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Research Report

Locomotory patterns, spatiotemporal organization of exploration and spatial memory in serotonin transporter knockout mice

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ABSTRACT

Serotonin transporter knockout (SERT–/–) mice are extensively used as a genetic model of several neuropsychiatric disorders, and consistently display anxiety-like behaviors and inactivity in different tests. To better understand how these mice organize their behavior, we assessed the open field and elevated plus maze spatiotemporal patterning of activity in adult male SERT wild type (+/+), heterozygous (+/–) and –/– mice on C57BL/6J genetic background using new videotracking and analytic procedures. In addition, we analyzed their spatial memory, assessing within- and between-trial habituation, and examined specific motor characteristics of their movement in these two tests. In the open field test, SERT–/– mice showed reduced vertical exploration throughout the arena, reduced central (but not peripheral) horizontal exploration, unaltered within-trial habituation, and slightly poorer between-trial habituation for horizontal activity. In the elevated plus maze, SERT–/– mice demonstrated anxiety-like avoidance of open arms, hypoactivity, as well as unaltered within-trial and between-trial habituation (except for poorer between-trial habituation of total horizontal activity). In both tests, SERT–/– mice showed greater prevalence of horizontal over vertical dimension of their exploration in the areas protected by the walls (open field periphery, plus maze closed arms), but not in open aversive areas, such as the center of the open field or center or open arms of the maze. In both arenas, SERT–/– mice consistently displayed increased turning behavior, potentially representing a perseverance-like phenotype or aberrant spatial strategies in novel environments. Overall, using a fine-graded behavioral analysis in two different novelty tests, this study revealed alterations in motor and spatiotemporal patterning of activity in SERT–/– mice. Given the relevance of exploratory strategies to human personality traits and brain disorders, our data may be useful for developing further neurobehavioral models using these mice.

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1. Introduction

Serotonin is a key neurotransmitter implicated in many brain disorders such as anxiety, depression, hyperactivity, autism, obsessive–compulsive disorders (OCDs) and schizophrenia (Gingrich and Hen, 2001; Hariri and Holmes, 2006; Holmes and Hariri, 2003; Lesch, 2005; Lesch et al., 1996, 2003; Sutcliffe et al., 2005; Yonan et al., 2003; Zhao et al., 2006). High-affinity

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serotonin transporter (SERT) is the main regulator of serotonergic neurotransmission, widely distributed throughout the brain and targeted by numerous psychotropic drugs (Blakely, 2001; Murphy et al., 2004; Torres et al., 2003; Wong and Licinio, 2004). SERT knockout (–/–) mice represent a useful tool to assess the role of serotonin and SERT in various normal and pathological brain mechanisms, and are extensively used in neuroscience research (Adamec et al., 2006; Bengel et al., 1998; Carroll et al., 2007; Li, 2006; Lira et al., 2003; Murphy et al., 2001, 2003, 2004; Salichon et al., 2001; Zhao et al., 2006).

Several studies have examined behavioral alterations in SERT–/– mice, reporting anxiety (manifest in reduced exploration and increased thigmotaxis – avoidance of aversive open zones) and overall hypolocomotion in different tests (Carroll et al., 2007; Holmes et al., 2002a,b, 2003a,b,c; Kalueff et al., 2006a, 2007a). While these studies do advance our understanding of the complexity of their behavioral phenotype, it still remains unclear how SERT–/– mice explore novel environments. For example, little is known about what exactly these mice do in different parts of novel arenas (i.e., center, corners, walls), and whether behavioral strategies and motor patterns of these mice differ as they move from periphery to the center.

In addition to examining traditional gross activity scores, in-depth analyses of patterning of animal behavior represent an

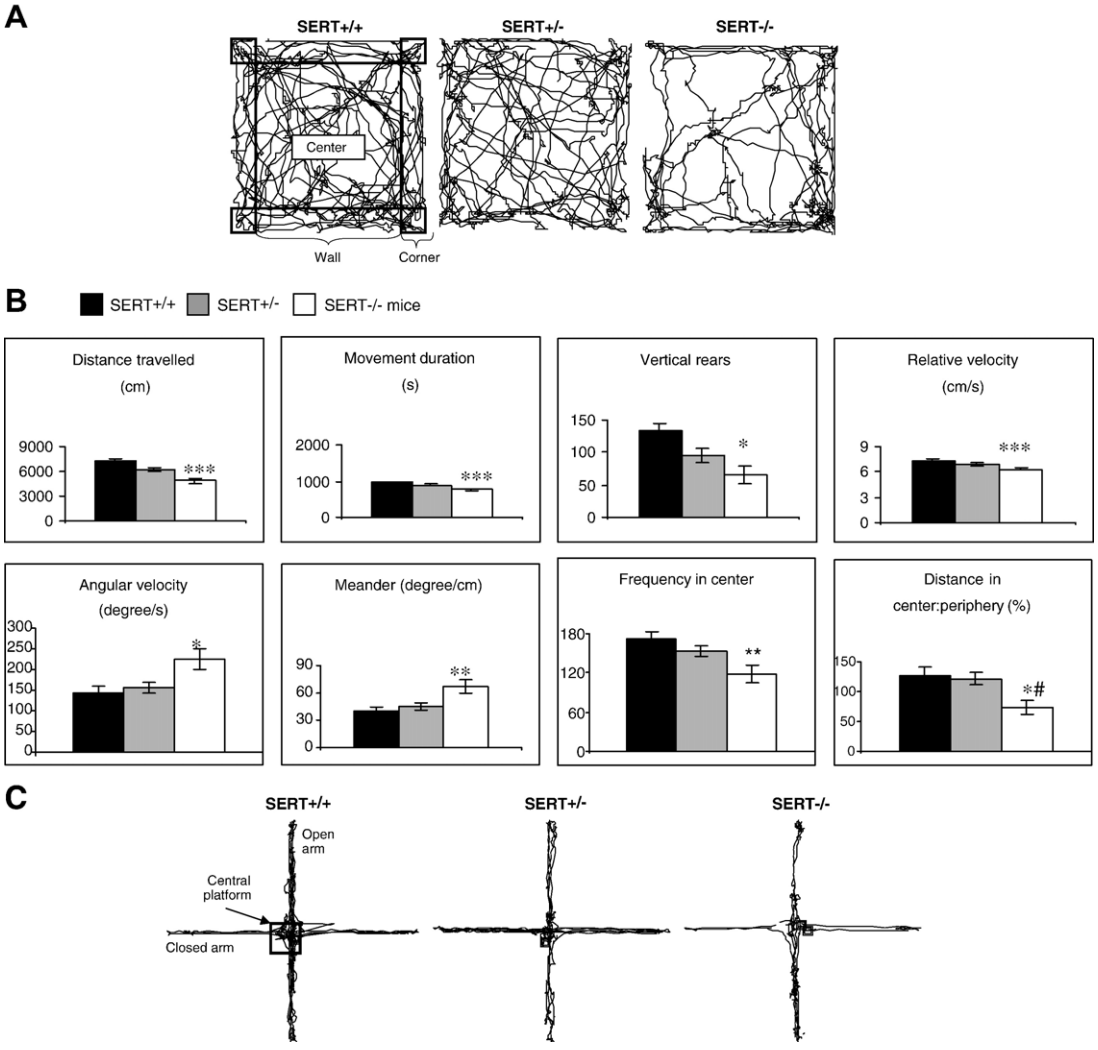

Fig. 1 – Behavioral performance of SERT+/+, +/– and –/– mice in the open field and elevated plus maze tests (Trial 1). *$P<0.05$, **$P<0.01$, ***$P<0.001$ (vs. SERT+/+ mice), #$P<0.05$ (vs. SERT+/– mice), Dunn's post-hoc test for significant Kruskal–Wallis data. (A) Exemplary open field movement patterns for the first 5 min of a representative animal of each genotype. Representative animal activity was pre-selected based on proximity to average total distance moved, by genotype. All activity patterns were then rated independently on scales of 1 to 5 for total activity and for thigmotaxis, and medians for each genotype were determined. Representative activity patterns were chosen based on these ratings. Different zones within the arena (center, corners, walls) are explained in the left diagram. (B) Behavioral scores and thigmotaxis in the open field test (20 min). (C) Exemplary elevated plus maze movement patterns for 5 min of a representative animal of each genotype (see Table 1 for total 20-min scores). Representative animal activity was pre-selected based on proximity to average total distance moved, by genotype. All activity patterns were then rated independently on scales of 1 to 5 for total activity and for open:closed arm preference, and medians for each genotype were determined. Representative activity patterns were chosen based on these ratings. Different zones within the elevated plus maze (center, open arms, closed arms) are explained in the left diagram.

important part of behavioral phenotyping (Dulawa et al., 1999; Fonio et al., 2006; Kalueff et al., 2006a; Nilsson et al., 2001). For example, the assessment of kinematics, geometrical patterns, as well as spatial, temporal and spatiotemporal organization of locomotion (Dulawa et al., 1999; Fonio et al., 2006; Kalueff et al., 2006a; Nilsson et al., 2001) may be a rich source of information for behavioral neuroscience and genetics in different species, including insects (Martin, 2004), fish (Keitsaro et al., 2003), rodents (Paulus and Geyer, 1993; Paulus et al., 1993, 1998, 1999), primates (Isbell et al., 1999) and humans (Uetake, 1992). These approaches have also been successfully used to detect behavioral differences in various inbred or mutant mice (Eilam, 2004; Geyer and Markou, 2002; Kafkafi and Elmer, 2005a,b; Kalueff, 2007; Lappanen et al., 2006; Lepicard et al., 2006; Nally et al., 2003, 2004; Nilsson et al., 2001; Paulus et al., 1999; Powell et al., 2006; Ralph et al., 2001).

Because the exploratory strategies may be relevant to both human personality traits and brain disorders, we hypothesized that spatiotemporal and locomotor characteristics of mouse exploration may be affected in SERT–/– mice. Using a careful fine-graded behavioral analysis, the present study aimed to characterize patterns of locomotion and spatial strategies in SERT wild type (+/+), heterozygous (+/–) and –/– mice in two traditional novelty-based models: the open field and elevated plus maze (EPM) tests (Carobrez and Bertoglio, 2005; Crawley, 1999, 2000; Izidio et al., 2005).

Because cognitive functions play a key role in animal exploration, with serotonin and SERT both implicated in the regulation of cognitive processes in animals and humans (Finger et al., 2007; Leussis and Bolivar, 2006; Roiser et al., 2006, 2007), we hypothesized that cognitive functions related to exploration, such as spatial memory, may also be affected in mice with reduced SERT function. Thus, the second aim of the present study was to compare temporal organization of exploration and habituation to novelty (as traditional measures of spatial memory (Bidzinski et al., 1998; Kalueff et al., 2006a; Nally et al., 2003)) in SERT+/+, +/– and –/– mice subjected to the above-mentioned popular novelty tests.

2. Results

Overall, we found several differences in locomotion and spatial strategies in SERT–/– mice tested in two traditional novelty-

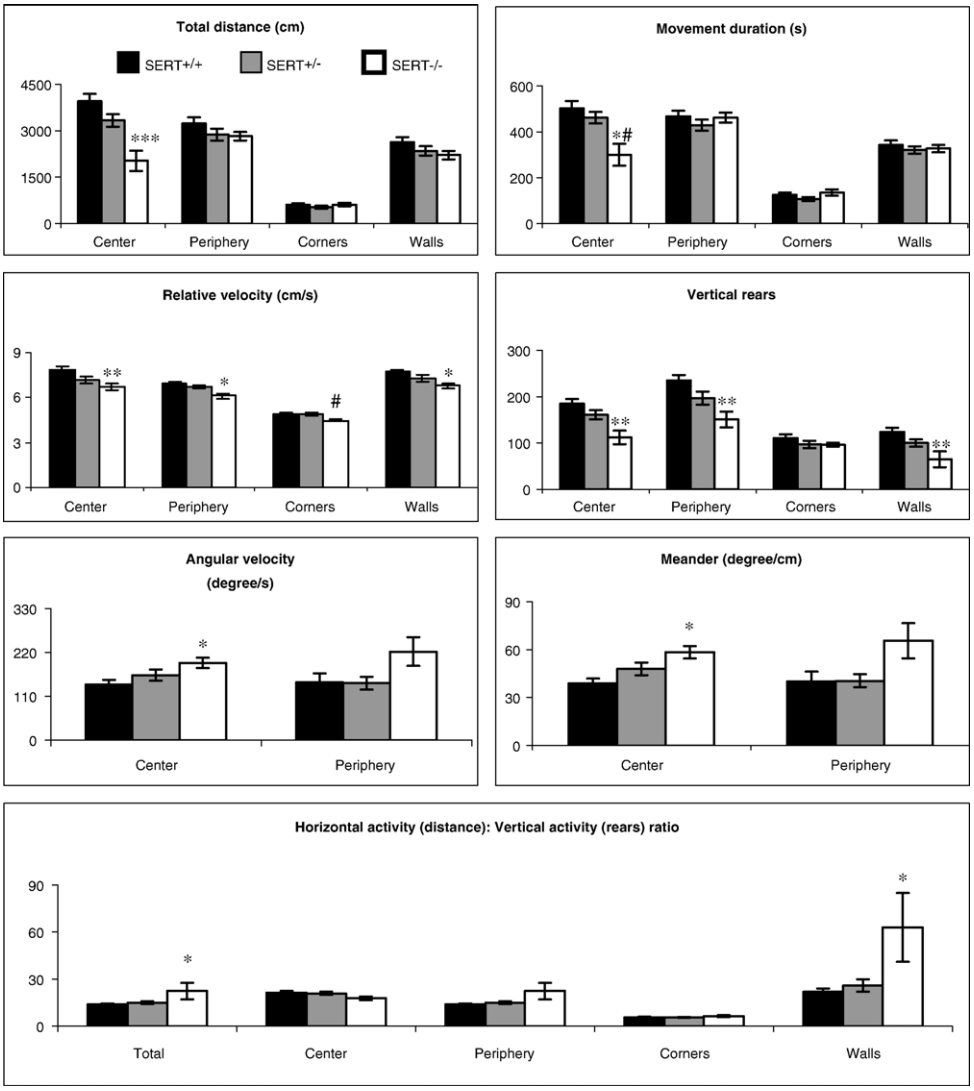

Fig. 2 – Spatial distribution of SERT–/– mouse activity (Trial 1) in the 20-min open field test. *$P<0.05$, **$P<0.01$, ***$P<0.001$ (vs. SERT+/+ mice), #$P<0.05$ (vs. SERT+/– mice), Dunn's post-hoc test for significant Kruskal–Wallis data.

based models: the open field and EPM. Figs. 1A and B show significant genotype differences in the open field horizontal activity (total distance traveled: $H=14.7$, $P=0.0006$; total duration of movement: $H=14.0$, $P=0.0009$) and vertical rears ($H=10.1$, $P=0.0063$), with a marked reduction in SERT–/– mice. There was also a significant reduction in relative velocity ($H=13.6$, $P=0.0011$) in this test, accompanied by robust thigmotaxis, manifest in fewer entries to the center ($H=9.9$, $P=0.0069$) and a significantly lower ratio of center:periphery distance traveled ($H=9.5$, $P=0.0086$) in SERT–/– mice. In addition, SERT–/– mice showed significantly more turning than did SERT+/+ mice, as assessed by increased angular velocity ($H=8.5$, $P=0.014$) and meander ($H=9.6$, $P=0.008$) in the open field test (Fig. 1B).

Fig. 2 summarizes spatial distribution of mouse open field activity. Overall, all three genotypes displayed similar distance traveled and duration of movement in periphery of the open field, while showing significant genotype differences for horizontal exploration in the center (distance traveled: $H=14.3$, $P=0.0008$; duration of movement: $H=11.9$, $P=0.0025$), but not in periphery of the open field (NS). In contrast, relative velocity was reduced in SERT–/– mice in both center and peripheral zones (center: $H=12.2$, $P=0.0023$; periphery: $H=7.9$, $P=0.019$; corners: $H=7.4$, $P=0.025$; walls: $H=6.7$, $P=0.035$), and vertical rears in the center ($H=12.6$, $P=0.002$), periphery ($H=11.8$, $P=0.0027$) and walls ($H=12.6$, $P=0.002$), but not in the corners (NS).

Analysis of the balance between different forms of exploration (assessed as horizontal:vertical activity ratio; Fig. 2) revealed the prevalence of horizontal over vertical dimension in SERT–/– mouse activity ($H=6.8$, $P=0.033$ total arena), especially pronounced near the walls ($H=7.9$, $P=0.019$) but not in the center or the corners of the open field arena (NS).

Compared with SERT+/+ mice, SERT–/– mice displayed significantly more turning behavior in the center (angular velocity: $H=8.1$, $P=0.018$; meander: $H=8.6$, $P=0.014$), with a similar trend, although non-significant, in the periphery of the arena (Fig. 2). To examine the relation between turning and other open field behaviors, we calculated correlation coefficients for meandering, angular velocity and horizontal and vertical activity measures. Although correlations were negative in all mice, they were not different in SERT+/+ and SERT+/– groups, whereas SERT–/– mice showed strong significant ($r\approx-0.9$, $P<0.05$) negative correlations between meandering scores and all horizontal and vertical activity measures (total distance traveled, relative velocity, duration of movement, vertical rears).

We next compared temporal organization of mouse exploration, using their habituation to open field novelty as traditional measures of spatial memory. Fig. 3 shows temporal organization (per-minute distribution) of mouse open field activity, with no genotype effects for mouse horizontal and vertical activity (distance traveled: $F(2,59)=0.42$, NS; travel duration: $F(2,59)=0.02$, NS; vertical rears: $F(2,59)=0.16$, NS). These results indicate that SERT–/– mice displayed unaltered temporal patterning of their exploration in novel arenas, and unaffected spatial working memory.

Assessing the mouse open field within-trial habituation using ratios of the first:last 5 and first:last 10 min (Fig. 4), we found unaltered habituation of horizontal and vertical activity, as well as meander and angular velocity, in all three genotypes (NS). Analyses of open field between-trial habituation (Fig. 4) showed that while all three genotypes display

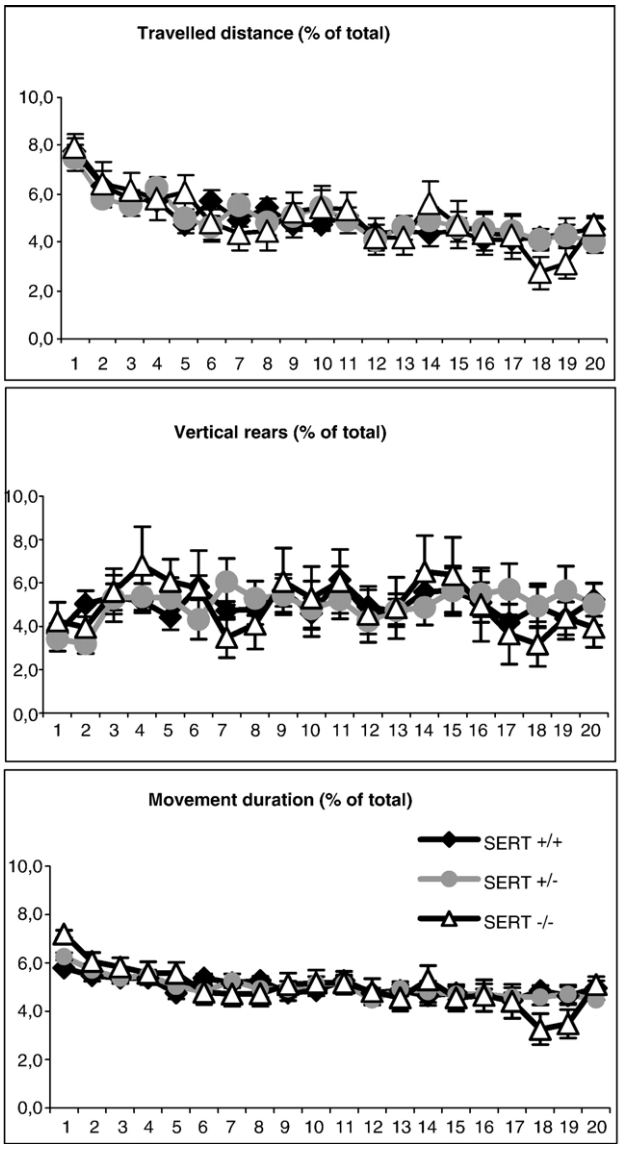

Fig. 3 – Similar temporal (per minute) distribution of SERT+/+, +/– and –/– mouse horizontal and vertical activity (Trial 1) in the 20-min open field test, % of total activity scores (100%).

habituation on Trial 2, it was slightly but significantly less for horizontal activity in SERT–/– mice (as assessed by Trial 2: Trial 1 ratios for total distance traveled: $H=10.3$, $P=0.006$; total duration of movement: $H=7.3$, $P=0.026$), but not for vertical rears, relative velocity and turning (meander, angular velocity; NS).

Table 1 summarizes behavioral performance of SERT+/+, +/– and –/– mice in the EPM test, representing another popular test of rodent exploration. Overall, there were significant Trial 1 genotype differences for horizontal and vertical activity, with a marked activity reduction in SERT–/– mice in all zones of EPM. Total motor activity scores (as assessed by open+closed horizontal and vertical activity scores) were also reduced in SERT–/– mice, indicating both hypoactivity and anxiety in this test. There was also a pronounced anxiety-like thigmotaxis in SERT–/– mice, manifest in significantly lesser time spent and distance traveled in aversive open arms and

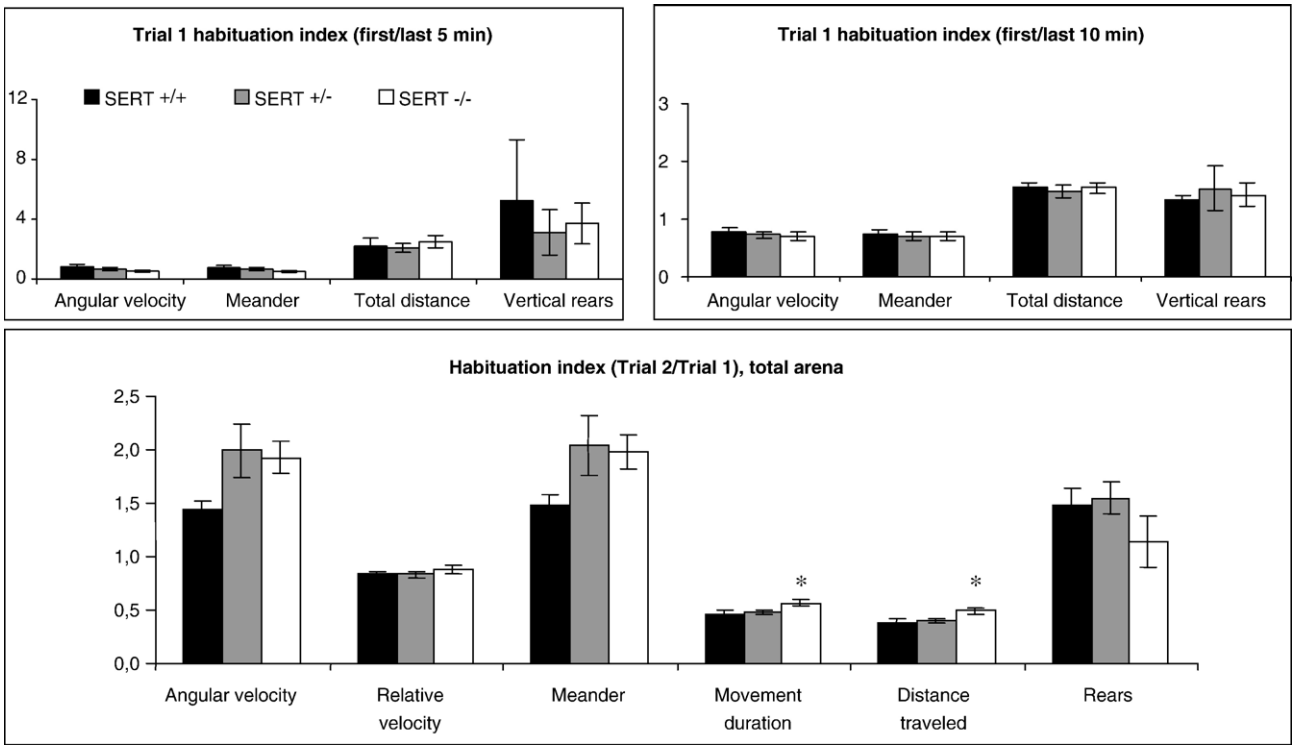

Fig. 4 – Within-trial (Trial 1) and between-trial (Trial 2 vs. Trial 1) habituation of SERT–/– mouse behaviors in the 20-min open field test. *$P<0.05$ (vs. SERT+/+ mice), Dunn's post-hoc test for significant ANOVA data.

central platform (see also similar trend for lesser open:closed and open:total ratios). In addition, SERT–/– mice produced significantly more turning, as assessed by increased angular velocity and meander in open and closed arms, but not in the central EPM platform, where animals of all three genotypes tended to move relatively straight.

Comparison of horizontal vs. vertical exploration (assessed as horizontal:vertical activity ratio) confirmed the prevalence of horizontal over vertical dimension in SERT–/– mouse activity in the closed arms area protected by walls, but not in the center or open arms of the maze (NS; Table 1).

Similarly to the open field experiments, we wanted to assess temporal organization of mouse EPM exploration, focusing in detail on their habituation responses. Analyzing mouse within-trial habituation in this test (using ratios of the first:last 5 min), we found similar habituation of horizontal, vertical activity and turning behaviors (meander, angular velocity) in all three genotypes (Table 1). Although EPM between-trial habituation was relatively unaltered in all three genotypes for most indices, SERT–/– mice produced a slightly lesser habituation for total (open+closed) horizontal distance traveled, as assessed by higher Trial 2/Trial 1 ratio (Table 1).

3. Discussion

Overall, this study led to three interesting observations in SERT–/– mice. First, we demonstrated aberrant spatial strategies of SERT–/– mice across different zones of novel arenas, accompanied by prevalence of horizontal dimension of activity over vertical, especially in protected areas close to walls (Figs. 1 and 2; Table 1). Second, we found unaltered within-trial habituation (spatial working memory index) but slightly reduced between-trial habituation of horizontal activity in SERT–/– mice in both tests (Figs. 3 and 4; Table 1). Finally, we showed that SERT–/– mice displayed specific higher turning behavior (Fig. 1; Table 1) in different zones of both novelty tests.

Examining spatial distribution of mouse open field activity, we noted that SERT–/– mice displayed a specific reduction of central horizontal activity (Fig. 1), generally consistent with their known thigmotaxis/anxiety-like responses (Holmes et al., 2003a; Kalueff et al., 2006b). Importantly, however, peripheral horizontal activity in this test remained unaltered in all three genotypes (Fig. 2), indicating that SERT–/– mice decreased movement in the more exposed and aversive center zone only, compared to SERT+/+ and +/– mice. The EPM data yielded similar results, showing a stronger reduction of exploration in more aversive open arms and central platform vs. protected closed arms (Table 1). Collectively, this suggests that SERT–/– mice seem to respond to novelty stress by spatial re-organization (reduction in potentially dangerous zones) rather than overall inhibition of horizontal locomotion. Because anxiety and hypoactivity domains seem to interplay in influencing the SERT–/– mouse behavioral phenotype (Holmes et al., 2003a; Kalueff et al., 2006b), our results are important, as they showed how anxiety domain can be separated from hypoactivity by studying spatial strategies in these mice.

Table 1 – Behavioral performance of SERT+/+ (n=11), SERT+/– (n=13) and SERT–/– (n=8) mice in the elevated plus maze test (two trials, 10 min each)

Behavioral parameters	Mouse genotype			H (P values)
	SERT+/+	SERT+/–	SERT–/–	
Trial 1 gross measures (total 10 min)				
Center distance moved (cm)	191±14a	167±19	83±17a	10.7 (<0.005)
Center time spent (s)	64±6	62±8	37±8	Trend
Central vertical rears	32±2a	25±4b	12±2ab	14.6 (<0.001)
Center angular velocity (deg/cm)	89±14	83±8	103±22	NS
Center meander (deg/cm)	43±7	42±5	54±11	NS
Open arms distance moved (cm)	859±89a	569±104	284±72a	12.3 (<0.005)
Open arms time spent (s)	292±38	223±48	168±49	Trend
Open arms vertical rears	19±1a	13±2	7±1a	12.8 (<0.005)
Open angular velocity (deg/cm)	114±6	127±9	148±23	NS
Open arms meander (deg/cm)	63±4	69±5	88±16	NS
Closed arms distance moved (cm)	875±95	798±114	557±54	Trend
Closed arms time spent (s)	245±34a	315±46	395±50a	6.3 (<0.05)
Closed arms vertical rears	27±3a	21±4	9±2a	10.1 (<0.01)
Closed angular velocity (deg/cm)	131±12a	156±23b	261±21ab	15.7 (<0.0005)
Closed arms meander (deg/cm)	68±6a	90±14b	160±11ab	15.6 (<0.0005)
Total (open+closed) distance moved (cm)	1734±74a	1367±94b	840±69ab	18.8 (<0.0001)
Total (open+closed) time spent (s)	537±6	538±8	564±8	Trend
Total (open+closed) vertical rears	46±4a	34±5	16±3a	14.5 (<0.001)
Trial 1 ethologically derived indices				
Spatial indices				
Open:closed distance moved ratio	1.2±0.2	2.7±1.5	0.6±0.2	NS
Open:closed time spent ratio	1.9±0.6	6.2±3.8	0.6±0.3	Trend
Open:total distance moved ratio	0.5±0.1	0.4±0.1	0.3±0.1	NS
Open:total time spent ratio	0.5±0.1	0.4±0.1	0.3±0.0	Trend
Horizontal:vertical activity indices				
Center	5.9±0.4	6.7±0.8	6.9±1.4	NS
Open arms	45±5	44±8	41±10	NS
Closed arms	34±3a	41±3b	73±13ab	18.9 (<0.0004)
Total arena	41±4	55±14	53±7	NS
Trial 1 within-trial habituation (first:last 5 min ratios)				
Center distance moved ratio	1.1±0.3	1.4±0.2	5.0±3.3	NS
Open arms distance moved ratio	4±1	15±11	4±2	NS
Closed arms distance moved ratio	0.8±0.1	1.1±0.2	1.0±0.2	NS
Total (open+closed) distance moved ratio	1.3±0.1	1.5±0.2	1.8±0.2	NS
Center time spent ratio	0.8±0.3	1.1±0.2	4.4±3.1	NS
Open arms time spent ratio	3±1	19±16	25±21	NS
Closed arms time spent ratio	0.5±0.1	0.6±0.1	0.4±0.1	NS
Total (open+closed) time spent ratio	1.1±0.1	1.0±0.1	0.9±0.1	NS
Center vertical rears ratio	1.3±0.3	1.2±0.2	2.0±1.0	NS
Open arms vertical rears ratio	3.4±1.7	2.0±0.6	2.8±1.8	NS
Closed arms vertical rears ratio	1.0±0.2	2.0±1.1	1.3±0.4	NS
Total (open+closed) vertical rears ratio	1.3±0.2	3.0±1.8	3.1±1.5	NS
Center angular velocity ratio	1.4±0.7	1.0±0.2	2.8±1.7	NS
Open arms angular velocity ratio	1.0±0.2	0.7±0.3	0.7±0.3	NS
Closed arms angular velocity ratio	0.7±0.3	0.6±0.1	0.5±0.1	NS
Center meander ratio	2.0±1.4	0.8±0.2	1.4±0.6	NS
Open arms meander ratio	1.1±0.2	0.4±0.4	0.6±0.2	NS
Closed arms meander ratio	0.7±0.2	0.6±0.1	0.4±0.1	NS
Between-trial habituation (Trial 2/Trial 1 ratios for total 10-min measures)				
Center distance moved ratio	1.0±0.2	0.8±0.2	1.0±0.2	NS
Center time spent ratio	1.2±0.3	0.8±0.2	0.8±0.1	NS
Central vertical rears ratio	1.0±0.2	1.6±0.9	1.0±0.2	NS
Center angular velocity ratio	1.3±0.2	1.2±0.2	1.7±0.7	NS
Center meander ratio	1.3±0.2	1.3±0.2	1.1±0.3	NS
Open arms distance moved ratio	0.5±0.1	0.5±0.1	3.0±1.7	NS
Open arms time spent ratio	0.5±0.1	0.4±0.1	3.4±2.7	NS
Open arms vertical rears ratio	0.8±0.2	1.3±0.8	0.9±0.3	NS
Open angular velocity ratio	0.8±0.1	0.9±0.1	0.6±0.1	NS

Table 1 (*continued*)

Behavioral parameters	Mouse genotype			*H* (*P* values)
	SERT+/+	SERT+/–	SERT–/–	
Between-trial habituation (Trial 2/Trial 1 ratios for total 10-min measures)				
Open arms meander ratio	0.7±0.1	0.8±0.1	0.6±0.1	NS
Closed arms distance moved ratio	1.6±0.3	3.4±1.6	1.4±0.3	NS
Closed arms time spent ratio	2.1±0.3	4.8±2.2	1.4±0.3	NS
Closed arms vertical rears ratio	1.3±0.3	2.6±1.2	3.0±1.7	NS
Closed angular velocity ratio	1.4±0.3	4.0±1.8	1.1±0.1	NS
Closed arms meander ratio	1.4±0.2	2.1±0.4	1.1±0.1	NS
Total (open+closed) distance moved ratio	0.7±0.1a	0.9±0.1b	1.9±0.4ab	12.1 (<0.005)
Total (open+closed) vertical rears ratio	0.9±0.3	1.7±0.7	2.1±0.6	NS

H – Kruskal–Wallis statistics for significant differences between genotypes (Trend: $P=0.05$–0.09). Genotypes sharing common letters are statistically different ($P<0.05$, Dunn's post-hoc test for significant Kruskal–Wallis data).

Unlike horizontal activity, SERT–/– mouse vertical rears were significantly reduced in both open field center and periphery (Fig. 2; also see similar data in all zones of the EPM (Table 1). This indicates that these two types of exploration were differentially affected by genetic ablation of SERT, and may reflect the fact that vertical exploration is more sensitive to anxiety than horizontal locomotion (Lapin et al., 1995). Clearly, this observation could be useful to future anxiety studies assessing behavioral activity patterns in these mice. Further evidence came from analysis of the balance between horizontal and vertical activity, as the nature of SERT–/– mouse exploration was clearly more "horizontal" than "vertical" in both tests, especially in protected areas close to walls (Fig. 2; Table 1). Although the exact meaning of this behavior requires further studies, these data again indicate that SERT–/– mice employed different behavioral strategies during their exploration of novel arenas, manifest in longer distance traveled between consecutive vertical rears in non-aversive zones.

Analysis of temporal organization of mouse open field behavior (Fig. 3) showed that although the levels of activity differed in all three genotypes (SERT+/+=SERT+/–>SERT–/– mice), they displayed similar temporal distribution of their Trial 1 novelty exploration. Unaltered within-trial habituation of horizontal and vertical exploration in all three genotypes in both open field and EPM tests suggests that short-term spatial memory in mice is unaffected by SERT genetic ablation. In general, these findings seem to be in agreement with recent pilot data on unimpaired learning in SERT–/– rats (Homberg et al., 2006), and on unimpaired habituation (Mar et al., 2002; Prinssen et al., 2007) and spatial memory/learning (Egashira et al., 2006; Steward and Reid, 2000) in rodents after treatment with SERT-inhibiting antidepressants. Our data also seem to be in line with recent clinical data on the lack of association between SERT genetic polymorphisms and memory (Payton et al., 2005; Reneman et al., 2006). However, in between-trial habituation in our mouse study, which was unimpaired for some measures in all three genotypes, was slightly but significantly reduced for horizontal activity scores in SERT–/– mice (Fig. 4; Table 1).

One explanation can be that SERT–/– mice may have somewhat poorer long-term spatial memory than SERT+/+ mice. At first glance, this contradicts to higher vulnerability of SERT–/– mice to repeated exposure to various stressors (Adamec et al., 2006; Carroll et al., 2007; Zhao et al., 2006), and positive correlation between serotonin levels and habituation (Bidzinski et al., 1998). Although this result may also conflict with recent clinical data showing somewhat improved memory and attention in carriers of short (less active) "s" SERT allele (Roiser et al., 2006, 2007), it is possible that *SERT* gene may play different roles in different types of memory. For example, although clinical data support the SERT role in augmented processing of aversive stimuli (Finger et al., 2007), its role in other forms of memory (such as spatial working and long-term memory) may not be crucial, as confirmed here.

It is also possible that other, non-cognitive factors modulated the SERT–/– mouse responses in our study. For example, with higher initial anxiety and pronounced fear-like freezing (both lowering horizontal activity scores on Trial 1), SERT–/– mouse behavior might become less inhibited on Trial 2, thus showing higher Trial 2:Trial 1 ratios reported here in the open field test. Our EPM data (Table 1) support this notion, as SERT–/– mice produced higher Trial 2:Trial 1 ratio for total horizontal activity.

Finally, SERT–/– mice displayed increased turning behavior in both novelty tests. Although increased turning was seen earlier in SERT–/– female mice (Kalueff et al., 2007a), the use of observation cylinders confounded these findings, as circling along the walls due to thigmotaxis (rather than meandering *per se*) might contribute to this phenomenon. In contrast, straight running along the walls in square open field or rectangular arms of EPM in our study is less likely to affect turning. As higher SERT–/– mouse meandering was also seen here away from walls (such as in the open field center; Fig. 2), this study provided a conclusive dissection of thigmotaxis from turning behavior, confirming the latter as a baseline phenotypical feature of SERT–/– mice, consistently observed in different novelty tests.

In general, several possibilities may be considered here. Despite motor and skeletal deficits reported in SERT–/– mice (Ansorge et al., 2003; Bliziotes et al., 2002), increased meandering on Trial 2 in both tests negates the possibility that this is a "tonic" neurological abnormality or a fatigue-related response, collectively suggesting that meandering is an interesting behavior in SERT–/– mice, reflecting a specific pattern of their locomotion in novel arenas. Can higher turning be due to reduced motor activity, generally seen in SERT–/– mice (Fig. 1; also see Holmes

et al., 2002b, 2003a; Kalueff et al., 2006b, 2007a)? Rodent studies have shown that the amount of animal activity may be independent of its geometrical patterning (Paulus and Geyer, 1993), implying that lower locomotion *per se* may not automatically lead to higher meandering in mice. Indeed, in the EPM (Table 1), higher meandering was seen in all three genotypes in the closed arms (where animals traveled more and spent more time), suggesting that increased meandering in SERT–/– mice is not due to their hypolocomotion.

To examine this possibility further, we calculated correlation coefficients for meandering and other open field behaviors, revealing strong negative correlations only in SERT–/– mice and implying genotype differences in SERT–/– mice in the relationship between turning and activity parameters. Moreover, open field meandering negatively correlated with vertical exploration, implying that an anxiety-related domain may also contribute to the high-meandering profile reported here. For example, higher meandering may reflect a different exploratory strategy in SERT–/– mice (i.e. a "cautious" locomotion), a geometrical complexity of mouse behaviours (Nilsson et al., 2001), a behavioral anomaly relevant to developmental barrel/corticolimbic brain abnormalities and aberrant somatosensory physiology in SERT–/– mice (Esaki et al., 2005; Persico et al., 2001; Xu et al., 2004), or a peculiar perseverative OCD-like behavior (consistent with the SERT involvement in human OCD (Hasler et al., 2006; Sutcliffe et al., 2005) and with other putative OCD-like behaviors in SERT–/– mice (Garner, 2005; Hill et al., 2007; Kalueff et al., 2007a; Lira et al., 2003)).

In summary, our study revealed altered spatial and motor patterns of SERT–/– mouse exploration in two novelty tests, but normal within-trial and slightly reduced between-trial habituation. While these features seem to reflect a complex interplay between motor, cognitive and anxiety factors, future studies are needed to dissect these profiles further. For example, using anxiolytic or anxiogenic drugs, we can assess further the role of anxiety in higher meandering reported here in SERT–/– mice, whereas psychostimulants may help evaluate potential motor component in specific responses reported here.

Given elevated serotonin and altered serotonergic pathways in SERT–/– mice (Li, 2006), an important question is whether these behavioral responses may be serotonergically mediated. For example, in line with potential utility of SERT mutant mice as a genetic model of serotonin syndrome (Kalueff et al., 2007a), it is possible to expect that aberrant patterns of locomotion observed here may be relevant to motor or mental serotonin syndrome-like symptoms (Goitz, 2002; Isbister and Buckley, 2005). Thus, pharmacological studies using different serotonergic drugs may be necessary to modulate these SERT–/– mouse phenotypes and assess their neurochemical underpinning. Finally, replicating our study using other relevant genetic models, such as mice lacking other monoamine transporters (Kalueff et al., 2007b; Torres et al., 2003) or brain-derived neurotrophic factor (Ren-Patterson et al., 2005), may help reveal further genetic interactions and their role in determining complex behavioral, motor and cognitive phenotypes. Based on these data, a better understanding of aberrant behaviors reported here may lead to new neurobehavioral models using genetic mouse models with reduced SERT function.

4. Experimental procedures

4.1. Animals

Animals were male SERT+/+ ($n=11$), SERT+/– ($n=13$), and SERT–/– ($n=8$) mice on a C57/BL6 background strain (Bengel et al., 1998). Mice were littermates produced by 20–21 heterozygous backcrosses. The animals were experimentally naïve and approximately 8 months old (37 ± 2 g) at the beginning of testing. Animals were weaned at 21 days of age, and group-housed (3–5 animals per cage) in standard plastic shoebox-style cages (29 × 19 × 13 cm^3) with wood shavings as a floor substrate, multi-ply gauze as nesting material, and *ad libitum* access to standard laboratory rodent food pellets and water. The animals were maintained throughout the study on a 12-h light/dark cycle (lights on at 06:00 h), in a virus/parasite-free facility approved by the American Association for Accreditation of Laboratory Animal Care. All three genotypes were examined in this study in order to more fully assess and compare their behavioral profiles.

4.2. Apparatus and procedures

4.2.1. Open field test

On the day of experiments, the mice were brought into a procedural room dimly lit by indirect red lighting and allowed to acclimate for at least 1 h prior to testing. During each trial (conducted during the light cycle, from 13:00 to 18:00 h), an individual mouse was placed in an open field arena (Plexiglas box 40 × 40 × 25 cm^3) with walls made opaque by attaching white paper outside the box. Each mouse was placed in the center of the arena and allowed to explore it freely for 20 min (between animals, the arena was cleaned with 70% ethanol, to remove olfactory cues).

A video recording camera was mounted to the ceiling above the observation chamber to record and input activity to a computer. Mouse behavior was recorded and analyzed using the Noldus Ethovision Video Tracking System (Version 3.0; Noldus, Wageningen, Netherlands). Parameters recorded included: horizontal activity (total distance traveled, cm), total duration of movement (s), vertical activity (number of rears), as well as angular velocity (deg/s) and meander (deg/cm), assessing overall turning of the animal. Data was then exported to Microsoft Excel and grouped by mouse genotype for analysis. In addition to these measures, we calculated the animal relative velocity (cm/s) and the ratio of horizontal:vertical exploration, as distance traveled divided by duration of movement or the number of vertical rears, respectively.

In order to obtain more information on spatiotemporal characteristics of animal behaviors, Noldus Ethovision system was used to quantify activity and behavior of each mouse, breaking down the activity by space and time. In addition to the entire arena scores, each behavioral measure was also analyzed in the following zones (Fig. 1A), previously established during tracking: the center (30 × 30 cm^2), the periphery (5 cm from the walls of the arena), the corners (5 × 5 cm^2) and the walls (calculated as periphery minus corners). To assess temporal patterning of behavior in Trial 1, the per-minute distribution of horizontal and vertical activity was analyzed, and calculated as percent (%) of total scores over the 20-min period.

To assess habituation (reduced responsivity to novelty) in SERT–/– mice, we studied within- and between-trial habituation. The within-trial habituation for each behavior was analyzed by computing ratios of first:last 5 and first:last 10 min (Leussis and Bolivar, 2006). In order to evaluate between-trial habituation in these mice, a second trial was repeated 3 days after Trial 1, as described above. Between-trial habituation was analyzed by computing the ratios of Trial 2 to Trial 1 for total 20-min scores for each individual behavior.

4.2.2. *The elevated plus maze (EPM)*

Two weeks after the open field test, the mice were tested in the EPM. The apparatus was made from Plexiglas and consisted of two open arms (30 cm × 5 cm) and two enclosed arms (30 cm × 5 cm; walls: 15 cm) extending from a common central platform (5 cm × 5 cm), elevated to a height of 50 cm. Experimental procedures were essentially the same as described above. During each trial, an individual mouse was placed in the center of the EPM (facing either open arm) and allowed to explore it freely for 10 min. Between animals, the apparatus was cleaned with 70% ethanol, to remove olfactory cues.

Using Noldus Ethovision system, each behavioral measure was analyzed in the following zones (Fig. 1C), previously established during tracking: the central platform, open arms and closed arms. Parameters recorded were: horizontal activity (cm), time spent (s), vertical activity (rears) and turning characteristics, as described previously for the open field test. As an additional measure of general activity, total activity scores were calculated in this test (a sum of open and closed arms scores). We also computed the animal relative velocity (cm/s) and the ratio of horizontal:vertical exploration in each zone (as described above). As conventional measures of EPM anxiety (Andreatini and Bacellar, 2000; Carobrez and Bertoglio, 2005), the ratios of open:closed and open:total activity (distance traveled, time spent and vertical rears) were also calculated for each genotype.

The within-trial habituation for each EPM behavior was analyzed by computing ratios of first:last 5 min. To assess between-trial habituation in these mice, a second trial was performed 3 days later, and the ratios of Trial 2 to Trial 1 for 10-min total scores were computed for each individual behavior.

4.3. *Statistical analysis*

All data are expressed as mean ± SEM. In both tests, data were analyzed by a Kruskal–Wallis test followed by a Dunn's post hoc test, using GraphPad Prism 4. Per-minute distribution of horizontal and vertical open field activity was analyzed using one-way analysis of variance (ANOVA, factor: genotype) for repeated measures (minutes of the test) followed by a Tukey's post-hoc test (www.StatPages.net). Correlations of total arena meander and angular velocity scores with other behaviors (including movement duration, total distance traveled, relative velocity, and vertical rears) in the open field test were calculated using non-parametrical Spearman's correlations (www.StatPages.net). A probability of less than 0.05 was considered statistically significant in all tests.

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