PREDICTION OF RAPID SPEECH SOUND STIMULI IN A *Dcdc2* KNOCKOUT RAT MODEL OF DYSLEXIA

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Introduction

Developmental dyslexia is the most common neurodevelopmental disorder and is characterized by below average reading scores in spite of normal nonverbal intelligence and adequate access to instruction (Peterson, Pennington, & Olson, 2014; Peterson & Pennington, 2012). Individuals diagnosed with dyslexia often struggle with low-level skills related to reading including phonological awareness (Swan & Goswami, 1997) and rapid automatized naming (RAN) skills (Tallal, 1980). Deficits in these skills interfere with reading acquisition and lead to significant lifelong consequences, both in an academic setting and daily life (Bretherton & Holmes, 2003; Boada & Pennington, 2006; Cassidy, Reggio, Shaywitz, Holahan, & Shaywitz, 2021; Raschle, Stering, Meissner, & Gaab, 2014). Developmental dyslexia has a rather high prevalence of roughly 7% in the general population (Snowling & Melby-Lervåg, 2016), with even larger prevalence in males (Rutter, 2004) and in lower socioeconomic status communities (Friend, Defries, & Olson, 2008). Within the population of those with dyslexia, there is significant variation in their specific phenotypes, and many do not make adequate gains in their reading abilities following intervention (Peterson & Pennington, 2012). These observed variations in phenotype and treatment effectiveness suggest that there are likely multiple causal factors leading to the various deficits in those with the diagnosis (Peterson, Pennington, & Olson, 2013; van Bergen, van der Leij, & Jong, 2014; Wolf et al., 1999).

Dyslexia is a highly heritable disorder and several candidate genes have been associated with the diagnosis. The most well-studied of these in humans are *KIAA0319, DCDC2, DYX1C1,* and *ROBO1* (Darki, Peyrard-Janvid, & Matsson, 2012; Galaburda, LoTurco, Ramus, Fitch, & Rosen, 2006; Marino et al., 2012; Mascheretti et al., 2017; Rendall, Tarker, Contreras-Mora, LoTurco, & Fitch, 2017; Wang et al., 2006). Current research suggests that each of these

candidate genes may contribute to the heterogeneity of dyslexia through separate pathways that each result in reading impairment (Centanni et al., 2018; Galaburda, LoTurco, Ramus, Fitch, & Rosen, 2006; Hancock, Pugh, & Hoeft, 2017; Liebig, Friederici, & Neef, 2020; Mascheretti et al., 2017; Peterson, Pennington, & Olson, 2013; Wolf et al., 1999). As such, it is important to better understand the specific mechanisms of each gene's contribution to the various deficits in dyslexia. One of the candidate genes for developmental dyslexia is *DCDC2* (Doublecortin domain-containing protein 2) a member of the *DYX2* gene family. *DCDC2* is found at the 6p.22 site in the human genome and contributes to the modulation or fine-tuning of neuronal migration by stabilizing the structure of the microtubules in the primary cilia, which in turn allow for typical migration from the ventricular to the pial surfaces. (Massinen et al., 2011; Meng et al., 2005). Variation in the expression of *DCDC2* alters the migration of neurons, including those critical to fluent reading skills that are located in the cerebellum and inferior and medial temporal cortices (Burbridge, Wang, & Volz, 2008; Che, Truong, Fitch, & Turco, 2016; Marino et al., 2014). Compared to the higher-order cortical regions that are also vital to the reading network, there are far fewer studies investigating the cerebellum and how an individual's reading and language capabilities may be impacted by structural changes to the cerebellum caused by *DCDC2* variations (Argyropoulos, 2016; Miall et al., 2016; Runnqvist et al., 2016).

The cerebellum is a critical component of the reading and language networks (D'Mello, Centanni, Gabrieli, & Christodoulou, 2020; D'Mello, Turkeltaub, & Stoodley, 2017; Runnqvist et al., 2016) but has been historically understudied. The cerebellum is critically involved in prediction, which allows an organism to use their prior experiences to develop an expectation about upcoming events so they may react accordingly (Pecenka, Engel, & Keller, 2013). This skill operates largely below conscious awareness but is critical for fundamental human behaviors

such as social communication, locomotion, and language (Grisoni, Mohr, & Pulvermuller, 2019; Maurer, Maurer, and Müller, 2015; Oestreich, Randeniya, Garrido, 2019). Even when controlling for comprehension ability, some individuals with dyslexia have longer reaction times to less predictable sentences than typically developed individuals, indicating that some individuals with dyslexia possess a linguistic prediction deficit (Engelhardt, Yuen, Kenning, & Filipovic, 2021; Huettig & Bruewer, 2015). Mutations in *DCDC2* in humans and rodent homologs are associated with abnormal structure of the cerebellum and altered connectivity with associated auditory neural pathways (Lesage, Morgan, Olson, Meyer, & Miall, 2012). These malformations in turn are associated with a reduction in cerebellar activity and increased rate of semantic prediction errors (Skipper & Lametti, 2021), both in speech and in reading (D'Mello, Centanni, Gabrieli, & Christodoulou, 2020; D'Mello, Turkeltaub, and Stoodley, 2017; Sihvonen, Virtala, Thiede, Laasonen, & Kujali, 2021; Wang et al., 2011). Given that variations in *DCDC2* alter the structure and connections of the cerebellum and that the cerebellum plays a critical role in making predictions, it is plausible that mutations in *DCDC2* may impact rapid stimulus processing in those with dyslexia.

Variation in *DCDC2* may contribute to the multiple deficits of developmental dyslexia through causing a deficit in prediction capabilities. Prediction deficits in individuals with *DCDC2* variations could make it more difficult to discriminate between rapidly presented speech sounds, which then would make it difficult to match a letter to the appropriate speech sound while reading. A significant difficulty with the rapid processing of auditory stimuli may impair the development of an automatic association between a speech sound and its associated grapheme (letter symbol), which could lead to reading impairment. This proposed mechanism is difficult to investigate using human participants because of the complex and varied genetic

profiles in those with dyslexia. To understand the role of *DCDC2* on rapid auditory processing and prediction, an animal model is needed in which genetic manipulation and sufficient environmental control is possible.

Rodent models have previously been used to investigate the role of *Dcdc2* (the rodent homolog of *DCDC2*) on auditory perception. *Dcdc2* knockout mouse models, where the expression of the gene product is entirely eliminated due to an artificial mutation, exhibit deficits in rapid auditory processing capabilities (Truong et al., 2014; Wang et al., 2011). While *Dcdc2* knockout mouse models are useful for assessing many of the neurological impacts of the gene, one limitation of this model is the inability of mice to be effectively trained and utilized for complex speech-sound discrimination tasks. Rat models, however, are capable of more complex behavioral tasks, including those using human speech sounds. One prior study investigated speech sound discrimination in a rat model with knockdown of *Dcdc2* by RNA interference, or RNAi (Centanni et al., 2016). Knockdown of *Dcdc2 in utero* using RNAi locally reduces the expression of *Dcdc2* and has been associated with an increase in neuronal migration errors (Burbridge et al., 2008), particularly in the periventricular region, similar to what is seen in humans with dyslexia (Marino et al., 2014). The previous work by Centanni and colleagues (2016) demonstrates that rats treated with *in utero Dcdc2* RNAi to express less Dcdc2 protein in auditory cortex have difficulties discriminating between consonant-vowel-consonant (CVC) speech-sounds presented at high speeds.

This prior work demonstrated that rats with suppressed *Dcdc2* exhibit impairment in their ability to discriminate between speech-sounds presented in random sequences at increased speeds, but there were two main limitations. First, RNAi knockdown of *Dcdc2* only affects roughly 1-2% of targeted neurons, so it may be the case that this incomplete gene product

elimination would have a different behavioral and neurological effect than a full genetic knockout. Second, the sample size in this study was notably small. The proposed studies were designed to address these limitations and expand on this prior work.

The aims of the current study were to 1) replicate the prior study using a full knockout rat and well-powered sample and 2) expand our existing task to evaluate prediction. We hypothesized that introduction of a reliable predictor to the rapid presentation portion of the speech-sound discrimination task would allow wild-type rats to improve speech-sound discrimination performance, but *Dcdc2* knockout rats would not show improved performance with the predictor present. This work lays the foundation for future studies of cerebellar volume, white matter structure, and neural plasticity.

Materials and Methods.

Animals. Subjects were Sprague-Dawley rats originally generated by genOway and bred at Charles River Laboratories. The rats were generated using CRISPR-Cas9 genetic manipulation and bred to have either two, one, or no insertions of a premature stop codon in exon 1 of the *Dcdc2* gene and were categorized as homozygous (HO), heterozygous (HE), or wild-type (WT), respectively. The litters produced in our facilities yielded only seven WT pups, three of which were trained, so data from a pilot study using WT Sprague-Dawley rats were included in the subsequent analyses. To first confirm that the non-littermate control WT rats were behaving similarly to the littermate control WT rats, a repeated-measures ANOVA was performed on response rate during the initial testing stage (no predictor cue available). This analysis revealed significant main effects of the presented sound (F (4,350) =292.47, $p < 0.001$), presented speed (F (5,350) = 56.17, $p < 0.001$), and group (F (1,350) = 32.57, $p < 0.001$). Also, the only significant interaction was between speed and sound (F (20,350) = 28.72, $p < 0.001$). *Post hoc*

two-tailed *t* tests found that there was no difference in the responses to the target sound at any speed ($ts(11) \leq 1.67$, $ps \geq 0.118$) aside from a trend in responding for non-littermate controls at 10 syllables per second ($t(11) = 1.95$, $p = 0.077$). Since the main effect of group was largely driven by the non-littermate controls slightly increased responding to distractors at 2 sps ($ts(11) \leq 2.793$, $ps \geq 0.018$) and the response patterns to the target sound were consistent between the groups, they were combined into the WT group for subsequent analyses. These non-littermate control pups were housed in identical conditions and went through the same training and handling procedures a few months prior to the start of training for the rats previously mentioned. All rats were housed between 69 and 72 degrees Fahrenheit and reared in a standard 24 hour light:dark (lights on, 07:00 am – 7:00 pm) cycle with free access to food and water. At least two weeks before they enter the training portion of the study, they were moved to a reverse 24 hour light:dark (lights on, 7:00 pm- 7:00 am) cycle to ensure behavioral training occurs during the rats' nocturnal circadian rhythm. Three days prior to the start of training, food restriction was initiated and animals were not allowed to fall below 85% of their pre-deprivation body weight. All animal protocols were approved by the Texas Christian University Institutional Animal Care and Use Committee.

Timeline. In this project, we collected data from 40 rats in total. Seven WT male, six WT female, six HE male, six HE female, eight HO male, and seven HO female rats were trained and tested. The rats were trained and tested in blocks of up to 24 rats, depending on litter sizes and available genotypes of the pups. Similar to the timelines of prior work in our lab using the same paradigm, each training block took between three and six months to get through behavior training and complete testing.

Behavioral Paradigm. Rats were trained to discriminate a target speech-sound (/dad/) from a randomized string of speech-sounds (/bad/, /gad/, /sad/, and /tad/) presented at varying speeds (2, 4, 5, 6.7, 10 and 20 syllables per second (sps)), as was done in prior work (Centanni et al., 2016). Rats were trained and tested in two 30-min sessions per day (5 days/week) using custom Matlab programming in an operant chamber with an infrared-monitored nose poke and pellet dispenser placed into a double-walled soundproofed booth (**Figure 1**). For descriptions of all training stages used and their respective threshold criteria, see Table 1. The first stage of training used autoshaping to teach the rat to place their nose in an infrared-monitored nose poke to associate the target /dad/ with the receipt of a 45 mg sugar pellet (sucrose) reward. After receiving at least 100 pellets in a single session, they were then trained to hold their nose in the nose poke until the target sound /dad/ is played, at which time withdrawal from the nosepoke resulted in sugar pellet delivery. Progression through training stages was dictated by previously demonstrated criteria (Centanni et al., 2016) using the d' value of each training session as an indicator of discrimination ability (**Table 1**). The d' value is defined as the Z-score of the distractor response rate subtracted from the z-score of the target response rate. After 10 nonconsecutive sessions at a d' $\geq$ 1.50, animals progressed through a series of training stages where each of the four distractors was incrementally introduced and with increasing levels of randomization. Upon completion of stage 11, the rats were trained to discriminate the target sound from the distractors at progressively increasing speeds by increasing the presentation rate of the speech-sound stimuli from 2 sps to 4 sps, followed by 5, 6.7, and 10 sps over the following stages until the final and fastest speed of 20 sps at stage 16. Upon completion of these training stages, they were placed into the final training stage, where the distractor sound /bad/ was converted to a predictor sound such that in 40% of trials, the predictor immediately precedes the target and is no longer

presented as a regular distractor. During the remaining 60% of trials, the target was presented randomly. The rat was then placed into the testing stage for ten sessions where their response rates and reaction times were recorded as dependent variables.

Statistics. All analyses were performed using custom code in Matlab. Response rate for each sound at each compression was defined as the total number of responses to each sound at each compression with respect to the total number of presentations. Reaction time was defined as the mean time to respond to the speech sound stimulus in milliseconds (ms) after onset. Repeated-measures analyses of variance (ANOVA) were utilized to assess response rate and reaction time (genotype x predictor x presentation rate). Any significant main effects and interactions were explored using post-hoc *t*-tests with the Bonferroni correction.

Results.

The first aim of this study was to replicate prior work that found that *Dcdc2* knockdown rats have a rapid auditory processing deficit, but in a novel *Dcdc2* knockout rat model. After confirming control validity, a repeated-measures ANOVA was performed on response rate during the initial testing stage (no predictor cue available) for each genotype to determine the impact of the speech sound itself and the presentation speed on response rates. In wild-type rats, this analysis revealed a significant main effect of the presented sound (F (4,360) = 408.84, $p <$ 0.001) and presentation speed (F (5,360) = 80.42, $p < 0.001$). There was also a significant interaction between presented sound and speed (F (20,360) = 25.94, $p < 0.001$; **Figure 2**). *Post hoc* analyses revealed a greater response rate to the target sound /dad/ than to any of the distractor sounds at all presentation rates (ps ≤ 0.001), and overall response rate decreased as the presentation rate increased from 2 to 20 sps. A two-tailed *t* test found that males did respond to the target significantly less than females at 2 sps (t(11) = -2.35, $p = 0.039$), but for all other

speeds there was no observed effect of sex on response rates to the target (ts(11) ≤ 1.10, ps ≥ 0.294). This overall pattern of behavior is consistent with prior work using this task (Centanni et al., 2014a, 2014b; Centanni et al., 2016).

Unexpectedly, the same patterns were observed for the heterozygous and homozygous knockout rats. In heterozygous rats, this analysis revealed a significant main effect of the presented sound (F (4,320) = 297.21, p < 0.001) and presentation speed (F (5,320) = 46.03, p < 0.001). There was also a significant interaction between presented sound and speed (F (20,320) = 17.67, p < 0.001; **Figure 3**). *Post hoc* analyses revealed a greater response rate to the target sound /dad/ than to any of the distractor sounds at all presentation rates (ps ≤ 0.011), and overall response rate decreased as the presentation rate increased from 2 to 20 sps. Though unexpected, this finding may be due to the fact that the heterozygous rats still possessed one functional copy of the *Dcdc2* gene which could be sufficient to produce enough *Dcdc2* protein and prevent any behavioral deficit. A two-tailed t test found that there was no observed effect of sex on response rates to the target in any condition (ts(10) ≤ 0.70, ps ≥ 0.500). In homozygous rats, this analysis revealed a significant main effect of the presented sound (F (4,420) = 391.76, p < 0.001) and presentation speed (F (5,420) = 55.86, p < 0.001). There was also a significant interaction between presented sound and speed (F (20,420) = 21.98, p < 0.001; **Figure 4**). *Post hoc* analyses revealed a greater response rate to the target sound /dad/ than to any of the distractor sounds at all presentation rates (ps ≤ 0.003), and overall response rate decreased as the presentation rate increased from 2 to 20 sps. A two-tailed t test found that there was no observed effect of sex on response rates to the target in any condition (ts(13) ≤ 1.11, ps ≥ 0.288). This behavioral pattern was unexpected given that prior work using this task found that rats with an RNAi knockdown of

Dcdc2 struggled to discriminate between speech sounds at increased speeds (Centanni et al., 2016).

The second aim of the study was to expand upon prior work to assess whether rats with a global knockout of *Dcdc2* are able to form predictions of upcoming auditory stimuli. A repeated-measures ANOVA was performed on response rate during the final testing stage for each genotype to determine the impact of the speech sound itself and the presentation speed on response rates. In wild-type rats, this analysis revealed significant main effects of predictor (F (1,740) = 93.05, $p < 0.001$), presented sound (F (4,740) = 478.49, $p < 0.001$), and presentation speed (F (5,740) = 78.33, $p < 0.001$). There were also significant interactions for predictor x sound (F (4,740) = 141.25, $p < 0.001$), predictor x speed (F (5,740) = 3.21, $p = 0.007$), and speed x sound (F (20,740) = 39.12, $p < 0.001$; **Figure 5**). As expected, there was a greater response rate to the target sound than to distractor sounds across all speeds and trial types ($ps < 0.026$). *Post hoc* analyses revealed that when the predictor was present, there was a significantly greater response rate to the target sound /dad/ than to any of the distractor sounds across all presentation speeds (adjusted ps ≤ 0.026). Response rates to the target were higher than the predictor at the slowest speed of 2 sps (adjusted ps < 0.001), but they did not differ at the faster presentation rates (adjusted ps ≥ 0.13) except for 6.7 sps, where they responded slightly more to the predictor than the target (adjusted ps ≥ 0.013). Regardless of the presence of the predictor, a two-tailed t test found that there was no observed effect of sex on response rates to the target in any condition (ts(11) ≤ 1.84, ps ≥ 0.093). This pattern was expected for the wild-type rats, as we hypothesized that they would be able to learn the meaning of the predictor.

Unexpectedly, these same patterns were observed in the heterozygous rats. This analysis revealed significant main effects of predictor (F (1,680) = 78.26, $p < 0.001$), presented sound (F

(4,680) = 497.66, $p < 0.001$), and presentation speed (F (5,680) = 59.38, $p < 0.001$). There were also significant interactions for predictor x sound (F (4,680) = 99.75, $p < 0.001$), predictor x speed (F (5,680) = 3.07, $p = 0.01$), and speed x sound (F (20,680) = 31.25, $p < 0.001$; **Figure 6**). There was a greater response rate to the target sound than to distractor sounds across all speeds and trial types ($ps < 0.028$). *Post hoc* analyses revealed that when the predictor was present, there was a significantly greater response rate to the target sound /dad/ than to any of the distractor sounds across all presentation rates (adjusted $ps \leq 0.028$). Response rates to the target were higher than the predictor at the slowest speed of 2 sps (adjusted $ps < 0.001$), but they did not differ at faster presentation rates ($ps \geq 0.094$). A two-tailed t test found that males were responding to the target marginally less than females when the predictor was present at the fastest speed ($t(10) = 2.14$, $p = 0.058$), but there was no observed effect of sex on response rates to the target at all other speeds, regardless of the presence of the predictor ($ts(10) \leq 1.28$, $ps \geq 0.230$). As with the results in the first aim, this behavioral pattern may be due to the presence of one functional copy of the *Dcdc2* gene which may be sufficient to produce enough Dcdc2 protein and prevent behavioral deficits.

Homozygous rat's response rates were also not as expected and exhibited patterns similar to the wild-type and heterozygous rats. This analysis revealed significant main effects of predictor (F (1,860) = 42.05, $p < 0.001$), presented sound (F (4,860) = 385.28, $p < 0.001$), and presentation speed (F (5,860) = 52.35, $p < 0.001$). There were also significant interactions for predictor x sound (F (4,860) = 100.11, $p < 0.001$), predictor x speed (F (5,860) = 3.65, $p = 0.003$), and speed x sound (F (20,860) = 29.58, $p < 0.001$; **Figure 7**). There was a greater response rate to the target sound than to distractor sounds across all speeds and trial types ($ps < 0.03$). *Post hoc* analyses revealed that when the predictor was present, there was a significantly

greater response rate to the target sound /dad/ than to any of the distractor sounds across all presentation rates (adjusted *p*s < 0.001). Response rates to the target were higher than the predictor at the slowest speed of 2 sps (adjusted *p*s < 0.001), but response rates to the predictor were higher than the target at 5 (adjusted $p = 0.004$) and 6.7 sps (adjusted $p = 0.015$). At all other speeds, there was no difference in response rates to the target and predictor (adjusted *p*s > 0.357). Regardless of the presence of the predictor, a two-tailed *t* test found that there was no observed effect of sex on response rates to the target in any condition (ts(13) ≤ 1.49, *p*s ≥ 0.160). Though unexpected, we saw that rats with a homozygous *Dcdc2* knockout have a similar response pattern to speech sounds in a predictable environment as what was seen in the wild-type and heterozygous rats.

Discussion.

In the first aim of this study, we hypothesized that wild-type rats would be able to discriminate between the speech sounds at increased speeds and rats with variation in *Dcdc2* (heterozygous and homozygous) would make more discrimination errors, but that is not the pattern that we observed. We saw that regardless of genotype, all rats were able to discriminate between the target speech sound and the distractors at increased speeds. This finding is in contrast with prior work with a *Dcdc2* rat model, which reported a deficit on the same task when there was variation in *Dcdc2* expression (Centanni et al., 2016). The present study differed from the prior work in that we used a novel *Dcdc2* rat model with a global knockout of the gene whereas the prior study, Centanni et al. (2016), used an *in utero* RNAi knockdown of the gene that prevented *Dcdc2* expression in 1-2% of neurons around the injection site in the auditory cortex. Given that these models differ in the degree and regions in which *Dcdc2* expression varies, it may be the case that a global knockout of the *Dcdc2* gene from the rat's genome does

not lead to the same deficit profile as a localized knockdown of *Dcdc2* expression during development. A local knockdown of *Dcdc2* in the auditory cortex may lead to impaired rapid auditory processing capabilities whereas a global knockout of *Dcdc2* does not impair this ability and may lead to other behavioral changes.

In the second aim of this study, we expected wild-type rats to be able to learn a predictive relationship between the former distractor speech sound and the target whereas rats with *Dcdc2* variation would struggle to learn this predictive relationship, but that is not the pattern observed in the rat's responses. We saw that both wild-type and heterozygous rats were able to learn the predictive relationship between the predictor and the target, as evidenced by the lack of responding to the predictor at the slowest speed but equal responses to the predictor and target sounds at all the faster speeds. Similarly and unexpectedly, we saw that homozygous rats were able to learn the predictive relationship between the predictor and target speech sounds, as evidenced by the lack of responding to the predictor at the slowest speed but equal responses to the predictor and target sounds at increased speeds. Homozygous rats also responded to the predictor more often than the target speech sound at the intermediate speeds of 5 and 6.7 sps. Anticipatory responses to the predictor were expected and indicate that the rat has predicted the upcoming target sound, but this anticipation appears to be amplified somewhat for the homozygous rats.

A potential explanation for this increased response to the predictor at intermediate speeds could be that *DCDC2* is not only associated with developmental dyslexia, but also with attention deficit/hyperactivity disorder, which is a common comorbid disorder (ADHD; Mascheretti et al., 2017; Sánchez-Morán et al., 2018). In particular, there is evidence suggesting that *DCDC2* variation is associated with increased impulsivity (Mascheretti et al., 2017). The response

patterns observed in our homozygous rats might suggest that the global knockout of *Dcdc2* did not prevent the rat from learning a predictive relationship but instead led the rat to be somewhat more impulsive in their responses. If this were the case, their responses to the target should have been faster than other responses and we would expect to see reduced reaction times to the target and more errors at increased speeds. However, no significant differences in reaction time or the number of errors were observed at any speed, so our results do not suggest that homozygous rats are more impulsive than wild-type rats. Though our results do not suggest an association between *Dcdc2* and impulsivity, the task used in this study does require a fast reaction time to begin with. Future studies that are specifically interested in impulsivity could investigate this further with a task that is more sensitive to differences in reaction time that are more subtle than this task could detect.

As our data do not suggest an effect on the rat's impulsivity, the lack of behavioral differences between wild-type and heterozygous or homozygous rats is most likely due to the global knockout of *Dcdc2* causing uniform dysregulation of neuronal migration across neural circuitry. *Dcdc2* encodes a cytoplasmic protein that binds to the microtubules of neurons, particularly to their primary cilia, to stabilize the cytoskeletal structure during neuronal migration and aid in the intra-cellular signaling that guides ciliary locomotion (Galaburda et al., 2006; Meng et al., 2005; Wang et al., 2011). Downregulation of *Dcdc2* expression impairs proper neuronal migration and leads to malformation, particularly in regions associated with reading and language (Burbridge et al., 2008). Prior work investigating *Dcdc2* using a speech sound discrimination paradigm used an *in utero* RNAi knockdown of the gene (Centanni et al., 2016). This approach eliminates expression of *Dcdc2* gene product in 1-2% of neurons near the injection site, which in this case was the auditory cortex, and led to impaired speech sound

discrimination capabilities. This differs from our model, which was a global knockout of *Dcdc2* from the entire body. In this model, no *Dcdc2* gene product was produced in any neuron and the behavioral deficits observed in prior studies were not seen. Some evidence suggests that other genes of the *DYX* family, which includes *DCDC2*, may be necessary for proper neuronal migration whereas *DCDC2* serves more so as a modulator of their activity (Meng et al., 2005; Wang et al., 2011), specifically in regions related to reading ability. This would explain why our global knockout model of *Dcdc2* did not produce the same behavioral deficits that were seen in models using local RNAi knockdown. Dysregulation of neuronal migration in a single region during development would cause only a small subpopulation of neurons to migrate improperly while all other regions in the circuit would migrate typically, thus impairing proper formation of the necessary circuitry for reading ability. However, uniform dysregulation of neuronal migration throughout the brain would not present the same issue during circuit formation and associated abilities should develop typically.

The findings of this study, though largely unexpected, provide much needed information regarding the mechanisms underlying *Dcdc2* and the use of genetic models of disorders in a broader sense. We see evidence that possessing one or two dysfunctional copies of *Dcdc2* in the rat genome does not lead to the potential behavioral deficits that were expected based on prior work investigating *Dcdc2*. Wild-type and homozygous rats displayed similar response patterns on trials where the predictor was present, though homozygous rats did make more anticipatory responses at intermediate speeds. We also see evidence that global knockout of *Dcdc2* does not lead to the behavioral deficits that a localized knockdown of the gene would induce. Prior work using a model with an RNAi knockdown of *Dcdc2* in the auditory cortex leads to rapid auditory processing deficits that are not seen in our model with a global knockout of the gene (Centanni et

al., 2016). Taken together, these findings show that the degree and region in which *Dcdc2* is expressed determines what behavioral changes may present, if any. This finding adds to the body of evidence supporting the notion that dyslexia is a heterogeneous disorder (Hancock et al., 2017; Peterson, Pennington, & Olson, 2013; Wolf et. al, 1999). Beyond the associated environmental and genetic factors, a single gene can vary in a number of ways that may still lead to the same diagnosis of dyslexia by differentially affecting the expression of the gene. Researchers that use genetic models of disorders should take this into consideration when interpreting results from these models and acknowledge that the way in which the genome is altered may be just as important as the specific gene that is being investigated.

There are a couple of limitations in the present study that should be noted. First, these rats were trained to discriminate human speech sounds, which are not ecologically valid to rats. Rats display speech sound discrimination capabilities that are on par with humans (Centanni et al., 2014b; Engineer et al., 2008; Porter, Rosenthal, Ranasinghe, & Kilgard, 2011; Ranasinghe, Vrana, Matney, & Kilgard, 2012; Reed, Howell, Sackin, Pizzimenti, & Rosen, 2003), but it may be the case that they may perform better or show different patterns with more ethologically relevant stimuli. This limitation is not exclusive to this study however, since all animal model work is limited in that it serves as an approximation of human behavior and should be treated as such. Second, this study aimed to determine the function of *Dcdc2* as it relates to rapid auditory processing and prediction skills but this genetic manipulation in this study may not be entirely representative of the variation that is seen in the human population. Another gene that is strongly associated with dyslexia in humans, *KIAA0319*, is located in the same chromosomal locus as *DCDC2* and shares some regulatory elements (Power et al., 2016; Trezzi et al., 2017). Though each gene is independently associated with dyslexia, variation in these shared regulatory

elements leads to greater behavioral deficits than the sum of the deficits due to variation at other sites in each gene (Trezzi et al., 2017). Our model assesses how complete elimination of *Dcdc2* gene expression in a rat alters behavior, which was the aim of the study, but it is worth noting that individuals with dyslexia are likely to have differences in regulation in multiple genes and these may interact with one another to produce different behavioral deficits than either would independently.

To conclude, this study presents the first behavioral analysis of the novel *Dcdc2* knockout rat model of dyslexia. We found that rapid auditory processing capabilities of speech sounds are not impaired in this model, which differs from what was expected based on other related models (Centanni et al., 2016; Wang et al., 2011). We also see that the homozygous *Dcdc2* knockout rat is able to predict an upcoming speech sound, like its wild-type and heterozygous counterparts, though these rats did make more anticipatory responses at intermediate speeds than their counterparts. This unexpected lack of behavioral deficits is most likely due to the differences in neuronal migration and proper circuit formation between a local RNAi knockdown of *Dcdc2*, as used in prior work, and the global knockout of *Dcdc2* that was used in our model. These findings suggest that behavioral deficits, as modeled in rodents, that are associated with *Dcdc2* are likely the result of differences in local regulation of *Dcdc2* expression in regions associated with auditory processing instead of a global elimination of *Dcdc2* expression. Taken together, these findings add to the body of literature supporting the heterogeneity of dyslexia, provide necessary understanding of the mechanisms underlying *Dcdc2*, and illuminate several potential avenues for further investigation. Future work should investigate the common degrees to which *DCDC2* varies in the population of individuals with dyslexia, specifically regarding the degree and regions where regulation of *DCDC2* varies, and work to apply those to an animal model. Further,

more representative animal models of dyslexia that manipulate both genetic and environmental factors should be developed and investigated to account for the observed heterogeneity of dyslexia and reading disability in the human population.

Table 1. Description of speech-discrimination training/testing stages and thresholds

Stages	Description	Thresholds
1	Autoshaping	One session with 100 pellets
2	Train to hold in nose poke until target sound **/dad/** is presented	10 nonconsecutive sessions with ≥ 30 pellets and d' > 1.5
3-6	Each stage introduces one of the four distractor sounds, **/tad/**, **/gad/**, **/sad/**, **/bad/**, with the target	Two sessions with ≥ 30 pellets and d' > 1.5
7-11	Each stage increases the number of distractors presented in a given block of trials, until all five sounds are presented	Two sessions with ≥ 30 pellets and d' > 1.5
12	Introducing faster presentation rate of 4 sps	Eight sessions with ≥ 30 pellets and d' > 1.5
13-16	Introduce rest of increased presentation rates of 5, 6.7, 10, and 20 sps	Four sessions with any d'
17	Randomized presentation rates	10 sessions with any d'
18	Convert distractor **/bad/** to a predictor, where **/dad/** always follows when presented	Two sessions with ≥ 30 pellets and d' > 1.5
19	Testing stage for prediction, 40% of initiated blocks of trials will have predictor **/bad/** presented	10 sessions with any d'

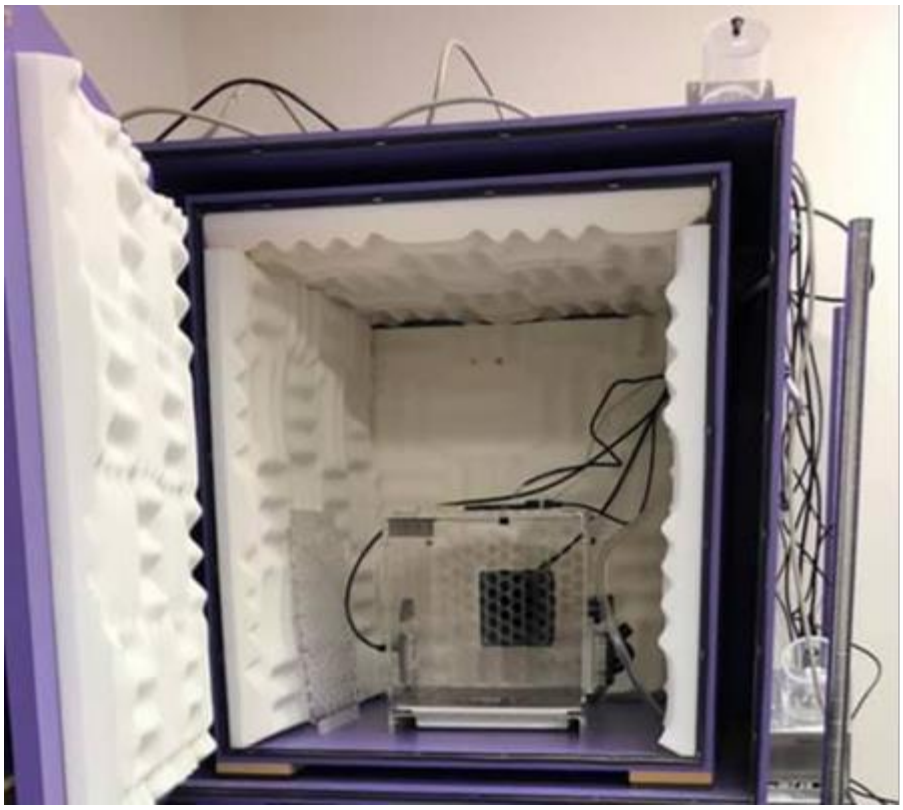

Figure 1. Layout of booth used in training/testing with infrared nose poke on left wall of booth and pellet dispenser on right. Booth is placed within a double-walled soundproof chamber.

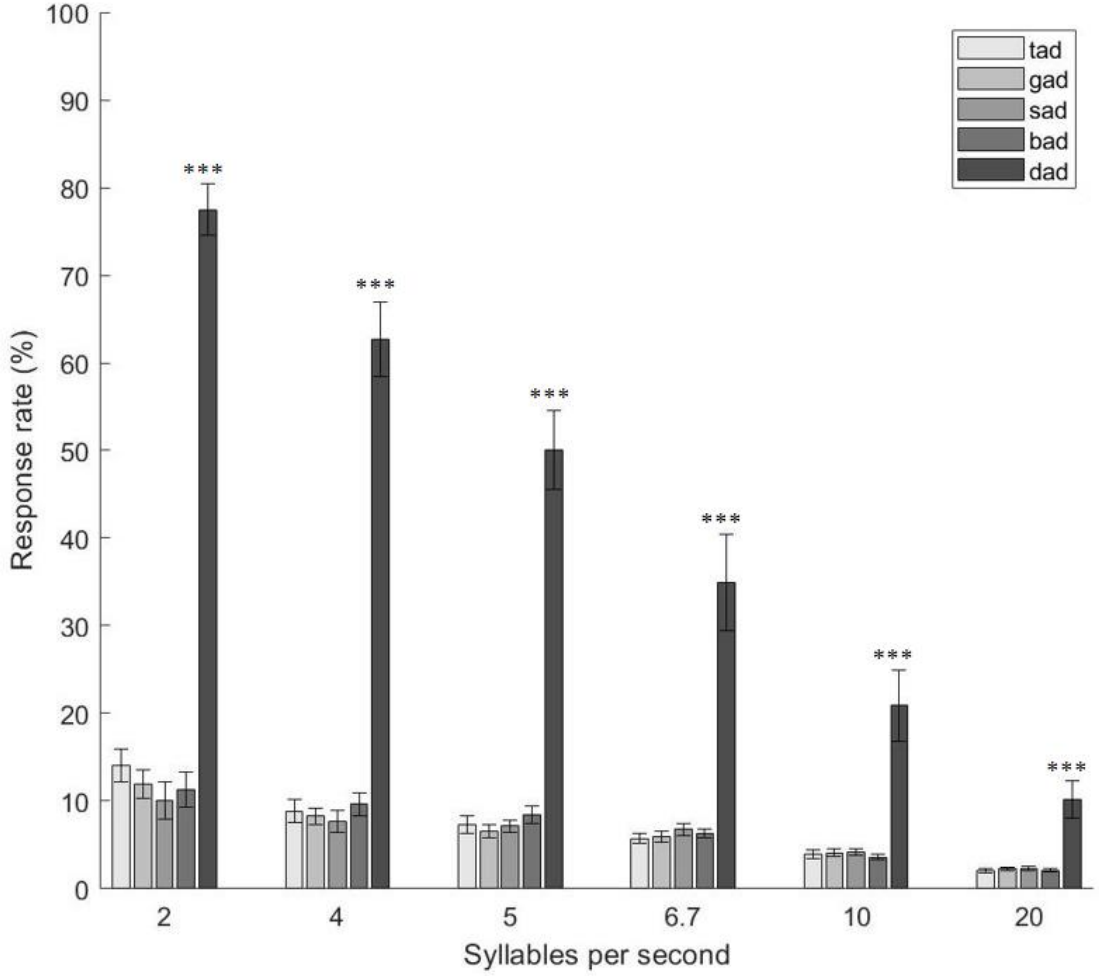

Figure 2. Response rates of 13 wild type rats to each speech sound stimuli at increasing speeds (2-20 sps) at stage 17 of training before /bad/ is a predictor. Error bars represent ± 1 SEM. ***$p \leq .001$

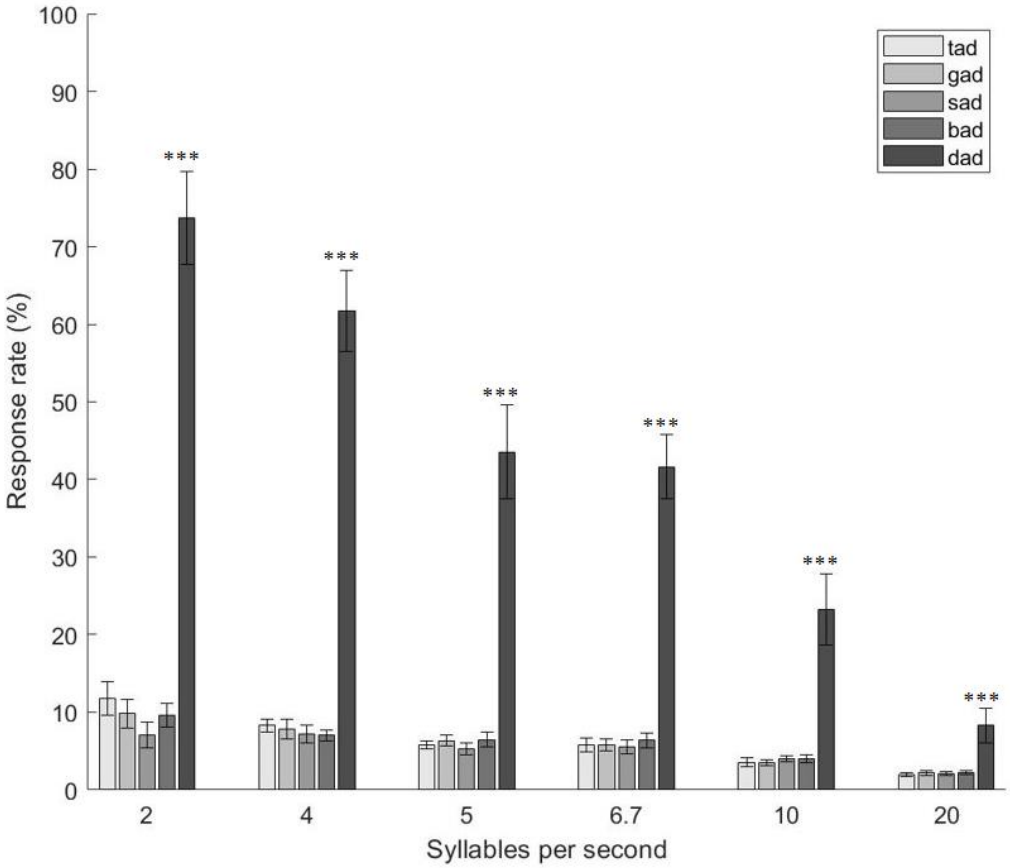

Figure 3. Response rates of 12 heterozygous rats to each speech sound stimuli at increasing speeds (2-20 sps) at stage 17 of training before /bad/ is a predictor. Error bars represent ± 1 SEM. ***$p \leq .001$

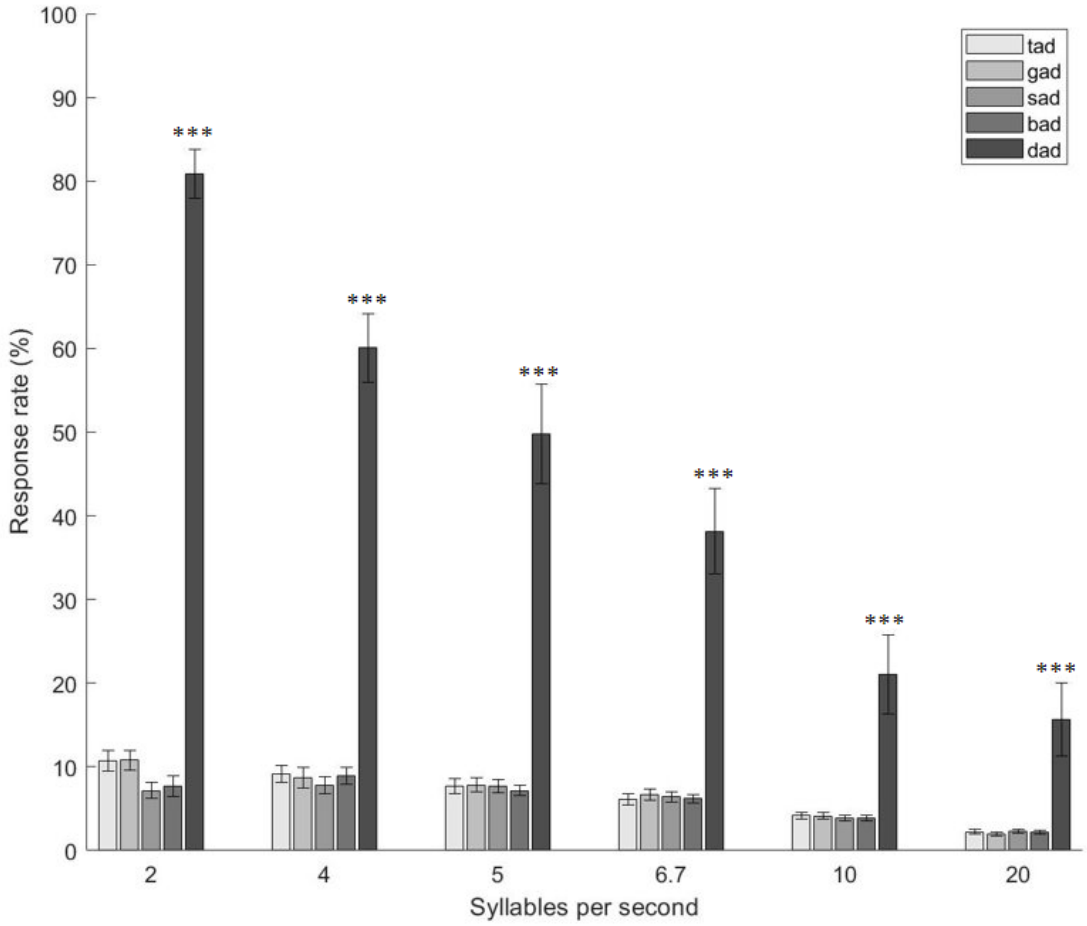

Figure 4. Response rates of 15 homozygous rats to each speech sound stimuli at increasing speeds (2-20 sps) at stage 17 of training before /bad/ is a predictor. Error bars represent ± 1 SEM. ***$p \leq .001$

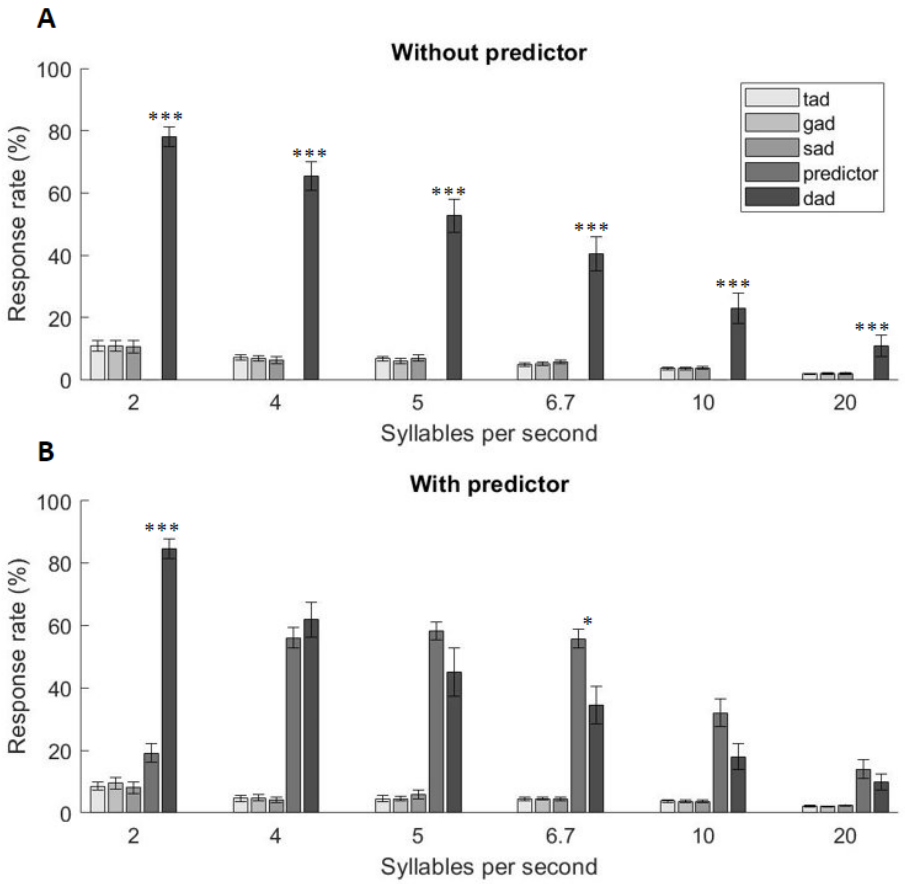

Figure 5. Wild type Sprague Dawley rats rate of responding to each speech sound stimulus (percentage) in the A) absence and B) presence of the predictor sound /bad/ at increasing speeds (2-20 sps). Error bars represent ± 1 SEM. *$p \leq .05$, **$p \leq .01$, ***$p \leq .001$

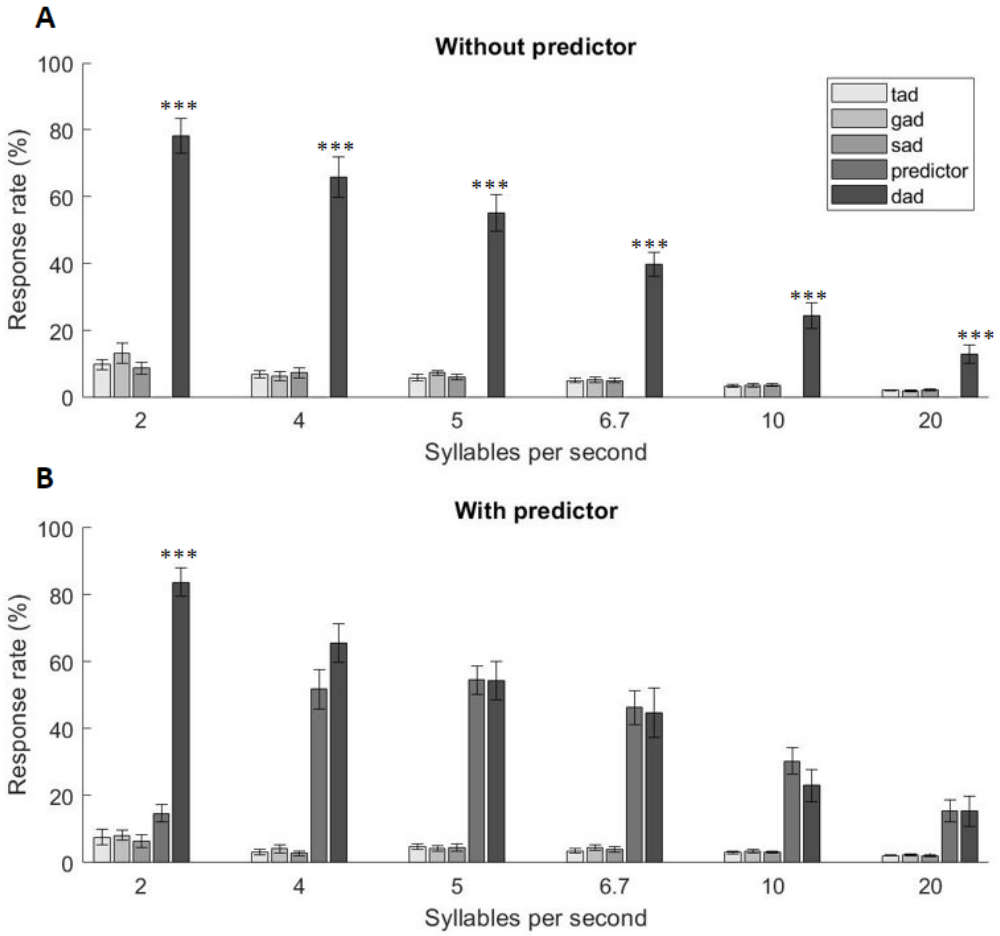

Figure 6. Heterozygous Sprague Dawley rats rate of responding to each speech sound stimulus (percentage) in the A) absence and B) presence of the predictor sound /bad/ at increasing speeds (2-20 sps). Error bars represent ± 1 SEM. *$p \leq .05$, **$p \leq .01$, ***$p \leq .001$

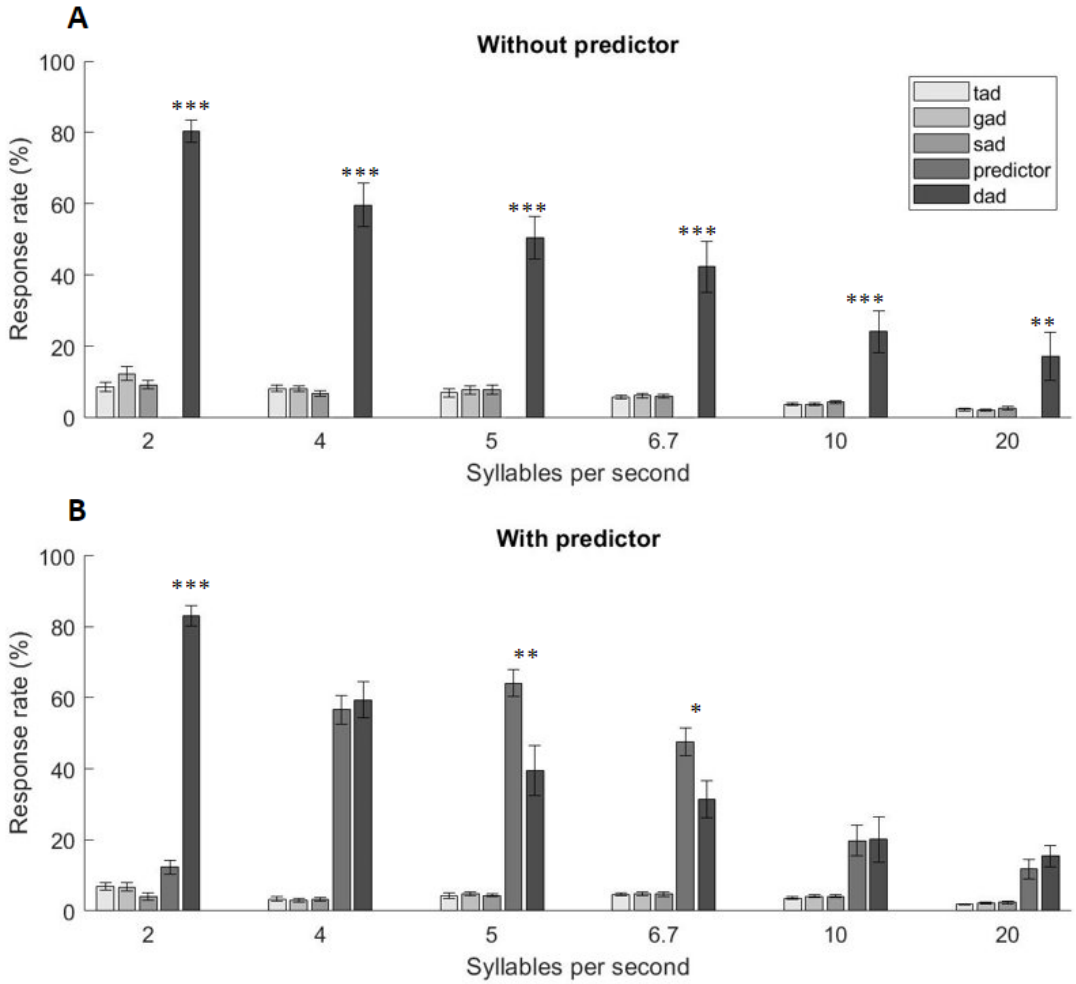

Figure 7. Homozygous Sprague Dawley rats rate of responding to each speech sound stimulus (percentage) in the A) absence and B) presence of the predictor sound /bad/ at increasing speeds (2-20 sps). Error bars represent ± 1 SEM. *$p \leq .05$, **$p \leq .01$, ***$p \leq .001$

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M., Pfeil, C., & Segal, D. (1999). The Double-Deficit Hypothesis for the Developmental Dyslexias. *Journal of Educational Psychology, 91*(3). Tunmer

VITA

Logun Presley K. Gunderson was born June 9th, 1999 to Kevin and Michele Gunderson, the younger brother of Paris and older brother of Makala. Logun graduated from D.C. Everest Senior High School in Schofield, WI in June 2017 before going on to the University of Nebraska in Lincoln, NE. There he graduated with a Bachelor of Science in Biological Sciences and Psychology in May 2021. Logun is currently attending Texas Christian University in Fort Worth, TX in the pursuit of a Master of Science in Experimental Psychology, and eventually a PhD in Experimental Psychology. Upon graduation, he plans to pursue a career in academia teaching neuroscience and researching his interests in how genetic and environmental factors influence the development of various disorders and the nervous system's immune response.

ABSTRACT

PREDICTION OF RAPID SPEECH SOUND STIMULI IN A *Dcdc2* KNOCKOUT RAT MODEL OF DYSLEXIA

By

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Developmental dyslexia is the most common neurodevelopmental disorder and is thought to be very heterogeneous, as it is associated with both genetic and environmental factors and individuals with dyslexia may have deficits in one or multiple specific sub-deficits that each result in reading impairment, such as rapid auditory processing or prediction. Variation in *DCDC2*, a gene associated with dyslexia in humans, is associated with atypical development of reading related regions, including the cerebellum. Variation in this gene is associated with rapid auditory processing deficits in both humans and rodents, though prediction deficits are also likely as the cerebellum plays a role in forming predictions. We developed a novel *Dcdc2* knockout rat model of dyslexia to determine whether variation in this gene is associated with deficits in rapid auditory processing and prediction capabilities. Using an extension of our rapid speech sound discrimination paradigm, we hypothesized that rats homozygous for the knockout would show impaired discrimination at increased speeds and an impaired ability to predict upcoming speech sounds, relative to wild-type and heterozygous rats. Counter to this hypothesis, variation in *Dcdc2* was not associated with deficits in either rapid auditory processing or prediction, likely due to uniform dysregulation of neuronal migration in this global knockout model of *Dcdc2*.