The Effect of Dyslexia Gene DCDC2 Knockout on Performance During a Prediction Task in Rats

Abby Thorne, Abby Engelhart, & Tracy Centanni

Department of Psychology, Texas Christian University

Introduction

- Dyslexia is a developmental disorder characterized by unexpected reading difficulty in children and adults with otherwise normal intelligence and nonverbal IQ (Shaywitz, 1998; Peterson & Pennington, 2012; Ferrer et al., 2009).
- Dyslexia is a heterogeneous disorder, and there are several plausible core deficits which can result in a diagnosis of dyslexia, including but not limited to theories of: phonological, cerebellar, low-level auditory, and low-level visual deficits (Valdois et al., 2004).
- The cerebellar theory of dyslexia posits that reading deficits associated with dyslexia are a symptom of a larger deficit in the cerebellum, leading to difficulty automizing tasks (Nicolson & Fawcett, 1990; Nicolson et al., 2001).
- There are several genes associated with dyslexia which may account for the observed causative differences, including: *DCDC2*, *KIAA0319*, *DYX1C1*, and *ROBO1.*
- Suppression of *Dcdc2* in rats has been shown to cause deficits in response to rapid stimuli (Centanni et al., 2016).
- The current study will use a *Dcdc2* knockout rat to further examine the role of *Dcdc2* in responding to rapidly presented auditory stimuli, as well as explore the effect of *Dcdc2* knockout on prediction ability associated with cerebellar deficit.

Methods

Animals

The subjects in this study were Sprague-Dawley knockout rats, targeting the gene *Dcdc2* and produced by GenOway (https://www.genoway.com). The animals ranged in age from 3 to 6 months at the time of study. The subjects included 2 wild type rats, 2 heterozygotes, and 1 homozygous knockout. Subjects were food deprived throughout training but maintained a body weight above 85% of their pre-deprivation weight.

Behavioral Paradigm

- Rats were trained on a 25-stage behavioral paradigm created to assess prediction ability in the context of rapidly presented speech sounds.
- Rats were presented with a sequence of English consonant-vowel-consonant (CVC) speech sounds and were trained to respond only to the target sound /dad/.
- Subjects were first trained under a shaping protocol to learn to associate the infrared-activated nose poke with the target sound /dad/ and the sugar pellet reward. Shaping was followed by hold training, in which animals were required to remain stationary in the nose poke until they heard the target sound /dad/. The animals were next trained in a series of stages to learn to respond to /dad/ and ignore several distractor sounds: /sad/, /tad/, /gad/, and /bad/ (Centanni et al., 2014). Rats were introduced to each distractor individually before progressing to stages in which distractors were presented in strings with the target. Criteria for advancement through the stages of the speech discrimination paradigm are shown in Table 1.
- Once trained to recognize /dad/, the animals advanced to the prediction paradigm in which the predictor sound /bad/ was always followed by the target sound /dad/. The target and predictor were presented in succession surrounding by a randomized stream of distractors: /gad/, /sad/, /tad/. Subjects first completed a stage in which they were exposed to the predictor /bad/ preceding the target sound /dad/ to establish the sound /bad/ as a reliable predictor. Next, rats completed an assessment stage in which they were exposed to the target sound /dad/ in the presence and absence of the predictor /bad/. The predictor sound /bad/ was presented prior to the target approximately 40% of the time, and the assessment session included all distractors. Criteria for rats to advance through the stages of the prediction paradigm are shown in Table 2.

Speech Discrimination

Stage	d'	Number
1	any	any
2	1.5	10
3-11	1.5	2
12	1.5	8
13-16	any	4
17	any	10

Table 1. Criteria required for rats to advance through stages of the speech discrimination paradigm.

Prediction

Stage	d'	Number
19	1.5	2
25	any	10

Table 2. Criteria required for rats to advance through stages of the prediction paradigm.

Statistics

- Analyses for training and prediction testing data were conducted using repeated-measures ANOVAs.
- To determine the accuracy of the groups in responding to the target /dad/, the sum of all false alarms was subtracted from the total number of hits. Response accuracy was determined by comparing this value to the total number of responses. Response rates were determined at each compression and compared within group. Significant main effects and interactions were then evaluated further using post-hoc t-tests.
- Speech discrimination training data were analyzed using a 3x2 ANOVA for genotype (wild type x heterozygous x homozygous) and sex (male x female). Prediction data was analyzed using a 3x2x2 ANOVA to account for genotype (wild type x heterozygous x homozygous), sex (male x female), and condition (predictor presence x predictor absence).

Results

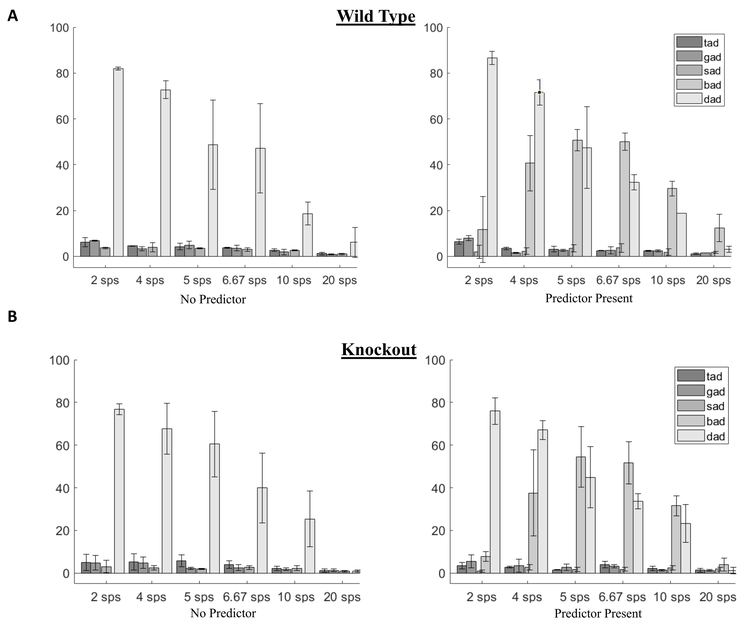

Figure 1. Response rates of Dcdc-2 knockout, heterozygous, and wild type rats to target /dad/ and all distractors (/tad/, /gad/, /sad/, /bad/) in the presence and absence of the predictor /bad/. **A.** Response rates to all stimuli of wild type rats in the presence and absence of the predictor /bad/. **B.** Response rates to all stimuli of Dcdc2-knockout rats in the presence and absence of the predictor /bad/.

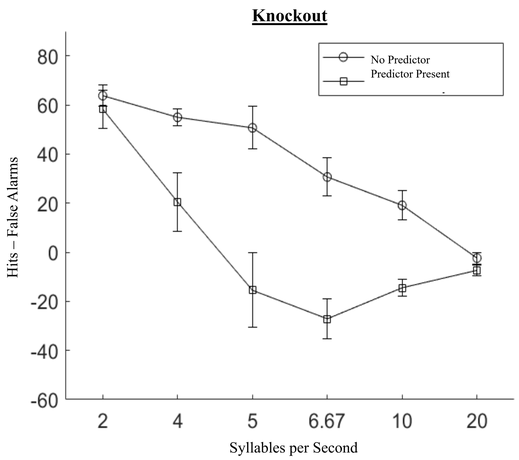

Figure 2. Results of prediction study in wild type and *Dcdc2*-variant rats. *Dcdc2*-variant rats' response to the target was significantly impaired in the presence of the predictor.

There were no significant differences between groups in response to the target /dad/ in the presence or absence of the predictor (Figure 1). However, knockout rats responded more to the distractors than did wild type, further supporting previous findings that *Dcdc2*-knockout impairs speech sound discrimination of rapidly-presented stimuli (Centanni et al., 2016).

As presentation rate increased, both wild type and knockout rats began to respond to the predictor /bad/ rather than the target /dad/ (Figure 1). This appears to be due to anticipation of the stimulus rather than stimulus generalization, as the effect is only observed for the predictor /bad/ and not observed for all distractors.

There were no significant differences between wild type and *Dcdc2*-variant rats when the predictor was not present (2-tailed unpaired t-test, t (df) = tstat, $p > 0.253$). There were also no significant differences between wild type and *Dcdc2*-variant rats when the predictor /bad/ was present (2-tailed unpaired t-test, t (df) = tstat, $p > 0.122$). Both the wild type and *Dcdc2*-variant rats performed significantly worse in the presence of the predictor /bad/ than in its absence (Figure 2). Notably, the *Dcdc2*-variants were more variable in response in the presence of the predictor than were the wild type. This could indicate a significant effect of the presence of the promoter which could be observed with a larger sample size.

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