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Open field modifications needed to measure, in the mouse, exploration-driven ambulation and fear of open space

José Vidal
Universitat de Barcelona

The open field test is used to assess ambulation and anxiety; one way to assess anxiety is to compare ambulation in the center with ambulation in the periphery: the more anxious is the mouse, the less it moves in the center. The results of this report cast doubts on the generality of that rule, because they show that ambulation, both in the center and in the periphery, depends on the mouse strain and on the size of the open field; specifically, in a brightly lit open-field of moderate size (38 x 31 x 25 cm), ambulation in the center reflects anxiety in Balb/c mice, but not in C57Bl/6 mice. Yet, a large open-field (100 x 100 x 30 cm), receiving approximately the same amount of light as in the mouse room, allows assessment of anxiety and exploration-driven ambulation in both strains of mice. To do that, the author of this report proposes (i) to express ambulation in normalized scores (i.e., ambulation per surface unit) to verify that ambulation in the periphery is higher than ambulation in the center, (ii) to use an open field sufficiently large so that mice of any strain ambulate more in the periphery than in the center, and (iii) to measure ambulation in concentric strips of the open field and plot ambulation against the distance of the strips from the wall: it is proposed that the intercept of the line reflects exploration-driven ambulation whereas the slope reflects fear of leaving the wall.
Keywords: *Open field, murine anxiety, ambulation in the open field, C57Bl/c, Balb/c.*

Modificaciones del campo abierto necesarias para medir, en el ratón, la deambulación motivada por la exploración y el miedo a los espacios abiertos

La prueba del campo abierto se utiliza para evaluar deambulación y ansiedad; una forma de evaluar ansiedad es comparar la deambulación en el

Correspondence: José Vidal, Universitat de Barcelona, Facultat de Psicologia, Departament de Personalitat, Passeig de la Vall d'Hebron, 171, 08035. Barcelona, Spain. E-mail: jvidal@ub.edu

centro con la deambulación en la periferia: contra más ansioso es el ratón, menos se mueve en el centro. Los resultados de este artículo ponen en duda la generalidad de esa regla, porque muestran que la deambulación, tanto en el centro como en la periferia, depende de la cepa de ratón y del tamaño del campo abierto. Concretamente, en un campo abierto de tamaño moderado (38 x 31 x 25 cm), e intensamente iluminado, deambulación en el centro refleja ansiedad en los ratones de la cepa Balb/c, pero no en los ratones de la cepa C57Bl/6. No obstante, el uso de un campo abierto grande (100 x 100 x 30 cm), con la misma iluminación que en la sala donde se alojan los ratones, permite la evaluación de la deambulación y de la ansiedad en las dos cepas murinas. Para ello, el autor de este artículo propone (i) expresar la deambulación como puntuaciones normalizadas (deambulación por unidad de superficie) para comprobar que la deambulación en la periferia es mayor que en el centro, (ii) utilizar un campo abierto lo suficientemente grande para que los ratones de cualquier cepa deambulen más en la periferia que en el centro, y (iii) medir la deambulación en franjas concéntricas del campo y representar la deambulación en función de la distancia de la franja a la pared del campo: se propone que la ordenada en el origen de la línea refleja la deambulación motivada por la exploración, mientras que la pendiente refleja el miedo a abandonar la pared.

Palabras clave: *campo abierto, ansiedad del ratón, deambulación en el campo abierto, C57Bl/6, Balb/c.*

Introduction

The open field is a widely used test in rodents. For murine work, researchers have used open-fields of different sizes: (a) rectangular: 28 x 28 cm (Cassano *et al.,* 2011), 40 x 40 cm (Bambico *et al.,* 2010; Branchi & Alleva, 2006; Careau, Ordonez, Bininda-Emonds, & Garland Jr., 2012; Mach, Grubbs, Price, Paton, & Lucot, 2004; Sharma, Elased, Garrett, & Lucot, 2010; Zhu *et al.,* 2007), 50 x 50 cm (Kindlundh-Högberg, Zhang, Svenningsson, 2009), 55 x 55 cm (Branchi, Alleva, & Costa, 2002), 72 x 72 cm (Clément, Martin, Venault, & Chapouthier, 1995), 80 x 80 cm (Choleris, Thomas, Kavaliers, Prato, 2001), 1 x 1 m (Suaudeau *et al.,* 2000), and (b) circular: 40 cm in diameter (Leppänen, Ravaja, & Ewalds-Kvist, 2008), 60 cm in diameter (Wilcoxon, Nadolski, Samarut, Chassande, & Redei, 2007), 180 cm diameter (Jain, Dvorkin, Fonio, Golani, Gross, 2012). It seems that the size of the open-field is of little relevance: a review reflects this conclusion (Gould, Dao, & Kovacsics, 2009), and the structure of locomotion is independent of the open field size (Eilam, 2003).

Thigmotaxis (i.e., the tendency of the mouse to stay close to the wall of the open field) has been used to assess anxiety (Choleris *et al.,* 2001; Simon, Dupuis, & Costentin, 1994; Treit & Fundytus, 1989). Researchers have measured thigmotaxis in the mouse in different ways: time spent in the corners and along the walls of the open-field (Branchi & Alleva, 2006; Cassano *et al.,* 2011; Choleris *et al.,* 2001), time spent in the periphery and central zones (Mach *et al.,* 2004 [central zone: 30 x 30 cm]; Sharma, Elased, Garrett, Lucot, 2010 [central zone: 20 x 20 cm]), activity in the central zone (30 x 30 cm; Bambico *et al.,* 2010), ambulation 1.75 cm from the wall (Kindlundh-Högberg, Zhang, Svenningsson, 2009), quotient «ambulation in the inner 24-cm-diameter circle divided by ambulation in the 40-cm-diameter open-field» (Leppänen, Ravaja, & EwaldsKvist, 2008), ambulation in the 20 cm x 20 cm center area (Zhu *et al.,* 2007), time in the 30-cm diameter inner circle (Wilcoxon, *et al.,* 2007), quotient «ambulation along the walls divided by total ambulation» (Suaudeau *et al.,* 2000; [40 x 40 cm open-field]), time and distance travelled close to the walls (Branchi *et al.,* 2002). The above review shows that there is no uniform way to assess fear of leaving the wall. On the whole, the open field test lacks standardization (Blizard, Takahashi, Galsworthy, Martin, & Koide, 2007; Stanford, 2007).

The goals of this report are (i) to confirm the use of a brightly lit, middle-sized open field for the assessment of anxiety in two murine strains that differed in anxiety (Balb/c and C57Bl/6; Crawley *et al.,* 1997; Milner & Crabbe, 2008), (ii) to find out if a moderately lit, large open field is appropriate to assess thigmotaxis in the above-mentioned murine strains. This paper shows that (i) a middle-sized open field (of 38 x 31 cm) yields misleading results when assessing anxiety in mice of the C57Bl/6 strain, and (ii) exploration-related ambulation and anxiety to leave the wall can be assessed severally (in both murine strains) by measuring ambulation in two concentric strips of a large (1 x 1 m) open field.

Method

Subjects

Male and female mice of the Balb/c and C57Bl/6 strains were purchased from Harlan Iberica (Barcelona, Spain). Eight Balb/c females were mated with eight Balb/c males, and the offspring were the subjects of the experiments reported here (replication 1); the same females were mated a second time with different males, and the offspring were the subjects of replication 2. Similarly, eight C57Bl/6 females were mated twice with eight C57Bl/6 males. The males were removed from the females 1 week before parturition.

Adult mice of the same sex were housed 3-5 per cage, at 21±1 ºC, under a 12 h light-dark cycle (lights on at 8:00 hours). Food and water were available ad libitum. At the time of the first open field test, the mice were approximately 8 weeks old. The illumination in the center of the mouse room was 227 lux.

The experimental procedures were approved by the University of Barcelona Ethics Committee on Animal Experimentation.

Open fields

Two open fields were used. Open field 1 was a rectangular enclosure made of plastic, 38.0 x 31.0 x 25.0 cm, with black walls; the brownish floor was divided by black lines in 49 rectangles according to a 7 x 7 pattern; each rectangle was 5.4 x 4.4 cm. This open field had an inner rectangular zone, 17.0 x 13.5 cm, divided in 9 rectangles. The open field was lit by a reflector bulb that yielded about 1554 lux in the center of the field.

Open field 2 was a square enclosure made of plastic, 100.0 x 100.0 x 30.0 cm, with gray walls and the gray floor; the floor was divided by black lines in 400 squares according to a 20 x 20 pattern; each square was 5 x 5 cm. For the purposes of this report, three inner and outer zones were defined: inner zone 1 was a 40 x 40-cm square situated at 30 cm from each wall (the remaining of the field was outer zone 1), inner zone 2 was a 80 x 80-cm square situated at 10 cm from each wall (the remaining of the field was outer zone 2), and inner zone 3 was a 90 x 90-cm square situated at 5 cm from each wall (the remaining was outer zone 3). The open field was lit by a neon tube that yielded about 180 lux in the center of the field.

Procedure

Mice of the Balb/c and C57Bl/6 strains were processed separately; results for each strain were confirmed in a second replication.

Mice took open field 1 when they were about 8 weeks old and open field 2 when they were about 12 weeks old. Each mouse was placed in a corner of the field and allowed to move freely for 5 minutes. These variables were recorded in open field 1: ambulation (number of rectangles crossed) in the outer zone, ambulation (number of rectangles crossed) in the inner zone, and defecation (number of fecal boli). These variables were recorded in open field 2: defection (number of fecal boli) and ambulation (number of squares crossed) in the three inner and outer zones. Each session, held between 14:45 and 19:00 hours was videotaped. The field was washed with disinfectant soap between two mouse sessions. The variables were scored visually by the author of this report.

Ambulation and defecation were recorded because ambulation is a reliable variable and is different from defecation.

Statistical analysis

The Spearman correlation coefficient was used to calculate the correlation between variables; this nonparametric coefficient was chosen because the scatterplots showed occasional extreme values. The statistical package STATISTICA v6.1 (Tulsa, Oklahoma) was used to calculate the correlation coefficients and to produce the figures below.

Results

Results in Balb/c mice

Male and female Balb/c mice ambulated more in the outer zone of open field 1 than in the inner zone (figure 1); this result is seen whether results are expressed as raw ambulation or as normalized ambulation (i.e., ambulation per dm^2 in each zone).

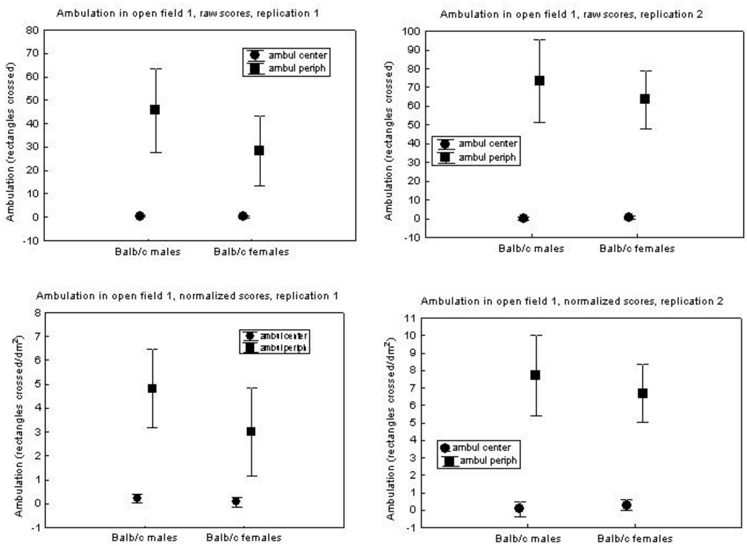

Figure 1. Ambulation of Balb/c mice in open field 1. The upper part represents ambulation expressed as raw scores; the lower part represents normalized ambulation (i.e., ambulation per dm^2 in each zone). Time for each mouse session: 5 minutes. Number of mice: in replication 1, 23 males and 18 females; in replication 2, 12 males and 24 females. Error bars are 95% confidence intervals.

Normalized ambulation in the inner zone was weakly correlated with normalized ambulation in the outer zone: in replication 1, the Spearman correlation coefficient in males was 0.25 (p=0.25, N=23), and the correlation coefficient in females was 0.26 (p=0.30, N=18); in replication 2, the Spearman correlation coefficient in males was 0.22 (p=0.49, N=12), and the correlation coefficient in females was 0.26 (p=0.21, N=24). Defecation scores (mean ± standard error) were (i) in replication 1, males, 6.8 ± 0.6; females, 5.6 ± 0.5; (ii); (ii) in replication 2, males, 6.2 ± 0.7; females, 4.9 ± 0.5.

Balb/c mice ambulated most of the time near the wall in open field 2 (i.e., they ambulated mostly in outer zone 3), barely entering inner zone 3; in replication 1, raw scores (mean ± standard error) of male mice were: 29.3 ± 7.7 (inner zone 3) and 188.5 ± 31.4 (outer zone 3); raw scores of female mice were 4.6 ± 1.3 (inner zone 3) and 82.1 ± 19.5 (outer zone 3); in replication 2, raw scores of male mice were 18.0 ± 7.3 (inner zone 3) and 181.58 ± 34.13 (outer zone 3); raw scores of female mice were 19.0 ± 6.3 (inner zone 3) and 163.7 ± 22.7 (outer zone 3). Defecation scores (mean ± standard error) were (i) in replication 1, males, 5.5 ± 0.6; females, 5.1 ± 0.4; (ii) in replication 2, males, 6.4 ± 0.7; females, 4.2 ± 0.5.

Results in C57Bl/6 mice

Male and female C57Bl/6 mice ambulated more in the outer zone of open field 1 than in the inner zone when the results were expressed as raw ambulation (figure 2, see next page), but ambulated to the same extent when results were expressed as normalized ambulation (figure 2). Defecation scores (mean ± standard error) were: (i) in replication 1, males, 0.6 ± 0.2; females, 0.3 ± 0.1; (ii) in replication 2, males, 0.8 ± 0.2; females, 0.3 ± 0.1.

In open field 2, results varied depending on whether ambulation was expressed as raw scores or as normalized scores: when ambulation was expressed as raw scores, ambulation in the periphery was higher than ambulation in the center, but only for zones 1 and 2 (upper part of figure 3, see page); when ambulation was expressed as normalized scores, mice ambulated more in the outer zones than in the inner zones (lower part of figure 3, see next page). Defecation scores (mean ± standard error) were: (i) in replication 1, males, 0.9 ± 0.3; females, 0.5 ± 0.2; (ii) in replication 2, males, 1.3 ± 0.3; females, 1.0 ± 0.2.

Ambulation as a function of the distance from the wall of open field 2

The above results show that ambulation decreases as the distance from the wall of open field 2 increases; i.e., as the mice move towards the center of the field. Yet, the above results do not lend themselves to quantitate that decrease. Therefore, ambulation in three concentric strips of the open field was plotted against the distance of each strip from the wall; figure 4 (see page 14) shows the three different strips. Both Balb/c and C57Bl/6 mice displayed a decrease in ambulation between strips 3 and 2, and another decrease, albeit less pronounced, between strips 2 and 1 (figure 5; see page 14). Balb/c mice steeply decreased ambulation as they moved away from the wall so that the mice barely entered a strip 15 cm away from the wall (figure 5); C57Bl/6 mice also decreased ambulation as they moved toward the center, but less abruptly than Balb/c mice (figure 5).

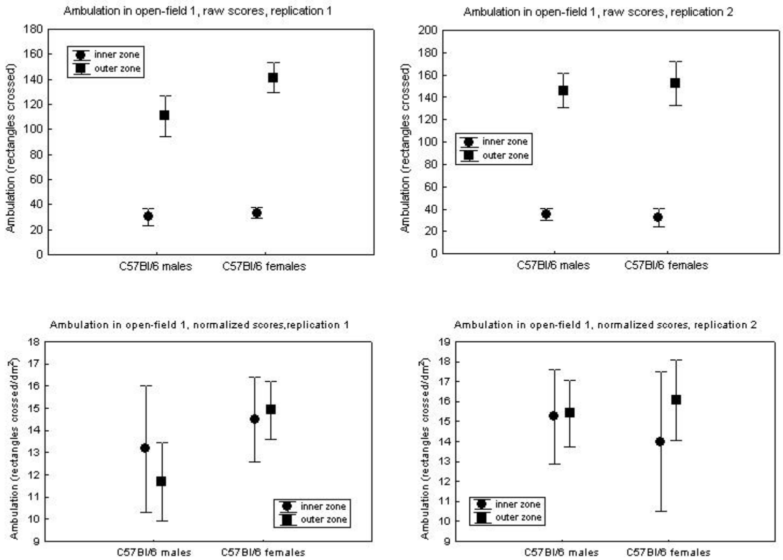

Figure 2. Ambulation of C57Bl/6 mice in open field 1. The upper part represents ambulation expressed as raw scores; the lower part represents normalized ambulation (i.e., ambulation per dm^2 in each zone). Time for each mouse session: 5 minutes. Number of mice: in replication 1, 13 males and 31 females; in replication 2, 28 males and 23 females. Error bars are 95% confidence intervals.

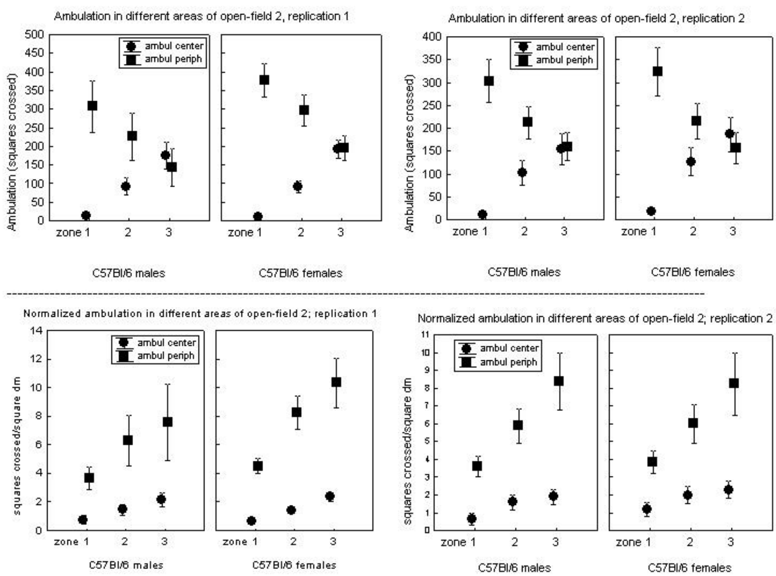

Figure 3. Ambulation of C57Bl/6 mice in open field 2. The upper part represents ambulation expressed as raw scores; the lower part represents normalized ambulation (i.e., ambulation per dm^2). Time for each mouse session: 5 minutes. Number of mice: in replication 1, 13 males and 31 females; in replication 2, 28 males and 23 females. Error bars are 95% confidence intervals.

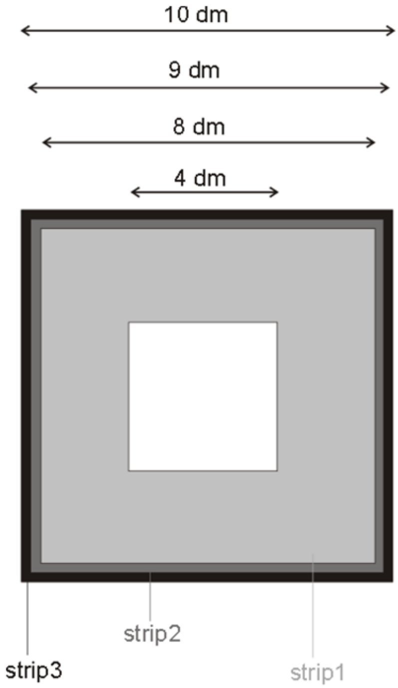

Figure 4. Strips in open field 2. Strips are indicated by the intensity of gray: the outer strip (strip 3) is black, the middle strip (strip 2) is dark gray, and the inner strip (strip 1) is light gray. The white square is not a strip. The open field was 10 x 10 dm.

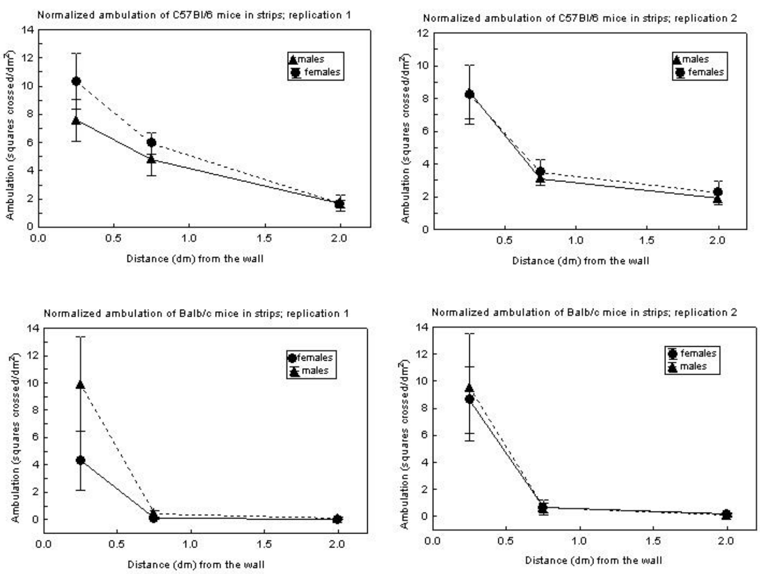

Figure 5. Ambulation of mice in concentric strips of open-field 2. Strips are the ones shown in figure 4. Distance of mid-strip3 to the wall: 0.25 dm; distance of mid-strip2: 0.75 dm; distance of mid-strip1: 2.00 dm. Error bars are 95% confidence intervals.

The curves in figure 5 accepted no satisfactory linear, second-order polynomial, or exponential equation fit (not shown); accordingly, each curve was approximated by two straight lines: one between strips 3 and 2 (figure 4) and another between strips 2 and 1 (figure 4). Table 1 shows the intercept and the slope of each line.

TABLE 1. INTERCEPTS AND SLOPES OF THE LINES SHOWN IN FIGURE 5.

segment	*intercept*	*slope*	*R*	*p*	*intercept*	*slope*	*R*	*p*
	C57Bl/6 males, replication 1				C57Bl/6 females, replication 1			
X<0.76	8.96±0.97	-5.50±1.74	0.54	0.004	12.53±1.17	-8.77±2.09	0.47	0.00009
X>0.74	6.72±0.72	-2.52±0.48	0.73	0.00002	8.51±0.48	-3.42±0.32	0.81	$1.8\text{x}10^{-15}$
	C57Bl/6 males, replication 2				C57Bl/6 females, replication 2			
X<0.76	11.05±0.92	-10.61±1.65	0.66	$4\text{x}10^{-8}$	10.62±10.63	-9.52±1.88	0.61	$8\text{x}10^{-6}$
X>0.74	3.80±0.31	-0.95±0.20	0.54	0.00002	4.23±0.61	-0.99±0.40	0.34	0.019
	Balb/c males, replication 1				Balb/c females, replication 1			
X<0.76	14.67±1.85	-18.99±3.31	0.65	$8\text{x}10^{-7}$	6.44±1.15	-8.50±2.06	0.58	0.0002
X>0.74	0.62±0.15	-0.26±0.10	0.36	0.015	0.11±0.03	-0.05±0.02	0.37	0.026
	Balb/c males, replication 2				Balb/c females, replication 2			
X<0.76	14.00±2.03	-17.76±3.63	0.72	$7\text{x}10^{-5}$	12.60±1.35	-15.94±2.41	0.70	$4\text{x}10^{-8}$
X>0.74	1.01±0.31	-0.45±0.21	0.42	0.040	0.93±0.22	-0.39±0.15	0.36	0.011

Each segment is identified by its abscissa in Figure 5: X<0.76 corresponds to a line between strips 3 and 2; X>0.74 corresponds to a line between strips 2 and 1. R: correlation coefficient; p: probability of the correlation coefficient. Intercepts and slopes are expressed as mean ± standard error.

The Spearman correlation coefficient of defecation (in open-field 2) and the slope of the first line (between strips 3 and 2 in Figure 5) were (i) in C57Bl/6 mice, replication 1, males, r=0.16 (N=13), p=0.60; females, r=0.10 (N=31), p=0.58; (ii) in C57Bl/6 mice, replication 2, males, r=0.28 (N=28), p=0.15; females, r=0.14 (N=23), p=0.51; (iii) in Balb/c mice, replication 1, males, r= -0.08 (N=23), p=0.71; females, r=0.05 (N=18), p=0.84; (iv) in replication 2, males, r= -0.13 (N=12), p=0.69; females, r=0.26 (N=24), p=0.23.

Discussion

Results in Balb/c mice are straightforward: in both open fields, the mice moved close to the wall of the open field and avoided the center (figure 1 and “Results”); besides, ambulation in the inner zone was weakly correlated with ambulation in the outer zone (see Results). These results are easily interpreted as ambulation in the periphery reflecting exploration, and ambulation in the center reflecting fear of open spaces (Blizard *et al.,* 2007); these results hold for both open fields; i.e., the size of the open field seems irrelevant, as it is commonly believed (Eilam, 2003; Gould *et al.,* 2009).

Results in C57Bl/6 mice are not so straightforward. In open field 1, the mice seemed to prefer the periphery over the center of the field (upper part of Figure 2); yet another interpretation is that the mice moved more in the periphery because they had more space to move. The latter interpretation is supported by the results shown in the lower part of figure 2: when ambulation was normalized (i.e., expressed as ambulation per surface unit), mice ambulated to a similar extent in the periphery and in the center of the open field. Therefore, results achieved with open field 1 cannot be construed as ambulation in the periphery assessing exploration and ambulation in the center assessing anxiety.

Results obtained with C57Bl/6 mice in open field 2 allow meaningful interpretation of ambulation, both in the center and in the periphery of the field. When raw scores of ambulation are considered, the ratio of ambulation in the center to ambulation in the periphery depends on what the center and the periphery are: when the periphery was a narrow strip close to the wall (zone 3), mice ambulated to a similar extent in the center and in the periphery (upper part of Figure 3). The correct interpretation of this finding is not that mice are not afraid of the inner zone, but that mice have more space to move in the inner zone (81 dm^2) than in the outer zone (19 dm^2). This conclusion is supported by expressing the results as normalized ambulation (ambulation per dm^2): in this case, mice consistently ambulated more near the wall than away from the wall (lower part of Figure 3); therefore, diminished ambulation in the center reflects lack of preference for the center; i.e., fear of the open space.

The ratio "distance traveled in the center of the open field/total traveled distance" has been used to assess anxiety (McIlwain, Merriweather, Yuva-Paylor & Paylor, 2001). The present study qualifies that anxiety index: in a small open field (e.g., open field 1), the above quotient may assess anxiety in Balb/c mice because they move more in the periphery than in the center, even if ambulation is expressed as normalized scores (figure 1), yet the above quotient yields misleading results in C57Bl/6 mice, because they move to a similar extent in both the center and the periphery (see normalized scores in figure 2). It is worth mentioning that McIlwain *et al.* (2001) used a 40x40x30-cm open field, whose dimensions are comparable to the dimensions of open field 1 reported here. Yet, the use of a large open field (open field 2) may generalize the assessment of anxiety because both Balb/c and C57Bl/6 mice ambulate more in the periphery than in the center (figure 3 and “Results”). Still, the question remains: what is a convenient index to assess fear of the open space? This question cannot be neatly answered with the above results, but measurements of ambulation in concentric strips in open field 2 (figure 4) may answer that question. A plot of ambulation in the strips against the distance of the strips from the wall yielded a curve (figure5): the intercept of the first segment of the curve (between strips 3 and 2; X<0.76, figure 5) may assess ambulation in touch with the wall (i.e., ambulation in relatively safe conditions), whereas the slope may assess the lack of inclination to move toward the center (i.e., a measure of fear of open spaces or a measure of risk taking). Table 1 shows that Balb/c mice displayed larger slopes (in absolute value) than C57Bl/6 mice: this result agrees with the more anxious nature of Balb/c mice (Crawley *et al.,* 1997). (Table 1 shows an exception to this rule: in replication 1, Balb/c females displayed a slope comparable to that of C57Bl/6 mice: that slope was atypically high (or low in absolute value) and probably is the exception rather than the rule.) A comprehensive analysis of ambulation along the wall and in the center of the open field has been carried out (Lipkind *et al.,* 2004); in this analysis, 16 end-points were established by means of a software (Software for the Exploration of the Exploration), and those end-points were used to discriminate behavior of two inbred strains of mice (C57Bl/6 and DBA/2). Although the method reported here is less thorough than the method by Lipkind *et al.,* it provides an easy index to assess fear to leave the wall.

A recurrent question is whether the open field can discriminate locomotion per se from anxiety-related locomotion: some authors have succeeded (Carola *et al.,* 2004; Trullas & Skolnick, 1993) but others not (Henderson, Turri, DeFries, & Flint, 2004; Milner & Crabbe, 2008). The curves shown in Figure 5 suggest that the intercept of the first segment probably assesses ambulation under the safety of the wall and, therefore, may be an index of ambulation not contaminated by anxiety (perhaps ambulation spurred by the need to explore?); on the contrary, the slope of the segment indicates the drop in ambulation that occurs as the mouse moves away from the wall (i.e., an index of fear).

Another question is whether defecation measures anxiety: it does according to some authors, but it does not according to other authors (see references in the report by Choleris *et al.,* 2001). The results of this paper reveal a low correlation between defecation in open field 2 and the slope of the first segment in Figure 5 (correlation coefficients lower than 0.28): therefore, defecation and the slope probably assess different constructs.

The results of this report may contribute to standardize the use of the open field, which is needed (Blizard *et al.,* 2007; Stanford, 2007).

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