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Intellectual outcome after a cortical lesion with versus without epilepsy: A life span neurodevelopmental view

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ABSTRACT

In patients with cortical lesions, the structure of intelligence has never been studied as a function of age at lesion onset and presence vs absence of lesional epilepsy over the life span.
Method: Two thousand one hundred eighty-six cases were assembled bearing unilateral cortical lesions occurring at all ages (1301 with seizures) with postlesion verbal intelligence quotient (IQ) (VIQ) and performance IQ (PIQ).
Results: Global IQ significantly and constantly *decreased* as a function of age at lesion onset in the cases without epilepsy, and *increased* in the cases with epilepsy. Beyond the lesion onset age of 12 years, VIQ was significantly *higher* than PIQ in the cases without epilepsy, and *lower* in the cases with epilepsy. The VIQ/PIQ × lesion-side interaction indicative of hemispheric specialization *increased* significantly linearly with age at lesion onset in the patients without epilepsy but ceased to progress at the lesion-onset age of 30 years and beyond in the cases with epilepsy.
Conclusion: Postlesion global IQ, the difference between VIQ and PIQ, and the laterality index all vary significantly as a function of age at lesion onset. In addition, these changes over the life span are all quite different between cases with and without epilepsy.

1. Introduction

The lesion method is still widely used in neuropsychology and behavioral neurology to analyze mental impairment, and from there, to determine how cognitive abilities might normally implement in the brain. However, there exists as of yet no detailed life span view of mental impairment due to brain lesions after various periods of normal development. One enormous complication for the lesion method is that epilepsy often sets in after a brain lesion, and very little is known about how this further channels mental impairment. Functional imaging appears as a much more direct and obviously nonintrusive method for studying brain function today. However, there remain several important findings that the lesion method can provide about cognitive brain development that functional imaging cannot access. For instance, intelligence cannot be functionally imaged but can be assessed after a lesion. The high cost of functional imaging precludes analysis of thousands of cases as can be done with files of patients with brain damage accumulated over many decades. Functional imaging cannot be done on neurotypical neonates, but the lesion method can assess the effect of lesions at occurring at any age — including before birth.

Intellectual development in childhood is extremely rapid, as indicated by doubling of raw IQ each year from age two to five years, then tapering off to nearly no change at all by the age of seven years [1]. Any tissue, including in the brain, is more at risk for teratogenic outcome if it suffers an insult during rapid development [2]. This rule could apply to intellectual functioning in humans. Young brains are particularly vulnerable to damage resulting from challenges to (a) the blood–brain barrier (e.g., fetal alcohol syndrome, lead poisoning syndrome), (b) the immune system (e.g., microcephaly from Zika infection), or (c) protection against mechanical trauma (e.g., shaken baby syndrome). On the other hand, certain specific cognitive functions seem to be more compensable in cases with early lesion onset (e.g., language recovers remarkably well after large left-hemisphere neonatal lesions), and of course, there are multitudes of vulnerabilities associated with senescence, ranging from cumulative damage to DNA [3] to progressive brain atrophy [4]. These deteriorations of the neurotypical aging brain are strongly reflected in the decline of raw intelligence, particularly the raw scores underlying the performance IQ (PIQ) of the Wechsler Adult Intelligence Scale (WAIS I-III). Of course, this effect is not reflected in the WAIS standard scores because the Wechsler scales are designed to maintain a population mean of 100 at all ages.

Very few studies have investigated age at lesion onset as a factor influencing cognitive outcome over the whole life span following brain injury in humans [5,6], particularly with the Wechsler scales of

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intelligence [7]. These studies followed the work of Margaret Kennard [8,9] on rats and monkeys, who observed that cognitive functions had a better prognosis when a brain lesion occurred earlier in life. Kennard studied the effects of lesions on cognitive performance at all ages and found a strong monotonic life span function. This is one of the most important findings in developmental cognitive neuroscience. This "Kennard effect" has since been challenged as far as full-scale IQ (FSIQ) is concerned [5,6]. These latter reports described a highly significant opposite effect. However, these studies did not take into account the role of epilepsy in intellectual outcome, nor of the neurodevelopmental difference between verbal IQ (VIQ) and PIQ of the Wechsler scales of intelligence. Kennard's work was based on surgical lesions that were uncomplicated by epilepsy.

Dennis [10] explains particularly well that the developmental stage of a given skill must be taken into account when considering the effects of early brain damage. In addition, the ongoing epileptic history of the patient over his or her entire life span is thought to be of paramount importance [11,12]. Epilepsy complicates cognitive recovery and intellectual development after a brain lesion, but the exact mechanism by which it does so remains unclear. The impact of epileptic seizures on intellectual development as a function of age of onset has been attracting increasing attention from clinicians and researchers alike. A single seizure provoked by injection of kainic acid in rat pups can lead to an autistic phenotype in adulthood [13]. In humans, early seizure onset has been linked to attention-deficit hyperactivity disorder [14]. Baldeweg and Skirrow [15] assert that there is an urgent need to identify the clinical factors that would ensure better long-term cognitive outcome in children suffering from epilepsy.

Studies in cognitive development in children with epilepsy have generally yielded a common finding: earlier onset of epileptic symptoms tends to result in worse intellectual outcome [16–24]. Early-onset epileptic disorders such as West and Lennox–Gastaut syndromes can have a catastrophic effect on cognitive development [25]. Duration of epilepsy is related to age at onset and appears to be an important negative predictor of intellectual outcome [26–28]. Early-onset epilepsy typically comes with brain pathology that is qualitatively different from late-onset epilepsy [26]. For example, cortical dysplasia is more common in early than late-onset epilepsy [29]. Early-onset epilepsy can be both the consequence [30] and cause [31] of brain damage. Even with epileptic spiking brought under control by antiepileptic drugs (AEDs), the benefit to intellectual outcome is partially compromised over the long term by the neurotoxic adverse effects of the medication [22, 32,33]; AEDs can also lead to reduced psychomotor speed [34], which in turn can affect performance in the timed tests composing some of the IQ scales. It thus appears possible that, in humans, effects of lesions could yield a "Kennard" effect while effects of epilepsy could yield an "anti-Kennard" effect.

Normal aging, which in senescence involves brain atrophy, affects raw performance (PIQ) intelligence far more than raw verbal (VIQ). Early terms used to describe age-resistant versus age-frail cognitive functions were *crystallized* versus *fluid* intelligence, respectively [35]. It was soon recognized that the WAIS VIQ raw score was resistant to aging whereas the WAIS PIQ raw score was not, because of the brain atrophy occurring naturally during senescence [36]. Stated otherwise, because PIQ includes an important working memory component, presents novel visual stimuli, and is under time constraint, it is less of a measure of overlearned cognitive habits than is VIQ; VIQ is a more direct measure of cultural learnedness [37]. This may explain why PIQ is apparently more susceptible to a practice effect than VIQ even in normal populations, gaining 8.4 points as opposed to 3.3 points for VIQ after retesting [38]. Naturally occurring brain atrophy in normal senescence particularly affects measures of fluid intelligence [39,40], especially for timed tasks [41]. In cases with focal lesions, PIQ appears to be intrinsically more affected than VIQ, especially in children [42,43].

Studies investigating VIQ and PIQ developmentally in people with epilepsy have been limited by small sample sizes, poor control of heterogeneous brain morbidity and lesions, as well as arbitrary and incomparable age groups, and have yielded contradictory findings. Hermann and collaborators [14] reported a lower PIQ than VIQ, with both scores improving at a second assessment. Luerding et al. [44] reported that, in a sample of 28 patients having undergone surgery between the ages of 13 and 53, PIQ tends to decline whereas VIQ tends to increase over time. In children between 7 and 35 months of age presenting with childhood spasms, PIQ was lower than VIQ by up to 17 points [45]. On the other hand, some studies have shown that VIQ is more vulnerable to epilepsy-related impairment [22, 46,47]. Bjornaes et al. [48] observed that both VIQ and PIQ remain stable between assessments in people with adult-onset epilepsy, but tend to decline in patients with juvenile-onset epilepsy.

Finally, it remains controversial whether in unilaterally lesioned patients, epilepsy typically *increases* cognitive effects of lesions revealing hemispheric specialization [49,50], *decreases* them [51], or *inverts* them in the early lesion-onset cases by forcing a shift in the hemispheric implementation of cognitive functions [52–55]. Another hypothesis is that early brain injury provokes abnormal asymmetry in infants by the shifting of hemispheric specialization through "crowding" of the right hemisphere. However, it is not yet clear whether epilepsy is necessary for crowding to occur [49,54–59]. It is important to understand that in the context of the present investigation, we searched for cases with focal cortical lesions, and the epilepsy could be of any type: strictly unilateral and focal on the one hand or generalized on the other hand. Epileptology studies aiming to investigate hemispheric specialization have been based only on the former type of epileptic presentation. Previous studies have therefore been unable to determine whether, with unilateral cortical lesions, epilepsy mostly aggravates the ipsilesional anatomy and physiology, producing an effect on cognitive abilities resembling a larger lesion, or whether the presence of seizures has a more widespread impact, producing the opposite effect on cognitive abilities as if epilepsy were so stressful for the whole brain that it hinders the implementation of hemispheric specialization altogether or might even redistribute it after it has been normally implemented. Given that controversy, it is even less well-established how such changes might occur as a function of age at lesion onset [60].

1.1. Purpose of the present investigation

To the best of our knowledge, no study has investigated the effects of age-related variables in lesional epilepsy with VIQ and PIQ in a sufficiently large sample to get any kind of life span perspective, in addition to controlling for lesion-related variables, particularly with regard to early brain development. The current investigation aimed to ascertain post-lesion VIQ and PIQ across the entire life span, with sufficient statistical power and extensive control of lesion-related variables — including precise age-tagging of lesion onset, symptom onset, and age at IQ testing. In particular, this investigation was designed to be able to clearly disentangle lesion effects from epilepsy effects on intellect in a developmental context spanning the entire life span.

2. Method

2.1. Patient selection

We ran extensive searches in Google Scholar using VIQ and PIQ or verbal or performance intelligence as keywords (>200,000 hits). Whenever a relevant report or group study was obtained, a thorough investigation of the paper's bibliography followed in order to obtain other reports that matched our criteria; 1820 cases were collected by us over two decades from existing scientific literature, and a further 366 cases were kindly collected for us by collaborators in medical files of 5 hospitals in eastern Canada. All handling of the data was done in full conformity with the Tri-council policy statement: Ethical conduct for research involving humans. Ottawa (ON): Canadian Institutes of Health