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Pediatric stroke: unique implications of the immature brain on injury and recovery

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Abstract

Pediatric stroke causes significant morbidity for children resulting in lifelong neurological disability. Although hyperacute recanalization therapies are available for pediatric patients, most patients are ineligible for these treatments. Therefore, the mainstay for pediatric stroke treatment relies on rehabilitation to improve outcomes. Little is known about ideal rehabilitation therapies for pediatric stroke patients and the unique interplay between the developing brain and our models of stroke recovery. In this review, we first discuss the consequences pediatric stroke. Second, we examine the scientific evidence that exists between the mechanisms of recovery and how they are different in the pediatric developing brain. Finally, we evaluate potential interventions that could improve outcomes.

Keywords

pediatric stroke; neural recovery; neurorehabilitation; brain injury

Introduction

Stroke is rare in children, but the consequences are significant and can impart lifelong neurologic disability. The care of stroke in adults has been revolutionized by the advent of hyperacute recanalization therapies to limit brain damage. By comparison, translational strategies to target recovery through neurorehabilitation have been disappointing, but this remains an important and active area of research with promising possibilities on the horizon. Much of the clinical care of pediatric stroke has been extrapolated from the adult experience. Similarly, the natural history of stroke recovery is based on adult models of stroke. The immature brain, however, is a dynamic environment with significant changes to cellular composition, neural circuitry, and blood flow occurring throughout childhood[1]. These changes influence the vulnerability of the immature brain to injury as well as mechanisms of recovery that are engaged after injury. Understanding how recovery varies across the age spectrum is essential to developing effective therapies for all stroke patients. Here we review the literature pertaining to stroke recovery in the immature brain, highlighting potential

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differences from what we know in adults. We also review some of the therapeutic strategies for promoting recovery in children who have suffered a stroke.

What toll does pediatric stroke take?

Stroke is a leading cause of death and disability worldwide and across all age groups[2]. National organizations have worked to raise awareness of the toll that stroke takes on children, and clinicians have developed centers committed to providing rapid diagnosis and advanced care for children with acute stroke[3,4]. While hyperacute recanalization therapies anchor the acute treatment of stroke in adults, the relatively rare occurrence and delays in diagnosis of stroke in children present a significant challenge to the successful implementation of such strategies on a comparable scale. More recent trials have extended the time windows for such therapies, which may eventually lead to more pediatric patients being considered eligible for treatment[5–7]. The relative plasticity of a child's brain, however, may offer significant possibilities for targeting the recovery phase after stroke with a much larger window of opportunity for intervention.

Epidemiology of Pediatric Stroke

Pediatric stroke is typically divided into perinatal stroke (<=28 days-old) and childhood stroke (29 days to 18 years-old) due to differences in etiology, risk factors, presentation, and outcomes between the two age groups. Perinatal stroke occurs in 1 in 2300 live births[8–10]; whereas, the incidence of childhood stroke has been reported as 2–13 per 100,000[8–10]. Most perinatal strokes present with focal seizures, and sensorimotor deficits developing later as the child ages. A subset of infants exhibits no symptoms in the perinatal period, and these patients are not detected until a hemiparesis emerges later in the first year. We refer to this group as presumed perinatal stroke. Conversely, childhood stroke typically presents with acute focal neurologic deficits such as hemiparesis.

In contrast to adult stroke where the most common risk factors include hypertension, diabetes and atherosclerosis, pediatric stroke risk factors are more diverse[11]. Common risk factors for perinatal stroke include cardiac disease, infection, blood clotting disorders and perinatal events; however, a direct cause is rarely identified[9,10]. For childhood stroke, the majority of risk factors break down into three categories: arteriopathy, cardiac disease and prothrombotic disorders[9]. Additional risk factors include infection, sickle cell disease, trauma, and genetic/metabolic disorders[10]. Not only are the demographics and risk factors different between adults and children, but more importantly, the developing brain has unique implications for injury and recovery.

Do Younger Brains Really Recover Better?

For decades both scientists and clinicians have wondered about the influence of age on recovery after brain injury. A widely held assumption is that younger brains naturally recover better than older brains. This is commonly referred to as the "Kennard principle" referring to Margaret A. Kennard who pioneered studies in the 1930's and 1940's investigating the effects of age on motor impairment after brain injury in monkeys[12]. She posited that the earlier a brain injury occurs the more likely compensatory mechanisms

could reduce negative effects of the injury, demonstrating improved outcomes. Around the same time a competing hypothesis of selective vulnerability emerged, exemplified in Hebb's studies of test score patterns in patients with brain injury either in early life or adulthood[13]. He demonstrated that intelligence and language test scores were worse for patients that had brain injury earlier in life compared to adulthood. Since these early studies numerous other findings have painted a much more nuanced picture of the interaction between age at injury, size of lesion, type of lesion, location of lesion, and neurologic function influencing outcome[14–16].

Outcomes after pediatric stroke

Despite a general assumption that children fare better after stroke than adults do, actual outcomes after pediatric stroke reported in the literature vary widely (Table 1). Studies from Switzerland identified moderate to severe disability (defined as a modified Rankin Scale score (mRS >2) in 20–30% of patients after childhood stroke[17,18]. A multicenter Canadian registry recently reported moderate-severe deficits in 32% of patients including both neonatal and childhood stroke[19]. A single center study from London reported poor outcome (defined as deficits interfering with daily life) in 60% of their patients[20], while a study from the Netherlands found no severe disability (defined by mRS > 2) in their population of 27 patients[21]. Such variability can be ascribed to differences in methodology including small population sizes, length of follow up, and inclusion criteria. The Pediatric Stroke Outcome Measure (PSOM) is a quantitative validated measure of outcome after pediatric stroke based on 5 domains of neurologic function: right sensorimotor, left sensorimotor, language expression, language comprehension, and cognitive/behavioral[22]. This measure may overestimate poor outcomes when compared to the mRS because the latter emphasizes function rather than neurologic impairment[23]. Conversely, the late emergence of deficits as neurodevelopment continues may underestimate the consequences of pediatric stroke[24–26]. The evolution of a child's neurologic exam and functional abilities represent a complex interaction between normal developmental plasticity and stroke recovery, thus making the study of stroke outcomes in children uniquely challenging.

Understanding outcome necessitates studying the process of recovery. Multiple studies in adult patients have shown that sensorimotor improvements occur spontaneously for the first 3 months after stroke, while cognitive and language gains continue to be made beyond this time point[27,28]. A theory of proportional recovery has been proposed with observations that the majority of adult patients with stroke recover approximately 70% of their initial upper limb sensorimotor deficits within 3 months post-stroke, and this is unchanged by current therapies[29,30]. The underlying basis for this sensitive period of recovery likely relies on a limited window of heightened plasticity.

Many believe the window for recovery is longer for children[31]. In preschool and school-aged children with stroke, Cooper and colleagues demonstrated a trend of improvement in gross motor skills but not fine motor skills over the first year, while neonates exhibited emerging deficits over that time[8]. These studies used developmental motor scales rather than specific measures of focal impairment. The same investigators also demonstrated that the motor subdomains of the PSOM stabilized between 6 months and one year after stroke, suggesting

the window for recovery of impairment may be inside of this timepoint[32]; however, the PSOM might not be sensitive enough to track more subtle changes that could occur outside of this time window. Although most studies investigate outcomes one year after pediatric stroke, one small study investigated the long term sensorimotor and psychosocial outcomes after childhood stroke when assessed in young adulthood in a small cohort of 26 patients[33]. In this study, outcomes were reported an average 10 years after stroke and the authors demonstrated that 80% of patients had complete recovery or mild deficit on a mRS but over 25% of them also self-identified as having mental illness[33], compared to approximately 5% of healthy children ages 3–17 years old with anxiety and depression[34]. Taken together, these results suggest that pediatric stroke has a complex interplay between developmental processes and neural injury resulting in emergence of certain deficits and improvement of others, and it is essential that we study pediatric stroke independently rather than extrapolation from studies of the mature adult brain.

How does the brain recover after neural injury?

The immature brain offers a unique substrate to investigate neural injury and repair. Prior work has compared the early recovery phase after stroke to critical periods of neural plasticity that occur during development[35,36]. The interaction between developmental plasticity and regenerative mechanisms needs to be more thoroughly explored.

Two mechanisms have been proposed by which recovery after neural injury such as stroke is made– behavioral restitution and compensation, both of which have clinical and research importance. First, “true recovery” or behavioral restitution is a process by which patients return to more normal patterns of motor control[37,38]. This requires repair of damaged neural networks to allow for return of behaviors that existed prior to neural injury[37]. Second, compensation is a process where patients use new behaviors to substitute for tasks which they can no longer accomplish after neural injury[37]. Compensation mechanisms require circuits of neural learning and adaptation. For example, children can pick up a cheerio with a fine grasp of their index finger and thumb, called a pincer grasp. If we assume a school age child has a right MCA stroke and loses significant ability to move her left hand, behavioral restitution would exist if after the stroke our patient were to recover the ability to grab small objects again with a left hand pincer grasp; whereas, compensation would exist if the child was instead able to rake an object towards her using all the fingers on her left hand to create a grasp (i.e. a raker grasp) or if she used her right hand to pick up the object.

Certain rehabilitation assessments give more weight to one recovery mechanism. For example, the Fugl-Meyer assesses individual joint movements to look for behavioral restitution of muscle activation without inappropriate synergies[39]. In contrast, the Modified Rankin Scale (mRS) assesses a patient’s ability to perform tasks of daily living where compensatory mechanisms are equally valued[40]. In pediatrics, the Pediatric Stroke Outcome Measure (PSOM) is the most widely used scale, which has limited aspects of both. Both compensatory and behavioral restitution mechanisms are important for rehabilitation after stroke; however, the therapeutic strategies and neural processes involved in each may be distinct.

Mechanisms of stroke recovery

When a stroke occurs, cells in the affected area are deprived of their normal metabolic substrates (e.g. oxygen, ATP), which results in apoptosis of neurons and cascades of cell death[41]. Much of what we know that happens in the acute period after stroke comes from stroke animal models. Many factors have been proposed to play a critical role during this period to facilitate recovery, some of which are similar to crucial periods of plasticity that occur during development[35,36,42]. These changes occur on multiple different levels– from molecular to networks of cells.

Molecular and cellular changes after stroke—Neural injury from stroke initiates a wave of regenerative responses resulting in neurogenesis, axonal growth, and synaptogenesis. Studies have shown that increasing activity over time in peri-infarct areas directly correlates with final clinical outcome[27,43]. Peri-infarct areas have high levels of growth related proteins similar to normal development (e.g. NeuroD, GAP43, synaptophysin, VEGF, BDNF)[35]. This wave of growth factor upregulation drives increased neurogenesis in the hippocampus and subventricular zone, producing new neurons that migrate towards the penumbra[44,45]. This neurogenic response correlates with recovery in preclinical models, although the mechanisms remain uncertain as very few newly generated cells survive and incorporate into local circuitry after stroke[46]. Neurogenesis declines with age, but migration of young neurons remains prevalent in early infancy[47,48]. We still do not know whether the effect of neurogenesis on stroke recovery varies by age, or whether cell-based therapies would be more effective in the immature brain.

Axonal growth and dendritic sprouting increase after stroke, both in the penumbra and in the non-stroke hemisphere, with subsequent pruning in a process similar to development[35,41]. Pro-inflammatory proteins such as brain-derived neurotrophic factor (BDNF) are upregulated after stroke, which leads to enhanced synaptogenesis[49]. Enhancement of these proteins and downstream cascades improve cortical restructuring and recovery in rats after stroke[50], possibly through mechanisms of motor learning since BDNF has been shown to increase with motor learning tasks in healthy adults[51]. However, the upregulation of these proteins are only present for a limited time after stroke, leading to the theory that there is a critical window by which to optimize these mechanisms to promote recovery[41]. Synaptic density increases during early childhood, peaking at around three years of age with subsequent pruning to adult levels during later childhood and adolescence[52]. The molecular signals driving synaptic remodeling during development may alter injury responses in the peri-infarct cortex and modify the window during which recovery can occur.

It is enticing to imagine that in children, naturally occurring growth and development might provide a longer window of recovery; the brain increases in size fourfold through preschool age[53]. Prenatally, brain development is mostly comprised of neurogenesis and the migration of those neurons; however, postnatally, changes consists predominately of glial cell proliferation, integration, and synaptic development to allow for the establishment of mature neural networks. While increased capacity for plasticity may be helpful for recovery after injury, interruption of the establishment of neural networks by stroke may also have detrimental consequences that are unique to the immature brain. After adult stroke

neurogenesis, gliogenesis, and synaptogenesis must be upregulated; however, in pediatric stroke it is not only the penumbra that is undergoing restructuring, but rather the entire brain. The interplay of developmental plasticity with neural injury and recovery remains poorly understood. One view is that post-stroke recovery recapitulates developmental programs, and indeed many genes and cellular processes typically seen during earlier stages of neurodevelopment are reactivated following injury[35]. Other studies, however, have shown substantial differences in gene expression between the immature brain and the adult peri-infarct cortex[54]. Understanding these differences may help to optimize therapeutic approaches to stroke in children compared to adults.

Synaptic plasticity underlies network restructuring after stroke—A localized brain injury disrupts the underlying balance of extensive networks that are responsible for nearly every facet of our activities as humans. As we learn new facts, practice new movements, create new memories the brain must have a way to constantly maintain, update and create new neural networks. It does this through synaptic plasticity, defined as the ability of synapses (i.e. connections between two cells) to increase or decrease their activity over time, which occurs both in normal development and recovery after stroke. Synaptic plasticity is regulated by two mechanisms which balance each other to develop neural networks– Hebbian and homeostatic plasticity[36,41].

Hebbian plasticity states that the strength of a synapse depends on the simultaneous activity of its neurons; stated more commonly “cells that fire together wire together.” The activity of a synapse is modified through mechanisms of long-term potentiation and long-term depression; which are underpinnings in the neural processes of learning and adaptation. However, unchecked Hebbian plasticity would make neurons reach a maximum plateau quickly and cells would be unable to make further changes. What balances this is homeostatic plasticity; homeostatic plasticity maintains average neuronal activity by allowing a neuron to modify its excitability relative to the entire neuronal network[36]. In other words, this brings neuronal activity back into a “normal range” so that it can continue to make further connections, allow for further learning, or recovery after neural injury. These processes are active throughout life but are some of the most important drivers for normal development in childhood.

In the first few days to weeks after stroke, synaptic activity is disrupted in both peri-infarct and distant cortical structures[41]. As a result, post stroke neuronal hyperactivity occurs with expanded receptive fields and spontaneous activity in the first few months of the recovery period[41,55]. This allows for increased synaptic plasticity. Hyperexcitability induced in the peri-infarct tissue is thought to be a result of homeostatic resetting, which in turn upregulates axonal sprouting allowing for new connections to form and redevelop the networks damaged by the stroke[56,57]. Pruning occurs though Hebbian and other learning-like mechanisms to strengthen the networks most beneficial and important to survival. The peri-infarct zone or “penumbra” has been shown in primates to be one area of significant plasticity after stroke[58]. In particular, one study showed facilitated processes of Hebbian plasticity in peri-infarct tissues 7–10 days after stroke[59].

The reorganization of neural networks can be visualized with imaging or assessed with noninvasive brain stimulation. Functional MRI studies show that after stroke, patients exhibit more activation in bilateral premotor cortices and contralesional primary motor cortex when using their affected hand compared to the unaffected limb, which has more localized unilateral activation of primary motor cortex[60–62]. In healthy newborns motor control involves bilateral activity[35,63]. As the child ages, progressive inhibition of the ipsilateral cortex occurs resulting in the adult pattern of contralateral motor control. One study using transcranial magnetic stimulation (TMS) in healthy children demonstrated significantly lower ipsilateral responses and longer ipsilateral latencies by 18 months of age[64]. Another study showed that by 10 years of age ipsilateral responses were not even detectable[63]. Subcortical or deep cortical control of movements in infants is one proposed reason why deficits in perinatal stroke appear to develop during the first year; as developmental synaptic plasticity progresses, and activation becomes contralateral, lesioned structures exhibit difficulty controlling movements. However, the characteristics of the ipsilateral connections differ between perinatal and adult stroke. Eyre et al. suggest that patients with congenital spastic cerebral palsy or perinatal stroke demonstrate a greater number of fast ipsilateral and contralateral projections from the nonlesioned hemisphere even compared to adult stroke patients[64]. This is supported by MRI studies showing increased size of corticospinal projections from the contralesional hemisphere in perinatal stroke patients[65]. In other words, because of the stroke, these infants do not have normal regression of the ipsilateral connections to the affected limb. In addition to motor outcomes, a small case series demonstrated with functional MRI that language function (which is most commonly lateralized to the left hemisphere) showed more bilateral recruitment in adults that suffered childhood left MCA strokes when compared to healthy controls and recovered adult stroke patients[66]. Taken together, research suggests that adults with bilateral cortical activation (e.g. compensatory mechanisms) have worse outcomes compared to those that have restructuring of neural networks (e.g. behavioral restitution) closer to the penumbra[67]. It is not yet clear of this holds true for infants and children.

What therapies can be utilized to promote recovery in pediatric stroke?

Little is known about the acute treatment and rehabilitation techniques important to pediatric stroke. For adult patients, management of acute stroke involves evaluation for possible treatment with recanalization strategies such as thrombolysis (i.e. tPA) and thrombectomy. In 2010, the National Institute of Neurological Disorders and Stroke (NINDS) funded the first prospective treatment trial in acute pediatric stroke entitled the Thrombolysis in Pediatric Stroke (TIPS) trial; however, due to lack of accrual, the study was closed in 2013[4]. Since that time, hospital systems have created pediatric stroke teams and standards for the diagnosis and treatment of pediatric stroke, yet due to delays in presentation, only about 2% of children are eligible for treatment with thrombolysis and thrombectomy[3].

The standard of care after pediatric stroke is to obtain physical, occupational, speech and language therapy, and neuropsychological evaluations once the patient is medically able to participate in these interventions. For an individual patient, recommendations can range between no therapy, outpatient therapy, in school therapy, and intensive inpatient rehabilitation. However, the benefit of the dose, timing and intensity of these treatments is

not well known. Some recent studies have suggested that within the current standards for adult patients there is limited functional improvement from these therapies[68]. That discussion is even more complex for pediatric patients. As has been stated previously, pediatric patients are unique in that sometimes deficits become apparent well after the stroke. For example, perinatal stroke patients might appear completely normal at the time of stroke. When should we have infants participate in physical therapy? Should they receive therapy when they have no deficits? Should we start therapy around 3 months of age when we expect they might start developing asymmetries in their neurological exam? Even more so, what effective therapies can be done with a 3 month-old?

Constraint induced movement therapy (CIMT) has been proposed as a potential option to improve motor outcomes after childhood stroke. Let's think about our patient earlier that had a right MCA stroke affecting the ability of her left hand to pick up a cheerio. In CIMT, we would place her right hand/arm in a cast or mitten, forcing her to continue to use her affected left hand to do all her normal activities. Patients typically complete 3 weeks in an intensive program where they receive multiple hours of therapy each day for 5 days a week but continue to wear the cast or mitten at home. Individual studies report variable effectiveness of CIMT in adults, but more recent systematic reviews suggest that it does not significantly impact their disability level compared to standard therapies[69]. For pediatric patients, studies have shown promising results for CIMT with improvement in use of affected limb that persists 3–12 months after the training sessions, however, these studies only have approximately 20 patients in them and there have been no large studies investigating the utility of CIMT in pediatric patients[70]. Moreover, the main outcome measures for these studies have been to quantify spontaneous use of the more affected extremity in life situations, and less is known about the quality of the movements and if this represents more compensatory mechanisms versus true biological restitution[70]. An additional unique concern in the pediatric population is that children are still developing skills with their "good" hand as well, and studies have shown that intensive bimanual therapy may be able to achieve comparable benefits[71]. Limited data suggest that the pattern of reorganization may be important in clinical outcomes and the response to CIMT, but larger studies are necessary to refine and validate this hypothesis[72,73].

One emerging avenue is the use of noninvasive brain stimulation to aid in the prognosis or modify outcomes of children after pediatric stroke. For example, lack of evoked motor responses assessed with transcranial magnetic stimulation (TMS) at 2 years of age, but not birth, was correlated with worse functional use of the affected hand[74]. Noninvasive brain stimulation is an emerging area that may prove beneficial as adjunctive treatments to promote recovery. One study combined both CIMT and repetitive TMS (rTMS) for children with chronic perinatal stroke and found additive benefits in upper extremity function at 6 months after the intervention[75]. A study of transcranial direct current stimulation (tDCS) found no objective benefits in upper extremity function, but improved patient satisfaction and subjective performance outcomes at one week after intervention, but diminishing by 2 months[74,76]. These preliminary studies suggest that noninvasive brain stimulation combined with movement therapies such as CIMT or motor learning paradigms might yield improved outcomes.

Motor learning studies have shown that stroke patients can exhibit more “normal” movement patterns through introduction of particular training environments and perturbations[77–79]. In particular, repeated training on a split-belt treadmill can improve symmetry of gait in adult stroke patients more than 6 months out from their stroke[80]. Robotic hand motor therapy which focused on precise repetitive movements of the affected limb showed improvement in hand motor function and changes in functional MRI[81]. Robotics and virtual reality environments are exciting tools that facilitate engagement for children to participate in repetitive training tasks that might benefit recovery. However, it is not yet understood if these same motor learning principles can be applied to pediatric stroke patients.

Pharmacologic interventions in the acute period after stroke have not been specifically studied in pediatric patients. For adult stroke patients, the FLAME trial in 2011 demonstrated improvement in the Fugl Meyer motor score for patients that received fluoxetine the first 90 days after stroke[82]; however, a more recent trial (FOCUS trial) showed no improvement in the modified Rankin Scale for patients receiving fluoxetine compared to placebo[83]. Although there were some differences in the study design between these two large studies, utility of fluoxetine to aid in the motor recovery of adult stroke patients is not completely clear[84]. Investigators need to study the effectiveness and safety of pharmacologic interventions such as fluoxetine in pediatric stroke directly, as clinical practice varies widely based on patient age and physician preference regarding this potential therapy.

Alternative therapies such as stem-cell based treatments have been explored in the research community. The majority of the studies investigate the feasibility and safety of cell-based therapies in the chronic phase of adult stroke[85]; more definitive efficacy trials are underway[86,87]. For pediatric stroke, there is even less evidence. One group has been completing small clinical trials using autologous cord blood (ACB) infusion in children with CP (not just perinatal stroke), and reported improved motor function in children receiving high doses of stem cells[88]. Yet, the authors also state that motor outcomes were better than predicted both for the experimental and control groups suggesting the highly motivated families participating in this study were more engaged in developmental therapies available[88]. The hypothesis and presumed mechanism of such studies is unclear, and likely will vary depending on the phase of stroke targeted. More rigorous studies are necessary in order to further advance cell-based therapy.

SUMMARY

The dearth of evidence regarding rehabilitation therapies after pediatric stroke offers tremendous potential for research. Pediatric stroke presents a unique condition in which we can study the physiologic interplay between neural development, injury and repair. Every parent asks the question, “what deficits will my child have as a result of this stroke?” or “what can I expect them to be able to do in the future?” Unfortunately, for many of these questions we cannot give reliable answers. Moreover, the limited information we do have is mostly with regards to motor outcomes, which is what this review focuses on; cognitive and language outcomes are even more difficult to predict. To better serve our patients, we need to understand when, how, and to what extent recovery can occur across all ages.

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Table 1:

Summary of pediatric stroke outcomes

Study	Country	N	Ages	Follow-Up Interval (years)		Favorable Outcome Definition	% Favorable Outcome
Ganesan 2000	United Kindgom	90	3m-15y	Median	3	Composite Score < 4 (“impairments unlikely to interfere with daily life”)	40%
				Range	0.25–13		
deVeber 2000	Canada	123	0–17.8y	Mean	2.07	PSOM Classification Normal-Mild (Total Score 0–0.5)	52%
				Range	0.01–17.59		
DeSchryver 2000	Netherlands	27	3m-14y	Mean	7.1	mRS 0–1	59%
				Range	0.25–20		
Steinlen 2004	Switzerland	16	6m-16.2y	Mean	7	mRS 0–1	56%
				Range	0.5–16.2		
Goeggel-Simonetti 2017	Switzerland	95	1m-16y	Median	6.9	mRS 0–1	56%
				IQR	4.7–9.4		
deVeber 2017	Canada	667	0–18y	Mean	3	Clinician Grading: Normal-Mild	68%
				IQR	2.8–3.2		