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# Neural Noise Hypothesis of Developmental Dyslexia

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**Developmental dyslexia (decoding-based reading disorder; RD) is a complex trait with multifactorial origins at the genetic, neural, and cognitive levels. There is evidence that low-level sensory-processing deficits precede and underlie phonological problems, which are one of the best-documented aspects of RD. RD is also associated with impairments in integrating visual symbols with their corresponding speech sounds. Although causal relationships between sensory processing, print–speech integration, and fluent reading, and their neural bases are debated, these processes all require precise timing mechanisms across distributed brain networks. Neural excitability and neural noise are fundamental to these timing mechanisms. Here, we propose that neural noise stemming from increased neural excitability in cortical networks implicated in reading is one key distal contributor to RD.**

## Premise of the Neural Noise Hypothesis

Developmental dyslexia (specific reading disabilities/disorders, or decoding-based RD) is a neurodevelopmental disorder contributed to by multiple genetic, neural, and cognitive factors [1], yet neurobiological models that account for the diversity of RD phenotypes remain elusive. An increasing number of studies have investigated the function of RD risk genes in animal models [2–13], and the neurobiological and behavioral consequences of genetic RD risk variants in humans [14–31], motivating the need for a synthesis of these findings, especially because they relate to emerging avenues of human research on the role of neurochemistry [32] and neural oscillations [33–36] in RD. Here, we present a timely integration of diverse lines of current research linking some of the key neural and behavioral deficits associated with RD to basic neural processes.

A variety of neurobiological contributors to RD have been proposed, ranging from disrupted structural and functional connectivity [37,38] to atypical neural migration [39]. Recent work has investigated the neural dynamics that support language and sensory processing [40–42] and how these dynamics may be altered in RD [36,43]. We integrate these emerging lines of research to propose that excess neural noise (Box 1) within cortical regions implicated in reading may be a distal contributor to RD. We suggest that multifactorial sources of neural noise, for example arising from neural hyperexcitability related to RD risk genes, disrupt two key processes important for reading [**phonological awareness** [44] (see Glossary) and **multisensory integration** of visual symbols with their corresponding speech sounds [45,46]] through the impact of excess noise on neural synchrony and sensory representations (Figure 1). The neural noise hypothesis of RD synthesizes a range of neurobiological findings, providing a mechanistic framework for understanding the deficits observed in RD and identifying targets for systems-level intervention. While the potential for noisy processing in RD has been previously considered at the levels of perceptual processes [47,48], phenomenological computational models [49,50], and subcortical neurophysiology [51], we present a novel neural hypothesis

### Trends

Increasing evidence from animal work suggests that reading-related risk genes affect cortical excitability and neural noise.

Oscillatory models of sensory processing indicate a close link between the regulation of excitation–inhibition cycles and stimulus encoding.

We propose neural noise as a distal mechanism in RD that can account for deficits in phonological processing and establishing multisensory grapheme–phoneme mappings through its effects on neural timing.

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### Box 1. Neural Noise

Broadly defined, 'neural noise' refers to sources of random variability in the firing activity of neural networks and membrane voltage of single neurons. Noise can originate from multiple sources, such as physical fluctuations in the function of ion channels and the release of neurotransmitters into the synapse, or synaptic activity from other neurons, mediated by network connectivity. Operationally, neural noise can be considered as stochastic variability in the neural response to repeated presentations of the same stimulus (as opposed to nonstochastic response variability, such as adaptation effects). For example, we consider a neuron that spikes at widely variable intervals in response to a repeated stimulus presentation to be nosier than one that spikes at nearly the same time following each presentation.

Neural noise, particularly that mediated by the activity of other neurons, is closely linked to neural excitability and the balance of excitatory and inhibitory activity within a neural network. Local excitatory neural activity produces feedback neural inhibition, through excitatory synaptic connections with inhibitory interneurons, which in turn synapse onto the original pyramidal cells (Figure 2A, main text). This produces a rapid rise in inhibitory synaptic conductance that is time-locked to the initial stimulus-dependent rise in excitation, producing a narrow time window for neural firing and enabling temporally precise and synchronized neural responses [110]. Dysregulation of the excitation–inhibition balance can lead to neural noise, reflected in increased variability in neural firing and a loss of spike timing precision (Figure 2B,C, main text).

Neural information processing may be optimal with respect to cognitive processing within a range of moderate noise. While we focus on the detrimental effects of excess neural noise, some level of neural noise can facilitate information transfer through stochastic resonance. Stochastic resonance occurs when weak periodic inputs combine with noise to trigger neuronal firing that is synchronized with the input. In the absence of noise, such weak inputs would normally be below the threshold for inducing neural activity and would be not be retransmitted through the brain, effectively increasing the signal:noise ratio of neural processing [113]. By contrast, when a neuron is close to or above the firing threshold, neural noise will lead to spontaneous neural activity that can reduce synchronization between neural activity within a network and external inputs. The neural noise hypothesis of RD is an attempt to account for some features of RD in terms of this noise-related loss of synchronization.

that grounds noisy processing in a neurobiological framework from genetics to behavioral phenotypes. We highlight potential sources of neural noise in RD, the potential impact of neural noise on sensory processing as it relates to phonological processing and reading, and how different regional sources of neural noise may produce deficits that can be relatively specific to reading and its subcomponent processes.

## Potential Sources of Neural Noise in RD

RD has a partially genetic basis [52] and is associated with neural anomalies that appear before formal literacy instruction [53]. These anomalous regions in temporoparietal and occipitotemporal cortices also show high expression of RD risk genes [28], although these genes are also expressed elsewhere in the brain. Several genetic risk variants have been associated with RD, with an average allele frequency of 0.28 in a US RD population [28]. In a German population, short *DCDC2* deletions were found in 18% of individuals with RD versus 9% of controls [30]. The moderate to high heritability of RD suggests that other, unidentified, genes are also involved in RD. Much of the research in humans and animal systems has focused on two RD risk genes: *KIAA0319* and *DCDC2*.

Severe disruptions, using gene-knockout or -knockdown techniques, to the rodent homologs of these two genes have been associated with abnormal neural migration in rodents. In humans, polymorphisms and small deletions in these RD risk genes have been associated with macroscopic changes in cortical structure [22,27] and functional activation [17,20] in analogous regions within the human reading network, and reading-related behavioral impairments in multiple languages [16,19,21,26,54]. Animal models inform speculation into the origins of RD, although there is a substantial gap between animal models and the effects of common allelic variants in the human brain. RD risk genes suggest two pathways (enhanced **glutamatergic** signaling and disrupted neural migration) to increased neural noise. Each of these pathways may increase neural noise by creating a state of neural hyperexcitability, in which the normal balance of neural excitation and inhibition is shifted. Balanced levels of

### Glossary

**Comorbidity:** the presence of multiple conditions, disorders, or symptoms within an individual, for example ADHD and RD. Highly frequent comorbidity may be evidence in favor of common origins.
**Functional connectivity:** the exchange of information between brain regions. Measures such as temporally correlated BOLD fluctuations and phase-locked EEG signals are often taken as evidence for functional connectivity in the human brain.
**Gamma aminobutyric acid (GABA):** the principal inhibitory neurotransmitter, released by interneurons.
**Glutamate:** the principal excitatory neurotransmitter, released by pyramidal cells.
**Homologous genes:** genes having common ancestry. Homologous genes may share large portions of their genetic sequence across species and serve similar functions.
**Magnetic resonance spectroscopy (MRS):** a technique that uses a conventional magnetic resonance imaging machine to measure the concentration of selected molecules *in vivo*. Notably, GABA and glutamate are visible in MRS.
**Multisensory integration:** the process through which sensory information from multiple modalities (e.g., visual and auditory) is integrated into a coherent representation. Multisensory integration is frequently associated with crossmodal interactions, in which the neural response to a stimulus in one modality is affected by a stimulus in another modality, depending on the timing and congruency of the stimuli.
***N*-methyl D-aspartate (NMDA):** a glutamate receptor that is particularly important in synaptic plasticity.
**Phase-locking:** occurs when a periodic signal, for example rhythmic neural activity, reaches the same point each time a second periodic signal, for example the speech envelope, reaches a given point.
**Phonological awareness:** the knowledge of the sound structure of words, including phonemes, syllables, and onset/rime structure, and ability to manipulate these units.
**Speech envelope:** the amplitude of the speech signal, changes in which

excitation and inhibition within cortical pyramidal-interneuron networks are important for the developmental tuning of cortex to sensory input, maintaining neural timing, and information processing [55] (Figure 2A). Hyperexcitability in these local networks can disrupt the excitation–inhibition balance and the precise timing of neural activity. Although neural noise can arise from multiple sources, we focus on cortical hyperexcitability as a plausible source of noise in RD. We review evidence for neural noise stemming from these two genetically mediated pathways in RD as examples of multiple noise sources in RD, and discuss the downstream consequences of increased neural noise as it relates to key reading-related processes.

provide syllabic, stress, and prosodic cues important for speech intelligibility and neural entrainment to the speech signal.

**Transcranial direct current stimulation (tDCS):** a non-invasive method of modulating cortical excitability over large regions by applying a weak electrical current to the scalp.

**Transcranial magnetic stimulation (TMS):** a non-invasive method of inducing and modulating cortical activity using a focal magnetic field. TMS can be used to both increase and decrease cortical excitability, depending on the stimulation parameters.

### Glutamatergic Signaling

Evidence that DCDC2 modifies neural activity within the excitatory glutamatergic pathway implicates increased neural excitability as a source of neural noise in RD. Mice with reduced or disabled function of the **homologous** *Dcdc2* gene have increased release of glutamate, expression of glutamate [***N*-methyl-D-aspartate** (NMDA)] receptor genes, NMDA excitability and spontaneous activity, and spike timing variability [5,56] in cortical neurons. These phenotypes can be rescued using NMDA antagonists [5]. Other *Dcdc2* animal models show impaired rapid auditory processing [3,8], similar to the deficits found in children at risk for RD [57]. These auditory deficits may be partially accounted for by the increase in glutamatergic excitability associated with the loss of *Dcdc2* function. As shown schematically in Figure 2B, increased glutamatergic activity disrupts the excitation–inhibition balance of cortical neurons, decreasing the precision of spike timing and increasing neural noise. Another RD risk gene homolog, *Kiaa0319*, has also been associated with greater trial-by-trial firing rate variability in response to speech and nonspeech sounds and with increased neural excitability in primary auditory cortex [10].

These models are complemented by human studies of neurochemistry and brain stimulation. Excitatory left hemisphere **transcranial direct current stimulation** (tDCS) has been shown to impair rapid auditory processing [58], consistent with a link between hyperexcitability and impairments in the prerequisite analysis of rapidly changing auditory stimuli needed for phonological processing [59]. However, excitatory tDCS [60] and **transcranial magnetic stimulation** (TMS) [61,62] over temporoparietal regions have also been found to improve reading skills, indicating a high degree of inconsistency in past findings. Even within studies, there are inconsistencies; for example, excitatory left temporoparietal tDCS was found to improve only speeded real-word reading, but not reading accuracy or nonword reading [60]. By contrast, excitatory TMS over either the right or left temporoparietal regions [including superior temporal gyrus (STG) and inferior parietal lobule (IPL)] yielded improvements only in nonword reading accuracy, but not real-word reading or speed in both typical adults and those with RD [61,62]. These studies suggest that modulating cortical excitability has consequences for reading. However, it is currently unclear which aspects of reading these techniques affect. These studies also provide conflicting evidence in terms of whether RD might be associated with high (as predicted by our hypothesis) or low excitability.

Studies of endogenous neurochemistry in humans also point towards increased excitability. A recent study reported increased levels of glutamate in RD, measured from occipital visual cortex using **magnetic resonance spectroscopy** (MRS), and an overall negative association between children's reading skill and glutamate [32]. Although MRS measurements of glutamate do not allow inference about a neural mechanism for increased excitability, MRS glutamate concentrations are positively correlated with cortical excitability [63]. More generally, left-lateralized expression of genes associated with glutamatergic function has been found within the STG and auditory cortex [64], suggestive of a relationship between glutamatergic signaling and lateralized auditory processing, which is thought to be significant in language processing [65]. Collectively, these studies suggest hyperexcitability in RD due to enhanced glutamatergic signaling as a source of deficits in rapid auditory processing and reading.

## Key Figure

### The Neural Noise Hypothesis

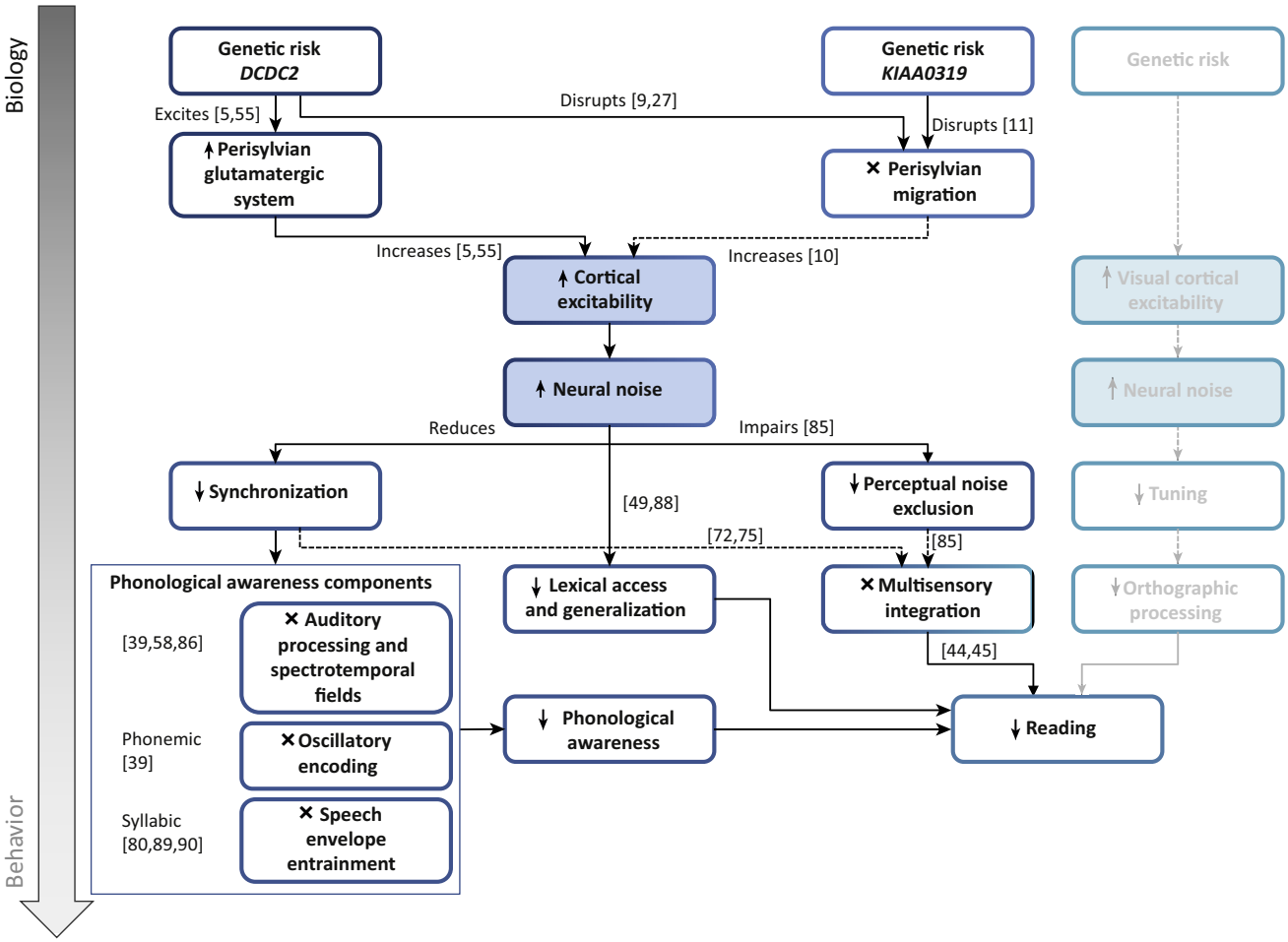


Figure 1. Schematic of the neural noise hypothesis, illustrated through two genetic pathways known to affect neural noise within the domain of auditory processing and their downstream consequences on reading. Some genetic risk factors, such as *DCDC2* mutations, increase neural noise through a direct effect on glutamatergic signaling and hyperexcitability. *DCDC2* and other genetic risk factors, such as *KIAA0319* mutations, may disrupt neural migration and the formation of local excitatory–inhibitory circuits, thereby increasing neural noise. There are likely other risk genes that act through similar pathways. Excess neural noise disrupts neural synchronization across multiple scales, leading to deficits in low-level temporal auditory processing, and the oscillatory neural processes that sample and encode sensory information. Loss of synchronization and precise neural spike timing also impairs multisensory integration. Ultimately, the downstream effects of neural noise may lead to impairments in phonological awareness and multisensory integration, two key components of reading development. Although we focus our discussion on the consequences of neural noise in the auditory domain, similar consequences are predicted in the visual domain, ultimately impacting orthographic processing and reading. This speculative pathway is shown on the right. Dashed arrows reflect more speculative links in need of further study. Processes in light text are not discussed in detail in the main text. Numbers by arrows refer to supporting references in the main text ([5,9,10,11,27,39,44,45,49,55,58,72,75,80,82,84,85,86,88,89,90]).

### Disrupted Neural Migration

A second source of hyperexcitability-related neural noise may arise from interactions between neurons. Local cortical circuits are networks of excitatory pyramidal neurons and inhibitory interneurons, and both excitatory and inhibitory synaptic connections are needed to maintain

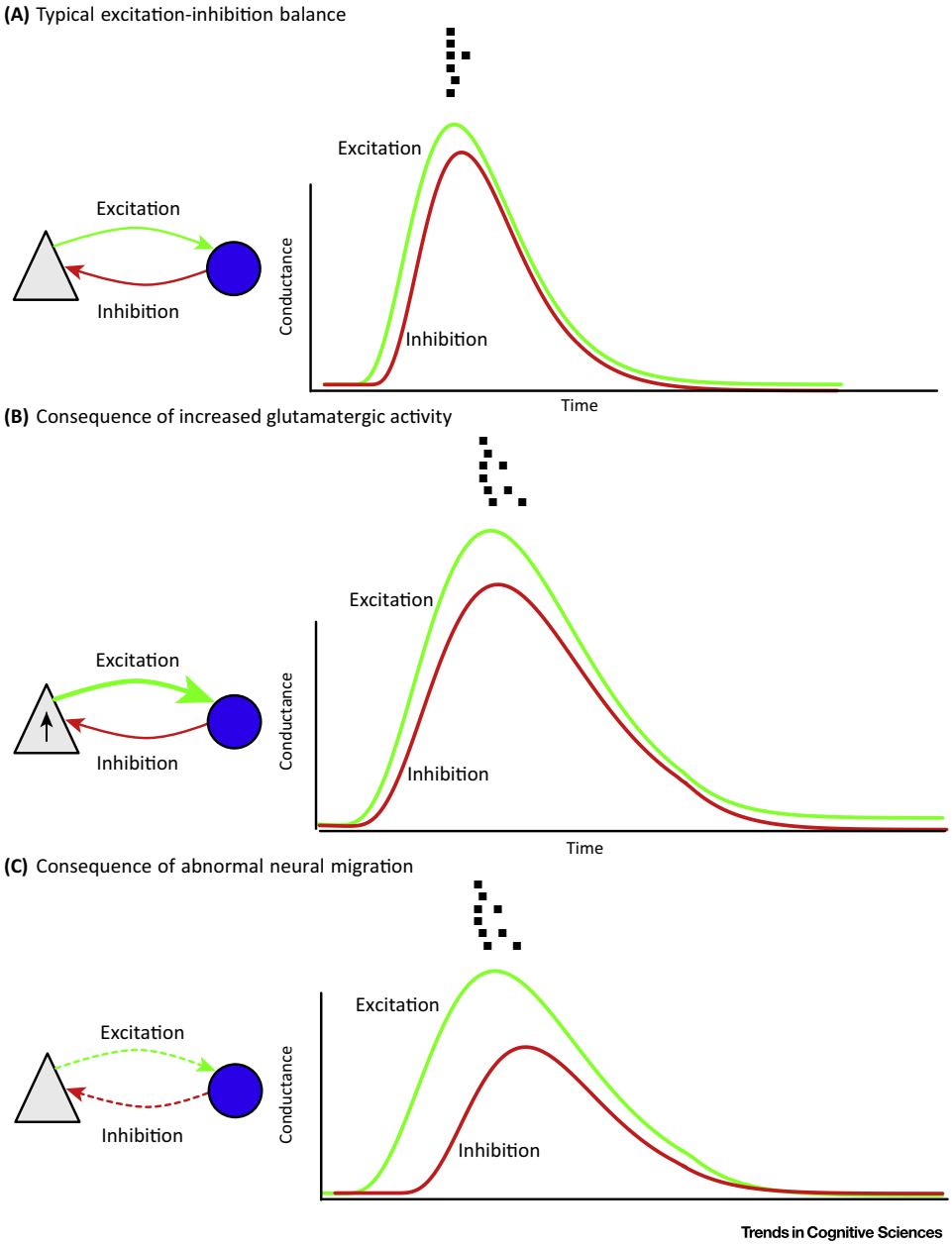


Figure 2. Possible Mechanisms of Neural Noise in Reading Disorder (RD). Schematic illustration of a excitation–inhibition imbalance within a local network of excitatory pyramidal cells (gray triangles) projecting to (green arrow) inhibitory GABAergic interneurons (blue circles) with feedback inhibition (red arrow). Corresponding trial-by-trial spiking activity are shown above the curves that indicate conductances. (A) Typical excitation–inhibition balance. In a balanced excitation–inhibition regimen, stimuli evoke excitatory synaptic conductances (green curve) followed by comparable inhibitory conductances (red curve) within a few milliseconds. Together, these conductances regulate spike activity to produce neural activity that is precisely timed with respect to the input. (B) Consequence of increased glutamatergic activity. Animal models suggest that RD risk genes modulate excitatory postsynaptic activity (thick green arrow), which may result in greater and more temporally extended increases in excitatory conductances and reduced spike-timing precision, in the absence of compensatory increases in feedback inhibition to restore excitation–inhibition balance. (C) Consequence of abnormal neural migration. RD risk genes have also been linked to disrupted neural migration and dendritic spine formation on pyramidal cells. One possible consequence of this is disrupted feedback connectivity (dashed arrows) between GABAergic interneurons and pyramidal cells, reducing feedback inhibition available to dampen neural activity and again producing temporally extended responses. Based on [110]. See also Box 1 (main text).

the excitation–inhibition balance. Thus, the synaptic structure of a cortical microcircuit is an important determinant of its noise characteristics, and disruptions to the development of typical interconnections may have consequences for neuronal excitability and noise (Figure 2C). Animal research suggests that RD risk genes have a role in neural migration processes, and that mutant versions of these genes produce abnormal cortical structure and synaptic connectivity. For example, *Dcdc2* has been linked to the abnormal migration of pyramidal neurons [28] and reduced dendrite growth, although *Dcdc2* mutations alone may not be sufficient to produce abnormal neural abnormalities [9]. Neural migration of both pyramidal and **GABAergic** interneurons is also associated with *Kiaa0319* [12] and *Dyx1c1*, another RD risk homolog [6]. On the macroscopic scale, there is convergent evidence for altered cortical structure in RD throughout the reading network [28,39,66], which may be mediated by risk genes, such as *DCDC2* [27,28]. While more work is needed to understand how disrupted neural migration associated with RD risk genes affects the organization of cortical microcircuits, it is unlikely that the excitation–inhibition balance is maintained in abnormally migrating circuits.

The animal research summarized here implicates two key RD risk genes (*DCDC2* and *KIAA0319*) in abnormal cortical development, increased neural noise, and degraded auditory processing, based on neural phenotypes found when expression of these genes is silenced or reduced. Translating these findings, which involve dramatic gene disruptions in rodents, to an understanding of how common variants affect the function of the human brain remains a challenge. Although the genetic variants associated with RD are suspected to result in reduced gene expression (for example, of *KIAA0319* [67,68]), the level of reduction may not be comparable to the levels induced in model organisms, so it is currently unknown how well these model phenotypes reflect those of humans with RD risk alleles. In addition, there is evidence that the interference technique used to produce knockdown phenotypes (used by Centanni *et al.* [3,10]) can have phenotypic effects unrelated to the target gene [69,70]. Finally, we note that these genes have also been associated with neurobiological phenotypes other than those discussed, such as corpus callosum area in rats (*Kiaa0319* [13]) and white matter integrity in humans in both corpus callosum and left arcuate fasciculus (*DCDC2*[25]).

Collectively, evidence from animal models, along with convergent findings in humans, suggests a link between RD risk genes and abnormal cortical microcircuits. Electrophysiological studies of RD risk gene function have provided direct evidence for hyperexcitability and increased neural noise (albeit in animals). Although more speculative as a mechanism, disrupted neural migration associated with genetic RD risk is also predicted to lead to hyperexcitability and noisy neural processing.

## Downstream Neural Effects of Neural Noise in RD

Neural noise has multiple consequences for cognition and brain function, particularly sensory processing [71]. Here, we highlight the loss of neural synchronization as a consequence of neural noise and discuss the impact of noise on encoding speech stimuli, a process particularly relevant to developing phonological awareness.

The synchronized activity of large numbers of neurons forms the basis for information processing [72], perception, particularly multisensory perception [73], and integrating and encoding sensory inputs. Synchronization at both exogenous and endogenous levels is important for sensory processing. At the exogenous level, the activity of the local circuits becomes entrained to external stimuli. At delta (2–4 Hz) and theta (4–7 Hz) frequencies, fluctuations in neural membrane potentials become entrained to quasiperiodic features in stimuli, for example speech stress patterns. Neural entrainment to external stimuli paces periods of local neural excitability, producing cross-frequency coupling with gamma oscillations (~30–50 Hz) [42,74,75], and may have a key role in encoding speech (Box 2).

### Box 2. Sensory Coding by Neural Oscillations

Sensory stimuli, such as speech, are processed in multiple time windows of neural processing. These windows determine the rate at which sensory information is sampled, which in turn determines which features of the sensory stimuli can be encoded and differentiated. Neural time windows for this process of temporal integration are closely linked to neural excitability. At the level of local neural circuits, excitatory activity triggers a closely following period of inhibition, during which sensory input is integrated in the interval before the next spike. This cyclic process, synchronized across a large number of neurons, imposes a physiological constraint on sensory processing [114], notably on the encoding of phonemic changes important in phonological processing. The excitation–inhibition balance is critical in regulating the frequency of these excitation–inhibition cycles [115]. Recent models [108,109] of this process show that phonemic transitions can be encoded in three such approximately 25-ms cycles of excitation–inhibition [or gamma cycles, referring to the frequency (~30–50 Hz) of the associated oscillations]. These models provide insight into the dependence of phonological representations on the frequency of neural oscillations and their dependence on neural noise and spike variability. In particular, stimulus representations become less robust (i.e., more easily confusable in terms of neural activity) in the presence of neural noise [109], which may be a source of phonological processing difficulty in RD (Figure 1, main text).

In addition to the general consequence of noise-induced synchronization loss, changes in the excitation–inhibition balance, as in the case of hyperexcitability, affect the time window available for sensory processing. Changes in the time window for sensory integration (either increases or decreases from the typical window period) are likely to have negative consequences for phonological processing. Reducing the time window of integration, effectively averaging stimulus changes over a shorter time period, can reduce the reliability of sensory processing. Increasing the integration window can reduce sensitivity to rapid changes in the stimulus, such as phonemic transitions, and produce overly broad phonetic sensitivity, which has been observed in RD [116,117].

Low-frequency phase resetting may also be important in multisensory integration [76], such as print–speech integration. Together, exogenous and endogenous synchronization are thought to form a basis for integrating and encoding sensory information over multiple timescales, from slow prosodic and stress contours to more rapid changes that distinguish phonemes.

Hyperexcitability can affect synchronous neural processing, the rate at which sensory stimuli are sampled and encoded, the precise spike timing needed for multisensory integration, and spike timing-dependent plasticity needed for learning multisensory associations [77–79]. At an exogenous level, thalamocortical projections deliver the filtered speech signal to auditory cortex. If the receiving neurons in auditory cortex are hyperexcitable, these thalamocortical projections could trigger spikes at input levels below those associated with onsets in the speech signal, disrupting delta/theta **phase-locking** that normally serves to entrain neural oscillations to speech [75]. As a consequence, periods of neural excitability within auditory cortex may become misaligned with the speech signal. Thus, hyperexcitability may provide a mechanism for the loss of exogenous synchronization between speech and neural oscillations found in RD. For example, low-frequency phase-locking of neural oscillations to the **speech envelope** is reduced in RD [43,80]. This failure to synchronize to external input at low frequencies has previously been proposed to account for many features of RD [81].

At the endogenous level, hyperexcitability may affect the sampling and encoding of speech, a prerequisite for phonological awareness. Gamma oscillations reflect underlying periods of neural excitability and the frequency of these oscillations may be a critical factor in how rapidly sensory stimuli are sampled (Box 2). Since phonemes are distinguished by fairly rapid acoustic changes, aligning the neural sampling rate is critical for establishing neural representations that distinguish phonemes. In RD, the rate of gamma oscillations has been found to be abnormally fast [35,36], which may link increased neural noise to atypical phonemic representations, leading to impaired phonological processing in RD.

## Reading-Related Consequences of Neural Noise Observed in RD

Reading development is a process of multimodal integration, critically dependent on tuning phonological and orthographic neural representations and establishing mappings between these. Reading relies on multiple component processes, including sensory processing (often under perceptually noisy conditions), intact phonological awareness, orthographic processing, and the ability to map graphemes to their corresponding speech sounds. The implications of neural noise for some of these critical processes are discussed below.

### Sensory Processing

As we have discussed above, neural noise can impact low-level perceptual processes, such as processing temporally varying auditory stimuli, that may contribute to the development of phonological representations [82]. A review [59] found a moderate effect size (d = 0.6) for impaired discrimination of frequency-modulated (FM) stimuli at slow (2 Hz) modulation rates in RD in both children and adults. Although FM discrimination has been found to be a predictor of reading ability [82], some studies have failed to find FM discrimination differences between RD and typical readers [83]. For example, a comparison between children with RD, and typical readers with and without hearing loss found that FM discrimination differed significantly only in the hearing loss group [84]. Another study found no behavioral difference in 5-Hz FM discrimination between adults with and without RD, but found reduced mismatch negativity amplitudes in adults with RD [83], suggesting that there are subtle auditory processing impairments in RD, even when these are not behaviorally evident.

### Perceptual Noise Exclusion and Learning

Behavioral studies in humans suggest that perceptual noise exclusion is impaired in RD in both visual [47,48] and auditory domains [85]. Results from modeling *in vivo* responses from gerbil primary auditory cortex in response to phonemes in noise suggest that the dynamic nonlinear control of neural thresholds, requiring both synaptic depression and gain adjustments, is critical for reducing the effects of perceptual noise [86]. In particular, synaptic depression was found to be necessary for suppressing additive perceptual noise of the type used in studies in noise exclusion in RD [85]. In the case of neural hyperexcitability, this necessary synaptic depression may be limited, producing the perceptual noise exclusion deficits found in RD. As Ziegler *et al.* [85] suggested, a perceptual noise exclusion deficit offers a simple explanation for RD: children cannot adequately extract phonemic information needed to learn phoneme–grapheme mappings in the noisy classroom environment. However, our hypothesis suggests that a deeper impairment (neural noise) limits the development of phonological awareness in RD, even under ideal listening conditions.

### Phonological Awareness

Phonological awareness is an early prerequisite skill for successfully learning to read and its deficit is often considered one of the central features of RD [44]. Phonological awareness includes the ability to identify and manipulate linguistic units at both the phonemic and syllabic levels. Sublinguistic acoustic features appear to be encoded within the spectrotemporal fields of auditory cortex [87], and may be expected to lead to phonological awareness deficits with less precision in the presence of neural noise (Box 2). More generally, excess neural noise also impairs the capacity of populations of neurons to maintain stable patterns of activity, which is detrimental to both forming and maintaining representations. Under low signal-to-noise ratio conditions, activity in neural populations, such as those tuned to represent phonemes and other higher order features [88], may spontaneously fluctuate [89], disrupting information processing. This consequence of neural noise has potentially wide implications in RD, from developing phonological awareness to degrading phonological memory.

Degraded phonemic representations (see above and Box 2) are expected to compromise phonological awareness at the phonemic level and lead to many of the behavioral deficits

observed in RD, as detailed in early connectionist models of noisy processing in RD [50]. Neural noise is also expected to impact awareness at the syllabic level through reduced neural synchronization to the speech envelope (above). We suggest that noisy firing at the arriving projections to local cortical circuits will prevent selective oscillatory entrainment to speech features, such as onsets [75]. Several studies have found that individuals with RD have reduced sensitivity to rhythmic patterns in the speech envelope, particularly at the syllabic rate [90,91], which some studies have attributed to impaired neural entrainment to the speech signal at low frequencies relevant to stress and syllabic segmentation [34]. There is also evidence for deficient phase-locking to both the fine structure of speech [92] and speech envelope in RD [81], consistent with the hyperexcitability-related spike timing variability observed in animal models [5,56].

### Learning Phoneme–Grapheme Mappings

Reading relies on the ability to reorganize left hemisphere speech and/or language-sensitive networks to allow print–speech integration [46,93–95], enabling phoneme–grapheme correspondences to be learned. The neural noise hypothesis predicts that multisensory integration, such as between print and speech, should be consistently impacted in RD. Neural noise may be present in specific subsets of the brain regions involved in reading, and these subsets may vary from individual to individual, producing individual variability in the RD phenotype. For example, disruptions to some reading subprocesses, such as orthographic or phonological processing, may be closely linked to cortical hyperexcitability in the corresponding visual or auditory sensory areas. However, multisensory integration deficits may arise from disruptions to any one of these processes or from hyperexcitability localized to heteromodal or crossmodal brain regions, such as temporoparietal cortex.

In addition to offering multiple spatial points of noise susceptibility, multimodal integration and coordinated processing across brain regions is also sensitive to the loss of spike timing precision. Multisensory integration occurs over a restricted time window [73,96] that may be susceptible to variability in neural spike activity and learning multisensory associations relies on spike timing-dependent synaptic plasticity during critical periods of development. Considering the number of possible paths to disrupted multisensory integration and its sensitivity on neural timing, deficits in multisensory processing are expected to be a reliable feature of RD, and several studies have reported deficits in print–speech integration in RD [45,95,97,98].

## Counter-Evidence to the Neural Noise Hypothesis and Considerations

The neural noise hypothesis draws on recent findings in animal models and the role of neural oscillations in sensory processing to suggest a specific pathway through which RD arises. However, the precise nature of neural noise in RD remains poorly characterized and other neurobiological mechanisms, such as atypical structural connectivity, are also supported. We briefly consider these alternative mechanisms and speculate on how variability in sources of neural noise may contribute to heterogeneity in RD and have specificity to reading-related processes.

We have emphasized cortical processing as the target of neural noise and source of RD impairments. However, other factors, such as connectivity between brain regions involved in reading, may also be important contributors to RD. For example, one study [37] provides evidence that poor access to phonological representations, arguably reflected in reduced functional connectivity with temporoparietal regions, is impaired, while phonological representations remain intact, although this study did not examine the detailed properties of phoneme encoding (as has been done in other studies [87]). RD risk mutations in *DCDC2* have also been linked to structural connectivity within the reading network [25] and children at risk for RD have

persistently reduced temporoparietal white matter integrity [99]. While these studies highlight the importance of connectivity in RD and the need for systems-levels approaches to studying RD, these results are not necessarily incompatible with the neural noise hypothesis. For example, neurochemistry has been related to **functional connectivity** [100]. It is currently unknown whether structural connectivity findings can be accounted for by excess neural noise (e.g., reflective of noise-driven differences in plasticity and axon growth) or whether these represent an independent neurobiological mechanism.

### Heterogeneity

We propose that local cortical abnormalities (as in other models of RD [39]) of cortical excitability disrupt the sensory and cognitive functions associated with those areas, but the location of dysregulated excitability is expected to vary across individuals, due to unidentified genetic and/or environmental factors. The location of an excitation–inhibition imbalance within the network of brain regions associated with reading will differentially affect reading subprocesses, producing heterogeneous phenotypes in RD. For example, a given case of RD might be characterized primarily by poor phonological awareness (if excitability is primarily increased in auditory cortex) or in decoding (if excitability is primarily increased in heteromodal regions important for print–speech integration). While accommodating wide, nonspecific variability may appear to lessen the strength of our model, this accurately reflects the complex genetic underpinnings of cortical development [101]. In addition, there is not a uniform level of cortical excitability across the brain: endogenous levels of GABA and glutamate also vary across the brain, and show regional correlations with specific functional networks [102]. However, our model predicts that multisensory integration of graphemes and phonemes should be consistently deficient in RD, due to the cascading effects of increased neural noise from both heteromodal and cross-modal regions on interregional synchronization and integration of possible poor representations across modalities.

### Specificity

Neural noise is not linked specifically to RD and has been proposed as an explanation for other neurodevelopmental disorders, notably autism [103] and schizophrenia [104]. Neural noise can result from multiple etiological sources and elucidating these neurobiological origins may improve the specificity of the neural noise hypothesis with respect to RD. For example, the neural noise hypothesis of RD can be readily distinguished from models of neural noise due to dopaminergic dysregulation [105], since RD deficits are predominately associated with brain regions that have little dopaminergic innervation.

In the case of RD, evidence suggests a more general source for hyperexcitability: an imbalance in the glutamatergic system. Since pyramidal-interneuron circuits comprise much of the neocortex, some explanation is needed for how the proposed glutamatergic imbalance might manifest in the comparatively restricted range of RD phenotypes. One possibility is that neural noise in RD stems from spatially localized genetic effects, such as those associated with *KIAA0319* or *DCDC2*. Indeed, polymorphisms on *KIAA0319* show regionally specific associations within language resting-state networks [17], illustrating that these genetic pathways may have relatively focal impacts on brain function (see also an fMRI study [20] of reading). Even among sources of hyperexcitability that may have some specificity to RD, different origins for hyperexcitability may produce subtle phenotypic differences. For example, both *Kiaa0319* and *Dcdc2* mutations produce phenotypes with increased neural excitability, but are associated with distinct auditory-processing deficits [3,10].

Although RD is not characterized by clinically significant general cognitive impairments, the deficits associated with RD are not limited to reading and related processes. A recent study

[106] showed that adults with RD do not exhibit a reduced neural response to repeated stimulus presentation (i.e., neural adaptation) to the same extent as typical readers. This reduced neural adaptation was found in response to both linguistic and nonlinguistic auditory and visual stimuli, suggesting a domain general feature of neural processing.

## Testing the Neural Noise Hypothesis

Our hypothesis is an effort to coherently synthesize a limited body of often-disconnected findings to provide a basis for future work. Our hypothesis is in principle directly falsifiable by showing that individuals with RD do not, in general, have noisy, hyperexcitable cortex. This is an empirically difficult, but not impossible, test. For example, induced pluripotent human stem cells from individuals with RD could be used to confirm or deny the prediction that noisy neural firing would be observed and correlated with reading ability. Our hypothesis also makes multiple links at multiple levels of analysis that can be readily investigated to produce results incompatible with our hypotheses. Some of these predictions, where negative findings would be clearly inconsistent with our hypothesis, are outlined below.

### Neurochemical Measurement of the Excitation–Inhibition Balance in Auditory Cortex Will Be Negatively Associated with Phonological Processing

Recently, it was shown that glutamate in occipital cortex is associated with a composite measure of reading skill [32]. However, this region is not strongly linked to reading and future studies need to examine the relationship between neurochemistry throughout the brain and phonological and orthographic processing. We predict that glutamate:GABA ratios in left superior temporal regions, but not prefrontal regions outside the reading network, will negatively correlate with phonological awareness.

### RD Risk Alleles Will Be Associated with Impaired Cortical Auditory Processing in Humans

Evidence from animal models that RD risk genes can impair the discrimination and processing of temporally dynamic auditory stimuli [3,10] provides a link from genetics to behavioral phenotypes. An important test for our hypothesis is whether similar loss of response consistency is present in humans carrying RD risk alleles. In the only study [31] to examine the association between RD risk genes and the consistency of human neural responses to auditory stimuli, *KIAA0391* risk alleles were associated with less-consistent auditory brainstem responses (ABRs) in preliterate children. In the same study, *DCDC2* risk alleles were associated with a trend towards more stable ABRs. While subcortical auditory function has an important role in RD, our hypothesis primarily draws on evidence for the effects of *Dcdc2* and *Kiaa0319* in pyramidal cells and the dynamics of cortical pyramidal-interneuron networks (rather than the lower auditory pathways, which have substantially different neural architecture) and it remains necessary to investigate cortical response variability in RD. Extending the results from rodent literature, we predict that cortical response consistency to auditory stimuli (e.g., using ERP measures or EEG phase-locking) will be reduced in individuals carrying RD risk alleles.

### Computational Models of Perceptual Noise Exclusion and Phonological Awareness

The neural noise hypothesis can most productively be tested through the use of biologically plausible neural models to generate, and then empirically test, novel hypotheses. For example, a previous study [86] used simple filter models to investigate the mechanisms involved in auditory noise exclusion, a deficit in RD [85]. Importantly, these models perform differently under different noise conditions, allowing them to be empirically distinguished *in vivo* (in gerbils). Spectrotemporal receptive fields can also be mapped in humans using fMRI [107]. More sophisticated models that parameterize neural excitability may predict results that depend on noise distributions, predictions that can then be tested in fMRI studies of RD. More generally, neural models of acoustic encoding [108,109] should be extended to model the effects of

excitation and/or inhibition on sensory processing and integrated, based on the fidelity with which phonemic features can be encoded, with more phenomenological models of reading [50].

## Concluding Remarks and Future Perspectives

We propose a biological mechanism (increased cortical excitability producing increased neural noise) that provides a mechanistic framework for disrupted unisensory and multisensory processing in RD that ultimately manifests as characteristic impairments in phonological awareness and/or grapheme–phoneme mapping. The hypothesis is consistent with current understanding of the neurogenetics of RD and accounts for deficits in processing rapidly presented auditory stimuli [3], and discriminating time-varying, but not static, auditory stimuli [110]. Our proposal also provides a novel foundation for intervention through brain-stimulation techniques, such as tDCS and TMS, or pharmacological agents. To date, only a few studies have examined the effects of brain stimulation on reading and related skills, with mixed results [60–62]. The ability to rescue phenotypes in RD risk gene animal models using NMDA antagonists [5] also raises the possibility of using pharmacological agents for RD intervention, although it is not possible to pharmacologically target specific brain regions. Research in this area has been limited to individuals with **comorbid** RD-attention deficit hyperactivity disorder (ADHD), where dopaminergic agonists [111] and norepinephrine reuptake inhibitors (with NMDA antagonist action) [112] have been found to improve reading. A recent study suggests that drug-related improvements in reading skill occur through mechanisms independent of those associated with ADHD symptom improvement, suggesting that these drugs act on the reading system beyond modulating attention and control [112].

Considerable research is still needed to test the neural noise hypothesis, resolve outstanding questions and translate this model into practice (see Outstanding Questions). Systems-level multimodal imaging studies that measure response variability in RD, such as using phase-locking measures in EEG or single-trial estimates of BOLD response, in conjunction with MRS from multiple cortical regions can provide a direct test of the basic premise of our hypothesis. Studies at this macroscopic scale also need to be linked more closely to underlying neurobiological and genetic risk factors to understand how specific sources of excitability can be linked to behavioral and cognitive deficits. Given that reading is a multifactorial process that recruits a broad network of brain regions, it also is important that future studies take a systems-level, individual-differences approach, ideally aided by biologically plausible neural models, to examining the biological factors underlying RD and probing the gene–brain–behavior pathway that we have outlined here.

## Outstanding Questions

How do the increases in single neuron excitability found in animal models (e.g., in *Dcdc2* knockdowns) affect processing at the level of cortical microcircuits? For example, are these increases in single-unit excitability also associated with changes in local connectivity?

How does disrupted neural migration, associated with *Dcdc2* and *Dyx1c1* for example affect local neural connectivity and function, particularly connectivity within pyramidal-interneuron networks?

What are the functional consequences of atypical neural migration in RD in terms of the excitation–inhibition balance?

How does the excitation–inhibition balance change through development and how does this affect neural plasticity during critical developmental stages?

How do neural noise characteristics differ in RD versus other conditions that have been associated with neural noise?

Are there regional differences in neural noise characteristics and neurochemistry that may drive neural noise? If so, what are the mechanisms that cause these regional differences?

Can hypothesis-driven pharmacological and magnetic/electrical brain modulation techniques in combination with multimodal imaging in humans be used to understand causal links between neural excitability and cognition?

Studies have yielded mixed evidence regarding noisy subcortical processing, measured in terms of variability in the auditory brainstem response. What is the relationship between noisy subcortical and cortical processing?

How is print–speech multisensory integration coordinated by neural oscillations across regions and what is the impact of trial-by-trial variability in synchronization on this integration? For example, is print–speech integration sensitive to phase resetting in auditory and/or visual cortices? How does neurochemistry affect print–speech integration?

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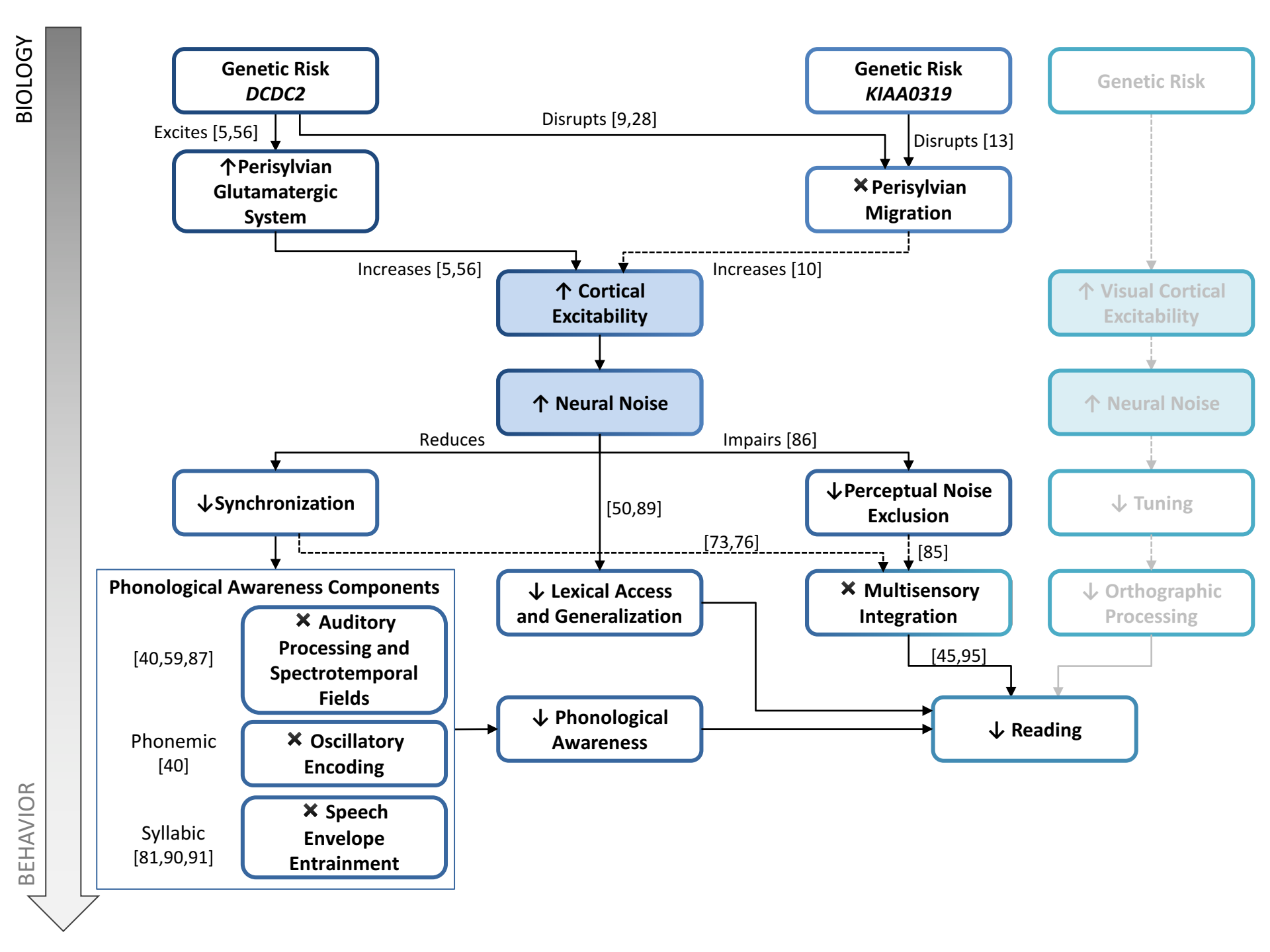
BIOLOGY
BEHAVIOR
Genetic Risk DCDC2
Genetic Risk KIAA0319
Genetic Risk
Excites [5,56]
Disrupts [9,28]
Disrupts [13]
↑ Perisylvian Glutamatergic System
✕ Perisylvian Migration
Increases [5,56]
Increases [10]
↑ Cortical Excitability
↑ Visual Cortical Excitability
↑ Neural Noise
↑ Neural Noise
Reduces
Impairs [86]
↓ Synchronization
[50,89]
↓ Perceptual Noise Exclusion
↓ Tuning
[73,76]
[85]
Phonological Awareness Components
↓ Lexical Access and Generalization
✕ Multisensory Integration
↓ Orthographic Processing
[40,59,87]
✕ Auditory Processing and Spectrotemporal Fields
[45,95]
Phonemic [40]
✕ Oscillatory Encoding
↓ Phonological Awareness
↓ Reading
Syllabic [81,90,91]
✕ Speech Envelope Entrainment

Schematic of the neural noise hypothesis, illustrated through two genetic pathways known to affect neural noise within the domain of auditory processing and their downstream consequences on reading. Some genetic risk factors, such as *DCDC2* mutations, increase neural noise through a direct effect on glutamatergic signaling and hyperexcitability. *DCDC2* and other genetic risk factors, such as *KIAA0319* mutations, may disrupt neural migration and the formation of local excitatory–inhibitory circuits, thereby increasing neural noise. There are likely other risk genes that act through similar pathways. Excess neural noise disrupts neural synchronization across multiple scales, leading to deficits in low-level temporal auditory processing, and the oscillatory neural processes that sample and encode sensory information. Loss of synchronization and precise neural spike timing also impairs multisensory integration. Ultimately, the downstream effects of neural noise may lead to impairments in phonological awareness and multisensory integration, two key components of reading development. Although we focus our discussion on the consequences of neural noise in the auditory domain, similar consequences are predicted in the visual domain, ultimately impacting orthographic processing and reading. This speculative pathway is shown on the right. Dashed arrows reflect more speculative links in need of further study. Processes in light text are not discussed in detail in the main text. Numbers by arrows refer to supporting references in the main text ([5, 9, 10, 13, 28, 40, 45, 50, 56, 59, 73, 76, 81, 85, 86, 87, 89, 90, 91, 95])