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Social order: Using the sequential structure of social interaction to discriminate abnormal social behavior in the rat

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ABSTRACT

Social interactions form the basis of a broad range of functions related to survival and mating. The complexity of social behaviors and the flexibility required for normal social interactions make social behavior particularly susceptible to disruption. The consequences of developmental insults in the social domain and the associated neurobiological factors are commonly studied in rodents. Though methods for investigating social interactions in the laboratory are diverse, animals are typically placed together in an apparatus for a brief period (under 30 min) and allowed to interact freely while behavior is recorded for subsequent analysis. A standard approach to the analysis of social behavior involves quantification of the frequency and duration of individual social behaviors. This approach provides information about the allocation of time to particular behaviors within a session, which is typically sufficient for detection of robust alterations in behavior. Virtually all social species, however, display complex sequences of social behavior that are not captured in the quantification of individual behaviors. Sequences of behavior may provide more sensitive indicators of disruptions in social behavior. Sophisticated analysis systems for quantification of behavior sequences have been available for many years; however, the required training and time to complete these analyses represent significant barriers to high-throughput assessments. We present a simple approach to the quantification of behavioral sequences that requires minimal additional analytical steps after individual behaviors are coded. We implement this approach to identify altered social behavior in rats exposed to alcohol during prenatal development, and show that the frequency of several pairwise sequences of behavior discriminate controls from ethanol-exposed rats when the frequency of individual behaviors involved in those sequences does not. Thus, the approach described here may be useful in detecting subtle deficits in the social domain and identifying neural circuits involved in the organization of social behavior.

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1. Introduction

Social interactions are complex and comprised of many constituent behaviors with distinct roles that support a broad range of functions including bonding, play, establishment of dominance hierarchies, and communication. The dynamic nature of social interactions present major challenges for social species, and to researchers engaged in the analysis of social behavior. For example, rough and tumble play is characterized by dynamic interactions that are topographically similar to genuine fighting, such that distinguishing play and fighting depends upon potentially subtle signals. In the rat, play behavior can be distinguished from other forms of behavior based on the target of "attacks", with the nape of the neck being the primary target of play compared to more posterior targets for aggressive behaviors (Pellis & Pellis, 1987, 2007). Although play fighting may appear to be stochastic, these behaviors are highly organized into sequences characterized by reciprocity among the individual animals (Pellis & Pellis, 1987) and both participants must engage in the appropriate sequential behaviors (Himmler, Himmler, Pellis, & Pellis, 2016). Such sequential processes are ubiquitous in the social domain and among social species. For example, verbal interactions among humans are typically characterized by reciprocity and complex temporal sequences of behavior (Levinson, 2016).

Normal social interactions require awareness of multiple factors, including the status of others (such as social dominance or sex) and sensitivity to contextual factors including temporal context and the behavior of conspecifics (Himmler et al., 2016). The neural circuitry involved in social behavior is commensurately complex and distributed, including limbic, subcortical, and neocortical regions including the prefrontal cortex (Numan, 2015). In rodents, the regions of the frontal cortex have been linked with abnormalities in social behavior (Bell, Pellis, & Kolb, 2010; Hamilton et al., 2010; Himmler, Pellis, & Kolb, 2013; Kolb, 1974; Pellis et al., 2006; Schneider & Koch, 2005) and the capacity for adaptation in the social domain. The hippocampus has also been implicated in the appropriate sequencing of social behavior (Maaswinkel, Gispen, & Spruijt, 1997). In addition to dependence on intact neural circuitry, social competencies depend critically upon adequate social experience during development (Pellis et al., 2006; Pellis & Pellis, 2007).

Owing to the complexity of neurobiological and experiential factors, abnormalities in social behavior are common consequences associated with disorders of the nervous system. During the past decade research in our laboratory has investigated the effects of moderate prenatal alcohol exposure (PAE) in a rat model of Fetal Alcohol Spectrum Disorders (FASD). FASD is an umbrella term that includes disorders associated with a broad range of negative consequences resulting from exposure to alcohol during prenatal development, including Fetal Alcohol Syndrome (FAS), partial FAS, and alcohol related neurodevelopmental disorders (ARND) (May et al., 2014; Riley, Infante, & Warren, 2011). The prevalence of FASD is approximately 2–5% in the United States (May et al., 2014). The consequences of heavy developmental alcohol exposure include facial dysmorphologies and severe deficits in cognition and behavior (Riley et al., 2011). The consequences of moderate PAE are more subtle, yet persistent, in humans and non-human animal models (Conry, 1990; Marquardt & Brigman, 2016; Streissguth, Barr, & Sampson, 1990; Streissguth et al., 1991; Valenzuela, Morton, Diaz, & Topper, 2012). Deficits in social behavior have been repeatedly observed in children with FASD (Disney, Iacono, McGue, Tully, & Legrand, 2008; Greenbaum, Stevens, Nash, Koren, & Rovet, 2009; Larkby, Goldschmidt, Hanusa, & Day, 2011) and in non-human animal models of FASD across a broad range of exposure doses (Cullen, Burne, Lavidis, & Moritz, 2013; Hamilton et al., 2010; Kelly & Tran, 1997; Middleton, Varlinskaya, & Mooney, 2012; Mooney and Varlinskaya, 2011; Parker et al., 2014; Tunc-Ozcan, Ullmann, Shukla, & Redei, 2013; Varlinskaya & Mooney, 2014; Wellmann, George, Brnouti, & Mooney, 2015). The detection of social behavior deficits with more moderate (e.g., Blood ethanol concentrations (BECs) of ~60–80 mg/dl) (Hamilton, Barto et al., 2014) or low exposure (e.g., BECs < ~40 mg/dl) (Cullen et al., 2013) can be more challenging tasks compared to detecting effects of heavy exposure (e.g., BECs > ~200 mg/dl).

Analyses of rodent social behavior typically include quantification of the frequency and duration of behaviors of interest. For example, in our previous studies we have utilized analysis of video recordings to code behaviors of interest using specialized software that creates a record of the precise onset and offset time of each coded behavior (Barto, Bird, Hamilton, & Fink, 2016). From these records, the overall frequency and total time spent engaged in each behavior are calculated for statistical analyses (Bird et al., 2017; Hamilton et al., 2010; Hamilton, Barto et al., 2014; Hamilton, Magcalas et al., 2014; Rodriguez et al., 2016). Similar approaches to quantification of social behavior are commonly utilized in the field. Considering that social behavior abnormalities following neurobiological or other experiential manipulations can be difficult to detect, analyses of the sequential structure of social behaviors could provide a more sensitive metric for detection of abnormalities. For example, Maaswinkel et al. (1997) observed alterations in the sequential structure of social behavior following hippocampal damage in the absence of gross changes in the frequency of individual behaviors. Analysis of behavioral sequences could also provide insight into the function of potentially ambiguous behaviors. For example, we demonstrated that adult male rats prenatally exposed to moderate levels of alcohol display increased wrestling behavior, however, attempts to disambiguate whether this reflects play or aggression based on the topography of the behavior (Hamilton, Barto et al., 2014) or ultrasonic vocalizations (Bird et al., 2017) have yielded mixed results. Quantification of behavioral sequences involving wrestling could contribute critical information needed for this disambiguation.

Several approaches exist for characterizing the sequential structure of behavior. For example, the Eshkol-Wachman Movement Notation method (Eshkol & Wachman, 1958) is a system in which body position in space and time is coded, providing a record of the temporal sequence of movements and their organization. These records can be performed separately on interacting organisms, and utilized to examine the relative spatiotemporal structure of behavior between individu-

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