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Opinion

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.

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.

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

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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