Time in the central area of the elevated plus-maze correlates with impulsivity-related measures during an operant task*

El tiempo en el área central del laberinto en cruz elevado correlaciona con medidas relacionadas a impulsividad durante una tarea operante

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ABSTRACT
Impulsivity-related measures have been obtained using operant-conditioning tasks. Although it has been suggested that impulsivity indices can also be obtained using the elevated plus-maze (EPM), an anxiety-related animal test, no studies have examined the relationship between anxiety-related variables in EPM and impulsivity-related indices obtained during operant conditioning. Correlations between EPM measures and performance in a 60-s fixed-interval schedule of reinforcement (FI 60s) were established in this study. Twenty-four female rats were exposed to the EPM before starting training in the FI 60-s schedule. A positive correlation was found between the percentage of time spent in the central area of the EPM and both the FI efficiency index and the inter-response times. In addition, these three measures were positively correlated within Factor 1 of a factor analysis. No correlations were observed between open-arms measures in EPM and operant performance. These results suggest that time in the central area of the EPM may be a useful index of impulsivity in rodents without a pre-determined trait of impulsivity.

Keywords
Anxiety; elevated plus-maze; impulsivity; operant conditioning; rats.

RESUMEN
Medidas relacionadas a impulsividad se han obtenido mediante tareas de condicionamiento operante. Aunque se ha sugerido que índices de impulsividad pueden ser también obtenidos usando el laberinto en cruz elevado (LCE), una prueba animal relacionada con ansiedad, ningún estudio ha examinado la relación entre las variables de ansiedad en el LCE e índices de impulsividad obtenidos durante condicionamiento operante. En este estudio se establecieron correlaciones entre medidas del LCE

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y el desempeño en un programa de reforzamiento de intervalo fijo 60-s (IF 60-s). Diecisiete ratas hembras fueron expuestas la LCE antes de iniciar el entrenamiento en el programa de IF 60-s. Se encontró una correlación positiva entre el porcentaje de tiempo de permanencia en el área central del LCE y tanto el índice de eficiencia como los tiempos entre respuestas en IF. Adicionalmente, estas tres medidas correlacionaron de forma positiva dentro del Factor 1 del análisis factorial. No se observaron correlaciones entre las medidas de los brazos abiertos del LCE y la ejecución operante. Los resultados sugieren que el tiempo en el área central del LCE podría ser un índice útil de impulsividad en roedores sin un perfil predeterminado de impulsividad.

Palabras clave
Ansiedad; condicionamiento operante; impulsividad; laberinto en cruz elevado; ratas.

The elevated plus-maze (EPM) is one of the most used animal tests in neuroscience to evaluate anxiety-related behaviors, screen anxiolytic drug and understand the biological basis of emotionality (for a review see Carobrez & Bertoglio, 2005). The EPM test is based on the natural tendency of rodents to avoid open spaces in favor of protected areas. The structure of rodent behavior in the EPM has been widely examined through factor analysis (for a review see Wall & Messier, 2001). The detection of at least two-factor models has been often reported across these analyses, in which anxiety-related measures (e.g. open-arms exploratory activity) loaded in the first factor and locomotion-related measures (e.g. number of closed entries) loaded in the second factor. Moreover, decision-making and waiting-capacity-related measures (e.g. time in the central area) have often been loaded on independent factors (Cruz, Frei, & Graeff, 1994; Rodger & Johnson, 1995; Fernandes & File, 1996).

Increase in the percentage of entries and time spent in the open-arms of the maze indicates reduction in rodent anxiety (Carobrez & Bertoglio, 2005; Pawlak, Karrenbauer, Schneider, & Ho, 2012). Interestingly, increase in the open-arms exploratory activity has been also taken to indicate a behavioral phenotype of impulsivity (Ueno et al., 2002; Langen & Dost, 2011; Pawlak, et al., 2012; Kishikawa et al., 2014).

Impulsivity is a multidimensional construct (Riaño-Hernández, Guillen, & Buela-Casal, 2015) and some definitions include the inability to stop a response in the face of negative consequences; preference for a small immediate reward versus a larger but delayed one; acting without forethought or before all necessary information is available; and novelty/sensation-seeking and an increased propensity to engage in risky behaviors (Bari & Robbins, 2013). Measurement of operant behavior in rodents has been used to analyze various dimensions of the impulsivity. For instance, schedules of reinforcement of the type differential reinforcement of low rate (DRL - Kirkpatrick, Marshall, Clarke, & Cain, 2013; Hankosky & Gulley, 2013) and fixed interval (FI - Berger & Sagvolden, 1998; Dellu-Hagedorn, 2006; Munn & McNaughton, 2008; Orduña, 2015) have been used to obtain measures of motor impulsivity. In some of these operant tasks, the ratio of reinforcements/number of responses and the inter-response time have been used as an indicator of impulsivity (Berger & Sagvolden, 1998; Dellu-Hagedorn, 2006; Perry, Sagvolden, & Faraone, 2010).

Alternatively, impulsivity-related indices have also been scored using the latency to explore a new environment (Gross et al., 2002), and behavioral measures from anxiety models such as the open field, the light-dark box (Binder, Droste, Ohl, & Reul, 2004; Colorado, Shumake, Conejo, Gonzalez-Pardo, & Gonzalez-Lima, 2006) and the EPM (Ueno et al., 2002; Langen & Dost, 2011; Kishikawa et al., 2014).

Considering the possible relationship between anxiety and impulsivity traits in animal models, the aim of this study was to establish relationships between the main anxiety-related behaviors in the EPM and fixed-interval performance in rats without a pre-determined trait of impulsive behavior.

Methods

Subjects

Twenty-four adult female Wistar rats (240-270gr) obtained from the breeding colony at Fundación Universitaria Konrad Lorenz were used in this study. Rats were housed in pairs in polycarbonate cages (42 x 20 x 20cm) which contained dust-free wood shaving bedding, and were kept in an animal room under a 12h light/dark cycle (lights on at 6:00 a.m.) with water and standard rodent pellets available *ad libitum*. The room temperature was maintained at 23±2°C with 55% relative humidity. All experimental procedures were performed in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals and were approved by our Institutional Animal Care and Use Committee (CICUAL-KL, SAC 006-08-2014).

Apparatus

An elevated plus-maze (EPM) was used to obtain anxiety and locomotion-related measures (Rogers & Johnson, 1995). The apparatus consisted of two open-arms (50 x 10-cm) crossed at right angles with two opposed closed arms of the same size. Closed arms were enclosed by 40-cm high black Plexiglas walls. The arms emerged from a central square (10x10cm). The floor of the plus-maze was made of black smooth Plexiglas and the entire apparatus was elevated 50cm from the ground. A Plexiglas edge (0.5-cm) surrounded the open arms in order to prevent rats from falling. The level of illumination of the test room was adjusted to 30 lux measured at the central area of the plus-maze.

Eight operant conditioning chambers (Med Associates Inc.) with stainless steel grid floor were used to train the rats. Each chamber (22 x 25 x 24 -cm) was fitted with two stainless-steel retractable levers and a feeder situated among the levers. Sucrose pellets were delivered in the feeder by a food dispenser when the rat pressed the lever. The chamber was enclosed in a sound-attenuating box and masking noise (80 dB) was provided by a fan. A computer and interface unit (Lafayette Instruments) controlled the schedule and recorded the behavioral data using the ABET II software (Lafayette Instruments).

Behavioral Procedures and Scoring

Elevated plus-maze. Behavioral tests in the EPM (Day 1) were conducted in the light phase of the cycle, i.e., between 08:00 and 13:00. Each rat was placed in the central area of the maze facing one of the closed arms, then it was allowed to freely explore for 5-min. At the end of each trial, the maze was cleaned with an ethanol solution and dried with a dry cloth. Experimental sessions were recorded using a video camera placed above the maze and connected to a digital video recorder in an adjacent room. Videos were subsequently scored and analyzed by a trained observer. Similar to the procedure previously described elsewhere (Rico, Penagos-Gil, Castañeda & Corredor, 2016), behavioral parameters were scored with the ethological scoring freeware X-PloRat, developed at the Laboratory of Exploratory Behavior USP/Ribeirao Preto, Brazil. The images of the maze's arms were divided into 10-cm squares on a transparent plastic mask placed over the computer screen. The number of entries and time spent in different parts of the maze were measured using the software, as well as the number of square crossings. Behavioral parameters comprised conventional spatiotemporal and ethological measures. The number of entries into the open and closed arms, the time spent in the open-arms, the time spent in the central area, the open and closed extremities (the last distal 10-cm squares in each arm) and the number of squares crossed were scored. An entry was scored after all four paws of the rat entered a square. In addition, frequency of *protected stretch-attend posture* (when animal stretches to its full length mainly with the forepaws and returns to the previous position into the closed arms or central area of the maze) and *head dips* (animal sticking the head outside the maze border and toward the floor) were also scored.

Operant tasks. The animals started operant-conditioning training three days after the EPM test (Day 4). Each rat was tested in the same operant chamber throughout the experiment. Since standard anxiety-related measurement in the EPM test does not entail the use of food or water deprivation regimen, rats were maintained with water and rodent pellets freely available in the home cage and sucrose pellets were used as reinforcers. During five consecutive daily sessions (Day 4 to 8), each subject was placed for 10 min into the chamber with 10 sucrose pellets available in the feeder (the levers of the operant chambers remained retracted). By Day 8, seventeen of the twenty-four rats were consuming 10 pellets before the end of 10-min session; thus, these seventeen subjects were subsequently trained to eat from the feeder (Day 11), whereas the remaining seven rats were excluded from the protocol. Between Day 12 to 14, bar-press responses of all subjects were manually shaped in 15-min daily sessions using successive approximations. On Day 15 and 16, all subjects were exposed to a continuous-reinforcement schedule (CRF). On Day 16, all rats were earning 30 reinforcements before the end of the 15-min CRF session (at this point the session ended), thus the FI 60-s schedule was introduced on Day 17. The mean of the time elapsed between responses (inter-response time - IRT), the frequency of bar-pressing, the number of reinforcements delivered and the ratio of reinforcements/number of responses (efficiency index) were scored during that single FI-60-s 15-min session (Day 17). In addition, the first 5 min of the session were scored separately in order to analyze the immediate (acute) effects of changing the schedule of reinforcement – e.g., having switched from CRF to an FI 60-s schedule.

Data analysis

Scored data from the EPM were used to calculate percentage of entries into the open-arms; percentage of time spent in the open-arms, the central area and the open and closed extremities of the arms. Data from the EPM and FI 60-s were correlated utilizing Pearson's correlation. The correlation coefficients were considered significant when $p < .05$. In order to expand variables correlation within the same model and across models, data obtained from the EPM and FI 60-s were subjected to a factor analysis. The main measures used for this procedure were the following: for the EPM, the percentage of entries in the open arms, open arms time, central area time, closed arms entries and protected SAP. For the FI 60-s, the inter-response time 15-min, efficiency index 15-min, inter-response time 5-min, and efficiency index 5-min. The factor analysis was performed by principal-component analysis followed by an orthogonal Varimax rotation. Factors with eigenvalues greater than 1.0 and loadings greater than 0.6 were kept.

Results

Significant negative correlations between open-arms exploratory activity and both the time spent in the protected areas of the apparatus and the frequency of protected stretch-attend posture were found in the EPM (Table 1). No significant correlations between the time spent in the central area of the maze and other measures scored in the EPM were found (Table 1).

TABLE 1

Main correlations amongst elevated plus-maze variables

Behavioral parameters	%OAT	%OAE	%OEx	%CAT	%CEx	CAC	pSAP
% Central area time (Cent)	-0.31	-0.05	-0.28	-0.03	0.06	0.04	0.21
% Open arms time (OAT)		0.81**	0.85**	-0.93**	-0.61**	-0.41	-0.75**
% Open arms entries (OAE)			0.53*	-0.84**	-0.33	-0.55*	-0.84**
% Open extremities time (OEx)				-0.79**	-0.49*	-0.08	-0.54*
% Closed arms time (CAT)					0.61**	0.41	0.71**
% Closed extremities time (CEx)						-0.01	0.21
Closed arms crosses (CAC)							0.35

Note. pSAP = Frequency of protected stretch-attend posture. * $p < 0.05$; ** $p < 0.01$
Source: own work

In the FI 60-s operant-conditioning task, high significant positive correlations between the inter-response time and the efficiency index were observed during both the first 5-min (r = 0.87, $p < 0.01$) and the15-min session (r = 0.91, $p < 0.01$). The main correlations between the FI 60-s operant task and the EPM measures are showed in the Table 2. None of the traditional anxiety- nor locomotion-related measures in the plus-maze correlated with the measures obtained from the FI 60-s operant task. However, significant correlations between time in the central area of the maze and operant measures were found.

TABLE 2

Main correlations between the FI 60-s operant task and the elevated plus-maze variables

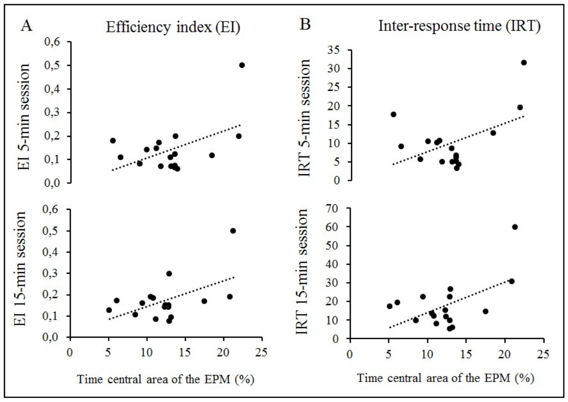
Behavioral parameters	% Cent	%OAT	%OAE	CAC	pSAP
Efficiency index 15-min	0.52*	-0.04	0.18	0.10	-0.03
Efficiency index 5-min	0.51*	-0.25	-0.05	0.25	0.22
Inter-response time 15-min	0.54*	-0.10	0.12	0.07	0.12
Inter-response time 5-min	0.48*	-0.35	-0.09	0.31	0.31

Note. % Central area time (Cent.); % Open arms time (OAT); % Open arms entries (OAE); Closed arms crosses (CAC); Frequency of protected stretch-attend posture (pSAP). * $p < 0.05$
Source: own work

Figure 1 and Table 2 show significant correlations between percentage of time spent in central area and the measures in the FI 60-s schedule. Positive correlations between the percentage of time spent by rats in the central area and the efficiency index during the first 5 and 15-min session of the operant task were found (Figure 1A). Similar to the efficiency index, positive correlations between time in the central area of the maze and the inter-response time were also found during the first five and 15-min session (Figure 1B). No significant correlations were found amongst other spatiotemporal and ethological measures scored in the EPM and impulsivity-related measures during the FI 60-s schedule.

Figure 1

Significant correlations (Pearson's coefficient, p < .05) between percentage of time spent in central area of the plus-maze and impulsivity-related measures in an operant task



Rats were exposed to the EPM for 5-min before starting training in the FI 60-s schedule. Data from (A) the efficiency index (EI) and (B) the inter-response time (IRT) were analyzed for the first 5-min and the total 15-min session of FI 60-s schedule
Source: own work

Results from the factor analysis are shown in Table 3. The main behavioral parameters obtained from EPM and FI 60-s were processed using principal-component analysis. After an orthogonal Varimax rotation, two factors representing 84.85% of the variance emerged. Factor 1, which accounted for 46.57% of the variance, was related to the impulsivity-related measures of the FI 60-s and the time spent in the central area of the EPM. Factor 2 was only associated with the anxiety-related measures of the EPM parameters. For the Factor 1, the time spent in the central area of the EPM correlated positively with the inter-response time and efficiency index of the operant task. Factor 2 showed that open-arms exploration negatively correlated with percentage of entries in the closed arms and protected SAP frequency. The time in the central area of the EPM did not correlate with the main measures of the EPM.

TABLE 3

Orthogonal factor loadings obtained from female Wistar rats exposed to the elevated plus-maze test and the operant conditioning task fixed-interval 60-s schedule of reinforcement

Behavioral parameter	Factor	
	F1-Impulsivity	F2-Anxiety
Elevated plus-maze test		
% entries open arms		-0.97
% time open arms		-0.89
% time central area	0.65	
% entries closed arms		0.97
Protected SAP frequency		0.90
60-s fixed-interval schedule of reinforcement		
Inter-response time 15-min	0.96	
Efficiency index 15-min	0.93	
Inter-response time 5-min	0.87	
Efficiency index 5-min	0.96	
% variance	46.57	38.28

Note. Principal-component analysis was followed by an orthogonal Varimax rotation. Factors with eigenvalues greater than 1.0 and loadings greater than 0.6 were kept. Minus signs (-) indicate the direction of the particular loading.
Source: own work

Discussion

Correlations between anxiety-related measures in the EPM and impulsivity-related indices during temporal operant conditioning (FI 60-s) were established in this study. The main findings were as follows: (a) rats that spent more time in the central area of the EPM also exhibited both better efficiency and greater inter-response time during a fixed-interval schedule of reinforcement; (b) the time in the central area of the EPM, the efficiency index and the inter-response time were also positively correlated within Factor 1 of the factor analysis (i.e., related to impulsivity); (c) open-arms exploration activity in the EPM and impulsivity-related measures in the FI 60-s schedule were not correlated.

Pearson's correlations showed that a greater permanence in the central area of the EPM was related to a better efficiency and a greater inter-response time. Both an increased efficiency index and an inter-response time suggest a better adjustment of the rats to the temporal constrains of the schedule of reinforcement. Factor analysis confirmed that the permanence in the central area of the EPM positively correlated with impulsivity-related measures scored during the operant task, which account for Factor 1. Anxiety-related measures observed within Factor 2 agree with the classic factor solution reported for the EPM parameters, where risk assessment (protected SAP frequency) negatively correlated with open arms exploration (Cruz et al., 1994; Rodger & Johnson, 1995).

Our data suggest that the percentage of time in the central area of the EPM could be a useful behavioral measure to identify an impulsive trait in naïve rats. Although no studies have reported a relationship between anxiety-related measures in the EPM and impulsivity indices during operant conditioning, the current results seem to be consistent with the data obtained from the factor-analysis techniques for the EPM measures. In mice exposed to an open EPM, time in central area loaded in a first factor, which was related to depth exploration (Sorregotti, Mendes-Gomes, Rico, Rodgers, & Nunes-de-Souza, 2013). However, center hub time or center hub time ratio measures have often been loaded in a third or four independent factors in the standard EPM and have been conceptualized as *decision-making* and *waiting-capacity-related* measures (Cruz et al., 1994; Rodger & Johnson, 1995; Fernandes & File, 1996). Impulsive decision-making and motor impulsivity seem to be the two main classifications of impulsivity (Winstanley, 2011; Bari & Robbins, 2013; Riaño-Hernández et al., 2015). Impulsive decision-making is referred to the inability to prioritize future rewards over satisfying the need for more immediate gratification, whereas motor impulsivity is often characterized by the inability to withhold from making a predominant motor response (Winstanley, 2011).

Conceptualized as *decision-making* and *waiting-capacity-related* measure, time in the central area of the plus-maze seems to be related with at least two main definitions of the multidimensional construct of impulsivity (for a review see Bari & Robbins, 2013). It seems that rats unable to withhold a response, such as stopping in the central area before entering any arm in the EPM, are also less effective in obtaining sucrose pellets (i.e., produce more responses than necessary to obtain each reinforcer); therefore, these rats are also more impulsive during both a schedule change and a temporally-defined schedule of reinforcement.

Research has shown that naturally-impulsive rats exhibit high open-arms exploration when exposed to the EPM. For instance, the spontaneously-hypertensive rat, a validated animal model of attention-deficit/hyperactivity disorder that includes a motor impulsivity phenotype (Sagvolden, 2000), typically shows high open-arms exploration in the EPM (Ueno et al., 2002; Fergunson & Gray, 2005; Langen & Dost, 2011). Accordingly, we hypothesized that rats exhibiting high open-arms exploration in the EPM could also be more impulsive during the operant task. Contrary to our expectations, we did not find any significant correlations between open-arms exploration in the EPM and impulsivity-related measures during FI 60-s task. It seems that the traditional anxiety-related measures in the EPM (open-arms time and entries) allow to detect spontaneously-impulsive rats' behavior but not the behavior of rats without that trait. Interestingly, the time spent in the central area of the EPM seems to be a sensitive measure to detect the behavior of rats without a predetermined trait of impulsivity.

In conclusion, our results suggest that low anxiety trait in the EPM do not correlate with high impulsivity profile during a temporally-defined operant-conditioning task, such as a FI 60-s schedule. However, low decision-making in the plus-maze correlated with high impulsive phenotype during a fixed-interval schedule of reinforcement. These results confirmed previous interpretation of the time in the central area of the EPM as a waiting-related measure, which in turn could be considered as a motor impulsivity parameter in rats without a predetermined trait of impulsive behavior. The EPM is a useful test that allows to obtain anxiety-related measures in a single and brief five-minute session without previous training. Whether a single measure, such as the time in the central area of the EPM, is sensitive to detect an impulsive trait in rats, thus the use of the EPM could also enhance our knowledge about the biological basis of impulsive behavior.

In order to extend variables correlation within the same model and across models (EPM and FI 60-s), we followed the suggestion of one the manuscript's reviewers to perform principal-components analysis. Considering that the reported findings are limited by the number of subjects and variables used, further studies could analyze (a) the factor solution with a larger sample of subjects, and (b) the relation between time in the central area of the EPM and impulsivity-related measures during other operant tasks, such as a differential reinforcement of low rates schedule (DRL).

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Notes

* Research Article.