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Review

Conserved role for the serotonin transporter gene in rat and mouse neurobehavioral endophenotypes

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ABSTRACT

The serotonin transporter knockout (SERT$^{-/-}$) mouse, generated in 1998, was followed by the SERT$^{-/-}$ rat, developed in 2006. The availability of SERT$^{-/-}$ rodents creates the unique possibility to study the conservation of gene function across species. Here we summarize SERT$^{-/-}$ mouse and rat data, and discuss species (dis)similarities in neurobehavioral endophenotypes. Both SERT$^{-/-}$ rodent models show a disturbed serotonergic system, altered nociception, higher anxiety, decreased social behavior, as well as increased negative emotionality, behavioral inhibition and decision making. Used to model a wide range of psychiatric disorders, SERT$^{-/-}$ rodents may be particularly valuable in research on neurodevelopmental disorders such as depression, anxiety, and possibly autism. We conclude that SERT function is conserved across mice and rats and that their behavioral profile arises from common neurodevelopmental alterations. Because mice and rats have species-specific characteristics that confer differential research advantages, a comparison of the two models has heuristic value in understanding the mechanisms and behavioral outcome of SERT genetic variation in humans.

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1. Introduction

Serotonin (5-HT) is a highly conserved neuromodulator that plays a key role in various brain processes, including emotion, motivation, cognition, feeding, sleep and nociception (Serretti et al., 2006). Extracellular 5-HT levels are regulated by the reuptake function of the 5-HT transporter (SERT) (Murphy et al., 2001, 2004, 2008). Created in 1998, the SERT knockout ($^{-/-}$) mouse (Bengel et al., 1998) soon became a popular model for translational biomedical research focusing on brain processes in health and disease (Adamec et al., 2006; Armando et al., 2003; Holmes et al., 2002b, 2003b; Murphy et al., 2001, 2003; Perona et al., 2008; Persico et al., 2001; Sora et al., 1998). Several different SERT$^{-/-}$ mouse strains are currently available for researchers, all demonstrating a substantial similarity in their neurobehavioral abnormalities (Gardier, 2009; Zhao et al., 2006), also see recent reviews in (Fox et al., 2007a; Murphy et al., 2008; Murphy and Lesch, 2008).

Because the rat is commonly used in behavioral, pharmacological, toxicological and neurochemical studies, attempts have been made to generate knockout rats using the 'mouse' homologous recombination technique in embryonic stem cells. Although this technique failed in rats, N-ethyl-N-nitrosuea (ENU)-driven target-selected mutagenesis has proven to be a promising alternative approach. Using this approach, several knockout rats have been generated (Smits et al., 2006), including a SERT$^{-/-}$ rat. In 2007, Homberg and co-workers presented the first data on characterization of the SERT$^{-/-}$ rat (Homberg et al., 2007a). This unique situation, when both mouse and rat SERT$^{-/-}$ models became available, was the focus of an international symposium on SERT knockout models, held in 2008 at Radboud University (Nijmegen, the Netherlands). Co-organized by AVK and JRH, this symposium was aimed at fostering a multidisciplinary dialogue between several SERT$^{-/-}$ mouse and rat laboratories, with a particular focus on (dis)similarities in neurobehavioral domains between the two species.

Notably, mice and rats not only differ in size, but there are also species differences in the number of chromosomes, genomic characteristics (Guryev et al., 2008), cognitive capabilities (this review), and receptor functions (Goodwin et al., 1985, 1987). Yet, the toolbox to manipulate the animal genome is far more extensive for mouse than for the rat. Because both mice and rats are used to model human health and disease, it is important to establish whether gene function is conserved across mouse and rat (Kalueff et al., 2008b; Kas et al., 2007).

Here we comprehensively evaluate SERT$^{-/-}$ mouse and rat endophenotypes, summarize their differences and similarities (Table 1), cluster these endophenotypes into major neuropsychiatric domains, and outline their common underlying mechanisms (Figs. 1 and 2). As discussed during the Nijmegen symposium, the overall SERT gene function in the brain appears to be conserved across mice and rats. We also posit that the wide range of endophenotypes displayed by SERT$^{-/-}$ rodents may be traced back to common neurodevelopmental changes, making these rodents particularly valuable for modeling developmental brain disorders. Because mice and rats have species-specific characteristics that confer research advantages, joining forces will have heuristic value to obtain new insights into the mechanisms and behavioral outcomes of SERT genetic variation in humans.

2. Brain neurochemistry

The function of the SERT is to reuptake 5-HT from the synaptic cleft into the presynaptic neuron for recycling or metabolic degradation. Under normal physiological conditions, the reuptake by SERT is the principle means for actively clearing 5-HT from the synaptic cleft. The major consequence of SERT inactivation is rapid increase in extraneuronal 5-HT levels, as determined by microdialysis in both SERT$^{-/-}$ mice (Fabre et al., 2000; Mathews et al., 2004; Murphy et al., 1999; Shen et al., 2004) and rats (Homberg et al., 2007a; Olivier et al., 2008c). The extent of this increase is quite similar (7–9-fold) in both SERT$^{-/-}$ mice and rats. SERT$^{-/-}$ mice show a lack of 5-HT uptake in brain synaptosomes (Bengel et al., 1998), and a very weak uptake in primary neuronal cultures derived from embryonic cells (Pan et al., 2001). In SERT$^{-/-}$ rat synaptosomes, 5-HT uptake is reduced, but not absent (Homberg et al., 2007a). Furthermore, a marked reduction in 5-HT tissue levels has been found in several brain regions of SERT$^{-/-}$ mice (Bengel et al., 1998; Fabre et al., 2000; Murphy et al., 1999) and rats (Homberg et al., 2007a). While reduced 5-HT uptake is a likely explanation, decreased 5-HT synthesis, as found in SERT$^{-/-}$ mice (Kim et al., 2005), could also contribute to lowered 5-HT levels.

As a consequence of the altered 5-HT homeostasis in SERT$^{-/-}$ animals, the density and/or function of 5-HT receptors are likely to change (Table 1). The presynaptic inhibitory 5-HT$_{1A}$ receptor in the raphe nuclei is important for regulation of raphe neuronal firing rate, whereas postsynaptic 5-HT$_{1A}$ receptors in terminal regions contribute to 5-HT neurotransmission. SERT$^{-/-}$ mice display decreased 5-HT$_{1A}$ binding sites, mRNA, and protein levels in the raphe nuclei and terminal regions (Li et al., 1999). Although inhibitory 5-HT$_{1A}$ receptors are desensitized in SERT$^{-/-}$ mice (Bouali, 2003; Gobbi et al., 2001; Mannoury la et al., 2001), the spontaneous firing rate of raphe neurons is decreased in these mice (Gobbi et al., 2001; Lira et al., 2003), possibly representing an additional mechanism to counteract the high extracellular 5-HT levels. The SERT$^{-/-}$ mouse postsynaptic 5-HT$_{1A}$ receptors in the hippocampus are unaltered in the CA1 area (Mannoury la et al., 2001) and less functional in the CA3 area (Gobbi et al., 2001), suggesting region-specific function of these receptors. Likewise, SERT$^{-/-}$ rats display decreased 5-HT$_{1A}$ receptor density in raphe nuclei and several terminal regions (Homberg et al., 2008a), as well as reduced firing rate of raphe neurons after 8-OH-DPAT application (Olivier et al., unpublished observations). In line with 5-HT$_{1A}$ receptor down-regulation, 8-OHDPAT- (Homberg et al., 2008a; Li et al., 1999) and flesinoxan-induced (Olivier et al., 2008a) hypothermia is reduced in mice and rats. Despite these consistent findings, the 5-HT$_{1A}$-receptor-mediated hypothermia in mice most likely reflects 5-HT$_{1A}$ autoreceptor desensitization, while the same response in rats is thought to be mediated by postsynaptic 5-HT$_{1A}$ receptors (Goodwin et al., 1985, 1987). Interestingly, 5-HT$_{1A}$ receptor antagonist-mediated reduction of stress-induced hyperthermia is still intact in SERT$^{-/-}$ rats (Olivier et al., 2008a), which could be due to the high endogenous 5-HT levels. While the hypothermic responses could reflect both receptor desensitization and/or increased receptor occupation, reduced 5-HT$_{1A}$ receptor density and firing in SERT$^{-/-}$ animals support the former.

Functional alterations have also been found for 5-HT$_{1B}$ receptors in SERT$^{-/-}$ mice and rats. In SERT$^{-/-}$ rats, the 5-HT$_{1B}$ receptor agonist CP94253 fails to potentiate cocaine's locomotor

Table 1
Summary of neurobehavioral phenotypes observed in SERT knockout rodent models.

Endpoints	SERT knockout mice		SERT knockout rats	
	Effect	References	Effect	References
I. Neurochemistry				
Extracellular 5-HT levels	↑	Fabre et al. (2000), Mathews et al. (2004), Shen et al. (2004)	↑	Homberg et al. (2007a), Olivier et al. (2008c)
5-HT tissue levels	↓	Bengel et al. (1998), Fabre et al. (2000), Murphy et al. (1999)	↓	Homberg et al. (2007a)
5-HT$_{1A}$ sensitivity	↓	Bouali (2003), Gobbi et al. (2001), Mannoury la et al. (2001)	↓	Homberg et al. (2008a), Olivier et al. (2008a)
5-HT$_{1A}$ binding/mRNA/protein	↓	Li et al. (1999)	↓	Homberg et al. (2008a)
Firing rate in raphe following 5-HT$_{1A}$ agonist administration	↓	Gobbi et al. (2001), Lira et al. (2003)	↓	*,**
5-HT$_{1A}$ agonist-induced hypothermia	↓	Li et al. (1999)	↓	Homberg et al. (2008a), Olivier et al. (2008a)
5-HT$_{1B}$ receptor sensitivity	↓	Holmes et al. (2002a), Fabre et al. (2000), Shanahan et al. (2009)	↓	Homberg et al. (2008a)
Brain synaptosomes 5-HT uptake	Absent	Bengel et al. (1998)	↓	Homberg et al. (2007a)
Number of 5-HT$_{1B}$ receptors	↓	Fabre et al. (2000), Shanahan et al. (2009)	=	Homberg et al. (2008a)
5-HT uptake in primary neuronal cultures	↓	Pan et al. (2001)		
5-HT synthesis	↓	Kim et al. (2005)		
5-HT$_{1B}$ receptor G-protein coupling	↓	Fabre et al. (2000)		
Density of 5-HT$_{2A}$ receptors	=	Qu et al. (2005), Rioux et al. (1999)		
5-HT$_{2A/2C}$ agonist-induced incorporation of arachidonic acid	↑	Basselin et al. (2009)		
Phospholipase A2 coupling of 5-HT$_{2A}$ receptors	↓	Qu et al. (2005), Rioux et al. (1999)		
Barrel-like patterns in somatosensory cortex	Absent	Persico et al. (2001)		
Functional integrity of barrel cortex	↓	Esaki et al. (2005)		
Maturity of thalamic axons	↓	Rebsam et al. (2002)		
Cell density in neocortex and macrocephaly	↑	Altamura et al. (2007), Page et al. (2009)		
Length of apical dendritic branches of prefrontal cortical pyramidal neurons	↑	Wellman et al. (2007)		
II. Nociception				
Thermal hyperalgesia after incomplete sciatic nerve injury (females)	↓	Vogel et al. (2003)		
Bilateral mechanical allodynia after nerve injury in females	↑	Vogel et al. (2003)		
Complete Freud's adjuvant-induced hyperalgesia (females)	↓	Palm et al. (2008)		
Mechanical, thermal, and formalin-induced nociception (males)	=	Kayser et al. (2007)		
III. Miscellaneous behaviors				
Grooming frequency	=	Kalueff et al. (2007a)	↑	*
5-HT syndrome behaviors	↑	Kalueff et al. (2007a)	=	*
Pharmacogenic 5-HT behaviors	↑	Fox et al. (2007a,b, 2009)		
Homecage activity	↓	Hariri and Holmes (2006)		
Marble burying and digging activity	↓	Kalueff et al. (2006)		
IV. Exploratory behavior				
Motor and neurological functions	=	Kalueff et al. (2007a, 2008a), Zhao et al. (2006)	=	Olivier et al. (2008d)
Open arm activity in the elevated plus maze	↓	Lira et al. (2003)	↓	Olivier et al. (2008c)
Open field central horizontal exploration	↓	Alexandre et al. (2006), Kalueff et al. (2007a)	↓	Olivier et al. (2008c)
Perseverance-like turning and meandering behavior	↑	Kalueff et al. (2007a,b), Shanahan et al. (2009)	↑	*
Open field vertical exploration	↓	Kalueff et al. (2007a)	=	Olivier et al. (2008c)
Between-trial habituation for horizontal activity	↓	Alexandre et al. (2006), Kalueff et al. (2007a)		
V. Negative emotionality: anxiety and fear				
Open arm time in the elevated plus maze	↓	Ansorge et al. (2004), Holmes et al. (2003a), Popa et al. (2008)	↓	Olivier et al. (2008a)
Latency to start eating in novelty suppressed feeding test	↑	Ansorge et al. (2004), Lira et al. (2003)[#]	↑	Olivier et al. (2008a)
Thigmotaxis on the open field	↑	Holmes et al. (2003a), Ansorge et al. (2004), Kalueff et al. (2007a)	↑	Olivier et al. (2008a)

Table 1 (*Continued*)

Endpoints	SERT knockout mice		SERT knockout rats	
	Effect	References	Effect	References
Locomotor activity in novel environment	↓	Ansorge et al. (2004), Alexandre et al. (2006), Holmes et al. (2003a,b), Kalueff et al. (2007a), Zhao et al. (2006)	=	Olivier et al. (2008a)
Aversion for open environments under red light	=	Adamec et al. (2006)		
Open arm time in the elevated plus maze with cat odor	↓	Adamec et al. (2006)		
Light time in the dark–light test	↓	Popa et al. (2008)		
Recall of conditioned fear	↑	Wellman et al. (2007)		
Escaping latency in the emergence test			↑	Olivier et al. (2008a)
VI. Negative emotionality: behavioral despair and anhedonia				
Immobility in forced swim test[#]	↑	Holmes et al. (2002b)[#], Lira et al. (2003)[#]	↑	Olivier et al. (2008a)
Sucrose preference[#]	↓	Popa et al. (2008)[#]	↓	Olivier et al. (2008a)
Sucrose preference	=	Kalueff et al. (2006)[#], Perona et al. (2008)[#]	↓	Olivier et al. (2008a)
Immobility in tail suspension test	↑	Alexandre et al. (2006)[#], Zhao et al. (2006)[#], Popa et al. (2008)[#]		
Immobility in repeated forced swim test	↑	Wellman et al. (2007)[#]		
Footshock-induced place aversion			↑	[*]
Latency foot shock escape	↑	Ansorge et al. (2004)		
VII. Positive emotionality				
Cocaine-induced conditioned place preference	↑	Sora et al. (1998, 2001)	↑	Homberg et al. (2008a)
Cocaine-induced dopamine release	=	Shen et al. (2004)	=	[**]
Intravenous cocaine self-administration	=	Thomsen et al. (2009)	↑	Homberg et al. (2008a)
Breakpoints in food-reinforced paradigm	↓	Sanders et al. (2007)		
Food intake			↑	Homberg et al. (2009)
Locomotor effects following cocaine administration			↑	Homberg et al. (2008a)
VIII. Social behavior				
Aggression in the resident-intruder test	↓	Holmes et al. (2002a)	↓	Homberg et al. (2007b)
Social interaction	↓	Kalueff et al. (2007a), Moy et al. (2009), Page et al. (2009)	=	Homberg et al. (2007b)
Play behavior			↓	Homberg et al. (2007c)
IX. Cognitive functions				
Spatial working memory (open field and elevated plus maze habituation)	=	Kalueff et al. (2007b)		
Premature responding in 5-choice serial reaction time task			↓	Homberg et al. (2007b)
Correct response latency in 5-choice serial reaction time task			↑	Homberg et al. (2007b)
Behavior in the Pavlovian-to-Instrumental transfer task	=	Sanders et al. (2007)		
Correct responding in serial spatial reversal learning task			=	Homberg et al. (2007b)
Emotional decision making in Iowa Gambling Task			↑	Homberg et al. (2008b)
Latency to find hidden platform in the Morris water maze			↑	Olivier et al. (2008d)
Object recognition after 8 h			↓	Olivier et al. (2009)
Acute tryptophan depletion-induced object memory			↓	Olivier et al. (2008b)

↑ Increased, ↓ reduced, = no difference. Bold text indicates domain similarities between mouse and rat phenotypes, gray color indicates phenotypes that show species-specific difference.

[*] Nonkes and Homberg, unpublished observations.

[**] Olivier, Homberg and Cremers, unpublished observations.

[#] Strain-specific effect (some other mouse strains show the opposite phenotype).

effects (Homberg et al., 2008a), while in SERT$^{-/-}$ mice the 5-HT$_{1A/1B}$ agonist RU24969 has no effects on locomotion (Holmes et al., 2002a) or prepulse inhibition (Fabre et al., 2000; Shanahan et al., 2009). In mice, such 5-HT$_{1B}$ receptor desensitization is due to reduced density of the 5-HT$_{1B}$ receptor (Fabre et al., 2000; Shanahan et al., 2009) and reduced G-protein coupling (Fabre et al., 2000). In SERT$^{-/-}$ rats, no changes were found in 5-HT$_{1B}$ receptor density (Homberg et al., 2008a), suggesting that solely G-protein uncoupling contributes to the receptor desensitization.

Examining 5-HT$_{2A}$ receptors, both the density and phospholipase A2 coupling of the receptors are region-specifically altered in SERT$^{-/-}$ mice (Qu et al., 2005; Rioux et al., 1999). Recent studies

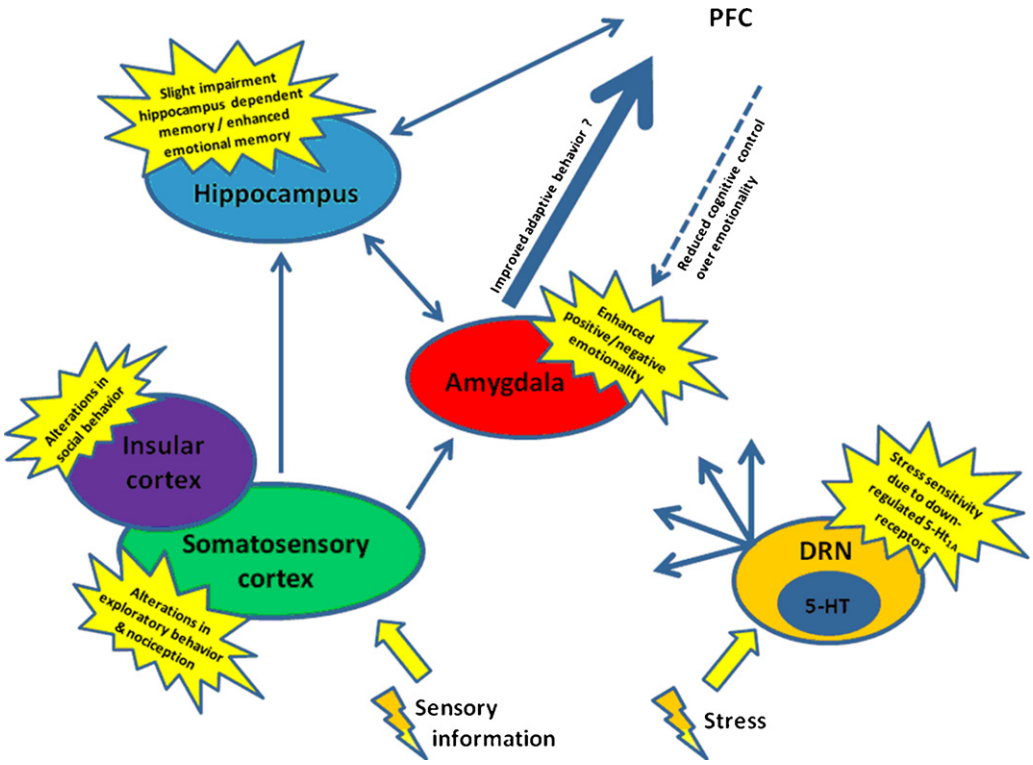

Fig. 1. A working model of how neurodevelopmental changes in multiple brain regions of SERT$^{-/-}$ rodents could account for the diversity of observed endophenotypes. Sensory information of the external and internal world is first processed by the somatosensory cortex and insular cortex. The absence of a barrel-like pattern in the somatosensory cortex (SERT$^{-/-}$ mouse; Persico et al., 2001) and the alterations in insula cortical gray matter (5-HTTLPR; Canli et al., 2005; Wassink et al., 2007) may account for the alterations in exploratory behavior, nociception and social behavior as observed in SERT$^{-/-}$ animals. The amygdala orchestrates the allocation of emotional values to sensory information, and its increased connectivity with the prefrontal cortex (PFC) (Heinz et al., 2005) may be important for associative learning and thereby adaptive behavior in response to environmental changes. Enhanced positive and negative emotionality is likely to arise from structural and functional changes in the amygdala of SERT$^{-/-}$ rodents (Wellman et al., 2007). Additional reduced PFC inhibitory control over the amygdala, as found in human s allele carriers, may be responsible for reduced cognitive control over emotion (Pezawas et al., 2005) and increased emotional memory (Wellman et al., 2007). Morphometric changes in the hippocampus (O'Hara et al., 2007) may contribute to altered contextual memory. Finally, SERT$^{-/-}$ rodents may be stress-sensitive because desensitization of the 5-HT$_{1A}$ receptor in the dorsal raphe nucleus (DRN) confers the animals a reduced capacity to buffer stress-induced increases in serotonin release (Uher, 2008).

reported elevated incorporation of arachidonic acid induced by DOI (a partial 5-HT$_{2A/2C}$ agonist) in SERT$^{-/-}$ mice, which may reflect tonic phospholipase A2 stimulation through 5-HT$_{2A/2C}$ receptors occupied by excess 5-HT (Basselin et al., 2009). This indicates that not all 5-HT receptors desensitize in response to constitutive high 5-HT levels. Apparently, 5-HT$_{2A}$ receptor signaling is necessary to compensate for SERT deficiency. It has been reported that 5-HT, via 5-HT$_{1A}$ and 5-HT$_{2A/C}$ receptor activation, regulates glutamate receptor function in prefrontal cortex (PFC) neurons in a counteractive manner (Yuen et al., 2008), suggesting that 5-HT$_{2A}$ receptor-mediated cortical glutamate transmission is important in modulating the serotonergic system. This may also render an individual susceptible to environmental factors because the capacity to buffer large fluctuations in 5-HT levels is lost (Uher, 2008).

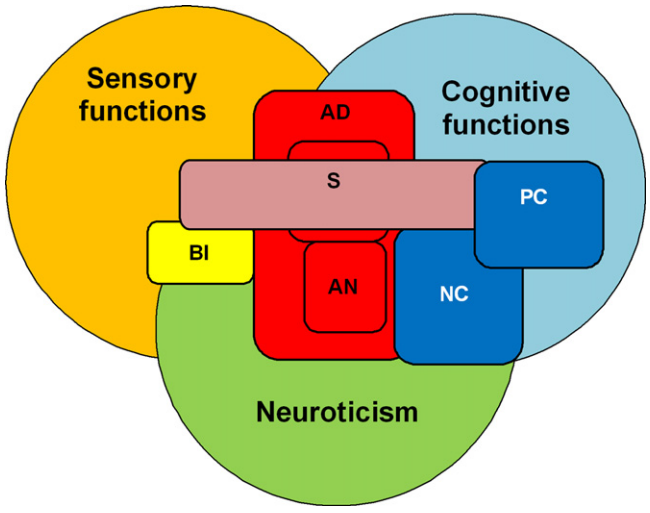

Fig. 2. Proposed domain structure of SERT knockout rodent phenotypes. S - reduced sociability, BI - behavioral instability, AD - affective disorders (D - depression, AN - anxiety), NC - negative cognitions, PC positive cognitions.

3. Serotonin syndrome

5-HT syndrome occurs when there is an excess of 5-HT in the brain, and its common symptoms include muscle rigidity, hyperreflexia and seizures (Isbister et al., 2004). The autonomic system also undergoes atypical stimulation resulting in accelerated heart beat, tremors, flushing and fever. Mental symptoms, such as anxiety, agitation and confusion, are also commonly observed (Kalueff et al., 2008a). Although the exact causes of 5-HT toxicity are unknown, an overdose of antidepressant drugs such as selective 5-HT reuptake inhibitors (SSRIs), resulting in accumulation of 5-HT in the brain, can cause these symptoms in humans. Life-threatening 5-HT toxicity is usually observed when two or more pharmacological compounds cause a synergistic serotonergic effect. However, due to the variability in genetic susceptibility to this syndrome, some individuals may be affected by a single drug alone (Isbister et al., 2004).

5-HT-like syndrome has been evoked in experimental animals, and may occur spontaneously in SERT$^{-/-}$ rodents. For example,

SERT$^{-/-}$ mice on C57BL/6J genetic background display spontaneous 5-HT syndrome-like behaviors, including low body posture, Straub tail, tremors, tics and backward gait (Kalueff et al., 2007b, 2008a). These studies, which lead to the first genetic animal model of 5-HT syndrome, were subsequently reconfirmed pharmacologically, using a wide spectrum of serotonergic drugs (Fox et al., 2007b, 2009). Interestingly, SERT$^{-/-}$ rats do not show spontaneous 5-HT syndrome-like behaviors, despite the fact that both SERT$^{-/-}$ mice and rats display elevated extracellular 5-HT levels. While the exact reason for these differences remains unclear, there may be species-specific differences in compensatory mechanisms for coping with elevated 5-HT levels. Another aspect to consider here is the potential contribution of states similar to 5-HT syndrome (Kalueff et al., 2008a) to animal exploratory behavior. For example, anxiety and confusion can be part of 5-HT-like syndrome in SERT$^{-/-}$ rodents, contributing to anxiety behavior reported in these animals (Kalueff et al., 2007b). Likewise, low/flat body posture and backward gait in SERT$^{-/-}$ mice may contribute to their reduced vertical exploration (Kalueff et al., 2007c) (see further).

4. Neurodevelopment

5-HT not only serves as a neurotransmitter, but also exerts morphogenic activity during early brain development (Gaspar et al., 2003), when axons with SERT follow the path taken by the serotonergic axons. By embryonic day 16–20, SERT is expressed in the cortex, olfactory bulbs and several other brain regions (Zhou et al., 2000). *In vivo* and *in vitro* evidence indicates that 5-HT and SERT can influence biochemical and morphological differentiation of raphe neurons and receptive target cells, implying that 5-HT modulates neurodevelopment, including neurite outgrowth, cell proliferation, migration, cell–cell coupling, synaptogenesis and maturation. These functions are mediated by a variety of 5-HT receptors that are expressed within specific time-windows (Lauder, 1990) and may modulate specific neurodevelopmental processes in SERT$^{-/-}$ mice and rats.

The non-aminergic neurons express SERT transiently, and belong to highly topographically organized sensory systems, such as the sensory relay thalamic neurons that form somatosensory maps. The importance of SERT in directing neuronal outgrowth is reflected by the finding that the barrel-like patterns in the somatosensory cortex are absent in SERT$^{-/-}$ mice (Persico et al., 2001), and that the functional integrity of the barrel cortex is reduced (Esaki et al., 2005). Specifically, the thalamic axons that carry sensory afferents from one whisker and form clusters in cortical layer IV (barrels), do not cluster and remain immature in SERT$^{-/-}$ mice (Rebsam et al., 2002). Other neurodevelopmental changes observed in SERT$^{-/-}$ mice include an increased cell density in the neocortex (Altamura et al., 2007), macrocephaly (Page et al., 2009), an increased length of the apical dendritic branches of PFC pyramidal neurons, and greater spine density of amygdalar pyramidal neurons (Wellman et al., 2007). Overall, these data suggest an important role for SERT in neurodevelopmental abnormalities, which may also contribute to the behavioral profile of SERT$^{-/-}$ rodents (see further).

5. Nociception

Endogenous 5-HT is implicated in the origin and maintenance of central neuropathic pain. SERT is also thought to play a role in nociceptive processing since antinociceptive effects are produced by SSRIs (Gatch et al., 1998; Schreiber et al., 1996). In support of the role for SERT in nociception, incomplete sciatic nerve injury in SERT$^{-/-}$ mice abolishes thermal hyperalgesia (Vogel et al., 2003), a pain-related syndrome associated with reduced 5-HT levels in the injured peripheral nerves. SERT$^{-/-}$ mice show bilateral mechanical allodynia after the nerve injury, which is also associated with decreased spinal 5-HT concentrations, or even a lack of spinal inhibition (Vogel et al., 2003). Another study found that intraplantar complete Freund's adjuvant injection attenuates hyperalgesia in SERT$^{-/-}$ mice, but can be reversed by an intraplantar injection of 5-HT (Palm et al., 2008). It is possible that diminished 5-HT levels seen in the injured peripheral nerve, and in nervous and adrenal tissue, causes the reduced hyperalgesia.

Nociception involves the neural processes of encoding and processing of noxious stimuli, from nociceptors in peripheral tissues to the somatosensory cortex via spinothalamic tracts. Given the structural changes that have been reported for the thalamocortical neurons in SERT$^{-/-}$ mice (Gaspar et al., 2003; Rebsam et al., 2002), it is possible that reduced hyperalgesia in SERT$^{-/-}$ mice could be related to neurodevelopmental changes in the thalamocortical projections and thereby the processing of pain information by the somatosensory cortex. The finding that microinjection of the SSRI paroxetine into the primary somatosensory cortex significantly attenuates thermal hyperalgesia in mice (Matsuzawa-Yanagida et al., 2008) strongly supports the role of SERT in both somatosensory function and nociception.

6. Exploratory behavior

Evaluation of the spatiotemporal patterning is extremely informative to understand how SERT$^{-/-}$ rodents organize their behavior. Because motor functions are not severely impaired in SERT$^{-/-}$ rodents (Kalueff et al., 2007b; Olivier et al., 2008c; Zhao et al., 2006), alterations in exploratory behavior are likely to be associated with anxiety, motivation and memory.

Extensive analysis of SERT$^{-/-}$ mouse exploratory behavior in the open field revealed reduced vertical exploration, reduced central (but not peripheral) horizontal exploration, unaltered within-trial habituation, and slightly poorer between-trial habituation for horizontal activity (Alexandre et al., 2006; Kalueff et al., 2007b). In the elevated plus maze (EPM) test, SERT$^{-/-}$ mice demonstrate anxiety-like avoidance of open arms, hypoactivity, as well as unaltered within-trial and between-trial habituation. In both tests, SERT$^{-/-}$ mice show greater prevalence of horizontal over vertical dimension of their exploration in the areas protected by the walls, but not in open aversive areas. Moreover, SERT$^{-/-}$ mice on C57BL/6 background consistently display increased turning behavior and meandering (Kalueff et al., 2007b,c) which may represent an altered spatial exploration strategy, as recently reconfirmed by Shanahan et al. (2009) using a mixed BALB/c-129SvEv genetic background. Because behavior of SERT$^{-/-}$ rodents is strongly cue-driven (Uher, 2008; see below), and several cues are encountered during exploration, it is possible that these findings reflect cue-induced switches in exploration path or direction consistent with an anxiety endophenotype.

Exploratory behavior in SERT$^{-/-}$ rats has been assessed in the open field and in the Phenotyper (Noldus Information Technology, Wageningen, The Netherlands), an automatic homecage behavior observation system equipped with an infrared camera on the top, a shelter, feeding station and two drinking bottles. Although SERT$^{-/-}$ rats do not display reduced locomotion (Olivier et al., 2008c), they, like SERT$^{-/-}$ mice, show elevated thigmotaxis (Olivier et al., 2008c), increased meandering, and a tendency to higher angular velocity (Nonkes and Homberg, unpublished observations). Interestingly, the frequency of immobility, mobility and high mobility are strongly increased in SERT$^{-/-}$ rats, as is the speed by which the rats move towards their shelter (Nonkes and Homberg, unpublished observations). The increased frequency of (im)mobility in SERT$^{-/-}$ rats suggest that they explore by running and stopping (rather than by

smooth controlled exploration, as is seen in wild type controls) indicative of an anxiety-like endophenotype.

Another interesting rodent behavior to consider is grooming. While grooming activity and its sequencing were unaffected in SERT$^{-/-}$ mice (Kalueff et al., 2007a; Kalueff, unpublished observations), SERT$^{-/-}$ rats did show increased self-grooming behavior (Nonkes, Homberg, unpublished observations). Since grooming behavior in rodents is highly relevant to anxiety and obsessive compulsive disorder (OCD) (Kalueff et al., 2007a; Kalueff and Tuohimaa, 2004; Kalueff and Tuohimaa, 2005), this finding is in line with elevated anxiety in SERT$^{-/-}$ rodents (Fig. 2).

In summary, SERT$^{-/-}$ rodents show increased anxiety-like behavior and aberrant strategy of exploration. At least in SERT$^{-/-}$ mice, these changes may also be due to neurodevelopmental changes in somatosensory cortex (Persico et al., 2001). For example, if the barrel cortex is less functional (Esaki et al., 2005), the animals will have to gather information by means other than their whiskers, and may use increased meandering/turning to aid in making the decision with respect to which direction to move.

7. Positive and negative emotionality

5-HT plays a key role in emotional regulation, including both negative (e.g., anxiety and depression) and positive, reward-related (e.g., obesity and drug addiction) disorders (Tops et al., 2009). Used in behavioral tests of rodent emotionality, SERT$^{-/-}$ mice and rats are very valuable to increase our insight into 5-HT's role in negative and positive emotionality.

7.1. Negative emotionality: anxiety and fear

5-HT is widely accepted to be implicated in the pathophysiology and treatment of anxiety-related disorders (Neumeister et al., 2002). Well-known supportive examples are the anxiolytic potentials of SSRIs and the link between the 5-HTTLPR and anxiety-related disorders (Brown and Harris, 2008). Nevertheless, it is still unclear how the serotonergic system contributes to the pathology underlying anxiety-related disorders.

SERT$^{-/-}$ mice generally show increased aversion for lit and open environments (Ansorge et al., 2004; Holmes et al., 2003a,b; Holmes and Hariri, 2003; Popa et al., 2008). However, strain differences may influence the behavioral outcomes of the SERT deficiency. For example, SERT$^{-/-}$ mice on 129S6/SvEv genetic background do not display anxiety-like behavior in the open field and EPM, but show higher anxiety in the novelty-induced suppressed feeding test (Lira et al., 2003). SERT$^{-/-}$ mice on CD-1 background show reduced locomotor activity in a novel environment (Alexandre et al., 2006), also found in SERT$^{-/-}$ mice on C57BL/6J background (Holmes et al., 2003a,c; Kalueff et al., 2007b; Zhao et al., 2006). Furthermore, while C57BL/6J SERT$^{-/-}$ mice fail to show anxiety-related behavior in the light-dark box under basal conditions, exposure to cat odor causes lasting anxiety in the EPM test in these mice (Adamec et al., 2006). Finally, in the fear conditioning test, C57/6J SERT$^{-/-}$ mice display increased recall of conditioned fear (Wellman et al., 2007), indicating that not only acute, but also conditioned responses to stress are increased. Overall, SERT$^{-/-}$ mice generally exhibit a robust anxiety-like behavior (Table 1).

In the open field test, SERT$^{-/-}$ rats show an increased aversion to the center of the field, indicating higher stress or anxiety (Olivier et al., 2008c). Moreover, in the EPM, SERT$^{-/-}$ rats spend less time on the open arms compared to the closed arms (Olivier et al., 2008c) and show unaltered total distance moved, suggesting that their thigmotaxis is unlikely to be due to differences in exploratory drive. In the novelty-suppressed feeding paradigm, an increased latency to start eating has been found in male, but not in female SERT$^{-/-}$ rats (Olivier et al., 2008c). Finally, in the home cage emergence test, SERT$^{-/-}$ rats demonstrate an increased latency for escaping from their home cage compared to SERT$^{+/+}$ rats (Olivier et al., 2008c), collectively confirming that loss of SERT induces anxiety-like behavior in SERT$^{-/-}$ rats as well. Importantly, there are also pronounced strain differences in neurobehavioral endophenotypes in rats (Yilmazer-Hanke, 2008). Thus far, only SERT$^{-/-}$ rats on a Wistar genetic background have been studied for the parameters described above (although the effect of genetic background on SERT$^{-/-}$ rat behavior is currently being studied in a genetic modifier screen). Considering the contribution of genetic background is important, because it may influence the correct interpretation of biobehavioral findings. Simultaneously, it may also provide an important tool to identify genetic modifiers of the SERT gene, and thereby new molecular pathways that could be valuable in treating patients that respond poorly to drugs like SSRIs.

7.2. Negative emotionality: behavioral despair and anhedonia

5-HT is strongly implicated in depression, with the most well-known example evidenced by the antidepressant potential of SSRIs. Although anxiety- and depression-related disorders share several endophenotypes, including increased negative (conditioned) emotionality and stress-sensitivity, depression more strongly involves behavioral despair and anhedonia.

In the forced swim test of behavioral despair, SERT$^{-/-}$ mice on 129S6 or CD1 backgrounds displayed increased immobility (Holmes et al., 2002b; Lira et al., 2003; Popa et al., 2008). In contrast, SERT$^{-/-}$ mice generated on C57BL/6J (Holmes et al., 2002b; Wellman et al., 2007) or mixed C57BL/6-129SvJ (Perona et al., 2008) genetic backgrounds showed unaltered responses in this test. Importantly, an increased immobility was observed in SERT mutants on C57BL/6J background following repeated exposure to the forced swim test (Wellman et al., 2007).

Depression-like behaviors were further examined in SERT$^{-/-}$ mice on CD-1 (Alexandre et al., 2006; Popa et al., 2008) or C57BL/6J (Zhao et al., 2006) genetic backgrounds, displaying an increased immobility in the tail suspension test. However, SERT$^{-/-}$ mice on 129S6 (Holmes et al., 2002b; Lira et al., 2003) or mixed C57BL/6-129SvJ (Perona et al., 2008) genetic backgrounds showed reduced immobility in this test, negating their higher baseline depression. Since anhedonia is a core symptom of depression (Orsetti et al., 2007), its assessment in SERT$^{-/-}$ mutant rodents represents an important direction of research. SERT$^{-/-}$ mice on C57BL/6 background did not show reduced preference of sucrose (Kalueff et al., 2006). Similar results were obtained in SERT$^{-/-}$ mice on mixed C57BL/6-129SvJ (Perona et al., 2008) genetic background, suggesting that anhedonia is not robustly affected in SERT mutant mice.

Depression-like behaviors have also been measured in SERT$^{-/-}$ rats, displaying increased immobility in the forced swim test, compared to SERT$^{+/+}$ rats (Olivier et al., 2008c). In a two-bottle paradigm with increasing concentrations of sucrose (2–10%), SERT$^{-/-}$ rats consumed significantly less sucrose compared to wild type rats (Olivier et al., 2008c). Although this is consistent with increased anhedonia, it is possible that cognitive mechanisms (i.e., 'learned' reduced sucrose preference) have contributed to these findings.

Clearly, there is general consensus that SERT$^{-/-}$ rodents display symptoms representing negative emotionality as seen in mood disorders (Fig. 1). Initially these findings were rather puzzling, since both SSRIs and SERT knockout increase 5-HT levels. However, it is possible that these symptoms arise from an inability of the 5-HTergic system to buffer stress-induced increases in 5-HT release (Uher, 2008), in line with a recent focus on SERT$^{-/-}$-related neurodevelopmental changes. For instance, a higher vigilance state

of the amygdala, as suggested for individuals carrying the s allelic variant of the 5-HTTLPR (Canli et al., 2005), may explain the increased responsivity to unconditioned adversity in SERT$^{-/-}$ rodents. Likewise, the loss of cortical top-down control over emotion, as reported in association with the 5-HTTLPR (Pezawas et al., 2005), could further contribute to increased fear memory as measured in the fear conditioning test (Wellman et al., 2007).

7.3. Positive emotionality: food intake and responsivity to psychostimulants

Although the rewarding effects of natural and drug reinforcers are generally thought to be mediated by dopamine, serotonin has also been implicated in reward. For example, serotonergic drugs have pronounced effects on food intake (Halford et al., 2007) and responsivity to psychostimulants (Walsh and Cunningham, 1997). A difficulty in interpreting most of these studies is that responsivity to natural reinforcers and drugs of abuse have often been measured in operant paradigms which are interspersed by associative and operant learning. Nevertheless, these tests may provide some insights into the role of 5-HT in positive emotionality. Examining natural reinforcers, it was found that baseline sucrose consumption is unaltered in SERT$^{-/-}$ mice (Kalueff et al., 2006). In contrast, SERT$^{-/-}$ mice have been found to reach lower break points in a food-reinforced progressive ratio paradigm (Sanders et al., 2007), suggesting reduced reward properties of food intake. Trigo et al. (2007) failed to replicate this finding, albeit there was a tendency for a reduced break point in SERT$^{-/-}$ mice.

Despite unaltered or reduced food intake, SERT$^{-/-}$ mice show an obesity phenotype that emerges at the age of 3 months and becomes more exaggerated throughout life (Murphy and Lesch, 2008). Reduced activity may contribute to this phenomenon in SERT$^{-/-}$ mice (Alexandre et al., 2006; Kalueff et al., 2007b). In SERT$^{-/-}$ rats, sucrose consumption is decreased (Olivier et al., 2008c), chow intake is slightly increased, and lard intake is unaltered (Homberg et al., 2009). Like SERT$^{-/-}$ mice (Murphy and Lesch, 2008), SERT$^{-/-}$ rats show obesity, which, however, does not involve an increase in body weight, but rather an increase in abdominal fat deposition (Homberg et al., 2009). Furthermore, this highly consistent and robust finding was only observed in female, but not male, SERT$^{-/-}$ rats, while obesity for SERT$^{-/-}$ mice has been reported for males. The nature of these species differences are unclear, but since there are age differences between the mouse and rat studies, it is possible that increased abdominal fat develops at an early age, while weight gain/obesity becomes overt later in life. Taken together, these data imply that there are some marginal differences in responsivity to natural (positive) rewards in SERT$^{-/-}$ rodents, although direct comparisons within and between species are hampered by a lack of coherence in test set-ups.

Among psychostimulant drugs, the effects of cocaine have been most extensively studied. Since cocaine inhibits the dopamine, noradrenaline and 5-HT transporters (Heikkila et al., 1975), the absence of SERT will affect the behavioral outcome of cocaine in SERT$^{-/-}$ rodents. Indeed, it has been reported that the psychomotor effects of cocaine are increased in SERT$^{-/-}$ rats (Homberg et al., 2008a). Cocaine-induced conditioned place preference is also increased in both SERT$^{-/-}$ mice and rats (Homberg et al., 2008a; Sora et al., 1998, 2001). In addition to producing place preference, cocaine also evoked conditioned locomotion response in SERT$^{-/-}$ mice, which habituated across the conditioning trials (Hall et al., 2009). Likewise, cocaine self-administration is increased in SERT$^{-/-}$ rats (Homberg et al., 2008a), but not in mice (Thomsen et al., 2009). While the reason for this discrepancy is unclear, these data show that SERT$^{-/-}$ rodents are more sensitive to cocaine.

Overall, these data suggest that sensitivity to natural rewards is reduced, while sensitivity to cocaine is increased, making it hard to conclude whether positive emotionality, like negative emotionality, is increased in SERT$^{-/-}$ animals. Likewise, 5-HT is not known to have rewarding effects, and it is currently unclear how 5-HT affects positively reinforced behavior. Since 5-HT promotes behaviors that lead to avoidance of adversity (Dayan and Huys, 2008), a possible mechanism could be that 5-HT increases reward by inhibition of behaviors that lead to a negative outcome. Alternatively, increased vigilance due to a hyper-arousal state of the amygdala (Canli et al., 2005) may not only lead to increased negative emotionality, but also to increased positive emotionality, since the amygdala processes both types of emotional information (Murray, 2007). Our data on cocaine conditioned place preference and foot shock-induced conditioned place aversion (Nonkes and Homberg, unpublished observations) seem to support the later idea. In line with this notion, recent imaging data (Bearer et al., 2009) showed markedly altered corticolimbic pathways in SERT$^{-/-}$ mice, biased towards reward circuits.

8. Social behaviors

In addition to modulating emotionality, 5-HT is an important regulator of social behavior, which is impaired in many psychiatric disorders caused by 5-HT imbalances. Therefore, it is important to examine and compare social behaviors in SERT$^{-/-}$ mice and rats. Several studies have reported abnormal social behaviors in SERT$^{-/-}$ mice. For example, isolated male SERT$^{-/-}$ mice show reduced aggression in the resident-intruder test (Holmes et al., 2002a). Compared to their wild type C57BL/6J littermates, SERT$^{-/-}$ mice are slower to initiate the first attack, and attack with a lower frequency and intensity. Furthermore, a repeated exposure to the intruder animal a week later increases the amount of aggression in SERT$^{+/+}$ and $^{+/-}$ mice, but not in SERT$^{-/-}$ animals (Holmes et al., 2002a).

While altered aggression indicates aberrant social domain in SERT$^{-/-}$ mice, additional studies were needed to examine their social behavior *per se*. The finding that social interaction is reduced in these mice (Kalueff et al., 2007b) suggests that SERT$^{-/-}$ mice may represent an animal model of autism spectrum disorders. This possibility was later supported by other studies showing that not only physical interactions, but also social approach behavior is strongly reduced in SERT$^{-/-}$ mice (Moy et al., 2009), as reflected by reduced time spent in the compartment containing a stimulus mouse (Page et al., 2009). Nevertheless, some caution is required while interpreting social behavior, since anxiety may be a confounding factor, and is highly expressed in SERT$^{-/-}$ mice.

Like SERT$^{-/-}$ mice, SERT$^{-/-}$ rats show reduced aggression behavior in the resident-intruder test (Homberg et al., 2007b). During multiple encounters, SERT$^{-/-}$ rats were less likely to initiate an attack than SERT$^{+/+}$ littermates, yet maintained unaltered levels of general social investigation (Homberg et al., 2007b; Olivier, Jans, unpublished findings).

The reduction in social behavior may well have a developmental nature, since social behavior is acquired during childhood and youth. As such, social play behavior, which takes place during the peri-adolescent period (~28–35 days), reflects behaviors found in adult sexual, affiliative and aggressive encounters (Baenninger, 1967; Bolles and Woods, 1964; Meaney and Sterwart, 1981; Poole and Fish, 1975), but displayed in an exaggerated and/or out-of-context fashion (Poole and Fish, 1975). Play behavior of SERT$^{+/+}$ rats has been compared to that of SERT$^{-/-}$ play couples. While play behavior is markedly reduced in SERT$^{-/-}$ rats, their non-playful social events remained unaffected. Strikingly, SERT$^{-/-}$ rats are interested in their play partner, spend a considerable amount of time chasing him, but display a markedly reduced initiation to play (Homberg et al., 2007c).

Collectively, these data indicate that social interaction and approach are impaired in SERT$^{-/-}$ rodents, suggesting a trait-like relationship (Higley and Linnoila, 1997). These SERT$^{-/-}$ rodent findings are in line with reduced gazing at faces and eyes in rhesus macaques carrying the 5-HTTLPR s allele (Watson et al., 2009), and parallel clinical findings implicating the SERT gene in autism (Huang and Santangelo, 2008; Moy et al., 2009; Raznahan et al., 2009; Serretti et al., 2006). Hyperserotonemia, reflecting increased blood platelet 5-HT levels, is consistently found in one-third of autistic subjects, suggesting that low brain 5-HT levels have neurodevelopmental consequences that may lead to autism-related symptoms (Whitaker-Azmitia, 2005). However, inconsistent findings have been reported for the association between the human SERT polymorphism and hyperserotonemia (Anderson et al., 2002; Coutinho et al., 2004; Hranilovic et al., 2008; Ramoz et al., 2006; but see Betancur et al., 2002; Tordjman et al., 2001). Furthermore, as SERT$^{-/-}$ rats (Homberg et al., 2006) exhibit very low 5-HT levels in blood platelets, but have high 5-HT levels in the brain (Homberg et al., 2007a; Olivier et al., 2008c), there seems to be no link between hyperserotonemia and reduced social behavior. Thus, although the role of SERT in social behaviors has begun to emerge, further research is needed to unveil its significance and relationship to the central and peripheral markers of autism.

9. Cognitive functions

The SERT and 5-HT receptor subtypes are highly expressed in cortical areas involved in cognitive functions, implying that 5-HT plays an important role in cognition, beyond emotionality and sociability. Additionally, 5-HT plays a role in inhibitory control, for which an inverse relationship between 5-HT and impulsivity has been suggested (Soubrié, 1986). 5-HT is also implicated in associative learning, which is supported by findings that chronic SSRI treatment potentiates conditioned reinforcement (Sasaki-Adams and Kelley, 2001) and appetitive Pavlovian conditioning (Valluzzi and Chan, 2007). Collectively, this implicates 5-HT in cognitive flexibility (Clarke et al., 2004, 2005), based on stimulus–response contingencies and new associative learning in response to changes in these contingencies. It has not yet been established whether response-outcome contingencies, which are implicated in goal-directed behavior and habit formation, are modulated by 5-HT. However, because flexibility in response-outcome contingencies requires associative learning, 5-HT may be involved in this form of flexibility as well. Not only is associative learning modulated by 5-HT, it has also been shown to mediate other forms of learning and memory, such as the consolidation of new information into long-term memory (Buhot et al., 2000). Clearly, 5-HT influences cognitive functions, and through its central role in emotionality, 5-HT may particularly affect those cognitive processes that are driven by emotional incentives. Cognition has received relatively little attention in SERT$^{-/-}$ research so far, but it is promising and may foster our understanding of the precise role of 5-HT in specific cognitive functions.

9.1. Inhibitory control

In the 5-choice serial reaction time task (5-CSRTT) it has been found that SERT$^{-/-}$ rats display a reduction in premature responding (Homberg et al., 2007b), indicative of decreased motor impulsivity. In addition, the correct response latency was increased in these rats. These findings are consistent with the hypothesis of an inverse relationship between 5-HT and impulsivity (Soubrié, 1986). As seen for social behavior, SERT$^{-/-}$ rats may have difficulties in initiating a response, or their behavior may be driven by the avoidance of a negative outcome. It is also possible that increased vigilance contributes to decreased impulsivity due to a strong focus on the food-predicting cue. Although no analogous test has been performed in SERT$^{-/-}$ mice, the finding that SERT$^{-/-}$ mice (Holmes et al., 2002a) and rats (Homberg et al., 2007b) are less aggressive is in line with inhibitory control being a core aspect of the SERT mutant endophenotype across species.

Other dimensions of impulsivity, which include an inability to inhibit ongoing behavior or to forego an immediate small reward in favor of a delayed larger reward (Torregrossa et al., 2008), have not been addressed so far in SERT$^{-/-}$ rodents. Pharmacological studies imply that 5-HT is involved in impulsive choices driven by delay (Denk et al., 2005; Eagle et al., 2009), but not in choices driven by probability and effort (Denk et al., 2005; Mobini et al., 2000), raising the expectation that SERT$^{-/-}$ rats may demonstrate improved 'waiting' when reward is delayed.

9.2. Associative learning and cognitive flexibility

Associative learning involves learning an association between reinforcers and environmental stimuli, and is utilized in several behavioral paradigms. For instance, increased cocaine-induced conditioned place preference in both SERT$^{-/-}$ mice and rats (Homberg et al., 2008a; Sora et al., 1998, 2001) may relate to increased associative learning beyond increased cocaine sensitivity. Increased recall of conditioned fear in SERT$^{-/-}$ mice (Wellman et al., 2007) may also reflect increased associative learning, although no changes in acquisition for fear conditioning have been found. Sanders et al. (2007) have tested the SERT$^{-/-}$ mouse in the Pavlovian-to-Instrumental transfer (PIT) task, measuring the ability of a conditioned stimulus to reinforce ongoing instrumental behavior. The fact that SERT$^{-/-}$ mice did not differ from SERT$^{+/+}$ mice in the PIT test (Sanders et al., 2007) suggests that transfer of conditioned responses is not altered in SERT$^{-/-}$ animals.

Cognitive flexibility reflects the ability to change contingencies between a stimulus and response, and is strongly PFC-dependent. In the serial spatial reversal learning task, which measures flexibility in stimulus–response contingencies, no genotype differences have been found between SERT$^{-/-}$, SERT$^{+/-}$ and SERT$^{+/+}$ rats in the percent of correct responses (Homberg et al., 2007b). This suggests that reversals of stimulus–response contingencies are not affected by SERT inactivation. Given that prefrontal/orbitofrontal 5-HT depletion impairs reversal learning and thereby induces perseveration (Clarke et al., 2004, 2005), this finding is quite unexpected. The discrepancy could relate to the fact that reversal learning deals with three different processes, namely extinction of the previously rewarded operandum, the acquisition of a new stimulus–response association, and learned indifference or anxiety to approach a new stimulus. In the Iowa Gambling Task, SERT$^{-/-}$ rats show increased emotional decision making (Homberg et al., 2008b), which requires adaptive behavior (shifting) when punishments are encountered. If adaptive behavior is increased, the acquisition of a new stimulus–response contingency should be facilitated. Furthermore, increased anxiety, as seen in SERT$^{-/-}$ rodents, could counteract such a facilitation of associative learning in the reversal learning paradigm. Otherwise, perseveration could neutralize increases in adaptive behavior in the reversal learning paradigm. Re-analysis of data, however, did not reveal genotype differences in new learning and perseveration (Homberg et al. unpublished observations). In relation to the 5-HTTLPR, improved performance of the Wisconsin Card Sorting test has been reported (Borg et al., 2009), implying that SERT genetic variation affects some forms of cognitive flexibility.

9.3. Memory

In addition to associative learning, other forms of learning have been measured in SERT$^{-/-}$ rodents. Analyzing short-term memory,

no genotype differences were found for within-trial habituation of horizontal and vertical exploration the open field and EPM tests in SERT$^{-/-}$ mice. Between-trial habituation, which assesses long-term memory, was slightly reduced in SERT$^{-/-}$ mice, most likely reflecting initial behavior inhibition during Trial 1, rather than poor habituation on Trial 2 (Kalueff et al., 2007c).

In SERT$^{-/-}$ rats, memory has been assessed in a variety of tasks. In the Morris water maze test, which assesses spatial hippocampal-dependent memory, SERT$^{-/-}$ rats are slightly impaired in finding the hidden platform. No motor coordination or vision differences were found between the genotypes, as assessed in both the visible platform test and the probe trial (Olivier et al., 2008d). In the object recognition test, which measures recognition memory, SERT$^{-/-}$ rats, compared to SERT$^{+/+}$ rats, are able to recognize a familiar object after 1-, 2-, 4-, but not 8-h interval (Olivier et al., 2009). Upon acute tryptophan depletion (ATD), object recognition memory after a 1-h interval is impaired in SERT$^{-/-}$ rats, but not SERT$^{+/+}$ rats, suggesting a stronger central depletion effect in these rats (Olivier et al., 2008b). These data suggest that the absence of the SERT slightly impairs hippocampus-dependent spatial/object memory, in striking contrast with improved amygdala-dependent emotional memory (e.g., fear conditioning) in SERT$^{-/-}$ rodents. Differential neurodevelopmental changes in the hippocampus and amygdala (Fig. 1) are likely to explain this discrepancy.

10. Understanding neural substrates and mechanisms

As emphasized here, genetic SERT inactivation has profound effects on brain chemistry and development, reflecting the dual function of 5-HT. We also show that SERT deficiency affects several important behavioral domains, which explains the widespread implication of 5-HT in health and disease. Specifically, SERT$^{-/-}$ mice and rats show anxiety-like exploratory behavior, increased negative (and perhaps positive) emotionality, reduced social approach, and altered nociception (Table 1). Changes in cognitive functions are also found in SERT$^{-/-}$ rodents, and point towards increased behavioral inhibition, improved decision making and reduced contextual memory. However, further research is needed to elaborate the role of SERT in different cognitive functions. Rather than being fragmented, these domains interact and may be traced back to a common process (Fig. 1). Indeed, most of these endophenotypes co-occur in complex neurodevelopmental neuropsychiatric disorders, such as anxiety, depression and possibly autism. An intriguing question then becomes: what are these common mechanisms, and how do they relate to changes in brain development, 5-HT neurotransmission, or both? In the design of therapies, these distinctions are becoming particularly crucial.

To answer this question, it is helpful to trace SERT$^{-/-}$ rodent endophenotypes back to findings related to the common 5-HTTLPR in humans. That is, the s allele reduces the transcriptional activity of the SERT gene (Lesch et al., 1996) and is strongly linked to several major psychiatric disorders. This implies that the 5-HTTLPR is biologically important, although its precise role in personality and related disorders remains unclear. Due to small effect sizes, ethnic differences and environmental factors, inconsistent findings have been reported for the 5-HTTLPR. Nonetheless, the general picture is that the s allele is associated with anxiety, social impairments, disorders of emotional regulation (Canli and Lesch, 2007; Dick et al., 2007; Mann et al., 2000; Schmitz et al., 2007), and perhaps improved cognitive functioning (Borg et al., 2009; Roiser et al., 2006; Strobel et al., 2007). The l allele seems to be associated with compulsive or repetitive elements in psychiatric conditions (Bloch et al., 2008). Disorders that combine emotional disturbances, social impairments and repetitive tendencies, such as autism and OCD, are associated with both the s and l allele (Bloch et al., 2008; Brune et al., 2006). Because the prevalence of major psychiatric disorders such as anxiety and depression is lower than that of the 5-HTTLPR, it is thought that the 5-HTTLPR shapes personality, which in combination with other genetic and environmental factors contributes to disease pathology (Lesch, 2009; Uher, 2008). Thus, the s allele, compared to the l allele may increase sensitivity to environmental challenges, leading to increased (negative) emotionality, and thereby adaptive behavior as reflected by reduced sociability, and possibly increased cognition. These characteristics are also seen in SERT$^{-/-}$ rodents, although their cognitive domain requires further research.

It is well established that the 5-HTTLPR is associated with brain endophenotypes, most likely arising from 5-HT's neurotrophic effects during brain development. Several studies have reported neurodevelopmental changes in SERT$^{-/-}$ mice as well (Altamura et al., 2007; Persico et al., 2001; Rebsam et al., 2002; Wellman et al., 2007). Although differences in applied morphometric techniques hampers the comparison between mouse and human data, the fact that changes are found in the same brain regions suggests that 5-HT's neurotrophic actions are conserved across species. For instance, SERT$^{-/-}$ mice show structural changes in the PFC and amygdala (Wellman et al., 2007), and s allele carriers, compared to l allele carriers, show alterations in the connectivity between these two brain regions, as well as volume changes (Hariri et al., 2002; Hariri and Holmes, 2006; Heinz et al., 2005; Pezawas et al., 2005).

It is possible that particular neurodevelopmental changes in the amygdala and cortical regions contribute to the endophenotypes associated with the 5-HTTLPR and in SERT$^{-/-}$ rodents (Fig. 1 and Table 1). Specifically, the s allele is associated with a smaller, but hyper-reactive (Hariri et al., 2002) and hyper-aroused (Canli et al., 2005, 2006) amygdala, leading to increased emotional vigilance. Thereby emotional stimuli, both negative and positive (Murray, 2007), may be perceived very strongly and drive the behavior, as reflected by increased anxiety-like behavior. Further, the 5-HTTLPR s allele is associated with an increased connectivity between the amygdala and PFC (Heinz et al., 2005), a pathway involved in associative learning (Phelps and LeDoux, 2005). The s allele has also been found to be associated with a functional uncoupling between the PFC and amygdala (Pezawas et al., 2005), a pathway that provides cortical top-down control over emotion. While the former may contribute to improved cognitive functions and perhaps increased adaptive behavior, the latter could lead to excessive emotional memories, as seen in s allele carriers and SERT$^{-/-}$ rodents. Therefore, neurodevelopmental changes in cortico-amygdala circuits may represent common pathways in the widespread behavioral endophenotypes exerted by SERT genetic variation, as postulated previously by others (Hariri and Holmes, 2006; Holmes, 2008). A volume reduction of the hippocampus in elderly (O'Hara et al., 2007), may be associated with poor memory, specifically contextual memory, as found in SERT$^{-/-}$ rats (Olivier et al., 2008d; Olivier et al., unpublished observations). Interestingly, the connectivity between the amygdala and hippocampus is altered by early life stress as a function of the 5-HTTLPR genotype (Canli et al., 2006). In line with this notion, increased emotional memory may be accompanied by poor contextual memory (as, for example, seen in depression).

Furthermore, in human s allele carriers and SERT$^{-/-}$ mice, alterations in neocortical and insular cortical gray matter (Canli et al., 2005; Wassink et al., 2007), as well as in neocortical cell density (Altamura et al., 2007; Persico et al., 2001) have been reported. The insula cortex is implicated in appraisal of self-relevance and empathy (Schmitz and Johnson, 2007). Hence, it is possible that insula cortex changes contribute to deficits in social interaction as seen in s allele carriers and SERT$^{-/-}$ rodents (Brune et al., 2006; Holmes et al., 2002a; Homberg et al., 2007b,c; Moy et al., 2009; Page et al., 2009; Watson et al., 2009). Because the insula is part of the ventral medial PFC-anterior cingulated–insula–

amygdala circuitry, insular functional changes could be directly related to the emotionality and cognitive functions mediated by the PFC-amygdala top-down control system.

Collectively, these data imply a strong neurodevelopmental basis for the widespread endophenotypes associated with the SERT$^{-/-}$ in rodents and the 5-HTTLPR in humans (as well as non-human primates). The recent finding that genetically induced 5-HT depletion increases fear conditioning (Dai et al., 2008) in SERT$^{-/-}$ mice exhibiting high 5-HT levels, suggests that 5-HT levels *per se* are not directly linked to a particular behavioral outcome. Nevertheless, because 5-HT depletion during early development reduces anxiety (Dai et al., 2008), there is heterogeneity in the outcome of 5-HT depletion *versus* 5-HT increment. As negative emotionality and reduced sociability have been well established in SERT$^{-/-}$ rodents, it can be argued that SERT$^{-/-}$ rodents are particularly suited to model the emotional and social aspects of neurodevelopmental disorders like anxiety (OCD), depression, and possibly autism. Whether SERT$^{-/-}$ rodents are useful to model cognitive domains of psychiatric disorders remains to be established.

While the s allele by itself does not cause diseases, but rather shapes the personality, the complete absence of the SERT may represent an exaggerated condition. A complete knockout of the SERT does not exist in humans, although some rare human mutations may lead to an almost complete loss of SERT function. However, we regard SERT$^{-/-}$ as models of the s allele of 5-HTTLPR, based on findings that SERT$^{-/-}$ rodents display increased negative emotionality and neurodevelopmental changes that are comparable to the effects of the s allele (Altamura et al., 2007; Hariri and Holmes, 2006; Holmes and Hariri, 2003; Homberg et al., 2008b; Wellman et al., 2007). SERT$^{+/-}$ would be more like the s allele from a molecular and biochemical point of view (Bengel et al., 1998; Hariri and Holmes, 2006; Homberg et al., 2007a), but generally they do not show such robustly affected endophenotypes compared to SERT$^{+/+}$ controls (see Kalueff et al., 2007d for details). However, upon early adverse life events (Carola et al., 2008), SERT$^{+/-}$ rodents may develop behavioral changes, consistent with the strong 5-HTTLPR × environment interaction in depression (Caspi et al., 2003; Lesch, 2009; Uher, 2008; but see Risch et al., 2009).

11. Concluding remarks

In summary, although SERT$^{-/-}$ mice and rats show some species-specific differences, overall these differences are small compared to major similarities in multiple neurobehavioral domains (Table 1), including altered nociception, anxiety-like exploratory behavior, impaired sociability, pronounced affective endophenotypes, and somewhat improved cognitive functions. What lessons can be learned from such cross-species comparisons? First, the fact that most endophenotypes are comparable between the two species indicates that SERT function and downstream neurobehavioral processes are highly conserved between species. Second, such comparisons strengthen the use of SERT$^{-/-}$ rodents in understanding human health and disease conditions, particularly from a neurodevelopmental point of view. The third important conclusion is that SERT$^{-/-}$ mice and rats are highly complementary for modeling serotonergic brain disorders. For example, while mice may be an excellent model for testing affective endophenotypes, SERT$^{-/-}$ rats may be valuable for research focusing on complex cognitive functions associated with SERT. Thus, while each species has its limitations, extrapolation of findings between species will increase our understanding of key affected brain mechanisms, representing a heuristic way to obtain new insights in SERT research. Fourth, one may use advantageously the relative simplicity and robustness of SERT$^{-/-}$ rodent neurobehavioral endophenotypes (vs. more complex human neuropsychiatric disorders). Analysis of simpler models and more distinguishable endophenotypes in mutant mice and rats allows for a better identification of key neuropsychiatric domains (Figs. 1 and 2) associated with SERT genetic differences. Finally, our analysis, summarized in Table 1, highlights the "white areas" of research where more knowledge needs to be generated in order to fully understand neurobehavioral abnormalities associated with SERT genetic knockout in animals. Serotonergic receptor differences, nociception, and especially cognitive functions require further efforts from biomedical researchers. The core role of cognitive endophenotypes in the pathobiology of various brain disorders has been emphasized recently (Kalueff and Nutt, 1996, 2007; Kalueff and Murphy, 2007; Korff and Harvey, 2006; McGrath et al., 1999). Therefore, it is likely that, in addition to neurodevelopmental abnormalities, cognitive deficits represent a common pathogenetic pathway (Figs. 1 and 2) underlying the rich spectrum of neurobehavioral domains (Table 1) in SERT$^{-/-}$ models.

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