

Toward a Theory of Stuttering

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Key Words

Brain · Hypoxia · Ischemia · Injury · Stuttering

Abstract

Stuttering affects about 1% of the general population and from 8 to 11% of children. The onset of persistent developmental stuttering (PDS) typically occurs between 2 and 4 years of age. The etiology of stuttering is unknown and a unifying hypothesis is lacking. Clues to the pathogenesis of stuttering include the following observations: PDS is associated with adverse perinatal outcomes and birth-associated trauma; stuttering can recur or develop in adulthood following traumatic events such as brain injury and stroke; PDS is associated with structural and functional abnormalities in the brain associated with speech and language; and stuttering resolves spontaneously in a high percentage of affected children. Evidence marshaled from the literature on stuttering and from related sources suggests the hypothesis that stuttering is a neuro-motor disorder resulting from perinatal or later-onset hypoxic-ischemic injury (HII), and that chronic stuttering and its behavioral correlates are manifestations of recurrent transient ischemic episodes affecting speech-motor pathways. The hypothesis could be tested by comparing children who stutter and nonstutterers (controls) in terms of the occurrence of perinatal trauma, based on birth records, and by determining rates of stuttering in children exposed to HII during the perinatal period. Subject to test-

ing, the hypothesis suggests that interventions to increase brain perfusion directly could be effective both in the treatment of stuttering and its prevention at the time of birth or later trauma.

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Background

The classic features of stuttering are blocks in speech, prolonging a word or sounds within a word, repetition of sounds, syllables and words, difficulty or inability to articulate certain syllables, or pauses within a word, and adding extra words such as ‘um’ if difficulty arises in speaking the next word. Speech difficulties are often accompanied by rapid eye blinks, tremors of the lips or jaw, facial tics, head jerks, clenched fists, facial flushing, pallor, perspiration, eye movements, and cardiovascular changes [1, 2].

Stuttering affects about 1% of the general population and from 8 to 11% of children, and about 8% of people experience the onset of stuttering during their lifetime (i.e., cumulative incidence rate) [3]. It is estimated that 70 million people worldwide exhibit severe stuttering [4]. In a cohort study of 1,619 Australian children recruited at 8 months of age, the cumulative incidence of stuttering onset by 3 years of age was 8.5%. Factors associated with stuttering onset, which often occurred suddenly over 1–3

days, included male gender, twin birth status, higher vocabulary scores at 2 years of age, and high maternal education. Yet these factors only accounted for 3.7% of the total variance [5]. Follow-up one year later showed that the cumulative incidence of stuttering onset had risen to 11.2% (95% CI 9.7–12.8) [6]. On the other hand, a survey of the parents and guardians of 119,367 children ages 3–17 years from the US Centers for Disease Control and Prevention reported lower prevalence rates of stuttering which, however, were twice as high among non-Hispanic black children compared to non-Hispanic whites (2.63 vs. 1.27%, $p < 0.05$), and intermediate (1.96%) for Hispanic groups overall [7].

The etiology of stuttering is still largely unknown and a unifying hypothesis of the pathogenesis is lacking [8]. One hypothesis is that stuttering is associated with temperamental or personality traits of shyness or anxiety [9]; a second is that stutterers know when they are about to stutter, and this awareness influences occurrences of stuttering and its treatment [10, 11]. A third hypothesis is that developmental stuttering is due to a basal ganglia defect involving a deficit in brain timing networks [12] and/or brain structural connectivity differences associated with impaired auditory-motor integration [13–15].

With regard to genetic factors in stuttering, mutations in the GNPTAB, GNPTG, and NAGPA genes related to the lysosomal enzyme-targeting pathway are found in <10% of unrelated stutterers with a family history of the disorder [16]. The GNPTAB and GNPTG genes in particular cause mucopolysaccharidosis types II and III, which are rare autosomal recessive lysosomal storage disorders associated with motor disabilities and delayed speech as well as pathologies of bone, connective tissue, liver, spleen, and brain [17]. It remains unclear how these gene mutations influence molecular and cellular mechanisms to cause stuttering.

Any theory proposed to explain stuttering should be able to account for the following observations:

- The risk factors for persistent developmental stuttering (PDS) include adverse perinatal outcomes and birth-associated trauma.
- Stuttering can recur or develop for the first time in later life following brain injury or pathology.
- PDS is associated with structural and functional abnormalities in the brain regions that modulate speech and language.
- Stuttering improves spontaneously in a high percentage of children with PDS, boys having a higher rate of persistence into adulthood than girls.

The Risk Factors for PDS Include Adverse Perinatal Outcomes and Birth-Associated Trauma

The circumstances surrounding the onset of PDS are not well defined, but evidence suggests that adverse perinatal outcomes and birth-associated trauma contribute to the pathogenesis of developmental stuttering [18, 19]. In a cohort study of speech and language skills at 6.5 years of age in children who had required neonatal intensive care (NIC), babbling was absent more commonly in those born at 23–27 weeks than in other preterm NIC children. Stuttering was also more common in preterm NIC children born at 23–27 weeks than among those born at >32 weeks [20]. In a study of 32 adults who stuttered, 41% had borderline childhood ADHD/ADD scores. Early neurological incidents including preterm birth, other birth complications and head injury were more common in this group than among those with low scores for ADHD [21]. In a longitudinal study of 97 preterm children and 93 term children as a control group, articulation defects, stuttering and dysgrammatism were more frequent in the preterm than in the term children, and more common in boys than in girls [22].

Stuttering Can Recur or Develop in Later Life Following Traumatic Events Such as Brain Injury and Stroke

Stuttering can recur or develop in adulthood secondary to neurological injury or pathology such as Parkinson's disease, a condition referred to as neurogenic stuttering [1, 23–25]. Among 10 individuals who had not stuttered as children but who had done so for 10–15 years after penetrating missile wounds during the Vietnam War, stuttering was associated with significant deficits in skilled rapid hand movements and in oral and speech movements, suggesting a motor control disorder [26]. In a study of stutterers with and without relatives who stuttered, 37% (21/57) of those without a family history of stuttering had experienced a head injury or birth complications compared to 2.7% (3/112) of those with a family history of stuttering [27], suggesting an important role for environmental factors.

PDS Is Associated with Structural and Functional Abnormalities in the Brain Regions That Modulate Speech and Language

In a high percentage of people who stutter, the brain areas and neural mechanisms that are affected are not the primary speech and language regions but rather deep structures such as the basal ganglia, which modulate the primary speech and language areas. The central control

abnormalities in stuttering tend to involve a systemic dysfunction, with evidence of structural and functional changes in the basal ganglia and related areas, suggesting that stuttering is a speech motor disorder associated with the initiation and termination of articulatory movements [1, 14, 28, 29].

Stuttering Improves Spontaneously in a High Percentage of Children with PDS, Boys Having a Higher Rate of Persistence into Adulthood than Girls

Based on large clinical caseloads from the 1940s, it was estimated that about 40% of childhood stutterers ceased to stutter without treatment by age 8 [3]. Recent reports suggest that recovery from stuttering may be as high as 91%, indicating that the vast majority of children outgrow it [3, 5]. Although the reported male-to-female ratio in very early stuttering is approximately 2:1, for persistent stuttering the ratio shifts to a range from 4:1 to 6:1 [30]. Boys are therefore several times more likely to experience persistent stuttering in later life than girls.

Toward a Theory of Stuttering

Based on these observations, the hypothesis proposed for consideration is that a common condition in the initiation of stuttering is hypoxic-ischemic injury (HII) to areas and pathways in the brain associated with speech motor control. Such injuries may be due to adverse perinatal outcomes, later onset brain trauma, or stroke. Prolonged hypoxemia leads to cardiac hypoxia, which leads to diminished cardiac output and ultimately to brain ischemia. Thus, brain injury resulting from asphyxia may be the consequence of ischemia superimposed on hypoxia [31]. HII can result in death or severe long-term neurological disability in children and adults. Birth asphyxia is also a major risk factor for interference in or failure to acquire language [32]. Infants and young children are more likely to experience events resulting in hypoxemia and brain hypoxia than older persons, which may explain the predominance of stuttering among children.

Alm [19] has similarly suggested that preterm birth, birth complications, and concussion are all related to hypoxia and hypothesized that, depending on its degree and duration, the effects of hypoxia, although subtle, could affect the dopaminergic system and result in neuronal loss in the basal ganglia and lead to stuttering. Alm and Risberg [21] proposed that the main mechanism causing acquired stuttering following head injury is rotational

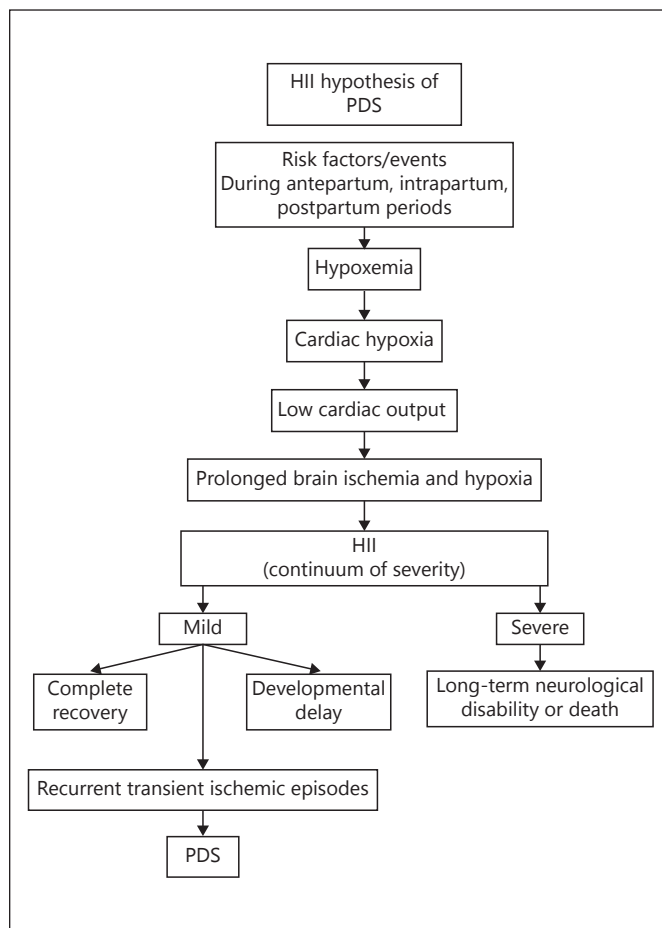


Fig. 1. HII hypothesis of PDS.

forces at the level of the midbrain and the substantia nigra, causing diffuse neuronal injury that affects several basal ganglia pathways. In sheep, repeated episodes of fetal asphyxia cause preferential damage to the striatum, with loss of medium-sized striatal GABAergic projection neurons to the globus pallidus and to the substantia nigra [33].

It is further suggested that stuttering associated with eye blinking, jaw jerking and involuntary head or other movements represents recurrent transient hypoxic-ischemic episodes affecting speech motor pathways. These episodic events may be exacerbated and perhaps perpetuated to some extent in children by the acute anxiety or panic evoked in the individual at the prospect of embarrassment and stigma, due to prior experiences of stuttering (fig. 1). Alternatively, given the close association between stuttering and anxiety disorder [34], both hyperventilation and panic associated with stuttering may signify abnormalities in cerebral blood flow and hence

cerebral hypoxia [35]. Persistent stuttering and panic disorder could thus be considered to be different manifestations of HII to the brain. This possibility receives support from a case–control study of anxiety disorder among 92 adults seeking speech therapy for stuttering and 920 age- and gender-matched controls. Conditional logistic regression analysis indicated that, compared with controls, those who stuttered as a group had a six- to sevenfold increased odds of meeting the diagnosis of anxiety disorder, a 16- to 34-fold increased odds of social phobia, a fourfold increased odds of generalized anxiety disorder, and a sixfold increased odds of panic disorder [36].

Hypoxic-Ischemic Injury

HII is a major cause of death and neurodevelopmental disability in term neonates, with estimated prevalence rates at 2–4 per 1,000 live term births [31, 37]. From 15 to 20% of infants exposed to HII die during the neonatal period and a further 25% develop permanent neurologic deficits [38]. The causes of birth asphyxia and trauma were determined in the 208 most severely affected infants of 10,995 consecutive live births. The most frequent causes of birth asphyxia and trauma were prolonged labor, mid-forceps or breech delivery in full-term infants; abruptio placentae; difficult breech delivery; maternal phenobarbital administration to prevent periventricular hemorrhage or neurological damage in preterm infants; and unattended precipitate deliveries in immature infants [39]. Brain injury is more likely to occur in premature infants because of the increased frequency of events potentially causing hypoperfusion – including respiratory distress syndrome, pneumothorax, patent ductus arteriosus and neonatal sepsis – and the relatively poor autoregulatory capacity of the premature brain [37, 40].

Clinical signs and symptoms of neonatal HII are non-specific and tend to evolve over a period of days [41]. Infants at highest risk can be identified on the basis of intrapartum distress (e.g., fetal heart rate abnormality, severe functional depression indicated by low 5-minute Apgar score), need for resuscitation in the delivery room, severe fetal acidemia, and an abnormal electroencephalogram [42]. In the first hours following a severe insult, neonates may demonstrate depressed consciousness, periodic breathing with apnea, and bradycardia. Mild cases of HII may recover completely or be somewhat developmentally delayed. It is infants in the latter category, we surmise, who develop PDS.

Implications for Understanding Stuttering

Age of Onset of PDS

How does the birth-associated HII hypothesis explain the fact that children who stutter are usually fluent speakers before they start stuttering [43]? A related question is why 65% of children with PDS begin stuttering before age 3, and 85% by 3.5 years of age. The peak ages when stuttering begins are the same years when major developments are occurring in the brain for the development of speech, language acquisition and articulatory skills [3]. This suggests that interference with these maturational processes contributes to stuttering. In fact, whole brain glucose metabolic rates at birth are only 30% lower than those attained in adulthood. These rates increase to adult levels by age 2 and exceed them by about age 3, after which they plateau from ages 4 to 9. At their peak, glucose metabolic rates are highest in the cerebral cortex, where they are two-fold higher than those of adults. In the phylogenetically older brainstem, cerebellum, thalamus and basal ganglia, glucose metabolic rates are relatively mature at birth, suggesting a hierarchy of energy demands, shifting from phylogenetically older to newer structures during early behavioral development. A cephalocaudal pattern of growth continues during infancy, peaking at age 3 when the human metabolic rate is the highest of the entire lifespan. The rate of physical growth then slows, reversing the cephalocaudal pattern of growth in infancy, with the rest of the body growing faster than the head [44].

Fluency in speaking is achieved by ages 2–3 and this may reflect the high level of oxygenation of the brain during those early years associated with the rapid growth and functional development of the speech-motor system. However, at about the age of 3, brain metabolic rates start to plateau. On the HII hypothesis, PDS tends to occur at this age because the period of slower growth is associated with relatively minor decrements in brain perfusion and that may be sufficient to trigger stuttering in a child predisposed to stutter due to HII during the perinatal period.

Decreased Heart Rate (HR)

Adults who stutter tend to show a decrease in HR in stressful speech situations compared with non-stutterers [45]. Consistent with the HII hypothesis that stuttering is associated with transient decrements in brain perfusion, hypoxic-ischemic states are also associated with decreased HR [46].

Gender Differences in Stuttering Outcomes

As noted, males are more likely to stutter and continue to stutter in adulthood when compared to females [6]. Clinical data similarly suggest a sex difference in the outcomes of HII, with males exhibiting more severe cognitive/behavioral deficits compared to matched females [47, 48]. The mechanisms underlying this gender difference remain unknown.

Effect of Singing

Singing tends to prevent stuttering and ameliorates dysfluency in other neurological conditions such as aphasia and Parkinsonian dysarthria [49, 50]. Respiratory factors have been suggested to explain the improved voice and fluency performance in singing [51, 52]. For instance, singing utilizes continuous phonation, which provides more fluid air flow and hence enables fluency in speech. It has been suggested that the effect of singing in aphasia is due to the effect of rhythm [53]. However, the unique therapeutic status of singing in neurological conditions remains uncertain [54]. In fact, there are shared and distinct neural correlates of singing and speaking [55–57]. Areas of activation common to all singing and speaking tasks include the inferior pre- and post-central gyrus, the superior temporal gyrus, and the superior temporal sulcus bilaterally, ‘indicating a large shared network for motor preparation and execution as well as sensory feedback/control for vocal production [58]’.

The HII hypothesis suggests that singing prevents stuttering due to the deep inspirations involved in the activity, resulting in an increased level of perfusion in the brain structures associated with speech. Increased inspired oxygen concentration appears to improve the oxygen supply to the brain, since increased lactate levels in brain tissue following severe head injury are reduced by increasing the fraction of inspired oxygen [59]. Further credibility for the HII hypothesis comes from a study of the effects of singing classes on pulmonary function in patients with chronic obstructive pulmonary disease, in which patients were randomly assigned to weekly classes of singing practice or handicrafts [60]. Consistent with the HII hypothesis, a significant increase in arterial oxygen saturation (SaO₂) was observed during the act of singing.

Remission of Stuttering

Children who stutter tend to show developmental anomalies, for example, less grey matter volume in the left brain [61]. These anomalies are also seen in adult persistent stutterers [62]. However, a subset of persistent stut-

terers recover unassisted in adulthood [63]. During speech, stutterers show anomalies in the left inferior frontal cortex and over-activation in right fronto-parietal brain regions [64]. Neuroimaging studies of stuttering show that children and adults who stutter can exhibit both decreases and increases in oxygenation/reduced blood flow in areas of the brain associated with speech/speech motor areas. Increased or decreased levels of perfusion in areas such as the basal ganglia can also vary depending on whether brain activity is measured at rest or during a speech task [65]. Differences in blood flow noted during tasks and at rest may reflect an underlying state of relative hypoxia-ischemia in speech-related brain areas compared to nonstutterers, possibly with compensatory changes in perfusion occurring in different situations. It has been found that whereas speech therapy can restrict over-activation to the ventral right and bilateral auditory cortex and can abolish over-activations in right lateral prefrontal and parietal regions, spontaneous (i.e., unassisted) recovery from stuttering is associated with fewer left inferior frontal structural anomalies. These results suggested that anatomical connectivity can normalize in the course of recovery and, like recovery from acute brain lesions, optimal brain repair for stuttering involves very focal changes [66]. Gray matter volume can also be increased during development and with motor training; for example, musical instrument practice [67]. The HII hypothesis suggests that reduced gray matter volume in persons who stutter may be due to the arrest of neural growth resulting from birth-associated hypoxic-ischemic trauma. Recovery from stuttering over time [3] may reflect maturational and/or behavior modification-induced changes in previously damaged brain structures, resulting in improved cerebrovascular perfusion.

Genetic Factors

With regard to mutations in the GNPTAB, GNPTG and NAGPA genes associated with lysosomal enzyme pathway associated with stuttering, the mutations encoded by NAGPA have been shown to reduce the overall cellular activity of the enzyme by about half, resulting in deficits in intracellular processing and trafficking that lead to a reduced cellular half-life [17]. The significance of this finding is that lysosomal enzymatic impairment results in the accumulation of undegraded glycosphingolipids in lysosomes and subsequent cell and microvascular dysfunctions, leading to cellular dysfunction, necrosis, apoptosis, inflammation, fibrosis, and poor target-organ perfusion [68]. The HII hypothesis suggests that genetic defects in lysosomal enzymatic processing are associated

with an increased risk of stuttering due to a reduced cellular half-life and poor target-organ perfusion, and hence increased host susceptibility to HII.

Conclusions

On the HII hypothesis, stuttering is a neurologic disorder resulting from perinatal or later-onset traumatic brain injury or from stroke-associated HII to brain structures involved in speech-motor control. It is proposed that chronic stuttering and its behavioral correlates are manifestations of recurrent, transient hypoxic-ischemic episodes. The HII hypothesis suggests that PDS typically begins at about 3 years of age because brain metabolic rates start to plateau at that time, and associated decrements in brain perfusion may be sufficient to trigger stuttering in a child who is predisposed to it due to HII during the perinatal period. Males may be more prone to stutter and less likely than females to attain fluency because of their greater susceptibility to HII-associated brain injury; singing may prevent stuttering because it involves deep inspirations, which in turn increase brain oxygenation; and stuttering may remit in later years due to maturational changes and/or speech motor training or therapy similarly associated with increased brain perfusion.

PDS is considered etiologically distinct from later-onset neurogenic stuttering, that is, unrelated to brain damage. However, given the considerable evidence of brain structural and functional involvement in PDS, differences between psychogenic and neurogenic stuttering may be continuous and reflect more severe HII and hence dysfluency caused by brain injury in adulthood. A common basis for the onset of persistent stuttering at any time in life may therefore involve HII to the brain, with PDS being caused by HII-associated events during the perinatal period. Such damage to the brain may be sufficient to cause recurrences of brain hypoxia-ischemia manifested as stuttering, other involuntary neuro-motor features and/or panic disorder, especially in

stressful situations. The cellular damage and neural deficits may, however, be repaired or corrected over time, as suggested above, due to maturational change and/or speech therapy, with eventual remission of stuttering. On the other hand, persons who stuttered as children but are exposed to relatively minor brain injury or pathology during adulthood may be at an increased risk of recurrence of stuttering due to a reduced threshold for HII. The HII hypothesis could be tested by comparing children who stutter and controls in terms of the occurrence of perinatal trauma, based on birth records, and by determining rates of stuttering in children exposed to HII during the perinatal period. Subject to testing, the hypothesis suggests that interventions to increase brain perfusion could be effective both in the treatment of stuttering and its prevention at the time of birth or later trauma.

Contributorship Statement

A.R.M. conceived the hypothesis and drafted the paper. N.T.R. provided clinical expertise on stuttering and both she and B.J. contributed data and ideas and critically revised the manuscript. All authors approved the version to be submitted and agreed to be accountable for all aspects of the work.

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Disclosure Statement

The authors declare no competing interests.

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