential susceptibility hypothesis* [7,8], homozygous s-allele carriers are assumed to express greater developmental plasticity and are thus expected to develop *more* psychiatric symptoms than homozygous l-allele carriers in an *adverse* environment but *less* in a *beneficial* environment. In this context, the 5-HTTLPR s allele can be understood as "plasticity" rather than "vulnerability" gene [6]. Indeed, differential susceptibility has been described in human studies on the 5-HTTLPR (for a meta-analysis, see [9]). For example, a recent study found the personality trait neuroticism to be *higher* in s-allele carriers than l-allele carriers after a series of negative life events, but *lower* after a series of positive life events, thus indicating higher plasticity in individuals with lower 5-HTT expression [10].

However, human studies in this field are mostly observational retrospective studies, and evidence for differential susceptibility from hypothesis-driven experiments is still missing. Translational studies in rodents may therefore help to investigate the predictions made by the differential susceptibility hypothesis. In this context, a 5-HTT knockout mouse model allowing systematic variation of 5-HTT expression is of particular interest [11]. Wildtype mice are characterized by normal 5-HTT expression, heterozygous 5-HTT knockout mice exhibit a 50% reduction of 5-HTT expression, thus resembling human s allele carriers most, and homozygous 5-HTT knockout mice are completely 5-HTT deficient. In fact, higher vulnerability to adverse experiences has been detected in the knockout mouse model: while homozygous 5-HTT knockout mice have been found to display a range of general behavioural traits that resemble symptoms of mood and anxiety disorders in humans [12–14], heterozygous 5-HTT knockout mice have been found to differ from wildtypes in terms of increased anxiety-like and depression-like behaviour only following adverse experiences [15–17]. Accordingly, especially the heterozygous knockouts seem to be well suited for studies on gene-by-environment interactions [17].

As so far studies in the 5-HTT knockout mouse model mainly investigated vulnerability to adversity (but see [18]), the overall aim of the present study was to investigate susceptibility to a beneficial social experience in mice with either normal or reduced 5-HTT expression. While vulnerability has usually been measured as increase in anxiety-like and decrease in exploratory locomotion, we chose a treatment that has previously been shown to exert opposite effects on these behaviours. As sexual experience has been found to reduce anxiety and increase exploration [19–21], we cohabitated male heterozygous 5-HTT knockout (HET) and 5-HTT wildtype (WT) mice with a female in oestrous (mating group) and compared them to naïve controls (control group). By testing for anxiety-like behaviour and exploratory locomotion shortly after the treatment, we sought to test the hypothesis that the beneficial experience of cohabitation would differentially affect behaviour in WT and HET mice. Specifically, we expected to observe an overall decrease in anxiety-like behaviour and an increase in exploratory locomotion in all male mice following the cohabitation period, with the strongest effects being present in HET mice, thus indicating a genotype-dependent susceptibility to beneficial experiences.

All animals included in this study were heterozygous 5-HTT knockout and wildtype mice backcrossed into a C57BL/6J genetic background for more than 10 generations, derived from the internal stock of the Department of Behavioural Biology in Münster. The original breeding stock was obtained from the Division of Molecular Psychiatry, University of Würzburg, Germany. In sum, 40 male mice were used as experimental animals ($n = 20$ per genotype), aged 4 to 5 months at the beginning of the experiments. Additionally, 20 sexually mature WT females that were unfamiliar to the experimental animals were used for the cohabitation treatment.

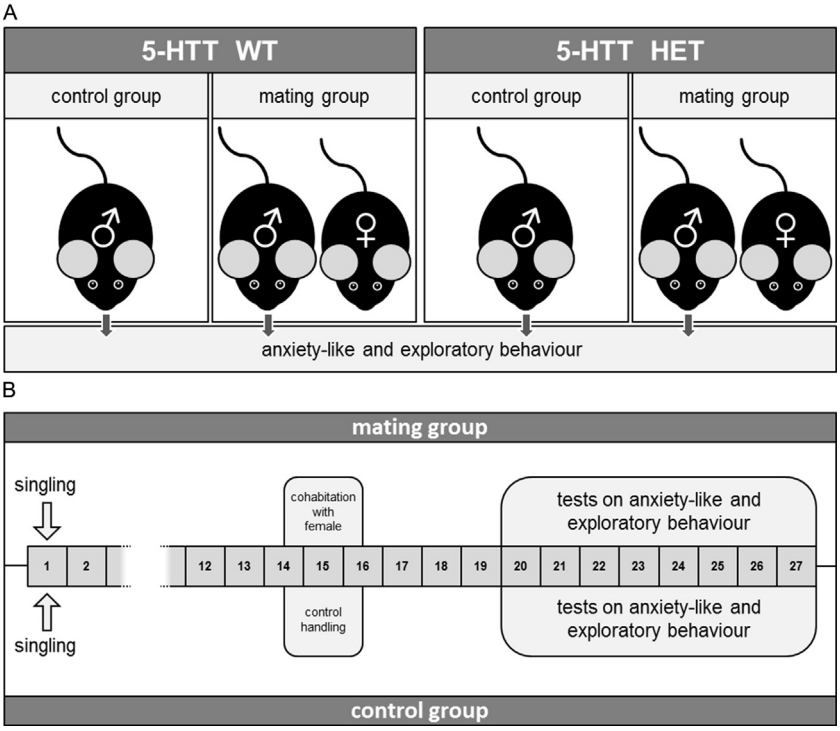

Fig. 1. *Experimental design.* (A) Experimental groups. 10 male 5-HTT wildtype (WT) and 10 male heterozygous 5-HTT knockout mice (HET) were either cohabitated with a female for 2 days (mating group) or kept as naïve controls in single-housing conditions (control group). (B) Time flow. Experimental animals were taken from their sibling groups on day 1. After two weeks, experimental groups were established, followed by behavioural testing between days 20 and 27.