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The effects of Kiaa0319 knockdown on cortical and subcortical anatomy in male rats

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Abstract

Developmental dyslexia is a disorder characterized by a specific deficit in reading despite adequate overall intelligence and educational resources. The neurological substrate underlying these significant behavioral impairments is not known. Studies of *post mortem* brain tissue from male and female dyslexic individuals revealed focal disruptions of neuronal migration concentrated in the left hemisphere, along with aberrant symmetry of the right and left the planum temporale, and changes in cell size distribution within the medial geniculate nucleus of the thalamus (Galaburda *et al.,* 1985; Humphreys *et al.*, 1990). More recent neuroimaging studies have identified several changes in the brains of dyslexic individuals, including regional changes in gray matter, changes in white matter, and changes in patterns of functional activation. In a further effort to elucidate the etiology of dyslexia, epidemiological and genetic studies have identified several candidate dyslexia susceptibility genes. Some recent work has investigated associations between some of these genetic variants and structural changes in the brain. Variants of one candidate dyslexia susceptibility gene, *KIAA0319,* have been linked to morphological changes in the cerebellum and functional activational changes in the superior temporal sulcus (Jamadar *et al.,* 2011; Pinel *et al.,* 2012). Animal models have been used to create a knockdown of *Kiaa0319* (the rodent homolog of the human gene) via *in utero* RNA interference in order to study the gene's effects on brain development and behavior. Studies using this animal model have demonstrated that knocking down the gene leads to focal disruptions of neuronal migration in the form of ectopias and heterotopias, similar to those observed in the brains of human dyslexics. However, further changes to the structure of the brain have not been studied following this genetic disruption. The current study sought to determine the effects of embryonic *Kiaa0319* knockdown on volume of the cortex and hippocampus, as well as midsagittal area of the corpus callosum in male rats. Results demonstrate that *Kiaa0319* knockdown did not change the volume of the cortex or hippocampus, but did result in a significant reduction in the midsagittal area of the corpus callosum. Taken in the context of previous reports of behavioral deficits following *Kiaa0319*

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knockdown (Szalkowski *et al.*, 2012), and reports that reductions of corpus callosum size are related to processing deficits in humans (Paul *et al.,* 2011), these results suggest that *Kiaa0319* has a specific involvement in neural systems important for temporal processing.

Keywords

Dyslexia; KIAA0319; RNA interference; Neuronal migration; Rapid auditory processing1

1. INTRODUCTION

Developmental dyslexia is a common disorder affecting 5–10% of the population (Peterson and Pennington, 2012), and is defined as a significant impairment in reading despite adequate intelligence and educational opportunity. While dyslexia is specifically considered a disorder of reading, it is in fact characterized by a wide array of more basic behavioral impairments, including deficits in phonological processing (Kovelman *et al.* 2012; Melby-Lervag *et al.* 2012; Peyrin *et al.,* 2012), short term and/or working memory (Beneventi *et al.,* 2010; Gathercole *et al.,* 2006; Menghini *et al.,* 2010, 2011; Smith-Spark and Fisk 2007), visuospatial attention (Franceschini *et al.,* 2012; Gabrieli and Norton 2012), and rapid auditory processing (Cohen-Mimran and Sapir 2007; Fitch and Szalkowski, 2012; Hamalainen *et al.,* 2012; Vandermosten *et al.,* 2011). Deficits in these core component behaviors, or "endophenotypes" vary greatly across individuals, but are thought to summate in various combinations—possibly as a function of risk factors, including genetics—to produce a high degree of heterogeneity in this population.

Despite years of research, the etiology of dyslexia is still not fully understood. However, studies that examined the *post mortem* brains of dyslexic individuals were among the first to report potential neurological markers for the disorder. Specifically, Galaburda *et al.,* (1985) and Humphreys *et al.,* (1990) observed microscopic focal disruptions to the cortex and underlying white matter in the form of ectopic collections of cells and aberrant microgyric infolding of the cortex, predominantly in the left hemisphere perisylvian regions of the brains of male and female dyslexic individuals. Additional anomalies were observed subcortically in the lateral (Livingstone *et al.,* 1991) and medial (Galaburda and Eidelberg, 1982; Galaburda *et al.,* 1994) geniculate nucleus of the thalamus of dyslexic subjects' brains, with a shift in the distribution to more small cells and fewer large cells as compared to the control subjects' brains. This finding suggested that the mechanism(s) underlying the apparent disruptions to neuronal migration also had widespread effects on the morphology of distal brain structures. However, the relationship between these anomalies regarding causation (i.e., whether cortical anomalies induced sub-cortical changes, or whether both phenomena evidence common underlying causal factors) is not well understood. The nature of these disruptions led researchers to conclude that the disruptive mechanism causing these widespread changes had likely taken place during prenatal life, and specifically during the process of neuronal migration. More recent studies have used *in vivo* neuroimaging to examine the brains of dyslexic patients in search of neurobiological markers of the disease. Studies of independent populations of dyslexic individuals from several different countries have indicated that there are also significant, region-specific reductions in gray matter in the cortex, subcortical structures, and cerebellum of dyslexic individuals as compared to age-matched controls (Brambati *et al.,* 2004; Kronbichler *et al.,* 2008; Menghini *et al.,* 2008; Siok *et al.,* 2008). Studies of changes in the corpus callosum have yielded conflicting results. In general, there are region specific changes, with some areas exhibiting increases in size and others exhibiting decreases in size in dyslexic individuals as compared to controls (Elnakib *et al.,* 2012; Hasan *et al.,* 2012; Paul *et al.,* 2011). Changes in functional activation, with associated microstructural changes in white matter, have also been reported in some

dyslexic populations (Carter *et al.,* 2009; Hoeft *et al.,* 2011; Pugh *et al.,* 2000; Rimrodt *et al.,* 2010; Wolf *et al.,* 2010). Additionally, these gross neurological anomalies have been significantly associated with specific behavioral deficits, such as performance on tasks of phonological processing and short term memory (Fine *et al.,* 2007; Leonard *et al.,* 2001). Moreover, recent work has demonstrated that many of these observed brain changes are present in children at risk for dyslexia, even before learning to read, and so they are present from birth and do not reflect experience-dependent changes (Raschle *et al.,* 2010).

Additional advances in understanding the etiology of dyslexia have been achieved through epidemiological and genetic studies of dyslexic populations. Recent work in this field has led to the identification of several candidate dyslexia susceptibility genes (Anthoni *et al.,* 2012; Francks *et al.,* 2004; Hannula-Jouppi *et al.,* 2005; Matsson *et al.,* 2011; Meng *et al.,* 2005; Poelmans *et al.,* 2008; Scerri *et al.,* 2010; Taipale *et al.,* 2003). Some recent reports have even used *in vivo* brain imaging to draw correlations between specific variants in these CDSGs and significant changes in gross brain structure and functional activation (Jamadar *et al.,* 2011 Pinel *et al.,* 2012). One of the discovered CDSGs, *KIAA0319*, has been linked to altered functional activation patterns in superior temporal sulcus and morphological changes in the cerebellum, both known language-related areas, in the brains of both dyslexic and unaffected individuals (Jamadar *et al.,* 2011; Pinel *et al.,* 2012).

In the wake of the discovery of CDSGs for dyslexia, animal models were developed to study neuroanatomical and behavioral effects following manipulation of the homologs of these genes. Studies utilizing RNA interference to embryonically knock down genes in rats have demonstrated that the rodent homologs of a handful of these genes, including *KIAA0319,* are involved in neuronal migration (Burbridge *et al.,* 2008; Meng *et al.,* 2005; Paracchini *et al.,* 2006; Peschansky *et al.,* 2010; Rosen *et al.,* 2007; Wang *et al.,* 2006). Knocking down these genes *in utero* leads to the development of ectopic and heterotopic collections of cells in the brains of adult animals; malformations that are strikingly similar to those observed by Galaburda *et al.,* (1985) and Humphreys *et al.,* (1990) in human dyslexic brains. There have not been any reports to date of gross changes in structural size or volume in the brains of animals following knockdown of *Kiaa0319* (or any of the other CDSGs). In fact, the specific function(s) of these genes (and their protein products) in brain development and growth in animal and human populations remains elusive. Current data suggests that the Kiaa0319 protein is important for cell adhesion. The Kiaa0319 protein is characterized by a large polycystic kidney domain, which is a structure known to play a role in intracellular adhesion in other proteins (Ibraghimov-Beskrovnaya *et al.,* 2000). Additionally, high magnification observation of *Kiaa0319* shRNA transfected neurons revealed loss of association between neurons and radial glial fibers, further suggesting that the protein is necessary for adhesion (Paracchini *et al.,* 2006). A potential role for *Kiaa0319* in extracellular signaling has also been suggested based on the observation that some variants of the protein are excreted into extracellular space (Velayos-Baeza *et al.,* 2008, 2009; 2010).

The current study sought to characterize the effects of embryonic *Kiaa0319* knockdown on specific structures in the brains of adult male rats. We specifically examined the effects of this genetic disruption on volume of the cortex, volume of the hippocampus, and midsagittal area of the corpus callosum in adulthood. We have previously reported on the behavioral deficits in this sample of animals (including impairments of rapidly changing/short duration acoustic stimuli, but not working memory), and so results from the current study may provide a better understanding of the biological underpinnings of the observed behavioral profile (see Szalkowski *et al.,* 2012 for review).

2. METHODS

Prepared brain sections from a total of 50 male Sprague-Dawley (Shams, n = 11; *Kiaa0319* shRNA, n = 14) and Wistar (Shams, n = 9; *Kiaa0319* shRNA, n = 16) rats were used for the current study. The histological sections analyzed in the current study were derived from the animals used in our recent report on the behavioral effects of *Kiaa0319* knockdown (Szalkowski *et al.,* 2012). Specifically, the Wistar rats in the current study are those that underwent rapid auditory processing testing in the Szalkowski *et al.,* 2012 paper, while the Sprague Dawley rats in the current study underwent spatial working memory testing in the 8 arm radial water maze. For detailed information on the housing and behavioral testing conditions that these rats were exposed to, refer to Szalkowski *et al.,* (2012). All animals were sacrificed at postnatal day 110 (P110), and so the brain sections used in the current study were derived from adult animals. All procedures were in accordance with National Institutes of Health guidelines and were approved by the University of Connecticut Institute for Animal Care and Use Committee.

2.1 In utero electroporation

In utero electroporation surgeries for these subjects were performed in two batches on embryonic day 15 (E15), as described in Szalkowski *et al*., 2012. Surgeries were performed by C.F. at the University of Connecticut. Briefly, time-mated Sprague Dawley or Wistar dams were anesthetized with an intraperitoneal injection of Ketamine (100 mg/kg) and Xylazine (15 mg/kg). A vertical incision was made through the skin and muscle of the lower abdomen and the uterine horns were exposed. Each pup received a single injection of either the *Kiaa0319* short hairpin RNA (shRNA) solution (see below) or the sham solution (see below) into one randomly chosen lateral ventricle. Injections were made with air pressure (General Valve Picospritzer) using pulled glass capillary needles. Fluorescent proteins were used as markers of transfection, with one color used to identify *Kiaa0319* shRNA transfection and a second color used to identify sham transfection in each batch of surgeries. The fluorescent proteins were then visualized after histological preparation of brain tissue and used to classify each subject as either shRNA or sham for subsequent data analyses. *Kiaa0319* shRNA injections consisted of 1.5 μg/μL of *Kiaa0319* shRNA (pU6shRNA-*Kiaa0319*) and 0.5 μg/μL enhanced green fluorescent protein (eGFP, used in Batch 1) or 0.5 μg/μL monomeric red fluorescent protein (mRFP, used in Batch 2). Note that the specificity and effectiveness of the vector used in the current study at knocking down Kiaa0319 protein translation has previously been reported (Paracchini *et al.,* 2006; Peschansky *et al.,* 2010). Sham injections consisted of 0.5 μg/μL of mRFP (in Batch 1) or eGFP (in Batch 2) alone. Following injection into the lateral ventricle, a pair of copper alloy plates (1 × .5 cm) were placed over the injection site and delivered a 70 mV electrical pulse. The paddle positions were then reversed and a second electrical pulse was delivered, leading to bilateral transfection of cells. This created a favorable electrical environment for the shRNA plasmids and fluorescent proteins to be taken up into the nuclei of transfected cells. Roughly equal numbers of sham and *Kiaa0319* shRNA injections were made in each litter. After all pups had received an injection the uterine horns were carefully placed back in the abdominal cavity and sutures were placed. Subcutaneous injections of 0.5% Metacam (2 mg/kg) were administered to alleviate post-operative pain.

2.2 Histology

At the end of behavioral testing, all animals were weighed, deeply anesthetized with Ketamine (100 mg/kg) and Xylazine (15 mg/kg) and were transcardially perfused with 0.4 M phosphate buffered saline, followed by 4% paraformaldehyde. Heads were removed and brains were extracted and shipped to GDR for histological preparation. Brains were cryoprotected in a 30% sucrose solution before being sliced at 40 μm in the coronal plane. A

1-in-10 series was mounted onto glass slides and stained for Thionin. An adjacent series of free-floating sections was analyzed with fluorescence microscopy for the presence of GFP or RFP (Chemicon, 1:200) using ABC protocols. A third adjacent series of sections was immunohistochemically processed for GFP and RFP antibodies. Nissl stained sections were examined with light microscopy for the presence of malformations in the form of ectopias and heterotopias.

2.3 Stereological Assessment: Midsagittal area of the corpus callosum measurement

Midsagittal area of the corpus callosum was measured for each subject using the Axio 2 Zeiss microscope and Stereo Investigator (MBFBioscience, Williston, VT). Measurements were taken at 10X magnification. The corpus callosum was analyzed on systemically sampled section, beginning rostrally where the corpus callosum was first seen to cross the midline and continuing caudally until the last section where the corpus callosum crossed the midline. On each coronal section measured, a line was drawn along the dorsal-ventral axis of the brain at the midline, extending beyond the dorsal and ventral boundaries of the corpus callosum, and we then measured the dorsal-ventral length of the midline of the corpus callosum. These measurements, along with the thickness of the mounted slices, and the distance between each counted section were entered into the Cavalieri equation, which yielded an estimate of the midsagittal area of the corpus callosum for each subject (see Newbury and Rosen, 2012; Rosen and Harry, 1990 for details).

2.4 Stereological Assessment: Cortical and hippocampal volume measurement

Volumes of the cerebral cortex and hippocampus were measured under 2.5X magnification on an Axio 2 Zeiss Microscope using Stereo Investigator software. The Cavalieri Estimator probe was used to overlay a grid of 600 μm × 600 μm on each section, and all points of intersection on the grid within the boundaries of the region of interest are counted.. Volume estimates for right and left cortex and hippocampus were calculated separately using Cavalieri's rule. An average of 10 sections each was counted for the cortex and hippocampus for each subject using the boundaries of Paxinos and Watson (2007). Specifically, all regions dorsal to the rhinal fissure were included in the cortex measurements, including areas extending up and onto the medial surface. The hippocampal measurements included the subiculum, dentate gyrus, CA1, CA2, and CA3.

2.5 Data analyses

Average midsagittal area of the corpus callosum, volume of the cortex, and volume of the hippocampus were compared for Strains (Wistar and Sprague Dawley) and Treatment (*Kiaa0319* shRNA and sham). Left and right cortex and hippocampus volumes (Hemisphere) were also compared within-subjects. All statistical analyses were performed using IBM SPSS Standard Statistics Package v. 19.0. All reported *P* values are two-tailed unless otherwise stated.

3. RESULTS

3.1 Body weight in Kiaa0319 shRNA and sham Wistar and Sprague Dawley subjects

Adult body weight was analyzed as a function of Strain and Treatment to ensure that any structural brain size differences found were not solely, or partly, reflections of overall differences in size or development (Table 1). A univariate ANOVA (Strain (2 levels) × Treatment (2 levels) revealed a significant Strain effect [$F(1,44) = 102.5$, $P < .01$]. There was not a significant Treatment effect, nor a Treatment × Strain interaction [$F(1,44) < 1$, NS for both effects]. The Strain effect reflects the fact that Wistar rats, across Treatment groups, were smaller than Sprague Dawley rats.

3.2 Midsagittal area of the corpus callosum in Kiaa0319 shRNA and sham subjects

A univariate analysis of variance (ANOVA) (Strain (2 levels) × Treatment (2 levels)) revealed a significant main effect of Strain [$F(1,46) = 10.8$, $P < .01$], and also a significant main effect of Treatment [$F(1,46) = 4.3$, $P < .05$ on midsagittal corpus callosum area (see Table 1). There was not a significant Strain × Treatment interaction [$F(1,46) < 1$, NS]. The main effect of Strain is reflective of the fact that Wistar rats were observed to have a larger midsagittal area of the corpus callosum than Sprague Dawley rats, across Treatment groups. Importantly, the main effect of Treatment indicates that, across Strain, *Kiaa0319* shRNA animals had a significantly smaller midsagittal area of the corpus callosum as compared to sham counterparts. The lack of a Strain × Treatment interaction tells us that the observed significant Treatment effects were also independent of the observed body size differences between Wistar and Sprague Dawley rats. (Note that an analysis of covariance with body weight as a covariate revealed that this variable did not significantly influence midsagittal area of corpus callosum [$F(1,42) = 1.7$, NS], and the Treatment effect remained significant [$F(1,42) = 4.927$, $P < .05$]). Because clinical data suggests that reductions in corpus callosum volume are relevant to impairments in reading and phonological processing in dyslexic individuals (Fine *et al.,* 2007; Paul *et al.,* 2011), we performed a bivariate correlation on the midsagittal area of the corpus callosum and performance scores from a rapid auditory processing test that had been used on all subjects in adulthood (mean attenuation scores on FM Sweep 125 ms task, see Szalkowski *et al.*, 2012 for further details). There was not a significant correlation between this measure of auditory performance and mean midsagittal corpus callosum area in sham [r = .30, NS] or *Kiaa0319* shRNA treated animals [r = −.16, NS].

3.3 Volume of the cortex in Kiaa0319 shRNA and sham subjects

A 2 between (Strain and Treatment) one within (Hemisphere) ANOVA was used to compare right and left cortex volume in *Kiaa0319* shRNA and sham treated Wistar and Sprague Dawley rats (see Figure 1). There was not a significant main effect of Hemisphere, Strain, nor Treatment [$F(1,44) < 1$, NS in all cases], nor were there significant interactions among these independent variables [$F(1,31) < 2$, NS for all effects]. These results indicate that there were no differences in cortical volume in *Kiaa0319* shRNA and sham subjects.

3.4 Volume of the hippocampus in Kiaa0319 shRNA and sham subjects

A 2 between (Strain and Treatment) one within (Hemisphere) was used to compare right and left hippocampus volume in *Kiaa0319* shRNA and sham treated Wistar and Sprague Dawley rats (see Figure 1). There was a significant main effect of Strain [$F(1,31) = 36.2$, $P < .001$]—Wistar animals have significantly larger hippocampal volumes than Sprague Dawley animals, across Treatment groups.. There were no significant main effects of Hemisphere or Treatment [$F(1,31) < 2$, NS for both effects], nor were there significant interactions among the independent variables [$F(1,31) < 2$, NS for all effects]. This indicates that there were no significant differences in hippocampal volume between *Kiaa0319* shRNA and sham subjects.

4. DISCUSSION

We find a significant reduction in midsagittal area of the corpus callosum in *Kiaa0319* shRNA transfected rats as compared to shams. General reductions in the midsagittal area of the corpus callosum are known to be associated with phonological processing deficits in human dyslexics. However, we did not find a significant correlation between this anatomical measure and rapid auditory processing abilities in *Kiaa0319* shRNA or sham animals. Finally, *Kiaa0319* knockdown did not affect volume of the cortex and hippocampus in this study.

4.1 Cortical dysgenesis and morphological changes in the brain: animal models

Studies have examined the impact of cortical dysgenesis on widespread changes to brain structure using other animal models of developmental brain disruption. Our lab has previously reported that whole brain volume, and specifically neocortical volume, are reduced in rats following induction of a microgyric lesion via a focal freezing probe on P1 (Peiffer *et al.,* 2003). An additional study from our lab demonstrated significant reductions in the volume of neocortex, corpus callosum, and hippocampus in a teratogenic model of nodular heterotopia in rats (Threlkeld *et al.,* 2009). A study that looked at differences in the midsagittal area of the corpus callosum and neocortical volume in strains of mice with spontaneously-occurring ectopias did not find any differences between mice with and without ectopias in these morphological measures (Rosen *et al.,* 1990). Taken together with the current results, these data suggest that the observed changes in the corpus callosum are not simply part of a generic cascade of reorganization that occurs following any disruption to neuronal migration. Instead it seems likely that the observed pattern of pathological brain changes in the *Kiaa0319* knockdown animals is due to specific effects of the genetic manipulation and not just to the resulting cortical dysgenesis.

4.2 Structural brain changes in developmental dyslexia

Several structural neural anomalies have been reported in dyslexic individuals. On a more general level, region-specific gray matter reductions are a consistent finding in language-impaired populations, with unilateral and bilateral volume reductions often reported in language-related cortical regions such as the superior temporal gyrus, fusiform gyrus, cerebellum, and planum temporale (Brambati *et al.,* 2004; Kronbichler *et al.,* 2008; Menghini *et al.,* 2008; Siok *et al.,* 2008; also see Sun *et al.,* 2010 for a complete review). Changes in white matter have also been reported in dyslexic individuals (Carter *et al.,* 2009; Elnakib *et al.,* 2012; Hasan *et al.,* 2012; Hoeft *et al.,* 2011; Paul *et al.,* 2011; Pugh *et al.,* 2000; Rimrodt *et al.,* 2010; Wolf *et al.,* 2010; see Vandermosten *et al.,* 2012 for a complete review). Region specific differences in the corpus callosum of dyslexics have been reported, but there is a great deal of variability in the findings across different studies. For example, increases in size have been reported in posterior aspects of the callosum, while decreases have been reported in anterior and middle aspects (Duara *et al.,* 1991; Hasan *et al.,* 2012; Kilian *et al.,* 2008; Rumsey *et al.*, 1996). Studies have also reported decreases in the area of the midbody of the corpus callosum in dyslexic individuals (Fine *et al.,* 2007). It has been suggested that this reduction in callosal midbody size has been linked to deficits in temporal processing (Aboitiz *et al.,* 1992; Fine *et al.,* 2007; Paul *et al.,* 2011). This is interesting given our current findings suggesting that *Kiaa0319* knockdown led to a reduction in callosal size in rats, and moreover in rats that had demonstrated specific deficits in rapid auditory processing (although we did not find these measures to be correlated).

The relatively small reduction in callosal size observed following *Kiaa0319* knockdown in the current study parallels the subtle changes to the callosum in clinical language impaired populations. In fact, as discussed above, changes in callosal size are typically apparent in specific subregions and not in measures of the total rostral-caudal area of the corpus callosum. Despite their subtlety, these small changes in callosal size are associated with impaired interhemispheric conduction and a range of sensory and cognitive impairments (see Paul *et al.,* 2011 for review). Thus, in spite of the lack of a significant correlation between midsagittal area of the corpus callosum and rapid auditory processing abilities in the current study, it is likely that the observed changes in callosal size are functionally significant. The lack of a correlation between the midsagittal area of the corpus callosum and the rapid auditory processing data from the animals in the current study may be explained several ways. First, it is possible that the overall reduction in callosal size observed here is the result of a large reduction in one particular area of the callosum that

may correlate more closely with sensory processing measures. It would be interesting to repeat this analysis using brain sections cut in the sagittal plane, which would enable us to analyze changes in callosal size by subregion. It is also worth noting that the correlation only compared RAP scores and callosal area in 16 animals that had experienced the *Kiaa0319* knockdown. It is possible that a correlation may become apparent with a larger sample size. Similarly, a correlation between auditory processing abilities and midsagittal area of the corpus callosum may become apparent following a greater reduction in callosal size. The degree of *Kiaa0319* knockdown achieved following electroporation may have influenced the degree of reduction of the midsagittal area of the corpus callosum, and it would be interesting to repeat this analysis in animals following a "larger" knockdown (perhaps via bilateral instead of unilateral injections of shRNA plasmids), or in a mouse model using a total genetic knockout. Moreover, we cannot verify whether or not genetic compensation may have dampened the effects of the *Kiaa0319* knockdown on callosal size; this would be a more likely scenario in a knockout model in which the gene/protein is absent from all cells throughout all of development, as opposed to the RNAi model that knocks down levels of the protein by affecting translation in a restricted subset of cells at a specific developmental time point. Finally, it is possible that this reduction in callosal size would correlate better with different tasks of auditory processing than with the task we tested our animals on (short frequency modulated (FM) sweep detection). Further studies are needed to explore the relationship between this genetically-mediated callosal size reduction and a broader range of auditory processing abilities, as well as abilities in other sensory and cognitive domains. Given human behavioral data showing that *KIAA0319* variants are specifically linked to deficits in phonological processing, along with animal work showing that *Kiaa0319* knockdown leads to temporal auditory processing deficits, and anatomical data suggesting that *Kiaa0319* knockdown results in reduced callosal size—which is related to temporal processing deficits in humans—it seems possible that *KIAA0319* may impact behavior at least in part through anatomical changes to the corpus callosum.

It is worth noting that anatomical findings are not consistent across all studies of dyslexic individuals, and in fact some studies have reported the opposite (that dyslexic individuals have region-specific increases in cortical volume as compared to controls) (Vinckenbosch *et al.,* 2005). The majority of papers reporting size differences in brain regions in dyslexic and control individuals use heterogeneous populations of dyslexics that are often recruited based on categorical diagnosis alone. Thus, it is difficult to say whether or not these anatomical findings would be present in every sub-population of dyslexic individuals. It seems possible that, like behavioral expression of the disorder, the neuroanatomical substrate of dyslexia may vary from one individual or sub-population to the next. It also seems plausible that different candidate dyslexia susceptibility genes may contribute uniquely to the patterns of disruptions of neuroanatomy in dyslexic individuals. For example, it is possible that reductions in cortical volume would not be detected in a population of dyslexics selected based on having a particular *KIAA0319* variant. It is even possible that different variants of the same gene may influence brain morphology differently, depending on the functional implication of the mutation. Further clinical neuroimaging studies using samples selected based on genotype will be necessary to address these issues.

4.3 The impact of KIAA0319 variants on human brain morphology and function

In the clinical literature, there are few reports detailing putative associations between variants in specific candidate dyslexia susceptibility genes and morphological changes in the brain. However, one recent study of a population of undiagnosed (i.e., not dyslexic) French adults demonstrated that a genomic region containing a variant of *KIAA0319*—a region found to be associated with dyslexia—significantly correlated with reduced functional symmetry in the superior temporal sulcus during a speech listening task (Pinel *et al.*, 2012).

This led the authors to hypothesize that *KIAA0319* may play a role in cortical lateralization of phonological processing abilities in both typical and impaired populations. Given that functional asymmetry in the superior temporal sulcus is present at birth in humans, it also seems possible that any effects of *KIAA0319* on the functional neuroanatomy of this region would be established early in development. Moreover, based on the superior temporal sulcus' known role in language, these neuroanatomic findings are complementary to other reports detailing the influence of *KIAA0319* variants on language-related behavioral traits in both dyslexic and control populations (Paracchini *et al.,* 2008; Scerri *et al.,* 2011).

Jamadar and colleagues reported on another clinical study that has investigated the relationship between specific *KIAA0319* variants and brain morphology. In their sample of control and schizophrenic patients, they found significant associations between dyslexia-related *KIAA0319* variants and gray matter volume in the inferior cerebellum, but not in the cortex, in both controls and schizophrenic individuals (2011). Specifically, a negative correlation was detected between the *KIAA0319* variant and cerebellar networks, suggesting that the genetic variant was related to reductions in cerebellar size. This is an interesting finding given the cerebellum's putative role in dyslexia, and reports of cerebellar structural abnormalities in dyslexic individuals (Stoodley and Stein, 2011). The latter supports the view that *KIAA0319* variants may differentially influence the structure of language-related regions in the brain.

5. CONCLUSIONS

We report novel findings of reduced midsagittal area of the corpus callosum in adult male rats following embryonic knockdown of *Kiaa0319*. The specific effects on the corpus callosum in the absence of volumetric anomalies the neocortex or hippocampus—which is in contrast to observations from other animal models of developmental brain disruption—suggest that this change may be due to specific genetic effects rather than a "side effect" or epiphenomena of disruption to neuronal migration. *Kiaa0319* knockdown has also been shown to specifically influence rapid auditory processing abilities in rats, which is interesting given clinical literature that suggests that reduced corpus callosum size is related to deficits in acoustic temporal processing. The neurological phenotype associated with *KIAA0319* variants in humans remains unclear, although preliminary evidence suggests that they are associated with changes in language-related brain structures. Further studies examining associations between brain morphology and CDSG variants are needed, and future work in our lab will continue to characterize the effects of knocking down other rodent homologs of CDSGs on rodent brain structure.

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Highlights

- We replicate reports that interference with *Kiaa0319* disrupts neuronal migration in rodents.
- *Kiaa0319* interference leads specific reductions in midsagittal area of the corpus callosum.
- *Kiaa0319* interference did not lead to changes in the size of the cortex of hippocampus.

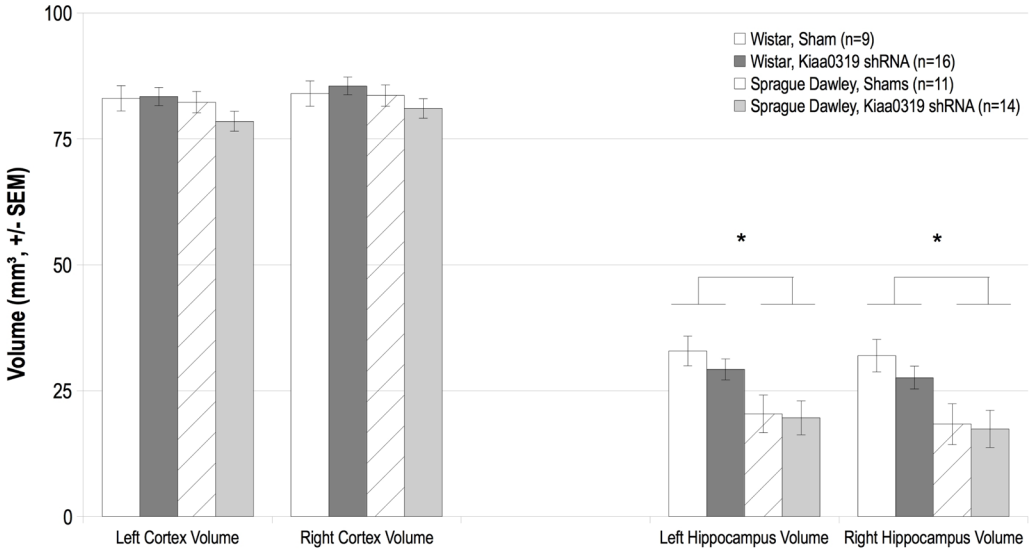

Figure 1.

Volume measurements from right and left cortex and hippocampus of Sprague and Wistar rats. There were no significant effects of Treatment, Strain, or Hemisphere, (nor any significant interactions) on cortex volume. There was a significant main effect of Strain on hippocampal volume, demonstrating that Wistar rats—across Treatment groups—had larger hippocampi than Sprague counterparts. However, the *Kiaa0319* shRNA treatment was not found to have an impact on hippocampal volume.

Table 1

Average adult body weight and Midsagittal Area of Corpus Callosum

	Average body weight (g)	Midsagittal Area of Corpus Callosum (mm^2)
Wistar Shams (n=9)	448 (23.2)	1.49 (.07)
Wistar *Kiaa0319* shRNA (n=16)	483.1 (17.5)	1.40 (.05)
Sprague Dawley Shams (n=11)	653.3 (18.9)	1.35 (.06)
Sprague Dawley *Kiaa0319* shRNA (n=14)	671.1 (17.5)	1.26 (.05)

* (Average body weight)

* (Midsagittal Area of Corpus Callosum)

Average weights and midsagittal area of corpus callosum, +/− SEM. For average body weight,

* indicates significant Strain effect (P < .01), with Sprague Dawley animals significantly larger than Wistar animals, across Treatment groups. There was an overall main effect of Treatment on Midsagittal area of corpus callosum, with Kiaa0319 shRNA animals having significantly (*, P < .05) smaller callosa than shams.