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Adaptação de modelo de impulsividade para o zebrafish (*Danio rerio*)

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RESUMO

O zebrafish (*Danio rerio*) é uma espécie de peixe que vem sendo cada vez mais utilizada como modelo animal para o estudo de fenômenos comportamentais. O desenvolvimento de modelos de impulsividade com tais sujeitos encontra-se em fase inicial, com apenas um modelo já desenvolvido, baseado na tarefa 5CSRTT. Modelos de ampla difusão na literatura, como o de desconto temporal, ainda não se encontram adaptados para tal espécie. O objetivo deste trabalho é a adaptação de um modelo de impulsividade, usando o zebrafish como sujeito, a partir de modelos já desenvolvidos para roedores. O trabalho está organizado em três artigos. No primeiro efetuou-se uma revisão de literatura de modelos animais de comportamento do tipo impulsivo. Embora os resultados apontem mais de 27 modelos diferentes, mais da metade dos artigos revisados usaram dois modelos, a saber, o paradigma de desconto temporal e a 5CSRTT, que correspondem a modelos de escolha impulsiva e ação impulsiva, respectivamente. Dado já haver modelo baseado na 5CSRTT adaptado para o zebrafish, optou-se pela adaptação de um modelo de desconto temporal. No segundo artigo estudou-se o responder do zebrafish sob um esquema de *peak procedure*. Os sujeitos não adquiriram o padrão típico de respostas em tal esquema, mas demonstraram discriminação temporal num esquema anterior de intervalo-fixo. Argumenta-se que os resultados negativos no *peak procedure* se devem a efeitos da idade dos sujeitos, devido à longa duração da coleta. No terceiro artigo estudou-se discriminação de quantidades de alimento pelo zebrafish. Os sujeitos não demonstraram discriminação em nenhuma das proporções testadas (1 vs. 2, 1 vs. 3, 1 vs. 4 e 2 vs. 3 itens). Embora tais sujeitos possam não discriminar quantidades de alimento, já se demonstrou que são capazes de discriminar quantidades de membros de sua espécie em cardumes. Conclui-se que, apesar dos resultados negativos encontrados por este estudo, seria possível o desenvolvimento de um modelo baseado em desconto temporal usando-se cardumes de tamanhos diferentes como reforçadores. Futuras pesquisas deveriam se concentrar em procedimentos diferentes dos adotados por este estudo.

Palavras-chave: comportamento animal, peixes, modelo animal, impulsividade.

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ABSTRACT

Zebrafish (*Danio rerio*) is becoming a very popular model for the study of behavioral phenomena. The development of impulsivity models using this species is only beginning, with only one model – based on the 5CSRTT – already adapted. Widespread models such as delay-discounting were not adapted yet. The objective of this work is the adaptation of a rodent impulsivity model using zebrafish as subjects. The work is organized into three articles. In the first one, we performed a review of impulsive-live behavioral models. Although the results show more than 27 different models, more than half of the reviewed papers used either one of two models: delay-discounting and 5CSRTT, which are models of impulsive choice and impulsive action, respectively. Because there is already a model based on the 5CSRTT adapted for the zebrafish, we decided to adapt a delay-discounting model for the species. In the second article, we investigated zebrafish responding under a peak procedure. The subjects did not acquire the typical response pattern in that task but showed time discrimination under a fixed-interval schedule. We argue that our results are due to the aging process of the subjects, given the long duration of training. In the third article, we investigated the discrimination of food quantities by zebrafish. The subjects did not discriminate between two different quantities in any of the ratios tested (1 vs. 2, 1 vs. 3, 1 vs. 4 e 2 vs. 3 items). Although such subjects may be unable to discriminate between different quantities of food, it has been shown that they are able to discriminate between different quantities of conspecifics in shoals. We conclude that, despite our negative results, the development of a delay-discounting based model using different shoal sizes as reinforcement could be possible. Future research should concentrate on different procedures than those adopted here.

Keywords: animal behavior, fish, animal model, impulsivity.

SUMÁRIO

Impulsivity can be defined as “actions that appear poorly conceived, prematurely expressed, unduly risky, or inappropriate to the situation and that often result in undesirable consequences” (Daruna & Barnes, 1993). Although some impulsive behavior can be beneficial to an individual, high levels of impulsivity can be considered harmful, as it is directly mentioned as a diagnostic criteria for several psychiatric disorders and is implied in the criteria for others, including Antisocial Personality Disorder, Borderline Personality Disorder, Substance Abuse, Bipolar Disorder, and Attention Deficit Hyperactivity Disorder (Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001). Thus, the development of animal models of impulsivity is important, especially because animal models are an essential component of pharmaceutical research.

Although rodents have been the animals of choice for the development of behavioral models in general, zebrafish (*Danio rerio*) is a teleost which is rapidly gaining acceptance in biomedical research (Gerlai, 2014). Its high fecundity, short generation time, transparent embryos and easy breeding protocols are often quoted as justification for its choice as a model in genetics (Müller, 2005). It is 4 cm long when fully grown and it prefers to stay in close proximity to its conspecifics, a behavior that allows investigators to house a large number of zebrafish in small fish tanks (Gerlai, 2014). It presents huge genetic homology with humans (Howe et al., 2013). It is a diurnal species that strongly relies on its vision, allowing for the manipulation of visual cues in experiments (Gerlai, 2014).

In behavioral sciences, the zebrafish has been shown as a promising model. It has been successfully used as subject in classical and operant conditioning procedures (Valente, Huang, Portugues, & Engert, 2012), has been trained to discriminate visual (Colwill, Raymond, Ferreira, & Escudero, 2005; Mueller & Neuhauss, 2012) and spatial cues (Karnik & Gerlai, 2012; Sison & Gerlai, 2010), and to avoid aversive stimuli (Xu, Scott-Scheiern, Kempker, & Simons, 2007). There has been also studies in the field of memory (Cognato et al., 2012; Gaikwad et al., 2011; Williams,

White, & Messer, 2002). Finally, it has been used as a subject in several anxiety-like behavior models (see Maximino et al., 2010 for a review).

When it comes to impulsivity models, however, very few studies have utilized zebrafish as a subject. We found only one adaptation of a rodent model for the zebrafish, that is, a 3-choice Serial Reaction Time Task (3CSRTT) (Parker et al., 2013; Parker, Millington, Combe, & Brennan, 2012). This model measures one aspect of impulsivity which has been classified as impulsive action ("the inability to withhold from making a response") (Winstanley, Eagle, & Robbins, 2006). Another aspect of impulsivity, not covered by this model, is what is called impulsive choice. As there are several successful models of impulsivity with rodents covering both aspects (see Winstanley, 2011 for a review), but only one adapted to the zebrafish, and covering only one aspect of impulsivity (i.e., impulsive action), our main objective was to adapt at least one of the several other existing models, especially trying to cover the lack of impulsive choice models. We understand that the field of impulsivity can greatly benefit from the introduction of a new species, especially one with so many advantages such as the zebrafish.

Thus, this work is organized into three articles. The first one is a review of animal models of impulsive-like behavior. Although there were previous reviews of impulsivity models (Dent & Isles, 2014; Winstanley, 2011), they were focused on rodent models only. As we were interested in developing a model for the zebrafish, a broader review, including other species, would be more useful. The objective of that article was to review the literature for animal behavioral models of impulsivity, to better understand the different existent models and to describe their measures. This would also help us to select one or more models to adapt. In that article we explore in more detail the concept of impulsivity, providing definitions for its aspects and classifications for the several models found. The article will be presented in the next section and the implication of its results to this work will be then discussed. The rationale for the second and third articles will be then

presented, as well as their full text. A final discussion then follows, bringing together the results of all studies here presented.

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REVIEW

Impulsive-Like Behavior: A Review of Animal Models

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Impulsivity is a component of several psychiatric disorders including attention-deficit/hyperactivity disorder (ADHD) and substance abuse. Different operational definitions for impulsivity have been proposed, and a plethora of behavioral models can be found in the literature. The main purpose of this review is to describe the most used models in the literature, presenting the different measures for each one of them. We follow the classification found in the literature dividing the models between impulsive action or impulsive choice models. The results show that the majority of models fall within the impulsive action category. Several models designed to measure anxiety are sometimes used to measure impulsivity. Individually, the most frequently used models are delay-discounting paradigms and the 5-choice serial reaction time task, accounting for impulsive choice and impulsive action, respectively. There is still space for the refinement and validation of other less popular models.

Keywords: behavior, impulsivity, model

Impulsivity, broadly defined as a tendency to act prematurely without foresight (Dalley, Everitt, & Robbins, 2011), is a common trait of human behavior. Although sometimes it can be beneficial to act on impulse, it can also bring undesirable consequences; impulsivity is considered to play a role in several psychiatric disorders including antisocial (ASPD) and borderline (BPD) personality disorders (Turner, Sebastian, & Tüscher, 2017), attention-deficit/hyperactivity disorder (ADHD; Nigg, 2013), bipolar disorder (BD; Newman & Meyer, 2014), and substance abuse (Argyriou, Um, Carron, & Cyders, 2017).

It is not easy, however, to find a precise and common definition of impulsivity across studies. It has been argued there is not a single unitary impulsivity, but rather "varieties of impulsivity" (Evenden, 1999) with different forms of impulsive behavior and, thus, possibly with different biological mechanisms underlying them. One definition that seems particularly frequent among studies states impulsivity as "actions that appear poorly conceived, prematurely expressed, unduly risky, or inappropriate to the situation and that often result in undesirable consequences" (Daruna & Barnes, 1993). This definition seems to encompass most of the aspects covered by models designed to assess impulsivity.

The measurement of impulsivity in humans is commonly done using self-report questionnaires such as the 11-point Barratt Impulsiveness Scale (BIS-11; Patton, Stanford, & Barratt, 1995). Factor analysis of such scales suggests that impulsivity comprises three major dimensions: motor (spontaneity or action without due

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consideration), nonplanning (lack of regard for the future), and attentional (the degree to which an individual can focus on the task at hand or tolerate cognitive complexity).

When it comes to animal behavioral models of impulsivity, researchers have usually classified them between two broad categories: those measuring impulsive action or motor impulsivity and those measuring impulsive choice or nonplanning impulsivity (Winstanley, Eagle, & Robbins, 2006). Impulsive action can be defined as "the inability to withhold from making a response" (Winstanley et al., 2006), and includes at least two aspects: (a) the ability to refrain from emitting a response, and (b) the ability to stop an already started response. Those two aspects have been called, respectively, "restraint" and "cancellation" in human literature (Schachar et al., 2007).

Impulsive choice regards "actions that fail to take into account other possible options or outcomes, and hence may be sub-optimal" (Dalley & Roiser, 2012). When studying impulsive choice, two types of tasks seem to be the most prevalent: those that base choice on delay of reinforcement and those that base choice on probability of reinforcement. Delay discount procedures (Rachlin, Raineri, & Cross, 1991) are based on choice between smaller immediate reinforcement and larger delayed reinforcement. Probability discount procedures (Ho, Mobini, Chiang, Bradshaw, & Szabadi, 1999) are similar to delay discount as subjects usually have to choose between small or large reinforcement, but instead of having it delivered immediately or with a delay, reinforcement is either delivered with a high or low probability.

To better understand the different impulsivity models existent, it is important to know what is being measured as impulsivity by the researchers. The objective of this study is to review the literature for animal behavioral models of impulsivity. We're interested in experimental studies that describe behavioral models of impulsivity, regardless of the main purpose of the study.

Method

To be included in this review, the articles should have been published in peer-reviewed journals, have been written in English or Portuguese, include one or more procedures designed or used to measure impulsivity or impulsive-like behavior, and have nonhuman animal subjects. Studies were excluded if they were not published in peer-reviewed journals, were written in any other language than English or Portuguese, did not include measures of impulsivity or impulsive-like behavior, had only human subjects, or were review articles.

We applied searches to PubMed and SCOPUS electronic databases. No limit was applied to the date range. The last search was performed on March 17, 2017. The following search terms were used: impulsiv* AND model AND behavior. The PubMed database provides a filter for studies with nonhuman animals, which was used. Because of the lack of such filter in the SCOPUS database, we included the term "animal" to the search, rendering the following search: impulsiv* AND model AND behavior AND animal.

The results were screened by the first author directly from the databases' websites. The full text was screened whenever the abstract did not provide enough information to decide whether the study met the inclusion criteria. After the screening, the selected articles were exported in BibTex format and then imported in a reference manager program (JabRef). The duplicates were then removed and the results were exported as a spreadsheet file for analysis.

Results and Discussion

We found 375 citations in PubMed and 829 in SCOPUS databases. From the 1004 citations, 582 articles were excluded after title/abstract screening for exclusion criteria (for having only human subjects or being review articles). From the 422 articles retrieved, 42 were excluded after full-text screen (for not including measures of impulsivity), resulting in a total of 380 articles selected. We then proceeded with analyses and classification of the impulsivity models. The articles found range from 1998 to 2017, covering almost 20 years of research.

Table 1 shows the models reviewed and their frequency. For space reasons, we decided to discuss only those models cited more than once. They were classified as either impulsive action or impulsive decision models. It should be noted, however, that several models included in the impulsive action category are more commonly used as anxiety-like models, with tasks

Table 1
Frequency, Percentage, and References of Impulsivity Models

Model	Frequency	Percentage	Reference
Delay discount	130	30.5	(Acheson et al., 2006; Adriani et al., 2009; Adriani et al., 2004; Adriani, Caprioli, Granstrem, Carli, & Laviola, 2003; Adriani, Romani, Manciocco, Vitale, & Laviola, 2013; Adriani, Zoratto, Romano, & Laviola, 2010; Adriani & Laviola, 2006; Amita, Kawamori, & Matsushima, 2010; Anderson & Diller, 2010; Anker, Zlebnik, Gliddon, & Carroll, 2009; Bañuelos et al., 2012; Barkus et al., 2012; Beckwith & Czachowski, 2014; Beeby & White, 2013; Bert, Harms, Langen, & Fink, 2006; Bizot et al., 2007, 2011; Blanchard & Hayden, 2015; Blanchard, Pearson, & Hayden, 2013; Blasio et al., 2012; Boomhower & Rasmussen, 2014; Boomhower, Rasmussen, & Doherty, 2013; Broos et al., 2015; Broos, Diergaarde, Schoffelmeer, Pattij, & De Vries, 2012; Bruno et al., 2007; Cardona et al., 2006; Cardona, López-Crespo, Sánchez-Amate, Flores, & Sánchez-Santed, 2011; Cervantes & Delville, 2007; Cheung & Cardinal, 2005; Counotte et al., 2009; Danysz et al., 2015; Dellu-Hagedorn, 2006; Diergaarde et al., 2008; Diergaarde, van Mourik, Pattij, Schoffelmeer, & De Vries, 2012; Doremus-Fitzwater, Barreto, & Spear, 2012; Dunnett, Heuer, Lelos, Brooks, & Rosser, 2012; Eubig, Noe, Floresco, Sable, & Schantz, 2014; Finger, Deacon, Burns, & Campbell, 2011; Flagel et al., 2010; Fodor et al., 2014; Foscue, Wood, & Schramm-Sapyta, 2012; Fox, Hand, & Reilly, 2008; Freund et al., 2014; Fuentes et al., 2014; Garcia & Kirkpatrick, 2013; Gondré-Lewis et al., 2016; Green & Estle, 2003; Hamilton, Czoty, & Nader, 2011; Harty, Whaley, Halperin, & Ranaldi, 2011; Harvey-Lewis & Franklin, 2015; Harvey-Lewis, Perdrizet, & Franklin, 2014; Hayden & Platt, 2007; Hellemans, Nobrega, & Olmstead, 2005; Helms, Reeves, & Mitchell, 2006; Henly et al., 2008; Holtz, Anker, Regier, Claxton, & Carroll, 2013; Íbias & Pellón, 2014; Johnson, Stein, Smits, & Madden, 2013; Juárez, Muñoz-Villegas, Guerrero-Álvarez, & Flores-Ocampo, 2013; Kayir, Semenova, & Markou, 2014; Kheramin et al., 2002, 2004; Koffarnus & Woods, 2013; Kolokotroni, Rodgers, & Harrison, 2014; Koot, van den Bos, Adriani, & Laviola, 2009; Lee & Goto, 2011; Leite-Almeida et al., 2013; Leo et al., 2009; Li, Zuo, Yu, Ping, & Cui, 2015; Locey & Dallery, 2009; Loiseau, Le Bihan, Hamon, & Thiébot, 2005; Loos et al., 2010; Lukkes, Freund, Thompson, Meda, & Andersen, 2016; Madden, Francisco, Brewer, & Stein, 2011; Mar, Walker, Theobald, Eagle, & Robbins, 2011; Marco et al., 2007; Mariano et al., 2009; Marusich, Darna, Charnigo, Dwoskin, & Bardo, 2011; McClure, Podos, & Richardson, 2014; Mejia-Toiber, Boutros, Markou, & Semenova, 2014; Mendez, Damborsky, Winzer-Serhan, Bizon, & Setlow, 2013; Mendez et al., 2010; Mobini et al., 2002; Moreno et al., 2010; Narayanaswami, Thompson, Cassis, Bardo, & Dwoskin, 2013; Navarrete, Pérez-Ortiz, & Manzanares, 2012; O'Tousa et al., 2015; Oberlin, Bristow, Heighton, & Grahame, 2010; Olmstead, Hellemans, & Paine, 2006; Orduña, 2015; Pardey, Homewood, Taylor, & Cornish, 2009; Perry, Larson, German, Madden, & Carroll, 2005; Perry, Nelson, Anderson, Morgan, & Carroll, 2007; Perry, Nelson, & Carroll, 2008; Regier, Carroll, & Meisel, 2012; Schippers, Binnekade, Schoffelmeer, Pattij, & De Vries, 2012; Schneider, Bizarro, Asherson, & Stolerman, 2012; Secci, Factor, Schindler, & Panlilio, 2016; Shimp, Mitchell, Beas, Bizon, & Setlow, 2015; Siesser, Zhao, Miller, Cheng, & McDonald, 2006; Simon et al., 2010; Simon, Mendez, & Setlow, 2007; Slezak & Anderson, 2011; Stanis, Burns, Sherrill, & Gulley, 2008; Stein et al., 2015; Stein, Pinkston, Brewer, Francisco, & Madden, 2012; Stein, Johnson, et al., 2013; Stein, Smits, et al., 2013; Stevens & Mühlhoff, 2012; Sukhotina et al., 2008; Tedford, Persons, & Napier, 2015; Turner, Wilding, Cassidy, & Dommett, 2013; Valencia-Torres et al., 2012; van Gaalen, van Koten, Schoffelmeer, & Vanderschuren, 2006; Walker & Kissler, 2013; Weston, Weston, Allen, & Cory-Slechta, 2014; Wilhelm, Reeves, Phillips, & Mitchell, 2007; Winstanley, Theobald, Dalley, Cardinal, & Robbins, 2006; Winstanley, Baunez, Theobald, & Robbins, 2005; Wiskerke, Schetters, et al., 2011; Wiskerke, Stoop, Schetters, Schoffelmeer, & Pattij, 2011; Woolverton, Myerson, & Green, 2007; Wright, Mills, & Pollux, 2012; Yamaguchi, Saeki, & Ito, 2015; Zlebnik & Carroll, 2015; Zoratto et al., 2013, 2012)

(*table continues*)

Table 1 (*continued*)

Model	Frequency	Percentage	Reference
5-choice serial reaction time task (5CSRTT)	88	20.7	(Abela, Dougherty, Fagen, Hill, & Chudasama, 2013; Adams et al., 2015; Agnoli & Carli, 2012; Amitai & Markou, 2009; Ansquer et al., 2014; Baviera, Invernizzi, & Carli, 2008; Bayless, Perez, & Daniel, 2015; Beaudin, Strupp, Strawderman, & Smith, 2017; Belin, Mar, Dalley, Robbins, & Everitt, 2008; Besson et al., 2013; Bird & Schenk, 2013; Blondeau & Dellu-Hagedorn, 2007; Caprioli et al., 2013, 2014; Carli, Baviera, Invernizzi, & Balducci, 2006; Counotte et al., 2009; Dalley, Lääne, et al., 2005; Dalley, Theobald, et al., 2005; Day et al., 2007; de Bruin et al., 2013; Diergaarde et al., 2008; Diergaarde, Pattij, Nawijn, Schoffelmeer, & De Vries, 2009; Dudley et al., 2013; Economidou, Pelloux, Robbins, Dalley, & Everitt, 2009; Fletcher, Tampakeras, Sinyard, & Higgins, 2007; Fuentes et al., 2014; Greco & Carli, 2006; Hamilton, Potenza, & Grunberg, 2014; Harati, Barbelivien, Cosquer, Majchrzak, & Cassel, 2008; Hehar, Yeates, Kolb, Esser, & Mychasiuk, 2015; Humby, Wilkinson, & Dawson, 2005; Humpston, Wood, & Robinson, 2013; Irimia, Tuong, Quach, & Parsons, 2014; Jupp et al., 2016; Kobayashi et al., 2013; Koskinen, Haapalinna, & Sirvi, 2003; Kramvis, Mansvelder, Loos, & Meredith, 2013; Lambourne et al., 2007; Lê Dzung et al., 2008; Leite-Almeida et al., 2013; Liu et al., 2008; Liu, Huang, Tung, & Lin, 2015; Liu, Tung, Lin, & Chuang, 2011; Lo et al., 2015; Loos et al., 2009; Loos et al., 2014; McNamara, Dalley, Robbins, Everitt, & Belin, 2010; McTighe, Neal, Lin, Hughes, & Smith, 2013; Middlemore-Risher, Buccafusco, & Terry, 2010; Miguel et al., 2015; Milstein, Dalley, & Robbins, 2010; Moreno et al., 2013; Moreno et al., 2010, 2012; Mychasiuk, Hehar, & Esser, 2015; Navarra et al., 2008; Nikiforuk, Hołuj, Potasiewicz, & Popik, 2015; Oliver, Ripley, & Stephens, 2009; Paine, Cooke, & Lowes, 2015; Paine, Slipp, & Carlezon, 2011; Parker, Brock, Sudwarts, & Brennan, 2014; Paterson, Ricciardi, Wetzler, & Hanania, 2011; Pattij, Schetters, Schoffelmeer, & van Gaalen, 2012; Pezze, Dalley, & Robbins, 2009; Pillidge, Porter, Vasili, Heal, & Stanford, 2014; Popik et al., 2015; Porter, Pillidge, Grabowska, & Stanford, 2015; Pozzi et al., 2011; Prasad, MacGregor, & Chudasama, 2013; Robinson, 2012; Sanchez-Roige, Baro, et al., 2014; Sanchez-Roige, Peña-Oliver, et al., 2014; Schneider et al., 2012; Stiles, Zheng, Darlington, & Smith, 2012; Terry et al., 2012, 2014; Turner, Young, McGrath, Eyles, & Burne, 2013; van den Bergh et al., 2006; Vancassel et al., 2007; Walker, Peña-Oliver, & Stephens, 2011; Weir et al., 2014; Wiskerke, Schetters, et al., 2011; Wiskerke, Stoop, et al., 2011; Wouda et al., 2011; Yan et al., 2011; Zheng et al., 2011)
Differential reinforcement of lower rates (DRL)	24	5.7	(Aleksandrova et al., 2013; Anastasio et al., 2011; Andrzejewski et al., 2011; Ardayfio et al., 2008; Bull, Reavill, Hagan, Overend, & Jones, 2000; R. K. Cheng, MacDonald, & Meck, 2006; Cho & Jeantet, 2010; Coppens, de Boer, et al., 2014; Flagel et al., 2010; Hill, Covarrubias, Terry, & Sanabria, 2012; Jayarajan, Nirogi, & Shinde, 2013; Kamphuis et al., 2017; Mangabeira, Garcia-Mijares, & Silva, 2015; Marek, 2012; McMillen, Means, & Matthews, 1998; Mejia, Ervin, Baker, & Palmour, 2002; Nikiforuk et al., 2010; Orduña, Valencia-Torres, & Bouzas, 2009; Sanabria & Killeen, 2008; Somkuwar, Kantak, Bardo, & Dwoskin, 2016; Stoffel & Cunningham, 2008; Sukhotina et al., 2008; Uslaner & Robinson, 2006; van den Bergh et al., 2006)
Elevated plus maze (EPM)	14	3.3	(Kishikawa et al., 2014; Knowles, de la Tremblaye, Azogu, & Plamondon, 2016; Ko et al., 2013; Logsdon et al., 2014; Lucke-Wold et al., 2015; Niimi et al., 2011; Sutin et al., 2014; Tchekalarova et al., 2014; Trantham-Davidson, Vazdarjanova, Dai, Terry, & Bergson, 2008; Turner et al., 2015; Vevera et al., 2016; Ye & Kim, 2015; Yoon et al., 2008; Zimmermann et al., 2015)
Go/No-go	10	2.4	(Anker et al., 2009; Berditchevskaia, Cazé, & Schultz, 2016; Gubner, Wilhelm, Phillips, & Mitchell, 2010; Hellemans et al., 2005; Koek, Gerak, & France, 2015; Marusich et al., 2011; Moschak & Mitchell, 2012; Moschak, Stang, & Mitchell, 2013; Tipps, Moschak, & Mitchell, 2014; Wilhelm et al., 2007)
Probability discount	9	2.1	(Acheson et al., 2006; Adriani et al., 2009; Adriani & Laviola, 2006; Flagel et al., 2010; Mendez et al., 2010; Mobini et al., 2002; Rokosik & Napier, 2011, 2012; Zoratto, Laviola, & Adriani, 2012)

(*table continues*)

Table 1 (*continued*)

Model	Frequency	Percentage	Reference
3-choice serial reaction time task (3CSRTT)	9	2.1	(Huang et al., 2015; Krueger et al., 2009; Maiti, Gregg, & McDonald, 2016; Ohmura et al., 2013; Parker, Millington, Combe, & Brennan, 2012; Scott & Taylor, 2014; Tsutsui-Kimura et al., 2009, 2010; Tsutsui-Kimura, Yoshida, Ohmura, Izumi, & Yoshioka, 2015)
Stop signal reaction time task (SSRT)	7	1.6	(Beckwith & Czachowski, 2016; Eagle et al., 2008, 2007; Humby, Eddy, Good, Reichelt, & Wilkinson, 2013; Liu, Heitz, & Bradberry, 2009; Mayse, Nelson, Park, Gallagher, & Lin, 2014; Walker & Kissler, 2013)
Electro-foot shock aversive water drinking test (EFSDT)	6	1.4	(Choi et al., 2012; dela Peña et al., 2013; Kim et al., 2012, 2014; Yang, Lu, Chen, & Fu, 2015; Yoon et al., 2013)
Open field task (OF)	6	1.4	(Colorado, Shumake, Conejo, Gonzalez-Pardo, & Gonzalez-Lima, 2006; Knowles et al., 2016; Marwitz, Woodie, & Blythe, 2015; Strekalova et al., 2015; Tchekalarova et al., 2014; Trantham-Davidson et al., 2008)
Rat gambling task (rGT)	6	1.4	(Aleksandrova et al., 2013; Barrus & Winstanley, 2016; Connolly, Kim, Tunstall, & Kearns, 2015; Rivalan, Valton, Seriès, Marchand, & Dellu-Hagedorn, 2013; Zeeb, Robbins, & Winstanley, 2009; Zeeb, Wong, & Winstanley, 2013)
Cliff avoidance	5	1.2	(Mouri et al., 2014; Sachs et al., 2013; Sasaki, Omotuyi, Ueda, Shinohara, & Ueda, 2015; Yamashita et al., 2013; Zhu et al., 2017)
Modified Vogel's drinking conflict model	5	1.2	(Svensson, Berntsson, Engel, & Söderpalm, 2000; Svensson, 2010; Svensson, Åkesson, Engel, & Söderpalm, 2003; Svensson, 2009)
1-choice serial reaction time task (1CSRTT)	5	1.2	(Anastasio et al., 2011, 2014; Cunningham et al., 2013; Fink et al., 2015; Trent et al., 2013)
Simultaneous visual discrimination task	5	1.2	(Perry, Sagvolden, & Faraone, 2010; Sagvolden, Dasbanerjee, Zhang-James, Middleton, & Faraone, 2008; Sagvolden, 2006, 2011; Sagvolden & Xu, 2008)
5-choice continuous performance task (5C-CPT)	4	.9	(Tomlinson et al., 2014; Turner et al., 2013; Young, Meves, & Geyer, 2013, 2011)
Multiple fixed-interval/ extinction schedules of reinforcement (FI/EXT)	4	.9	(Berger & Sagvolden, 1998; Boix, Qiao, Kolpus, & Sagvolden, 1998; Dellu-Hagedorn, 2006; Oorschot, Voss, Covey, Bilkey, & Saunders, 2007)
Variable interval (VI)	4	.9	(Coppens, Coolen, et al., 2014; Coppens, de Boer, et al., 2014; Coppens, de Boer, Steimer, & Koolhaas, 2012; Coppens, de Boer, Steimer, & Koolhaas, 2013)
Elevated zero maze	3	.7	(Couch et al., 2016; Skelton et al., 2008; Zörner et al., 2003)
Fixed minimum interval (FMI)	3	.7	(Hill et al., 2012; Mika et al., 2012; Watterson, Mazur, & Sanabria, 2015)
Intruder challenge test	3	.7	(Fairbanks et al., 2004; Fairbanks, Way, Breidenthal, Bailey, & Jorgensen, 2012; Schwandt et al., 2010)
Light-dark	3	.7	(Angoa-Pérez et al., 2012; Colorado et al., 2006; Van der Jeugd, Vermaercke, Halliday, Staufenbiel, & Götz, 2016)
Passive avoidance	3	.7	(Camp & Johnson, 2015; Marusich et al., 2011; Matzel, Babiarz, Townsend, Grossman, & Grumet, 2008)
Reaction time task	3	.7	(Pineda et al., 2014; Sesia et al., 2010; Summerson, Aazhang, & Kemere, 2014)

(*table continues*)

Table 1 (*continued*)

Model	Frequency	Percentage	Reference
Resident-intruder task	3	.7	(Angoa-Pérez et al., 2012; Bouwknecht et al., 2001; Deslauriers, Belleville, Beaudet, Sarret, & Grignon, 2016)
"Waiting-for-reward" paradigm	3	.7	(Bowen, Hannigan, & Cooper, 2009; Bowen & McDonald, 2009; Whitney & Wenger, 2013)
Fixed consecutive number (FCN)	2	.5	(Dellu-Hagedorn, 2006; Rivalan, Grégoire, & Dellu-Hagedorn, 2007)
Mouse Iowa gambling task (mIGT)	2	.5	(Sanchez-Roige et al., 2014; van Enkhuizen, Geyer, & Young, 2013)
Restraint test	2	.5	(Azarbar, McIntyre, & Gilby, 2010; Gilby, Jans, & McIntyre, 2009)
Variable delay-to-signal (VDS)	2	.5	(Leite-Almeida et al., 2013; Melo, Leite-Almeida, Ferreira, Sousa, & Pêgo, 2016)
Other models (each with 1 occurrence only)	53	12.2	(Andrzejewski et al., 2011; Angoa-Pérez et al., 2012; Ash et al., 2013; Atalar, Uzbay, & Karakaş, 2016; Brooks, Jones, & Dunnett, 2012; Carr, Jenkins, Weinberger, & Papaleo, 2013; Cheng & Li, 2013; Cheung & Cardinal, 2005; Clements & Wainwright, 2006; Cocker, Hosking, Benoit, & Winstanley, 2012; Coyne et al., 2015; Dallaire, Meagher, Díez-León, Garner, & Mason, 2011; Decamp & Schneider, 2006; Dervola et al., 2012; Espinoza et al., 2015; Gallistel et al., 2014; Galtress & Kirkpatrick, 2010; Gerasimova, Sidorina, Kuleshova, & Merzhanova, 2015; Gipson et al., 2012; Golub et al., 2005; Hand, Fox, & Reilly, 2006; Jentsch, Roth, & Taylor, 2000; Johansen, Killeen, & Sagvolden, 2007; Johnson, Madden, Brewer, Pinkston, & Fowler, 2011; Juárez et al., 2013; Kawaura, Karasawa, Chaki, & Hikichi, 2014; Kim, Bobeica, Gamo, Arnsten, & Lee, 2012; Krueger et al., 2006; Kumar et al., 2016; Lee & Goto, 2011; Leite-Almeida et al., 2012; Logue, Swartz, & Wehner, 1998; Mahoney, Silveira, & Olmstead, 2013; Moers-Hornikx et al., 2009; Moon et al., 2006; Muñoz-Villegas, Rodríguez, Giordano, & Juárez, 2017; Murphy, Robinson, Theobald, Dalley, & Robbins, 2008; Pezzato, Silveira, Novais, & Hoshino, 2012; Puumala & Sirviö, 1998; Radwanska & Kaczmarek, 2012; Ramos, Carreiro, Scorza, & Cysneiros, 2016; Richardson et al., 2015; Sanabria & Killeen, 2008; Simon, Gregory, Wood, & Moghaddam, 2013; Strekalova et al., 2015; Tan & Vyas, 2016; Thanos et al., 2010; Tremblay et al., 2017; Viñals et al., 2012; Wooters & Bardo, 2011; Yates, Darna, Gipson, Dwoskin, & Bardo, 2015)

based on conflict situations. Because the authors using such models consider the behaviors measured to be indicative of behavioral disinhibition, we decided to group them along the impulsive action models, providing the rationale given by the original authors in each case.

Impulsive Action Models

The models classified as impulsive action are shown in Table 2. They account for the majority of the models reviewed in this study, and this category also holds a greater variety of procedures than the impulsive choice category. The impulsive action models are described below.

5-choice serial RT task. Among the impulsive action models, the 5-choice serial RT task (5CSRTT; Carli, Robbins, Evenden, & Everitt, 1983) is the most frequent one, and it is the second most frequent model overall. It is derived from the Continuous Performance Task (CPT). A cue light is presented for a brief period of time in one of five different spatial locations and the subject has to respond (for instance, by nosepoking a hole in the case of rodent subjects) at the correct location to receive reinforcement. This task was originally developed to assess sustained spatial attention, measured by choice accuracy (Robbins, 2002), but different measures such as errors of omission and commission can also be taken. Responding before the cue light is presented is considered "premature responding" and can also be considered a measure of impulsivity. There are simplified versions of this task with lesser choices available, such as the 3CSRTT and the 1CSRTT.

The effects of drugs on the rodent performance in 5CSRTT has been extensively described. Psychostimulants such as amphetamine and methylphenidate are most commonly ad-

Table 2
Impulsive Action Models and Their Main Measures

Model	Impulsivity measures
5C-CPT	Premature responding (responding before the cue light is presented); responding during the presentation of all lights
5CSRT	Premature responding (responding before the cue light is presented)
Cliff avoidance	Falling and jumping
DRL	Leftward peak deviation; low reinforcement to response ratio
EFSDT	Increased frequency to drink water even with the presentation of an aversive consequence
Elevated plus maze	Time spent in the open arms; number of entries in any arm
Elevated zero maze	Time spent in the open quadrants; number of head dips
FCN	Short chain lengths
FI/EXT	Response bursts with short IRTs (about 1 s)
FMI	Short mean time IRTs
Go/No-go	Number of responses during "no-go" signal
Intruder challenge test	Short latency to approach with risky, assertive, and aggressive behaviors directed toward the intruder
Light-dark	Speed ambulation; time spent in the lighted side; latency to emerge to the lighted side
Modified Vogel's drinking conflict	Number of shocks accepted
Open field	Ambulation speed; center time; abnormally increased total activity
Passive avoidance	Low latency for emission of the behavior
Reaction time task	Number of premature responses; ratio of premature responses to total responses
Resident-intruder	Aggressive behavior; latency of the first attack
Response inhibition task (waiting-for-reward)	Mean wait time per session
Restraint test	Percentage of time spent struggling
Simultaneous visual discrimination task	Number of responses with short inter-response times (IRTs, $< .67$ s)
SSRT	Longer stop-signal reaction times
Variable delay-to-signal	Number of premature responses
VI	Total of responses during the VI15 sessions; total of responses during an extinction session following the VI15 sessions

ministered treatments for ADHD, causing reduction in impulsive behavior (among other effects). Although those drugs have been shown to decrease impulsivity in human CPT, amphetamine and methylphenidate increase premature responding as measured by this model in rats (Blondeau & Dellu-Hagedorn, 2007). Such results show that, at least for those drugs, this model is less consistent between rats and humans than other models. On the other hand, atomoxetine (Blondeau & Dellu-Hagedorn, 2007) and desipramine (Pattij, Schetters, Schoffelmeer, & van Gaalen, 2012) have been shown to decrease impulsivity in rats, a result similar to the effect of the same drugs in humans. In monkeys, guanfacine, an FDA approved drug for the treatment of ADHD, has been shown to decrease 5CSRTT impulsivity (Terry, Callahan, Schade, Kille, & Plagenhoef, 2014). Additionally, atomoxetine has also been shown to reduce 5CSRTT impulsivity in zebrafish (Parker, Brock, Sudwarts, & Brennan, 2014).

The 5CSRTT has been recommended for the evaluation of new compounds because of its good characterization; moreover, it is affected by all drugs that also affect motor impulsivity in humans, even though the effects can be opposing (Winstanley, 2011). The number of sessions needed for baseline establishment and the complexity of training are, however, disadvantages of this model.

Differential reinforcement of lower rates. Differential reinforcement of lower rates (Ferster & Skinner, 1953), or DRL, is a reinforcement schedule that consists in delivering the reinforcement only if a given period of time has passed since the last response was emitted. For this task, different measures of impulsivity are used. When plotting the distribution of responses per time, a peak is formed around the minimum interval stipulated. Deviations of such peak to the left (i.e., to lower intervals) usually are used as measures of impulsivity. Another measure is to compare the number of reinforcements delivered and the number of responses emitted. The optimal behavior under such tasks is a ratio closer to 1. Smaller ratios, that is, more responses than reinforcements, can be also interpreted as impulsivity. In both cases, the impulsive subject is incapable of "waiting" for the proper amount of time.

DRL schedules have been shown to be sensitive to the effects of psychostimulants (Anastasio et al., 2011; Stoffel & Cunningham, 2008) and serotoninergic manipulations (Anastasio et al., 2011; Ardayfio et al., 2008). Although such results could strengthen this model, the results with methylphenidate have been inconsistent: some studies show no improvement by methylphenidate (van den Bergh et al., 2006), whereas others show it to deteriorate behavioral inhibition in this task (Orduña, Valencia-Torres, & Bouzas, 2009). As mentioned earlier, methylphenidate is the drug of choice for treating ADHD in humans. Some authors suggest that inferences on behavioral inhibition drawn from DRL data are highly dependent on procedural parameters, and are therefore not reliable (Hill, Covarrubias, Terry, & Sanabria, 2012).

Elevated plus maze and elevated zero maze. The elevated plus maze (EPM) was originally developed as a model for the study of fear-induced behavior (Handley & Mithani, 1984). It is a plus-shaped maze elevated 50 cm above ground, with alternating open and enclosed arms. The subject is placed in the maze and the time spent at the arms or center, as well as and the number of entries are measured. The number of entries and time spent in the enclosed arms are usually taken as measures of anxiety. Some authors interpret the time spent in the open arms as a measure of impulsivity (Trantham-Davidson, Vazdarjanova, Dai, Terry, & Bergson, 2008; Yoon et al., 2008), whereas others measure the number of entries in any arm as a measure of total activity, with high values as a measure of impulsivity (Vevera et al., 2016).

The elevated zero maze (Shepherd, Grewal, Fletcher, Bill, & Dourish, 1994) is a modification of the EPM, consisting of an elevated annular platform with two opposite, enclosed quadrants and two open quadrants. Its design removes any ambiguity in the interpretation of the time spent in the central square of the EPM. Usual measures are the time in the open quadrants and the number of head dips.

As these tasks are more commonly used to measure anxiety-like behaviors, it is necessary to separate impulsivity from anxiety measures. The reasoning offered by one of the studies regards differences between the number of opened arm entries and time spent in the opened arms of an elevated plus maze by rats with lesions in the habenula, which plays an important role in regulation of monoamine transmis-

sion in widespread brain areas including the prefrontal cortex and nucleus accumbens (Lee & Goto, 2011). Rats submitted to neonatal habenula lesion (NHL) showed an increased number of opened arm entries compared with control subjects, whereas the time spent in the opened arms (a measure of anxiety) did not differ between NHL and control subjects. As the elevated number of entries in the opened arms could also be attributable to hyperlocomotion, the authors tested the correlation between locomotion distance and arms entries. They found a significant correlation between locomotion distance and enclosed arm entries, but no correlation between locomotion distance and opened arm entries. Thus, the elevated number of entries in the opened arms could not be attributed to hyperlocomotion or anxiolysis. Although these results strengthen the reasoning for considering these measures as impulsivity ones, such distinction is not made by all authors and, in many cases, there is no clear distinction between high levels of impulsivity and low levels of anxiety.

The spontaneously hypertensive rat (SHR), frequently used as an animal model for ADHD, usually displays behaviors that can be considered impulsive in other behavioral models (see the electro-footshock aversive water drinking test, simultaneous visual discrimination task, and multiple fixed-interval fixed-interval/extinction schedules sections of this review). Surprisingly, a substrain (SHR/Izm) showed no significant difference from Wistar rats in percentage of entries into the open arms or time in the open arms. Methylphenidate at a low dose did not affect the percentage of entries into open arms or time in open arms in any of the strains, whereas high doses of methylphenidate increased the percentage of time in open arms only in Wistar rats (Kishikawa et al., 2014). As the SHR/Izm showed other ADHD behaviors, the authors suggest that it represents a unique animal model of ADHD without anxiety-related impulsive behavior. It could as well mean that this model is not best suited to measure impulsive behavior at least in SHR/Izm. On the other hand, a mice model of ADHD with impaired actin dynamics (Zimmermann et al., 2015) submitted to this task showed a preference for the opened arms that was ameliorated by methylphenidate. The lack of consistency in the results among different species can be seen as a weakness of this model.

Although this model provides measures simple to be obtained (as it requires no previous training), the lack of a clear distinction between impulsivity and anxiety measures can be seen as a clear disadvantage in its usage as an impulsivity model.

Go/no-go. Go/no-go tasks (Terman & Terman, 1973) are successive discrimination tasks where responses during the presentation of a "go" signal are reinforced and responses during the presentation of a "no-go" signal are extinct (Hellemans, Nobrega, & Olmstead, 2005) or punished (Berditchevskaia, Cazé, & Schultz, 2016). In some variations, reinforcement is presented if no responses are emitted during the "no-go" signal (Wilhelm, Reeves, Phillips, & Mitchell, 2007). In such tasks, impulsivity is measured by the number of responses emitted during the "no-go" signal.

Even though this task seems to be sensitive to drug treatment in humans, some studies have found difficulties in translating those effects to animal subjects. For instance, acute ethanol administration promotes impulsive behavior in humans but does not seem to affect this measure of impulsivity in rats (Hellemans et al., 2005; Moschak & Mitchell, 2012). Amphetamine, which decreases false alarms without having significant effects on performance during go trials in humans, decreases responding during no-go trials in rhesus monkeys, but only at doses that also decrease responding during go trials. Unlike the studies in humans, morphine decreases responding in rhesus monkeys during go trials but not during no-go trials (Koek, Gerak, & France, 2015). Other manipulations, such as rearing condition (one rat per cage, two rats per cage, or group housed with toys), do not seem to have an effect on impulsivity as measured by this model (Hellemans et al., 2005).

Although this model presents good face validity, the results of pharmacological manipulations on go/no-go performance seems to indicate that it does not translate accurately between species.

Stop signal RT task. The stop signal RT (SSRT) task is the only one among the models found in this review to represent the cancellation type of impulsive action. The subject has to respond as fast as possible, usually under a limited hold schedule (see Verbruggen & Lo-

gan, 2009 for a review). On a subset of trials, a "stop" signal is presented at varying delays after the go signal and the subject must refrain from responding. This task is based on a race model proposing that "stop" and "go" processes are independent of one another and that a race occurs between them. If the go process wins, the response occurs; if the stop process wins, the response is withheld. The greater the delay for the presentation of the stop signal, the harder it is for the subject to withhold the response. The stop signal RT (SSRT) cannot be measured directly but is rather estimated from methods based on the assumptions of the independent horse-race model. It corresponds to the time interval between the start of the stop process (i.e., the presentation of the stop signal) and the point at which the stop process finishes (see Verbruggen & Logan, 2009 for an elaborate explanation on how the stop point is estimated). Impulsive subjects have longer SSRTs.

Modafinil, a nonstimulant drug that has been used with success to treat ADHD and decreased SSRT in adults, has also been shown to decrease SSRT in rats with slow baseline SSRTs. Methylphenidate decreases SSRT for slow baseline responder rats but increases SSRT in fast responders. The effects of both modafinil and methylphenidate on rat SSRT-task performance are thus compatible with the effects of such drugs in human subjects (Eagle, Tufft, Goodchild, & Robbins, 2007). In mice, the SSRT task was successfully modeled (Humby, Eddy, Good, Reichelt, & Wilkinson, 2013), having been shown to be sensitive to prefrontal cortex dysfunction and drug treatments: excitotoxic lesions of medial prefrontal cortex impaired stopping, and methylphenidate and atomoxetine enhanced stopping abilities, results that are qualitatively similar to humans and other rat models. Rhesus monkeys that had self-administered cocaine, followed by 18 months of abstinence, displayed increased SSRTs than control animals, a result consistent with human data (Liu, Heitz, & Bradberry, 2009). Such results attest the good predictive validity of the model.

One shortcoming of this task is that, because of its complexity, it can take a high number of sessions to establish a stable baseline.

Electro-footshock aversive water drinking test. In the electro-footshock aversive water drinking test (EFSDT; Kim et al., 2012) water-deprived subjects have to pass over an electrified quadrant of an apparatus to drink water. Animals considered impulsive are those who show increased frequency to drink water even with the presentation of an aversive consequence.

This model is based on the punishment/extinction paradigm of impulsivity, where impulsive subjects are those that persevere with responding despite having punished or unreinforced responses. It was developed at first to be used with the spontaneously hypertensive rat (SHR), considered the most validated animal model of ADHD (Kim et al., 2012). Even though the SHR has been shown to be impulsive in delay-discounting paradigms, there is a difficulty in showing similar results in the 5CSRTT. The authors of this model suggest that it may be because of the complexity of the 5CSRTT, and proposed the EFSDT as an easier behavioral model.

SHR has been shown to be more impulsive than Wistar-Kyoto rats (WKY) in this task, and methylphenidate reduced impulsive drinking frequency in both strains, providing pharmacological validation to the task. Oroxylin A, a flavonoid isolated from the root of *Scutellaria baicalensis* that acts as a γ-aminobutyric acid-A (GABA-A) receptor antagonist, has also been shown to reduce impulsivity in SHR as measured by this task (dela Peña et al., 2013; Yoon et al., 2013).

This model has the advantages of being simple to implement (only two 10-min training sessions and one 10-min test session) when compared with other models such as the 5CSRTT, also allowing the use of many subjects in a short time. However, being a conflict-based model, it could be argued that as the modified Vogel's drinking conflict model below, is better suited to measure anxiety rather than impulsivity.

Open field. The open field task (Hall & Ballachey, 1932) is a long established model for anxiety. It usually consists of placing the subject inside an apparatus marked with a grid and enclosed with walls on all sides. Several behaviors can be measured, such as the number of line crossings, time spent at the center, and time spent near the walls. The behaviors that have been used as impulsivity measures in this task are ambulation speed (Colorado, Shumake, Conejo, Gonzalez-Pardo, & Gonzalez-Lima,

2006; Strekalova et al., 2015) and center time (Colorado et al., 2006; Knowles, de la Tremblaye, Azogu, & Plamondon, 2016; Marwitz, Woodie, & Blythe, 2015; Trantham-Davidson et al., 2008). One of the studies reviewed considered the abnormally increased total activity in this test as an index of impulsivity, reflecting disinhibited hyperactive behavior (Tchekalarova et al., 2014).

Ambulation speed can be regarded as a measure of hyperactivity rather than impulsivity. Time spent in the center can be considered risk-taking behavior, as the animal can be more exposed to danger in the central portion than in the sides, where the walls can offer some protection from possible predators (Colorado et al., 2006). Some of the reasoning provided for these measures being related to impulsivity is quite indirect. For instance, because rats submitted to hypoxia-ischemia showed heightened impulsivity in 5CSRT in a different study, some authors suggest that maybe behavioral impulsivity in ischemic rats contributes to the 'anxiolytic' response profile and propensity of ischemic animals in their study to venture more in the open areas of the open field (Knowles et al., 2016). Thus, one difficulty of using this model to measure impulsivity is to separate it from low anxiety.

Simultaneous visual discrimination task. Five papers (Perry, Sagvolden, & Faraone, 2010; Sagvolden, DasBanerjee, Zhang-James, Middleton, & Faraone, 2008; Sagvolden, 2006, 2011; Sagvolden & Xu, 2008) used a simultaneous visual discrimination task to assess impulsivity. The task consists in presenting two levers for responding, one of them with an unpredictable random-interval schedule in effect (signaled by a constantly lit cue light above the lever) and the other with an extinction schedule in effect (with no cue light associated).

This task has been used to measure ADHD related behaviors, especially in the spontaneously hypertensive rat (SHR; Sagvolden, 2006), which displays hyperactivity, impulsiveness, and deficits in sustained attention. To this end, different measures are related to different symptoms of ADHD. The total number of lever presses is said to be an expression of the general activity level and therefore a measure of the degree of overactivity. The percentage of correct lever choices of the total number of lever presses when the reinforcers are delivered infrequently is a measure of sustained attention. The measure of impulsivity in those studies is the number of responses with short interresponse times (IRTs, <0.67 s), as it could be interpreted that the subject was incapable of withholding a response even if it is an unnecessary one.

It has been shown that SHR have their impulsive behaviors, as measured by this task, reduced by drugs commonly used for the treatment of ADHD, such as guanfacine (an alpha-2A adrenoceptor agonist; Sagvolden, 2006), acute d-amphetamine (Sagvolden & Xu, 2008), and chronic high-dose l-amphetamine (Sagvolden, 2011).

The predictive validity of this model can be seen as one of its advantages, whereas the number of training sessions required (at least 15) as a disadvantage.

Modified Vogel's drinking conflict model. In the modified Vogel's drinking conflict model (Svensson, Berntsson, Engel, & Söderpalm, 2000), water-deprived subjects are allowed to drink water from a drinking spout for a small amount of time after which an electric shock is delivered. Upon every further attempt to drink, an electric shock is administered. Impulsivity is then measured by the number of shocks accepted.

Disinhibited behaviors in conflict models such as the Vogel's drinking conflict model are commonly interpreted to reflect anxiolytic effects, but it has been suggested that it may reflect impulsive behavior rather than anxiolysis (Soubrié, 1986).

This model has been mostly used in studies assessing the effects of testosterone on impulsivity (Svensson, Åkesson, Engel, & Söderpalm, 2003). Testosterone increases the number of shocks accepted by male rats (Svensson, 2010; Svensson et al., 2003). Gonadectomy enhances shock-induced behavioral inhibition in adult male rats, whereas testosterone-substitution following gonadectomy prevents this effect (Svensson, Söderpalm, & Engel, 2000). Gonadectomy also reduces disinhibitory behavior in 5-HT depleted rats (Svensson et al., 2000). These results seem to be consistent with the effects of testosterone on impulsivity in humans. However, the lack of more studies, especially with pharmacological treatments, leaves the validity of this model as a measure of impulsivity to be questioned.

Thus, even though the model has the advantage of being easily implemented, it's validity still is unclear. As with the EFSDT model above, its measure can be confounded as anxiolysis.

5-choice continuous performance task. The 5-Choice Continuous Performance Task (5C-CPT; Young, Light, Marston, Sharp, & Geyer, 2009) is an elaboration of the 5CSRTT, where light is presented for a brief period of time in one of five different spatial locations and the subject has to respond at the correct location to receive reinforcement. In addition to this, subjects are also required to inhibit responding when lights in all five locations are lit, to make it consistent with human's CPT. This task allows for an additional measure of impulsivity than the 5CSRTT, that is, false alarms, responding during the presentation of all lights. Response inhibition impairment in the form of increased false alarm responding often accompanies or mediates impaired CPT performances; impulsivity in the human CPT measured as false alarms to nonsignal stimuli has been linked to dopaminergic mechanisms (Young, Powell, Scott, Zhou, & Geyer, 2011).

Mice with reduced dopamine D4 receptor (DRD4) expression show impaired 5C-CPT performance while premature responding remains unaffected. The 5-HT_{2C} antagonist SB242084 increases premature responding without affecting 5C-CPT performance. This suggests that premature responses and false alarms are measures of different aspects of impulsivity (Young et al., 2011).

In another study (Tomlinson et al., 2014), rats selected to represent different subtypes of ADHD (low-attentive, high-attentive, high-impulsive and low-impulsive) had their performance in the 5C-CPT affected differently by methylphenidate and atomoxetine. Methylphenidate and atomoxetine reduced premature responding in high impulsive animals (consistent with results in treating human ADHD), but only atomoxetine also improved the second form of impulsivity, response inhibition.

Further validation of this model comes from the fact that nicotine improved and scopolamine disrupted normal performance of the task in mice, consistent with healthy humans in the CPT (Young, Meves, & Geyer, 2013).

Although this model presents some advantages over the 5CSRTT, it shares some of the same disadvantages such as the complexity of training and the time spent to establish baseline responding.

Cliff avoidance. Cliff avoidance reaction (CAR) refers to the natural tendency of animals to avoid a potential fall from a height (Yamashita et al., 2013). The cliff avoidance test (Matsuoka et al., 2005) puts rodents over a round platform, usually a cylinder, of a height of twice or more the length of the animal, and falling and jumping behavior is then measured. CAR impairment is thought to result from deficient behavioral inhibition (Mouri et al., 2014; Sachs et al., 2013; Sasaki, Omotuyi, Ueda, Shinohara, & Ueda, 2015; Yamashita et al., 2013).

Dopamine transporter knockout (DAT-KO) mice, an animal model of ADHD, have been shown to have impaired CAR, exhibiting perseverative exploration at the edge of the platform with bursts of sniffing and peering repetitively over the platform edges, where there is risk of falling. Methylphenidate and the selective norepinephrine transporter blocker nisoxetine ameliorated the impairment (Yamashita et al., 2013). Methylphenidate also improves cliff avoidance in mice subjected to prenatal nicotine exposure (Zhu et al., 2017). It has also been shown that maternal separation increases behavioral disinhibition (CAR impairment) in mice (tryptophan hydroxylase 2 knock-in) with low levels of brain serotonin. Maternal separation is one of the most common early life stress models and it has been reported to induce anxiety-like behaviors in rodents and nonhuman primates (Sachs et al., 2013).

As with other models based on unlearned behavior, this task can be easily implemented, though its measures can also be taken as representing anxiolysis rather than impulsivity.

Multiple fixed-interval/extinction schedules. Multiple fixed-interval/extinction schedules of reinforcement (FI/EXT; Ferster & Skinner, 1957a) consist of presenting two schedules alternately. During FI schedules, reinforcement is delivered only for the first response emitted after a time interval has elapsed. Responses that occur during the interval are not reinforced. During extinction schedules, all responses emitted go unreinforced. The fixed-interval component is said to measure motor impulsiveness (behavioral inhibition). The main measure is response bursts with short IRTs (about 1 s; Berger & Sagvolden, 1998; Boix, Qiao, Kolpus,

& Sagvolden, 1998; Dellu-Hagedorn, 2006; Oorschot, Voss, Covey, Bilkey, & Saunders, 2007).

This schedule, such as the simultaneous visual discrimination task discussed above, has been used to assess impulsivity especially in the SHR (Berger & Sagvolden, 1998; Boix et al., 1998). Male and female human ADHD patients show different behavioral problems: girls tend to be more inattentive whereas boys tend to be more impulsive and overactive. SHR have been shown to display parallel differences between sexes as male subjects display lever press bursts in this schedule that are similar to the impulsivity seen in hyperactive boys in an analogous task (Berger & Sagvolden, 1998).

Among the four studies reviewed that used this model, only one tested the effect of a drug in this schedule. L-Deprenyl, a monoamine oxidase-B inhibitor, effectively relieves the problems of patients with Parkinson's disease caused by reduced dopamine in the neostriatum. Because dopamine functions seem to be downregulated in SHR, SHR subjects were treated with L-deprenyl to investigate whether it would normalize aspects of SHR behavior. The chronic administration of L-deprenyl reduced impulsiveness/bursting in SHR without affecting either general overactivity or deficient sustained attention, an effect that could be attributed to a restoration of normal dopamine function in the prefrontal cortex (Boix et al., 1998).

This task has been proven useful to differentiate ADHD and control behavior, SHR and control behavior (Boix et al., 1998) and produces quite similar behavior in animals and humans. Unfortunately, there are not sufficient data (as found by this review) to determine whether the effects of different pharmacological manipulations translates comparably between humans and other species.

Fixed minimum interval. The fixed minimum interval (FMI; Mechner & Guevrekian, 1962) is a reinforcement schedule commonly used to study response inhibition. In a common implementation with rats, trial onset is signaled by the introduction of a lever to the experimental chamber. The first lever press starts an IRT that ends with a head entry in the food hopper. IRTs longer than a programmed interval *t* are reinforced according to a VI90s schedule. IRTs shorter than a programmed interval *t* go unreinforced. In this task, impulsivity is expressed by short mean time IRTs.

Behavioral validation research on FMI (Watterson, Mazur, & Sanabria, 2015) shows that it is not vulnerable to problems that affect other models such as the 5CSRTT and DRL. Pharmacological treatments that elevate response inhibition indices in humans do not elevate such indices in 5CSRTT and systematically lower them in DRL. Also, the response inhibition indices in both 5CRSRTT and DRL are influenced by changes in motivation. None of these problems affect the FMI model. It seems, however, that the response inhibition index given by FMI is vulnerable to learning effects (Watterson et al., 2015). Methylphenidate has been shown to enhance inhibitory capacity as measured by FMI, a result that is consistent with evidence from human research (Hill et al., 2012).

Therefore this model presents advantages over other popular models such as the 5SCRTT and DRL, as its measure is free from potentially confounding factors and results of pharmacological manipulations are more consistent to those from human research. However, its training can take several sessions (up to 38 in one study).

Intruder challenge test. The intruder challenge test is a standardized method developed with vervet monkeys to measure impulsivity in a social situation and is a variant of the resident-intruder paradigm (Fairbanks, 2001). It consists in placing three or four subjects in their home enclosures and placing an unfamiliar conspecific (the intruder) in an individual cage at the edge of the home enclosure, within arm's reach of the subject animals. Impulsivity is then assessed by the Social Impulsivity Index, which combines short latency to approach with risky, assertive, and aggressive behaviors directed toward the intruder (standing or sitting within 1 m and touching, sniffing, displaying to, and threatening the intruder). Animals with high social impulsivity scores "rush over to the intruder immediately without taking the time to assess the situation. They place themselves at risk of injury by standing and sitting within arm's reach and by touching, challenging, and threatening the stranger" (Fairbanks et al., 2004).

The validity of this scale as a measure of impulsivity is said to be supported by its relationship to age and social competence in vervet monkeys (Fairbanks, 2001), as its scores peaks

in adolescence and decline in adulthood, with the most socially successful individuals in the groups scoring in the midrange. Furthermore, high scores on the Social Impulsivity Index scale have been related to low indicators of serotonin metabolism (Fairbanks et al., 2004). Using this model, researchers have been able to demonstrate heritability of social impulsivity in adolescent and adult vervet monkeys (Fairbanks et al., 2004).

This test can be implemented easily, does not require long periods of observation or prior knowledge of the animals. However, its applications have been limited to nonhuman primates.

Light-dark. The light-dark test (Crawley & Goodwin, 1980) is usually used to assess anxiety. It consists in placing the subject in a chamber divided into two zones, one brightly lit and the other covered and dark. It is said to provide a risk-taking index and thus it could measure such kind of impulsivity. There are different measures for impulsivity in this test, and they vary according to the specific procedure.

Some authors, for instance, start the test placing the animal in the lighted compartment (Colorado et al., 2006), then measuring ambulation speed and time spent in the lighted side. Bursts of fast ambulation are said to serve as an index of impulsivity analogous to what is observed in the impulsive/hyperactive type of ADHD. Time spent in the lighted side is said to represent risk-taking behavior. Other authors start placing the animal in the dark side facing away from the opening between chambers and the time taken to emerge into the lighted side is measured (Angoa-Pérez et al., 2012).

Frontotemporal lobar degeneration (FTLD) is characterized by atrophy of the frontal and temporal lobes and deposition of abnormal protein aggregates in these areas. The three syndromes associated with FTLD are classified as frontotemporal dementia (FTD) and include the behavioral variant frontotemporal dementia (bvFTD), which is characterized by, among several other symptoms, poor impulse control leading to compulsive behaviors. Tau58-2/B mice, a model of bvFTD, showed lower latencies to emerge into the light than wild-type control animals. They also spend more time on the lighted side than control animals (Van der Jeugd, Vermaercke, Halliday, Staufenbiel, & Götz, 2016). These results indicate higher impulsivity/risk taking behavior which is similar to FTD patients' impulsive and risky behavior.

Additionally, mice genetically depleted of brain serotonin emerge faster to the light than wild-type control animals (Angoa-Pérez et al., 2012), a result that is consistent with existing evidence suggesting that low serotonin levels can contribute to increased impulsivity.

One advantage of procedures such as that explained above is that they do not rely on learning tasks; although there is a possibility of a confound in that learning deficits could be interpreted as impulsivity, this would not affect tasks like this, which rely on voluntary risk-taking.

Passive avoidance. Passive avoidance tests usually place the subject in a situation where it must emit a given response, after which an aversive stimulus is presented (e.g., an electric shock). The subject is then placed again in the same situation and the latency for the emission of the behavior is measured. Lower latencies are interpreted as a failure to suppress behavior (Camp & Johnson, 2015; Marusich, Darna, Charnigo, Dwoskin, & Bardo, 2011; Matzel, Babiarz, Townsend, Grossman, & Grumet, 2008).

One of the papers that considered this model to measure impulsive behaviors did so in justification for an unexpected result of repeated stress exposure over retention latency in a passive avoidance task for Fischer rats using a light-dark apparatus with electric shock presented in the dark chamber. The authors expected that "enhanced association between the dark chamber and foot shock during conditioning would increase latencies to enter the dark chamber in stressed animals." However, the animals exposed to chronic mild stress (CMS) for four days displayed lower latencies in a similar task than control animals (Camp & Johnson, 2015). The authors argue that this lower latency indicates increased impulsivity in the stressed animals, as it is known that stress exposure can increase impulsive behaviors such as drug abuse, risk taking behavior, and food intake.

In another study, mice subjected to a brain-wide deletion of the gene for the neuronal cell adhesion molecule (Nr-CAM, a molecule which is believed to play a critical role in cell adhesion and migration, axonal growth, guidance, target recognition and synapse formation) had their

performance reduced in a passive avoidance task (Matzel et al., 2008). The authors present this arguing that "these animals may be abnormally impulsive, a result consistent with their propensity to explore stressful areas of a novel open field" (Marusich et al., 2011). This result can be explained by the differences in types of impulsivity measured by such procedures, but it also could be attributable to the fact that this model measures anxiety rather than impulsivity.

Even though this task is easily implemented as it requires little training, it seems more suitable to measure anxiety rather than impulsivity.

Resident-intruder. In resident-intruder tasks, the resident subject is habituated to a cage for a given amount of time. After such period, a conspecific intruder is placed in the cage and social and aggressive behaviors are measured. Impulsivity in such tasks is correlated with aggressive behavior, often labeled impulsive aggressiveness. One possible measure is latency before the first attack (Angoa-Pérez et al., 2012; Bouwknecht et al., 2001; Deslauriers, Belleville, Beaudet, Sarret, & Grignon, 2016).

Most of the information regarding the validation of this measure for impulsivity as found by this review come from studies using serotonin-depleted mice models. Low levels of serotonin are associated to increased impulsivity in humans; accordingly, mice submitted to genetic depletion of serotonin show reduced latency to attack compared with wild-type control animals (Angoa-Pérez et al., 2012) and increased general behavioral disinhibition (Bouwknecht et al., 2001).

Schizophrenia patients show high rates of suicide. Impulsivity is one among suicide-trait–related behaviors and clozapine has prominent suicide prevention effects. Mice exposed to prenatal polyinosinic:polycytidylic acid and postweaning social isolation, a rodent model of schizophrenia, had the latency to attack increased by clozapine treatment (Deslauriers et al., 2016).

Like the intruder challenge test above, this model is simple to implement, as it requires no previous training. However, this model presents ethical and animal welfare issues owing to the harm and injury inflicted on the defeated intruder.

Variable interval reinforcement schedule. Some authors (Coppens, Coolen, de Boer, & Koolhaas, 2014; Coppens, de Boer, Steimer, & Koolhaas, 2013) use variable interval (VI) reinforcement schedules (Ferster & Skinner, 1957b) to evaluate impulsivity. During VI schedules, reinforcement is delivered only for the first response emitted after a mean time interval has elapsed (in the case of the papers reviewed, 2–32 s, VI15). Responses that occur during the interval are not reinforced. The measure of impulsivity in such cases is the total of responses during the VI15 sessions and sometimes the total of responses during an extinction session following the VI15 sessions.

Two studies that used this model to measure impulsivity worked with Roman rat lines selected for high (RHA) or low (RLA) levels of active avoidance in a shuttle box. Low emotional reactivity and a proactive coping style are said to result in impulsive behavior, and accordingly, the RHA rats showed higher amounts of lever pressing in the VI15 schedule than RLA rats (Coppens et al., 2013). Even though it could be reasoned that the differences in responding could be attributed to differences in activity and not impulsivity, the authors argue that the performance of both strains was similar under a predictable (fixed-ratio) schedule. They conclude, however, that it "remains a question to what extent behavior measured in the VI-15 schedule relates to impulsivity" (Coppens, de Boer, Buwalda, & Koolhaas, 2014). This unsolved question could be considered a weakness of this model. As for one strength, it should be noted that VI schedules are relatively easy to train (one of the studies mentioned here required 10 training sessions).

Waiting-for-reward paradigm. Three studies (Bowen, Hannigan, & Cooper, 2009; Bowen & McDonald, 2009; Whitney & Wenger, 2013) used a response inhibition task also known as the waiting-for-reward paradigm. The subjects are trained to press one of two levers (the right one) in the presence of the lever and a cue light. The number of responses required for delivery of reinforcement is increased progressively from a fixed-ratio 1 (FR1) schedule to a higher schedule, FR30 for instance. When the response is stable, a wait component is introduced. When the subject completes the number of responses required (30, for instance), the right lever is retracted, the cue light goes off and the left lever is introduced, with a cue light over it. During the wait component, free reinforcements are delivered at increasing time in-

tervals (2s, 4s, 6s, etc.). The subject continues to receive reinforcements until a lever press is emitted on the wait lever. When this happens, the FR component is reinstated and the levers return to the original position. Because this is a response inhibition task, the main measure usually is the mean wait time per session.

Earlier studies using this paradigm have shown that desipramine, clomipramine, indalpine, zimelidine, nialamide, and clenbuterol (all drugs commonly used as antidepressants) increased the wait time in rats (Bizot, Thiébot, Le Bihan, Soubrié, & Simon, 1988). These results are consistent with the observation that antidepressants have been shown to ameliorate pathologies characterized by impulse control deficiency, such as obsessive–compulsive disorder (OCD).

Among the studies reviewed, two of them assessed the effects of the inhalant toluene on impulsivity as measured by this model. Children born to pregnant women with occupational exposures to toluene showed increases in impulsivity, but the offspring of Sprague–Dawley rats exposed to toluene showed altered performance in this task that are not consistent with increased impulsivity or impaired behavioral inhibition (Bowen et al., 2009). Additionally, Swiss Webster mice submitted to repeated toluene exposure did not have increased impulsivity measures. These results do not contribute to the validity of this model.

Conflicting results with pharmacological manipulations seem to advice against this model as a measure of impulsivity. However, the studies here reviewed did not explore the effects of drugs commonly used to treat impulsivity, thus further research is advised.

Fixed consecutive number schedule. The fixed consecutive number (FCN; Mechner & Guevrekian, 1962) schedule measures the ability of rats to carry out a chain of sequential acts to achieve a goal. The task usually consists in the subject pressing one lever a number of consecutive times (for instance, eight) and then pressing a second lever once and receiving reinforcement. If the chain is shorter than the set number, no reinforcement is presented and the subject has to start a new chain. If the chain is longer, the reinforcement is delivered as usual when the subject presses the second lever. The main measure of impulsivity in this task is chain length: shorter chains indicate impulsive behavior. The introduction of a cue to indicate the number of responses required (for instance, a light that goes out when the required number is achieved) can improve the performance of rats in this task, because of the removal of the requirement of nonspecific capacities such as time estimation. Low doses of amphetamine have been shown to increase chain length under such conditions (Rivalan, Grégoire, & Dellu-Hagedorn, 2007), a result that is consistent with the clinically observed reduction of some aspects of impulsive behavior by psychostimulants.

One advantage of this schedule is that it demands little attention and thus allows more rapid measurements of inhibitory capacities compared with tasks such as the go/no-go, DRL and 5CSRTT. However, this task is sensitive to changes in time estimation, a shortcoming that can be amended by introducing discriminative stimulus to indicate the number of responses required.

Reaction time task. The RT task (see Blokland, 1998 for a review), also called lateralized RT task is usually composed of four phases: a holding phase, lever-pressing phase, reward phase and time-out phase. Each trial begins with a cue light turning on and then the subject has to emit a sustained response (usually a nose poke) for a given time. Once completing successfully this phase, a cue light is lit in either side of the central position and the subject has to emit a new response (a nose poke or lever press) in the according side. This response is reinforced with food or water and is considered a "correct" response. If the subject responds on the side that is not the target in that trial, a time-out period takes place. If the subject does not sustain the response until the end of the hold period, a "premature response" is scored. Impulsivity measures in this task can be either the number of premature responses or the ratio of premature responses to total responses (Sesia et al., 2010; Summerson, Aazhang, & Kemere, 2014).

Validation of this task comes from deep brain stimulation studies (DBS). Dysfunction of the nucleus accumbens (NAc) is held responsible for some of the key symptoms of several psychiatric disorders including OCD, and DBS is considered as a therapy for refractory psychiatric disorders. It has been shown that deep brain stimulation of the NAc shell increases impul-

sive action as measured by this task and increases DA and 5-HT levels, while DBS of the dorsal parts of the NAc core decreases impulsive action (Sesia et al., 2010), a result that is in line with the clinical application of NAc DBS for OCD. Additionally, this task has also been used to show that hemi-Parkinsonian rats display increased impulsivity, a result consistent with previous reports on the impulsivity of this rodent model (Summerson et al., 2014).

One shortcoming of this task is that its training can be time consuming, taking up to six weeks to achieve stable performance.

Restraint test. In restraint test the subject (a rat) is placed in the wide end of a cone-shaped plastic bag with a hole in the narrow end. Once the rat is secured in the bag, the wide end is taped close leaving the tail out. The bag snugly fits the rat, allowing limited movement. The rat is then placed on a table for 10 min of observation. The percentage of time spent struggling is recorded and is considered a measure of impulsivity (or hyperactivity): the more time spent struggling, the more impulsive the subject is (Azarbar, McIntyre, & Gilby, 2010; Gilby, Jans, & McIntyre, 2009).

The reasoning for this interpretation is based on the performance of rats with fast (seizure-prone) or slow (seizure-resistant) amygdala kindling epileptogenesis. Fast rats are less anxious than slow rats, but when exposed to different stressors each strain behaves differently (Anisman et al., 1997). Fast rats show more pronounced immobility when exposed to a predator (a ferret) than slow rats, but in contrast, slow rats struggle much less when restrained than fast rats. Rather than indices of fear or arousal, the different immobility responses are considered to reflect a difference in impulsivity between strains. This seems to be validated with chronic omega-3 supplementation (which has been reported to be useful in treating impulsivity): fast rats treated with omega-3 reduced struggling to reach levels similar to slow rats (Gilby et al., 2009). However, more studies are necessary to verify if this task can be useful in measuring impulsivity.

This model has the advantage of being easily implemented, as it requires no training, but it has the disadvantage of lacking a larger number of studies to support its validity and usefulness as an impulsivity model.

Variable delay-to-signal. In variable delay-to-signal (VDS) task (Leite-Almeida et al., 2013) subjects must emit a response (a nose poke) during the presentation of a light at the response aperture. Each trial begins with only the house light on (delay period); the light in the response aperture is presented after a variable delay from the trial onset and its duration is 60 seconds. The session starts with a block of 3-s delay trials, followed by a block with large and variable delays (randomized between 6 and 12 s) before a final block again with a 3-s delay. Impulsivity is measured by the number of premature responses (responses that occur before the presentation of the light).

This task was validated with methamphetamine and the NDMA antagonist MK-801 (dizocilpine). Methamphetamine is used as a second-line treatment for ADHD, and MK-801 is known to increase impulsivity. Accordingly, rats treated acutely with MK-801 had their number and rate of premature responses increased, while acute challenge with methamphetamine prevented the increase of premature responses displayed by control animals in the last 3s delay block.

One advantage of this model over more well-established ones such as the 5CSRTT or DD is the time needed for training (10 twice daily sessions for VDS vs. 35–55 days for 5CSRTT and DD). It also requires only one testing session and is resistant to multiple testing. However, there were almost no significant correlations between impulsive behaviors in the VDS and the 5CSRTT (Leite-Almeida et al., 2013), probably indicating different types of impulsivity assessed by the two tasks.

Impulsive Choice Models

The impulsive choice models are shown in Table 3. Only four different models were found

Table 3
Impulsive Choice Models and Their Main Measures

Model	Impulsivity measures
Delay discount	Selection of smaller but sooner reinforcement
Probability discount	Selection of smaller but surer reinforcement
rGT/mIGT	Choosing the options linked to larger reinforcements

to belong in this category, but they account for approximately one third of all studies reviewed. This is largely a result of the number of studies (n = 130) using delay-discounting procedures. These models were divided in delay-based and probability-based, as follows.

Delay-based procedures. Delay-discounting tasks, sometimes called intolerance to delay tasks, (Rachlin et al., 1991) were the most frequently used model of impulsivity found in this review. In such procedures subjects usually choose between smaller immediate reinforcement and larger delayed reinforcement. This can be achieved by different types of procedures, such as choosing to press between two levers, choosing to nose-poke between two holes, or choosing between two arms of a T maze. Impulsive subjects are those who select the smaller but immediate reinforcement instead of the larger but delayed one.

As with the second most popular model found by this review, the 5CSRTT, delay-discounting procedures have been extensively tested with pharmacological manipulations. For example, atomoxetine, desipramine, d-amphetamine, and methylphenidate (drugs that, as previously described, are successful in treating impulsive behavior) have all been shown to decrease impulsivity in a T maze implementation of this model (Bizot, David, & Trovero, 2011).

Although the different procedures assessing delay-discounting are commonly treated as one single model, differences in parameters in this procedure can have impacts on the measures taken. For instance, reward bundling can have an effect on responding toward the larger but later choice (Stein, Smits, Johnson, Liston, & Madden, 2013).

This seems to be the model of choice when it comes to evaluating impulsive choice, probably because of its high face and predictive values (Winstanley, 2011). However, as with the most popular impulsive action model (the 5CSRTT), it requires a high number of training sessions to establish baseline responding.

Probability-based procedures.

Probability discount. Probability (or sometimes probabilistic) discount procedures (Ho et al., 1999) have the subject choosing between small reinforcement with a high probability or large reinforcement with a low probability. Selecting the smaller but surer reinforcement is considered impulsive behavior.

This model has been shown to demonstrate comparable effects in humans and rodents. Pramipexole, used for the treatment of movement dysfunction in Parkinson's disease, increases probability discounting in a rodent model of Parkinson's disease, thus emulating the clinical scenario (Rokosik & Napier, 2012). Rats submitted to lesions of the orbital prefrontal cortex (OPFC) have shown an increased preference for both smaller but sooner and smaller but surer reinforcement, a result similar to that shown by human patients with OPFC lesions in similar tasks (Mobini et al., 2002).

Even though probability discounting tasks seem similar to delay-discounting tasks, drugs can produce dissimilar effects on both. For instance, self-administered cocaine can cause a long-lasting increase in impulsive choice as measured by delay discount, but not as measured by probability discount (Mendez et al., 2010). This dissociation between the two processes has been shown even in drug free animals, as Wistar adolescent rats preferred smaller but sooner reinforcements in an intolerance to delay procedure, but developed a stable preference for large/luck-linked reinforcements, even when the two options (smaller but surer and large/luck-linked) were predicted and demonstrated to be indifferent. These results led the authors to suggest that probability discount procedures do not reflect impulsivity, but rather resemble the features of gambling (Adriani & Laviola, 2006). However, some session parameters as timeout duration and session length have also been shown to influence rats performance in this task. Shorter sessions (60 min), and thus lower gambling opportunities, produce a stable large/luck-linked preference in rats (Zoratto, Laviola, & Adriani, 2012). Even though this task has good face validity, it has the disadvantage of being difficult to train.

Rat gambling task and mouse Iowa gambling task. The rat gambling task (rGT) and its variation for mice, the mouse Iowa gambling task (mIGT), are loosely based on the Iowa Gambling Task (Bechara, Damasio, Damasio, & Anderson, 1994). The subject chooses between four options, each one associated with a different amount of reinforcement and a different probability and duration of punishing timeout periods when no reinforcement can be

earned. The schedules are programmed so that choosing the options linked to larger reinforcements leads to fewer pellets earned per unit time, and this behavior is considered impulsive (risk-preference). One critical feature of this model is the risk of losing, "that is, the resources staked on a favorable outcome are lost when a wager is unsuccessful," as probability discounting models deal only with failing to win, "that is, the absence of any additional gain" (Zeeb, Robbins, & Winstanley, 2009).

In rGT, d-amphetamine and the 5-HT1A receptor agonist, 8-OH-DPAT, have been shown to impair the performance, whereas eticlopride, a dopamine D2 receptor antagonist, improved performance. The effect of 8-OH-DPAT is consistent with data indicating that dysfunction within the serotoninergic system contributes to pathological gambling (Zeeb et al., 2009). In mIGT, C57BL/6 *N* mice developed a preference for the safe option, which was potentiated by amphetamine administration. When treated with modafinil and the selective DAT inhibitor GBR12909, these subjects had their risk preference slightly increased. Such effects are seen in rats and humans in corresponding IGT tasks, supporting the translational validity of the task (van Enkhuizen, Geyer, & Young, 2013).

Besides having good validity as an impulsive choice model, this model also has the advantage of allowing the measurement of impulsive action (by measuring the number of premature responses, which happen before the choice stimuli appear). However, repeated training in the IGT may impede drug-induced risk-taking effects (van Enkhuizen et al., 2013).

Conclusion

The objective of this study was to review the literature for behavioral animal models of impulsivity. The results show a variety of different models using both nonlearned and learned behavior. The five most frequently used models are delay-discounting, 5-choice Serial Reaction Time Task, differential reinforcement of lower rates, elevated plus maze, and go/no-go.

Although a plethora of models was found, more than half of the papers reviewed use either delay-discounting models or the 5CSRTT. Each of these models measures a different dimension of impulsivity (impulsive choice and impulsive action, respectively).

It should be noted that several models—namely the elevated plus maze, elevated zero maze, open field, cliff avoidance, light-dark, and passive avoidance—are commonly used to measure anxiety. Behavior that is considered to indicate high levels of anxiety in such models (time spent in the closed arms of an elevated plus maze, time spent at the edges of an open field, time spent in the dark zone of light-dark chambers) is what is considered to indicate low levels of impulsivity; conversely, behavior that indicates low levels of anxiety also indicates high levels of impulsivity. The reasoning is that impulsive behavior is the opposite of risk aversion. This interpretation seems to contradict clinical data on anxiety and impulsivity, which points out a positive correlation between them (see Jakuszkowiak-Wojten, Landowski, Wiglusz, & Cubała, 2015 for a review).

Even though the field of impulsivity counts with well-established models such as the 5CSRTT and delay-discounting, which respond well to drugs and have good a translational value between humans and other species, those do not come without shortcomings, such as complexity of training and time needed to establish baseline responding. We understand that there is still space for the refinement and validation of other less popular models.

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3. Brief discussion of review results and outlining of a model adaptation

Although the results of the previous article show more than twenty-seven different models, more than half of the papers reviewed used one of either two paradigms: delay-discounting models (Rachlin, Raineri, & Cross, 1991) or the 5-choice Serial Reaction Time Task (5CSRTT) (Carli, Robbins, Evenden, & Everitt, 1983) . The former (with 130 citations found in the review) measures impulsive choice, while the later (with 88 citations) measures impulsive action. As mentioned earlier, the only model adapted for the zebrafish is the 3CSRTT, and it is a simplified version of the 5CSRTT. Thus, we decided to adapt for the zebrafish the most cited model in the literature, that is, the delay-discounting model.

In delay-discounting tasks, the subject usually chooses between smaller immediate reinforcement and larger delayed reinforcement. The choice for the smaller but immediate reinforcement is called impulsive choice. There are two distinct causes for this preference: either an increased aversion to delay, or a decreased sensitivity to reinforcement size (McClure, Podos, & Richardson, 2014). In order to adapt such a model, it would be necessary to verify whether the zebrafish is (a) sensible to delay and (b) sensible to reinforcement size or quantity. These two specific objectives were discussed in the second and third articles.

The second article investigated the performance of zebrafish under a peak-interval timing task (or peak procedure) (Roberts, 1981). This procedure is an operant task commonly used to investigate temporal control of behavior. It has been shown that rats that showed greater discrimination in a peak interval task showed less impulsivity in a delay discounting task which kept the reinforcement size constant (McClure et al., 2014). If we could demonstrate temporal discrimination in zebrafish, we could then cross such data with delay discounting.

In the third article, we investigated whether zebrafish could discriminate between two different quantities of food. This ability is necessary for the adaptation of delay discounting models

for the zebrafish. In the following sessions, we present the second and third articles and, afterward, a general discussion about our results.

4. Zebrafish Performance Under a Peak Procedure[1]

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Abstract

The peak procedure is a task commonly used to investigate time discrimination. Most studies employing this procedure utilized rats or pigeons as subjects, but none of them used zebrafish as subjects. Zebrafish is considered a promising model in behavioral studies, thus this study investigated peak procedure performance in zebrafish. Twenty-six adult zebrafish were trained to perform a peak procedure task. Only three fish completed training. The typical result of peak-procedure training is a curve showing the response rate within a trial reaching a maximum at about the time the reinforcement is delivered. None of the subjects in this study produced such curve. However, the same subjects have shown some time discrimination under a fixed-interval schedule. The lack of time discrimination during peak procedure sessions can be attributable to problems of experiment design and aging of the subjects. More studies using this procedure are needed to reach clearer conclusions.

Keywords: peak procedure, zebrafish, time discrimination, learning.

1 Manuscript to be submitted to *Psychology & Neuroscience* (eISSN: 1983-3288).

The peak procedure, sometimes called peak-interval procedure, is commonly utilized to evaluate time discrimination in animals. It was developed by Roberts (1981) based on a procedure first proposed by Catania (1970). It is a discrete-trial procedure with randomly mixed fixed-interval (also called food trials) and extinction (also called empty or probe) trials. On food trials, food is delivered after the first response after a set time has elapsed, and the trial ends. On empty trials, no food is given and the trial usually lasts twice or more than the set time for food trials. Empty trials usually last twice or three times longer than food trials. The typical result of peak-procedure training is a curve showing the response rate within a trial reaching a maximum at about the time the reinforcement is delivered (Roberts, 1981). The time of maximal responding is called peak time and the standard deviation of the function, the peak spread, grows in direct proportion of the interval being timed. The peak time is interpreted as a subjects estimate of the expected time of reinforcement, and the peak spread as a measure of confidence in the accuracy of this estimate (Matell & Portugal, 2007).

This procedure has been used to study time discrimination with pigeons (Roberts & Boisvert, 1998) and rats (Matell & Portugal, 2007; Wiener, Magaro, & Matell, 2008). There is at least one reported usage of this procedure in its respondent version with goldfish (Drew, Couvillon, Zupan, Cooke, & Balsam, 2005). However, so far no studies on time discrimination using this procedure have been done with zebrafish. Zebrafish is considered a promising model in behavioral sciences, having been used to study classical and operant conditioning (Valente, Huang, Portugues, & Engert, 2012), spatial learning (Karnik & Gerlai, 2012; Sison & Gerlai, 2010), visual discrimination (Colwill, Raymond, Ferreira, & Escudero, 2005; Mueller & Neuhauss, 2012), and active avoidance (Xu, Scott-Scheiern, Kempker, & Simons, 2007), to name a few examples. The study of time discrimination in zebrafish can open new possibilities of investigation, such as impulsivity models.

Thus, in this experiment, we investigate the performance of zebrafish under peak procedure.

Method

Subjects

Twenty-six experimentally naÿve wild type zebrafish of both sexes were used. They were housed under two conditions: twelve of them individually and fourteen in pairs. The subjects kept in pairs had a companion conspecific that was not exposed to the procedures. The individuals were housed in 1.2 l plastic tanks and the pairs in 3.45 l. The temperature of the water was maintained at 26-28 °C, with constant mechanical and biological filtering. The tanks were additionally cleaned from debris three times a week. There was a 14 hr:10 hr light-dark cycle (fluorescent lights on at 6 a.m.). The subjects were fed twice a day, one time during the procedures and the other in the opposite turn. The experiments were run 5 days a week, from Monday to Friday.

Apparatus

The apparatus used was similar to the described by (Manabe, Dooling, & Takaku, 2013). The response key consisted of a 2 mm-diameter-polymer-optical fiber for the presentation of color stimuli and a fiber sensor for detection of an approach to the response key. A tricolor LED illuminated the tip of the glass fiber. The apparatus was placed over a 1.2 l plastic tank (9 cm x 13.5 cm x 10.5 cm) and the water column at 8.5 cm. The response key operated a feeder consisting of a servo motor, a brass tube with the inner diameter of 600 μm, a 406-μm-diameter electric-guitar wire inserted in the brass tube, a vibrator and a white LED (feeder light). The reinforcement used was decapsulated brine shrimp eggs. During reinforcement the feeder light turned on, the servo motor pulled the wire, the vibrator operated and the food was loaded in to the brass tube, the servo motor pushed the food out of the tube and into the water. The feeder light then flashed 5 times at a 0.2-s interval.

Procedure

The response training (feeder training and auto-shaping) procedure followed the parameters described by Manabe et al., 2013. The subjects were transported from their tanks to the test tank and

sessions would start after an acclimation period of 3 minutes. After each session, the subjects were returned to their tanks.

Feeder training. The subjects were trained to consume the shrimp eggs delivered from the feeder according to a variable-time (VT) 20-s schedule. Sessions ended after 80 reinforcement deliveries. Subjects were submitted to 5 sessions of feeder traning before the auto-shaping phase started.

Auto-shaping. During auto-shaping sessions, the LED at the tip of the response key was lit for 5 seconds according to a VT 20-s schedule. If the subject responded by swimming under the fiber session within the 5 seconds, reinforcement was delivered immediately. If no response was emitted during the 5 seconds, the reinforcement was delivered. Sessions ended after 80 reinforcement deliveries. The training was complete after the subjects responded within the 5 seconds in at least 75% of the trials.

Fixed-Ratio. After the response training was complete, a Fixed-Ratio (FR) 1 reinforcement schedule was implemented. Sessions lasted 80 reinforcement deliveries or 60 minutes, whatever happened first. If the subject received 80 reinforcements within-session for 3 consecutive sessions, the FR value was increased on the next session, according to the following progression: 1, 2, 3, 5, 7, 10. If the subject failed to respond enough to receive at least 60 reinforcements for 5 consecutive sessions, the FR value was decreased. After reaching the advancing criteria under FR 10, a Fixed-Interval 10 s (FI 10) schedule was implemented.

Fixed-Interval. After the FI 10 schedule was implemented, if the subject received 80 reinforcements for 3 consecutive 60 minutes sessions, the FI value was increased in 1 second on the next session. Once the subjects reached FI 20, they were kept under this schedule until the response pattern was the typically observed under FI schedules (i.e., the fixed-interval scallop). This happened within 113 to 186 sessions. After this, the subjects were ready to be submitted to peak-procedure sessions.

Peak Interval. In this phase, subjects were submitted to the Peak Interval timing procedure with 80% Fixed-Interval (FI 20) trials and 20% unreinforced probe trials. Each unreinforced probe trial lasted 60 s. A mean inter-trial interval of 20 s was present. In each session, the first four trials are FI 20 ones, with the fifth being a probe trial. After the fifth trial, a probe trial is randomly inserted within each block of five trials.

Data analysis

For each subject, a response-rate function – the number of responses in each bin divided by the time spent in that bin (1 s) – was generated.

Results

Of all twenty-six subjects submitted to the procedure, only three reached the last stage of training (peak procedure), two of them were housed individually and one housed in pairs. Some subjects did not advance to later stages, while others died during the process.

Figure 1 shows curves generated from the response rate for each 1-second bin during peak trials. The values shown are the mean rates of four sessions for each subject. For the sake of comparison, it also includes the curves generated from sessions 83-86 under the FI 20 schedule. The response rates per second were converted to percentage of responses per second to make the comparison clearer.

Discussion

As mentioned earlier, the typical result of peak-procedure training is a curve showing the response rate within a trial reaching a maximum at about the time the reinforcement is delivered, then decreasing with the passage of additional time.

In our findings, none of the subjects generated such curve (Figure 1). The peak expected would be around 20 s, and the subject with the closest peak to this bin is I5a, with a peak around 24 s. One subject (D4b) showed earlier peaks, around 1 and 11 s, and the other (I3) did not seem to show any clear sign of discrimination, even showing a 0 response rate around the 20-seconds bin.

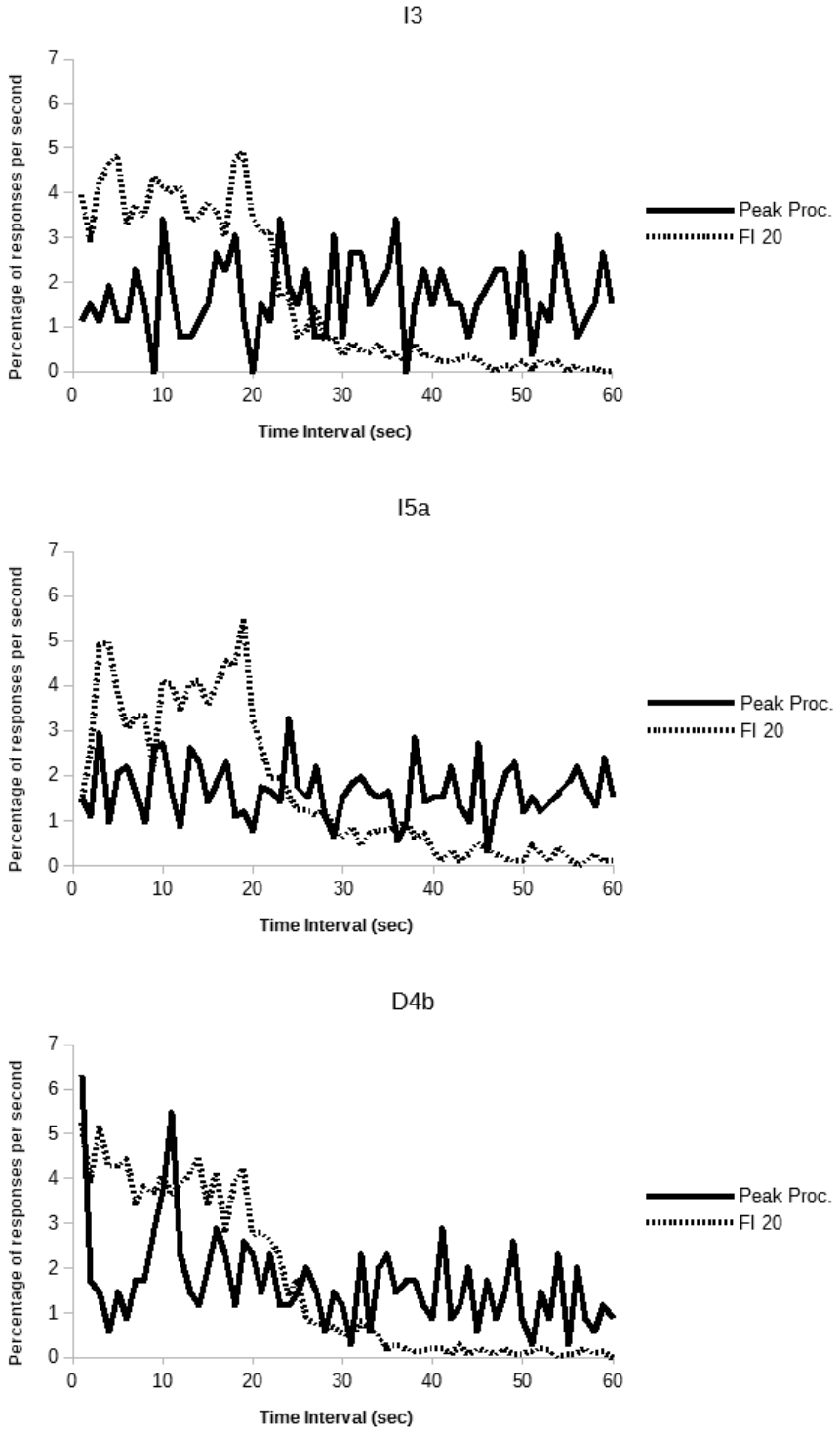

Figure 1. Performance of subjects I3, I5a and D4b under peak procedure and FI 20. For peak procedure the response rates are a mean of four sessions. For FI 20, the response rates are a mean of sessions 83-86.

Such results could mean that the subjects' responding was not under control of the elapsed time. However, that did not seem to be the case under the FI 20 schedule. Figure 2 shows the curves generated by each subject after 86 sessions under FI 20. For all three subjects, there is a high rate of responses before the time specified by the schedule, followed by a quick decline in the rate after such time. This illustrates that the responses were under at least some control of the elapsed time. The pattern was disrupted as sessions went by.

One possible explanation is the aging of the subjects. Unpublished data from the third author suggests that 15-month-old subjects show poor or no discrimination of time under FI 20 schedule. In an active avoidance learning task, 7-month-old zebrafish showed increased learning ability compared to 15-month-old subjects (Yang, Kajiwara, Tonoki, & Itoh, 2018). Two-year-old zebrafish showed learning deficits in a color discrimination paradigm for associative learning, while one-year-old subjects showed no such deficits (Ruhl et al., 2015). In our study, the minimum number of sessions to reach the peak procedure phase was 177 sessions. As we ran experiments 5 days a week, 177 sessions would take aproximately 35 weeks or almost 8 months. Given the fact that the subjects in our experiment were adult (90 days at least), some fish were at least 11 months old when reaching the peak procedure phase. Their performances were thus probably hindered by their aging process.

Our results should not be taken as a sign that zebrafish cannot discriminate time under peak procedure. Instead, it is rather a sign of difficulties with the procedure. Our experiment was performed along an overly extended period of time, partly due to demanding criteria for advancing from one phase to another. As we established three consecutive sessions of 80 reinforcements as a criterion for advancing from one schedule to another, any subject would take at least 39 sessions to reach the FI20 schedule. Many subjects took more than three sessions to advance from one schedule to another, sometimes having to regress to earlier schedules when failing to respond enough to receive at least 60 reinforcements for 5 consecutive sessions. The high number of training sessions

can be lowered with less demanding advance criteria. For instance, preliminary results from the third author's laboratory show that zebrafish show responding with a peak time of 20 seconds an FI 20 schedule with as few as 20 sessions of training in that schedule.

It is also possible that the size of the interval was too big for the subjects. For instance, subject's D4b response rate shows a peak around 10 seconds. Maybe a smaller interval (FI 10 or FI 5) could yield better results. It has been shown that zebrafish can acquire responding when the response produced a reinforcer after a 0.5 and 1-s delay (Kuroda & Mizutani, 2018). It seems that zebrafish is sensitive to delay of reinforcement up to a 6-s limit. Moreover, unpublished results from the first author's laboratory of experiments with zebrafish submitted to DRLL schedules show that these subjects can discriminate time intervals up to 5-s. A smaller FI value would also make the traning period shorter, possibly reducing the effects of aging over the learning abilities of the subjects.

In conclusion, in this study we investigated the performance of zebrafish under a peak procedure. Our subjects failed to produce the typical response pattern under this procudedure. Although it could indicate that zebrafish are unable to discriminate time intervals, our results with the FI 20 schedule, with high response rates around the 20-s bin, indicates that zebrafish responding can be brought under the control of time intervals. Future studies should focus on different training procedures to evaluate whether a comparable performance can be achieved under peak procedure.

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5. Zebrafish Do Not Discriminate Between Two Discrete Quantities of Food[2]

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Abstract

The ability to discriminate quantities is widespread among non-human animals and is present in mammals, birds, fish, and insects. There are few quantity discrimination studies using zebrafish as subjects, most using conspecifics as choice stimuli, but none using food items. In this study, we evaluated if zebrafish can discriminate between sets with different quantities of food items. The subjects were divided into four groups, each with different contrasting ratios (1 vs. 2, 1 vs. 3, 1 vs. 4, and 2 vs. 3 items) and were exposed to 5 daily forced-trial sessions and 5 daily free-trial sessions. The subjects were unable to discriminate between food quantities in all ratios. Their performance did not improve along the sessions. The results seem to contradict previous ones that showed quantity discrimination in zebrafish. Such contradiction can be attributed to differences in the procedures and nature of the task.

Keywords: quantity discrimination, food choice, zebrafish.

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The ability to discriminate quantities is widespread among non-human animals, being present, for instance, in mammals such as monkeys (Beran, 2008), dogs (Macpherson & Roberts, 2013), and horses (Uller & Lewis, 2009), birds such as domestic chicks (Rugani, Regolin, & Vallortigara, 2008), and insects, such as honey bees (Howard, Garcia, Greentree, & Dyer, 2018). Such abilities are also present in several species of fish (see Agrillo & Bisazza, 2018 for a review). Of particular interest, the zebrafish (*Danio rerio*) is a model organism for genetics, physiology and development research, with increasing applications in behavioral studies (Gerlai, 2014). However, only a few studies assessed quantity discrimination in zebrafish.

For instance, in a study investigating the influence of shoal size and activity in shoal choice (Pritchard, Lawrence, Butlin, & Krause, 2001), zebrafish have been shown to prefer larger shoals. The test subjects were placed in the center of a tank with two smaller stimulus tanks, positioned at either end of the test tank, and the time spent near either stimulus tank was recorded. The stimulus tanks held different shoal sizes: one side held four fish, while the other held one, two, three or four fish. The level of activity of the stimulus shoal was also manipulated through changes in water temperature, with more or less active shoals placed in warm or cold water. The subjects in this study have been shown to prefer the larger shoal when faced with 4 vs. 1 and 4 vs. 2 ratios. The level of activity of the stimulus shoal also played a role in the preference, with zebrafish preferring the more active shoal.

Another study (Potrich, Sovrano, Stancher, & Vallortigara, 2015) has shown that male zebrafish prefer the larger of two female shoals. The male subjects were placed at the center of a plastic rectangular tank with two isolated sectors located in either short side of the tank. Those sectors held different numbers of female individuals. One part of the two sectors was transparent, allowing for the stimulus fish to be fully observed by the test fish in the center, while the other part was opaque. In each trial, test subjects were placed within a transparent cylinder at the center of the test tank allowed to observe the two different stimuli shoals during a short period (5 or 30 s). At the

end of the observation period, a number of females (depending on the shoal size) was moved to the opaque part of the isolated sector, so that only one fish was visible in either side of the tank. The test fish was then released and the first choice for either side was recorded. In this experiment, subjects prefered the larger shoal in ratios of 2 vs. 1, 3 vs. 2, 4 vs. 2, 4 vs. 6 and 8 vs. 4 individuals, but shown no significant preference in 4 vs. 3, 6 vs. 4 or 8 vs. 6 individuals.

A third study (Seguin & Gerlai, 2017) has demonstrated that zebrafish chose the larger shoal for contrasted ratios above or equal to 2:1. In this study, subjects were placed in the center of a tank with two containment areas created by perforated plexiglass dividers placed 5 cm away from each short side. The time spent in the zones near each containment area and the number of entries in each zone were recorded. The following contrasts were used for stimuli shoals: 4 versus 0, 4 versus 1, 8 versus 2, 6 versus 2, 6 versus 3 and 8 versus 4. The subjects in this study have shown significant preference for the larger shoal in all contrasts except when each of the two contrasted shoals had at least 4 members (8 vs. 4 stimulus fish). Thus, even though there is not a clear agreement between all reports when it comes to ratios, it seems that zebrafish have some ability to discriminate quantities, at least when the choice stimulus is a shoal of conspecifics.

Zebrafish have also been successfully trained to discriminate between different quantities of abstract items (Agrillo, Petrazzini, Tagliapietra, & Bisazza, 2012). In this study, subjects of five different species (*Xenotoca eiseni*, *Poecilia reticulata*, *Betta splendens*, *Pterophyllum scalare* and *Danio rerio*) were placed in a rectangular tank and presented with two sets of black geometric figures differing in numerosity inserted in a white background. Soon after the stimuli were inserted into the tank, reinforcement (nauplii of *A. salina*) was released near the reinforced numerosity. Half the subjects received reinforcement to the larger numerosities and the other half received reinforcement to the smaller numerosities. After 12 training trials, the subjects were tested in 12 probe trials with the same numerosities presented during training and 8 probe trials to observe generalization to small (2 vs. 4) and large (25 vs. 50) numbers. The dependent variable was the

proportion of time spent in the choice areas during probe trials. Zebrafish in this study successfully learned to discriminate between 5 vs. 10 items and 6 vs. 12 items. However, only six out of forty-eight fish reached the learning criterion. Those that learned were able to generalize to sets of 8 vs. 12 items.

It seems the ability to discriminate quantities of food has not been studied in zebrafish. Other species of fish such as guppies (*Poecilia reticulata*) have been shown to prefer the larger quantity of similar-sized food items up to a 2:1 to ratio (4 vs. 1 and 4 vs. 2, but not 3 vs. 2 or 4 vs. 3 items) (Lucon-Xiccato, Miletto Petrazzini, Agrillo, & Bisazza, 2015). They also seem to prioritize the item size over the total amount, selecting the set with larger items even when the other set with smaller items contained the double quantity of food. No such data is available regarding zebrafish behavior.

Thus, in this study, we investigate whether zebrafish can discriminate between different quantities of food items. This ability has clear survival advantages as it benefits foraging efficiency.

Method

Subjects

Twenty-four adult zebrafish of both sexes were used. They were housed individually in 1,2 l tanks with gravel bottom in a system with shared water with mechanical and biological filtering. The temperature of the water was maintained at 26-28 °C. There was a 14 hr:10 hr light-dark cycle (fluorescent lights on at 6 a.m.). The subjects were fed twice a day, only during the procedures.

Apparatus and stimuli

The experimental apparatus (Figure 1) was a glass tank (40 cm length, 10 cm width and 10 cm height) with a 10 cm long wall in the middle of one of its shorter walls, dividing it into two chambers. Two plastic guillotine doors were used, one to isolate the fish at ¼ of the tank's length (10 cm) at the beginning of each trial, and a smaller one to isolate one of the choice chambers

during forced trials. The tank was placed inside a cardboard box to avoid distracting stimuli from outside the tank.

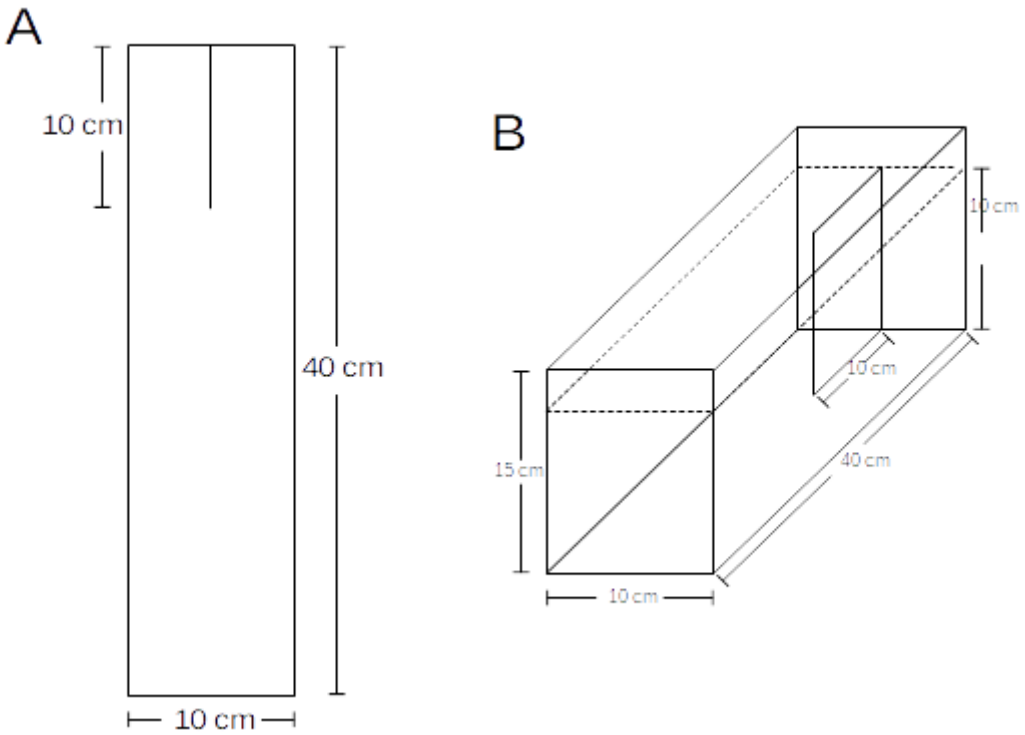

Figure 1: Diagram of the test tank used as seen from above (A) and in a three dimensions (B), showing the choice chambers in one of the short walls

The stimuli were small pieces of commercial food flakes (Bettagran, Sera GmbH, Heinsberg, Germany). The items used were of the same size for each trial.

Procedure

The subjects were divided into 4 groups with 6 subjects. Each group was submitted to a different discrimination ratio: 1 vs. 2, 1 vs. 3, 1 vs. 4, and 2 vs. 3 items. Each group was submitted to two types of sessions: forced-trial sessions were used to teach the subjects the amount of food to be found in each side and free-trial sessions were used to evaluate the subjects preference for either side.

During forced-trial sessions, the subjects were placed in the test tank and after 1 minute of free exploration, they were brought to the side opposite to the choice chambers and held there with a plastic guillotine door placed at ¼ of the tank's length (10 cm) for one minute. During that period, one of the choice chambers was closed with a plastic guillotine door and food was placed on the surface of the water in the other choice chamber, close to the outer corner. After the inter-trial period, the guillotine door holding the subject was removed and it was given one minute to consume the food in the opened choice-chamber. After this period, the subject was brought back to the side opposite to the choice chambers and a new trial begun. The food was placed on alternate sides for each trial, 3 times on the right and 3 times on the left, for a total of 6 forced trials. One side would always have more food than the other. Half the subjects would receive the larger amount on the left side and the other half on the right side.

During free-trial sessions, the procedure was the same, but instead of closing one of the choice chambers during the intertrial period, food was placed on both choice chambers, which were left open. When the subject was released and chose one side, the guillotine door was placed on the opposite side to prevent the subject from eating the food placed there. Each session lasted for a total of five trials.

For each group a total of 10 sessions was conducted over 6 days, 5 forced-trial sessions (in the afternoon) and 5 free-trial sessions (in the morning).

Data analysis

The number of choices made by each subject on either side was recorded. Percentage of choices for the side with the larger number of food items were computed for each fish. One-sample two-tailed *t* tests were used to assess whether the preference for either number of items and either side was greater than chance (50%) for each group (ratio). We also conducted analyses of variance (ANOVAs) to compare the preference for the larger number of items among all groups (ratios) for each session and among days for each group (ratio).

Results

Subjects chose the side with the larger quantitiy in 54.89 ± 23.82 % of the trials when facing choices of 1 vs. 2 items, 54.00 ± 26.34 % when facing 1 vs. 3 items, 48.67 ± 17.17 % when facing 1 vs. 4 items, and 48.00 ± 31.34 % when facing 2 vs. 3 items. None of these preferences were greater than chance (1 vs. 2, $t(29) = 1.12$, $p = 0.272$; 1 vs. 3, $t(29) = 0.83$, $p = 0.412$; 1 vs. 4, $t(29) = -0.43$, $p = 0,674$; 2 vs. 3, $t(29) = -0,35$, $p = 0,729$).

To assess if subjects had a preference for a given side, regardless of the quantity present in either of them, a one-sample two-tailed t test was performed between the percentage of choices for each side in all groups. Subjects in the 1 vs. 2 group chose the right side in 46 ± 24 % of the trials ($t(29) = -0,96$, $p = 0,345$), 48 ± 27 % for the ones in the 1 vs. 3 group ($t(29) = -0,41$, $p = 0,683$), 51 ± 17 % in the 1 vs. 4 group ($t(29) = 0,21$, $p = 0,833$) and 43 ± 31% for the subjects in the 2 vs. 3 group ($t(29) = -1,19$, $p = 0,243$). Even though three out of four groups showed a higher preference for the left side, none of these preferences were above chance level.

As the subjects were submitted to forced-trial sessions every day, some learning effect could be expected, with more choices for the larger quantity as the days passed. That was not the case, as shown in Figure 2. A session by session analysis within groups shows the choice for the larger quantity was higher in the last day, compared to the first one, for the 1 vs. 2 group, equal for the 2 vs. 3 group and lower for 1 vs. 3 and 1 vs. 4 groups. However, none of these differences were statistically significant ($F(12, 80) = 1.17$, $p = 0.321$).

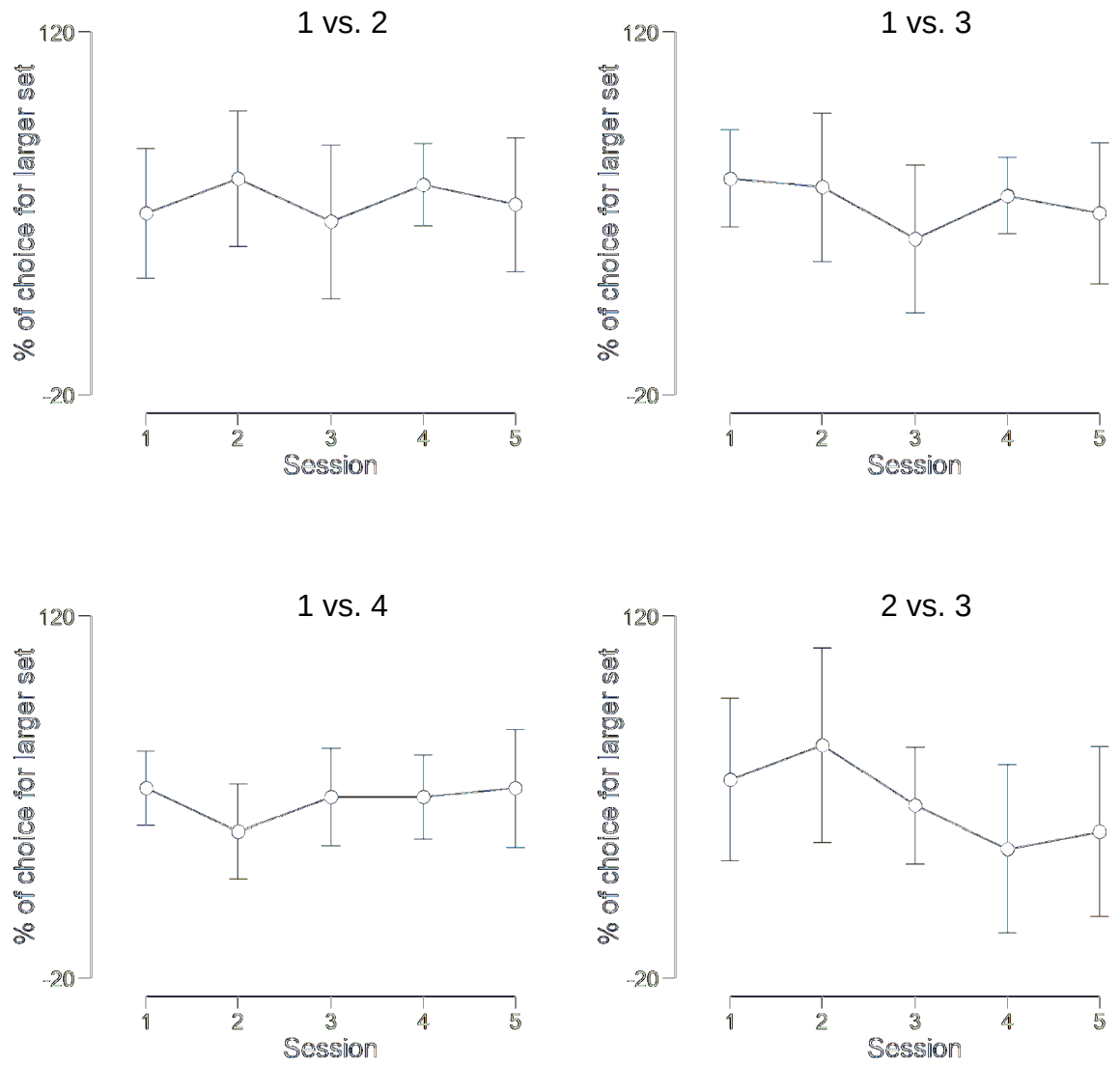

Figure 2. Percentage of choice for the larger set of food items in each session for all four groups (1 vs. 2, 1 vs. 3, 1 vs. 4 and 2 vs.3 items). The graphs show the mean preference and the standard deviation. There was no statistically significant difference between sessions in none of the groups ($p < 0.05$).

Finally, the ANOVAs performed for each session using groups as a between-subjects factor revealed no significant effects (one way ANOVA, Session 1: $F(3, 20) = 0.37$, $p = 0.778$; Session 2: $F(3, 20) = 1.40$, $p = 0.273$; Session 3: $F(3, 20) = 0.16$, $p = 0.919$; Session 4: $F(3, 20) = 2.98$, $p = 0.056$; Session 5: $F(3, 20) = 0.54$, $p = 0.661$), as shown in Figure 3.

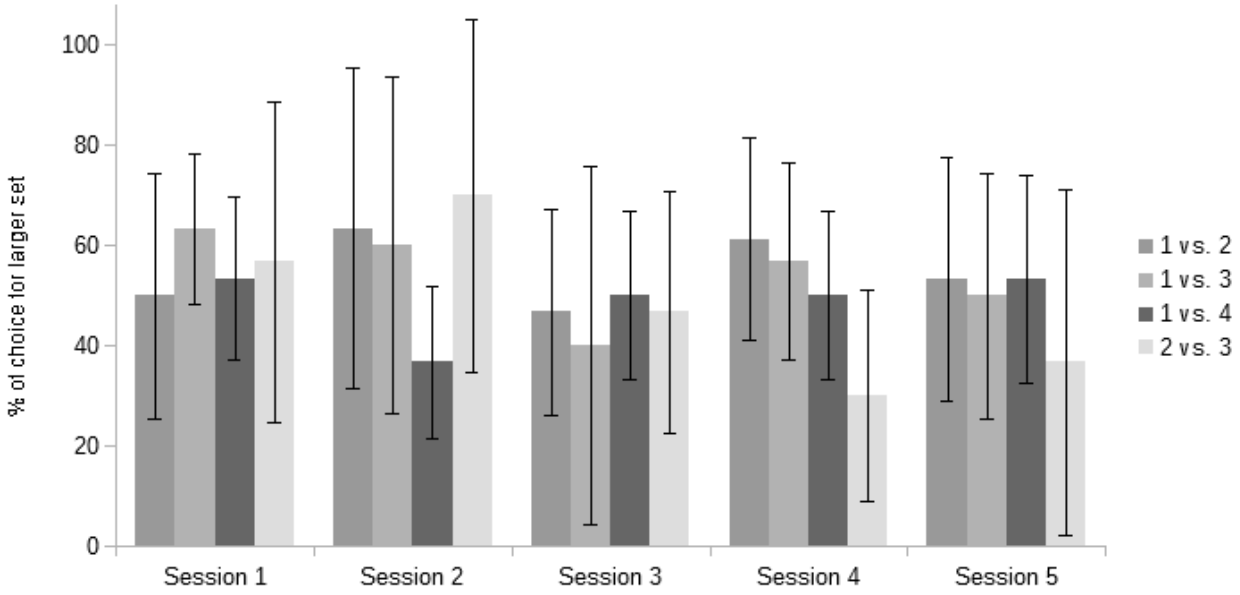

Figure 3. Percentage of choice for the larger set of food items in each group session by session. The graphs show the mean preference and the standard deviation. There was no statistically significant difference between groups in none of the sessions ($p < 0.05$).

Discussion

The results reported by this study seem to contradict earlier results on quantity discrimination in zebrafish (Agrillo et al., 2012; Potrich et al., 2015; Pritchard et al., 2001; Seguin & Gerlai, 2017). Even though this species has been demonstrated to discriminate the larger quantity of conspecifics in sets of several different ratios, in our experiment, zebrafish failed to discriminate between food quantities in all ratios tested. There are differences between these studies, especially regarding the procedures and the choice stimuli. The reasons for the difference between the results could then be explained by aspects of the procedure and nature of the task.

Most of the experiments that investigated quantity discrimination in zebrafish used conspecifics as choice stimuli, and the procedures did not require previous training as they were based on shoaling (Pritchard et al., 2001; Seguin & Gerlai, 2017) or courtship-based (Potrich et al., 2015) behavior. Our experiment, however, used food as choice stimuli and relied on training because the subjects faced a choice between different quantities of food that were visible only after

the fish was released from the initial enclosure, at the start of each trial. The food was placed on the surface of the water, and it is possible the fish could not see all items when choosing one side or the other for the first time. The forced-trial sessions served as training for the subjects, so even if the fish failed to see all the items in some trials, the repetition of forced trials should expose them to the different amounts in each side. Thus, it is possible that part of the difficulty of the subjects in discriminating the different quantities of food came from difficulties in learning the task. For instance, Agrillo et al. (2012) argued that one reason why only six out of forty-eight zebrafish reached the learning criteria in their experiment was attributable not to "a specific deficit of zebrafish regarding numerical skills", but to "a more general inability of this species in discrimination learning". They mention zebrafish performed much worse than the control species (redtail splitfin) in a simple shape discrimination task. Moreover, in our experiment, we saw no improvement in the performance (that is, increase in choices for the larger quantity of food items) as the number of training sessions increased. As the subjects were exposed to only 5 training sessions, it is possible that a longer training period would be necessary for the discrimination to be learned.

It also should be noted that we only investigated the ability to discriminate discrete quantities. As mentioned earlier, guppies prioritize item size over total amount when discriminating quantities (Lucon-Xiccato et al., 2015). Thus it is possible that zebrafish are not able of discriminating quantities based on number, but could be capable of discriminating based on item size. That possibility remains to be investigated.

Given that the ability to discriminate larger sources of food is of clear importance to the success of foraging strategies, the results here presented should encourage new studies to confirm or deny them, possibly with different procedures and extended training. The further investigation of whether zebrafish are able to discriminate quantities based on item size is also recommended.

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6. General Discussion

Our main objective was to adapt a model of impulsivity from the rodent literature to the zebrafish. In order to select a model to adapt, we performed a review of the literature of animal models of impulsive-like behavior. We found a variety of more than twenty-seven different impulsivity models. However, more than half of the papers used either delay-discounting tasks or the 5CSRTT. Each of those models represents one aspect of impulsivity: impulsive choice or impulsive action. From all those models, only one was already adapted for the zebrafish, that is, the 3CSRTT, a variation of the 5CSRTT with lesser choices. Because this model was of the impulsive action kind, we decided to adapt an impulsive choice model for the zebrafish based on the delay-discounting paradigm.

In delay-discounting tasks, the subject chooses between a smaller but immediate quantity of reinforcement and a larger but delayed quantity. Thus, two variables are manipulated in such tasks: reinforcement size and delay duration. It is then necessary to subjects in such tasks to be sensible to both manipulations. We then studied the timing and quantity discrimination abilities of zebrafish in two separate articles.

To study zebrafish's timing abilities, we used a peak procedure. In such procedures subjects have to respond in discrete trials under two randomly alternating schedule: in some trials, the subjects respond under a fixed-interval schedule (or food trials) and in some other trials (called empty or probe trials) under an extinction schedule (Roberts, 1981). The typical result of this task is a Gaussian or peak-shaped curve showing the average response rate in probe trials. The time of maximal responding in these trials, the peak time, falls close to the criterion duration (the fixed-interval value in food trials), while the standard deviation of this function, or peak spread, grows in direct proportion of the interval being timed. The peak is interpreted as the subject's estimate of the expected time of reinforcement. (Matell & Portugal, 2007).

In our study, zebrafish were trained to respond under a FI 20 schedule and then were submitted to peak procedure sessions. Of twenty-six subjects submitted to the procedure, only three reached peak procedure training. Their responding did not generate the mentioned Gaussian curve. While one subject showed a peak around some time intervals within the probe sessions, this peak time was earlier than the set time.

This can be interpreted as the subjects responding not being under control of the elapsed time. However, under FI 20 the subjects showed peak times around 20 seconds, even if their responding rate in earlier times was also high. This and other unpublished results show that zebrafish can learn to discriminate time intervals. Our hypothesis is that the duration of the whole training was too long (8 months in some cases) and the subjects learning abilities were hindered by their aging process.

Our results should not be taken as a sign of the impossibility of developing impulsivity models based on time discrimination by zebrafish. For instance, it has been shown that zebrafish can acquire responding when the response produces reinforcers with delays up to a 6-s limit (Kuroda & Mizutani, 2018). Moreover, unpublished results from our laboratory show that zebrafish trained in a DRLL procedure are able to discriminate time in 5-s intervals. It is possible then that smaller intervals, of 10 or maybe 5-s, could yield better results.

We also trained zebrafish in a quantity discrimination procedure. Our subjects were exposed to choices between 1 vs. 2, 1 vs. 3, 1 vs. 4 and 2 vs. 3 items. The subjects could not discriminate between quantities above chance level in any of these ratios. Our result could mean that zebrafish are unable to discriminate between different quantities of food, but it does not mean that this species is not capable of discriminating quantities at all. There are reports that zebrafish are able to discriminate between different quantities of conspecifics (Potrich, Sovrano, Stancher, & Vallortigara, 2015; Pritchard, Lawrence, Butlin, & Krause, 2001; Seguin & Gerlai, 2017). This is important for the development of impulsivity models based on impulsive choice because it has also

been shown that the sight of conspecifics has reinforcing properties (Al-Imari & Gerlai, 2008; Pather & Gerlai, 2009).

Given that zebrafish have been shown to be sensitive to delay of reinforcement and that conspecifics can work as reinforcement for zebrafish's responses, a delay-discounting model could be developed using sight of conspecifics as reinforcement, varying shoal and delay sizes. However, it should be noted that while most zebrafish could acquire responding with delays of 0, 0.5 and 1-s, only a few could do it up to 3s and even fewer could do it up to 6-s (Kuroda & Mizutani, 2018). It should also be noted that even if some zebrafish were capable of discriminating between two different shoal sizes, only six out of forty-eight subjects reached the learning criteria (Agrillo, Petrazzini, Tagliapietra, & Bisazza, 2012). According to the authors of that study, the reason why so few subjects learned the task could be attributed to a general inability of the species in discrimination learning. In that sense, it is possible that even a delay-discounting model using conspecifics as reinforcement could be difficult for zebrafish to learn.

In conclusion, even though zebrafish has been proven a useful model in behavioral sciences, being capable of learning several different tasks, the only impulsivity task that has been successfuly developed for this species is the 3CSRTT (Parker et al., 2013, 2012). Future studies on the subject should concentrate on different tasks and take into account the fact that this species, at least according to our procedures, has difficulties discriminating between different quantities of food.

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ANEXO I

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Your Submission PNE-2017-0169R3 - [EMID:8876b3eb29d59d52]

Psychology and Neuroscience <em@editorialmanager.com> 19 de junho de 2018 17:44
Responder a: Psychology and Neuroscience <sbarnold@apa.org>
Para: Guilherme Chirinéa <chirinea@gmail.com>

PNE-2017-0169R3
Impulsive-like Behavior: a Review of Animal Models
Psychology & Neuroscience

Dear Mr. Chirinéa,

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ANEXO II

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COMISSÃO DE ÉTICA EM USO DE ANIMAIS
(CEUA - IMS/CAT - UFBA)

PARECER DE APROVAÇÃO

PROJETO DE PESQUISA - Protocolo 058/2018 - Apreciação em 24/04/2018 - Aprovado sem restrições

Título: Discriminação de quantidade de alimento em *Danio rerio* (zebrafish).

Protocolo: 058/2018

Pesquisador: Guilherme Chirinéa

Instituição: Instituto Multidisciplinar em Saúde - Campus Anísio Teixeira - UFBA

CERTIFICADO

A Comissão de Ética em Uso de Animais (CEUA - IMS/CAT - UFBA) certifica que o projeto de pesquisa "**Discriminação de quantidade de alimento em *Danio rerio* (zebrafish)**", Protocolo **nº 058/2018**, do pesquisador **Guilherme Chirinéa**, que foi submetido à avaliação desta Comissão, está de acordo com os princípios éticos da experimentação animal e foi **aprovado na 19ª reunião ordinária no dia 24/04/2018**.

CERTIFICATE

The Ethics Committee on Animal Use (CEUA - IMS / CAT - UFBA) certifies that the research project **"Discrimination of food quantity in *Danio rerio* (zebrafish)"** Protocol No. 058/2018 by researcher **Guilherme Chirinéa** which was submitted to the evaluation of this Commission is in accordance with the ethical principles of animal experimentation and was **approved at the 19th ordinary meeting on 04/24/2018**.

Vitória da Conquista, 24 de abril de 2018.

P/ Ricardo Evangelista Fragá
Coordenador CEUA - IMS/CAT – UFBA

ANEXO III

Gmail

Guilherme Chirinéa <chirinea@gmail.com>

Submission Confirmation for Zebrafish Do Not Discriminate Between Two Discrete Quantities of Food - [EMID:8ec05866255877b0]

1 mensagem

Psychology and Neuroscience <em@editorialmanager.com> 21 de novembro de 2018 04:35
Responder a: Psychology and Neuroscience <sbarnold@apa.org>
Para: Guilherme Chirinéa <chirinea@gmail.com>

Dear Mr. Chirinéa,

Your submission "Zebrafish Do Not Discriminate Between Two Discrete Quantities of Food" has been received by Psychology & Neuroscience.

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