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Neurocognitive Outcome After Pediatric Epilepsy Surgery: A Review of the Literature

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Surgical resection is increasingly employed for treatment of intractable seizures in children. However, although the effects of epilepsy surgery on cognition in adults are relatively well known, comparable information with regards to children remains sparse. Further delineation of the risks and benefits of surgery in children would clearly be useful to clinicians involved in the assessment and treatment of pediatric epilepsy patients. This paper provides an overview of existing research on neurocognitive functioning after pediatric epilepsy surgery. Effects on intellectual functioning, language, memory, visual-spatial skills, attention, and executive functioning are reviewed with respect to the most commonly-studied surgical interventions in children, including temporal lobectomy, hemispherectomy, and focal cortical resections. Methodological limitations of existing research and conceptual issues inherent in assessing cognitive abilities in children are also discussed.

Resultados Neurocognitivos Posteriores a la Cirugía de la Epilepsia Pediátrica: Una Revisión de la Literatura

La resección quirúrgica es ampliamente empleada para tratar las criris epilépticas intratables en niños. Sin embargo, aunque los efectos de la cirugía sobre la cognición en adultos se conocen relativamente bien, no hay información similar respecto a los niños. La clarificación respecto a los riesgos y beneficios de la cirugía en niños seria útil para los clínicos involucrados en la evaluación y tratamiento de estos pacientes. Este documento ofrece una revisión de la investigación existente sobre el funcionamiento neurocognitivo posterior a la cirugía de epilepsia. Se revisan los efectos sobre el funcionamiento intelectual, el lenguaje, la memoria, las habilidades visuo-espaciales, atención y funcionamiento ejecutivo con respecto a la intervención quirúrgica más estudiada en niños, incluyendo la lobotomía temporal, hemisferectomía y reseciones corticales focales. Adicionalmente, se discuten las limitaciones metodológicas de las investigaciones existentes así como las aspectos conceptuales inherentes en la evaluación de habilidades cognitivas en niños.

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Epilepsy surgery is increasingly used for treating intractable seizures in children, likely due to mounting evidence that earlier surgical interventions lead to better outcomes (Falconer, 1972; Mizrahi et al., 1990; Shewmon et al., 1990). Resection is seen as a treatment that may reduce or eliminate intractable seizures and lead to better functional outcome while causing few cognitive or motor side effects. In children, there is also the assumption that after surgery, any adverse cognitive sequelae may be minimized by the young brain's inherent plasticity. However, emerging research suggests that surgery in children may also be associated with a degree of cognitive risk, as is the case in adults. Often, these risks may be mitigated by the benefits of reduced antiepileptic medication (AEDs) and reduced cognitive and psychosocial interference from seizures. Evidently, an informed analysis of cognitive risks and benefits remains an important aspect of surgical decision making in pediatric epilepsy.

This paper examines the existing literature on neurocognitive outcome in children after epilepsy surgery, with particular emphasis on the cognitive benefits and costs of common neurosurgical procedures such as temporal lobectomy, hemispherectomy, and other focal cortical resections. The effects of these different surgical approaches on outcome will be reviewed with respect to intellectual abilities, language, memory skills, visual-spatial skills, and attention/executive functioning. Methodological and conceptual limitations of existing research will also be discussed (for outcome after less frequently employed specialized surgical procedures such as subpial transection and corpus callosotomy, the reader is referred to works such as those by Sass et al., 1992 and Grote, Slyke, & Hoeppner, 1999).

Temporal Lobectomy

Temporal lobectomy in children is an effective treatment for reducing seizures: approximately 56 to 93% of children become seizure-free or have a 90% reduction in seizures after surgery (Goldstein et al., 1996). It should be noted that children who undergo temporal lobectomy are a heterogeneous group; they present with a variety of etiologies, including mesial temporal sclerosis (MTS), cortical dysplasias, and tumors. Compared to the relatively voluminous literature on cognitive outcome after temporal lobectomy in adults, pediatric studies on cognitive outcomes are few. However, existing literature suggests similarities between the cognitive effects of this procedure in adults and in children.

Intelligence

In a comprehensive review of the literature, Strauss and Westerveld (in press) concluded that after temporal lobectomy, children show few changes in verbal or nonverbal intelligence, regardless of the side of resection. Large-scale studies (Westerveld et al., in press) and studies on smaller samples (Adams et al., 1990; Caplan et al., 1993; Gilliam et al., 1997; Meyer et al., 1986; Szabo et al., 1998) support this conclusion. This is consistent with the adult literature.

Although these studies are informative in their own right, the conclusion that temporal lobectomy is not associated with any changes in intellectual ability in children is somewhat tempered by the fact that the use of empirically based techniques for measuring change is uncommon in the pediatric literature. These techniques, well studied in the adult literature, allow the researcher to account for confounding factors that influence postsurgical scores (for a review, see Chelune et al., 1993; Hermann et al., 1991; Hermann et al., 1996; McSweeney et al., 1993; Sawrie et al., 1996). Such confounding factors include practice effects, measurement error, test-retest reliability, and regression towards the mean. For example, Szabo et al. (1998) note that minimal or no change in cognitive functioning after surgery may indicate an actual decrease in IQ due to the fact that normal children evidence significant practice effects on IQ tests. In pediatric populations, there is also the additional factor of maturation, which may influence re-test values in different ways depending on the child’s age at pre-test.

Memory

In many adult patients, temporal lobectomy is associated with material-specific changes in memory skills consisting of verbal memory decline after left temporal resections and, somewhat less reliably, visual memory decline after right temporal resections (e.g., Barr et al., 1997; Helmstaedter & Elger, 1996; Gleibner, Helmstaedter, & Elger, 1997). Along with resection side, there are also additional factors that predict the risk of post-surgical changes in memory in adults. These include preoperative variables such as type of pathology, presurgical cognitive levels, extent of resection, age at seizure onset, age at surgery, and degree of post-operative seizure control (e.g., Chelune, Naugle, Luders, & Awad, 1991; Helmstaedter & Elger, 1996; Hermann, Seidenberg, Haltimer, & Wyler, 1995). Among existing factors, risk in adults appears to depend most strongly on whether surgery removes a functional or a dysfunctional hippocampus (Chelune & Najm, in press). This is the crux of Chelune's (1995) hippocampal adequacy model, which dictates that the risk for memory decline is inversely related to the functional adequacy of the tissue to be resected. Thus, patients with mesial temporal sclerosis (MTS) are at much lower risk of memory decline than patients without signs of memory dysfunction or pathology. A small number of studies suggest a similar situation in children.

For example, Adams et al. (1990) studied a group of 28 children under the age of 16 years. At six months post-surgery, verbal memory scores had declined after left temporal lobectomy whereas non-verbal memory was unchanged, regardless of resection side. These authors found that the extent of verbal memory loss tended to be worse in those with better preoperative verbal memory scores. Similar findings were reported on a group of 11 children by Szabo et al. (1998). As in adult studies, Adams et al. found that children with MTS were less affected by verbal memory loss post-surgery.

Certain pediatric studies have reported inconsistency or lack of laterality effects (i.e., side of resection/side of focus) across memory measures (Adams et al., 1990; Meyer et al., 1986; Szabo et al., 1998). In some studies, these results are interpreted as possibly reflecting differences between the organization of memory systems of children and adults (Szabo et al., 1998). Other explanations, such as memory suppression effects of AEDs (Rausch, 1991) and a lack of sensitivity of some memory measures to lateralized deficits (Adams et al., 1990; Barr et al., 1997) are also possible.

A study by Helmstaedter and Elger (1998) involving a mixed sample of 104 adults and children suggests that there may be one major difference between children and adults when it comes to postsurgical memory functioning, namely, that children are at less risk for certain kinds of memory decline after dominant hemisphere resections than are adults. The authors compared verbal long-term memory (posited to reflect mesial/limbic temporal functioning) to short-term memory or working memory (presumed to reflect neocortical functioning). Although younger patients incurred similar losses in verbal long-term memory post-surgery, unlike the older patients, no patient aged younger than 15 years experienced a significant deterioration in verbal short-term memory. The authors posited that short-term memory could be compensated for by other left hemisphere functions in young people but that this capacity for compensation declines with age. Although minimal information was provided on their epilepsy control group, this is the only study published to date in the pediatric literature that used a statistical method to measure change in memory skills following surgery based on data from epilepsy controls (i.e., the reliable change index).

One often mentioned and potentially devastating outcome of temporal lobectomy is global amnesia. Specifically, a small number of unfortunate adult surgical patients have been rendered amnesic following unilateral temporal lobectomy in adults, typically because of undiagnosed temporal pathology in the non-resected hemisphere (see Loring, 1994, for review). No such case has yet been reported in the pediatric literature. Though the young brain's plasticity may reduce the chances of this rare and devastating condition, this assumed advantage might be offset by the fact that the hippocampus is an early-developing structure in primates (see Baron, Fennell, & Voeller, 1995). If neuroanatomical structures subserving memory become functionally dedicated at an early age, the critical period for preservation of memory is likely to have passed for all but the youngest of surgery candidates. Despite the absence of reported pediatric amnesic cases, this suggests that a global amnestic syndrome is clearly not an impossibility in children. This is a major reason for the routine use of the intracarotid amobarbital procedure (e.g., Wada test) prior to pediatric epilepsy surgery in order to rule out dysfunctional memory systems in the non-resected temporal lobe.

Language

In adults, some studies have documented language deficits consisting of naming problems and transient aphasia after left temporal lobectomy (Rausch, 1991; Saykin, Stafiniak, Robinson et al., 1995). These post-surgical language problems appear restricted to epilepsy patients without documented evidence of mesial temporal sclerosis (Seidenberg, Hermann, Wyler et al., 1998). Unfortunately, there are relatively few published reports on language functioning after temporal lobectomy in children; of those published studies, specifics regarding the measures used are often not reported (e.g., Mizrahi et al., 1990). However, the results from a study by Adams et al. highlight some of the similarities between findings from adult and pediatric series following surgery to the dominant temporal lobe. The researchers found that children with left temporal lobectomies assessed at 3 to 6 weeks following surgery had mild but significant declines in object naming. However, naming skills were back to baseline levels at 6 months post-surgery. Only one child with an unspecified degenerative condition had a lasting acquired impairment in comprehension. In comparison, the children with right temporal lobectomy actually demonstrated an improvement in language comprehension 6 months after surgery, presumably because of reduced interference from seizures. The authors did not indicate whether the presence of MTS was predictive of language functioning post-surgery, as is the case in the adult literature.

Attention and Executive Functioning

Research on attention and executive functioning (i.e., organization, planning, self-monitoring, response inhibition) in children with epilepsy is extremely rare. Rarer still are studies assessing these abilities pre- and post-operatively and in specific subgroups of children undergoing epilepsy surgery. One study with relevance to this field is a study by Caplan et al. (1993). The authors administered thought disorder and discourse analysis measures to children before and after left temporal lobectomy and found that the children improved on a measure of illogical thinking (i.e., inappropriate reasoning in causal and non-causal utterances presented to the listener). They interpreted this finding as possibly reflecting improved prefrontal lobe functioning secondary to increased seizure control. Studies in adults support this tentative hypothesis. For example, improved executive functioning following temporal lobectomy in adults has been interpreted as reflecting reduced interference in prefrontal systems from seizure activity originating in the temporal lobe (Hermann, Wyler, & Richey, 1988).

Hemispherectomy

Surgically removing a hemisphere to relieve refractory seizures in children is never undertaken lightly. However, hemispherectomy and related procedures (i.e., hemispherotomy, functional hemispherectomy, hemicorticectomy) are at times the only remaining treatment for some children with medically refractory seizures and widespread unilateral hemispheric abnormalities. Hemispherectomy is considered in cases of severe cortical dysplasia with primarily unilateral pathology (e.g., hemimegancephaly), other developmental conditions such as Sturge-Weber syndrome, or severe neurological conditions such as ischemic events leading to widespread damage in one hemisphere (Vining, Freeman, Carson, & Brandt, 1990). Hemispherectomy is also frequently the only recourse in children who develop Rasmussen’s encephalitis (RE), an inflammatory progressive brain disease of unknown etiology associated with intractable seizures in previously neurologically normal children that is often lateralized to a single hemisphere (Andermann & Rasmussen, 1991). From the point of view of seizure control and functional impairment, children undergoing hemispherectomy often represent some of the more severely affected children seen in surgical centers.

Intellectual Abilities

Unfortunately, many research reports on intellectual outcome after hemispherectomy in children contain significant methodological limitations such as poorly defined cognitive outcome measures, retrospective ratings, heterogeneous samples, and small sample sizes. However, some general principles have emerged from this important literature concerning intellectual outcome. Despite the radical nature of the surgery, cognitive levels in many children do not appear to be altered significantly by hemispherectomy. Several researchers have also noted increases in the intellectual functioning of some children following this procedure (Honovar, Janota & Polkey, 1992; Vining, Freeman, Brandt, Carson, & Uematsu, 1993; Vining, Freeman, Pillas et al., 1997). These findings appear to apply to all children who undergo hemispherectomy, regardless of the etiology of the intractable seizure disorder (Vining et al., 1997). Other evidence suggests that early age at surgery is a predictor of positive intellectual outcome, though reports are restricted to case studies and small patient series (e.g., Taylor, 1991).

Despite the extensive nature of the resection, explanations for the lack of decline in intellectual functioning following hemispherectomy have not yet been well elucidated. Contributing factors likely include the global nature of deficits pre-operatively in many children. In addition, the presence of floor effects in measurement tools may preclude the detection of subtle post-surgical changes. Cognitive improvements secondary to reduction in seizures and AEDs may also compensate for any surgery related losses. As noted above, Chelune has hypothesized that in the case of adult temporal lobectomy (1995), the ability to predict post-surgical changes in cognitive ability is more highly dependent on the functional adequacy of the to-be-removed tissue than on that of non-resected areas. This hypothesis may be a useful model for understanding and predicting cognitive outcome in hemispherectomy in future studies.

Language

From the point of view of language functioning, dominant hemispherectomy and other lesions that cause damage of a similar magnitude are profoundly impairing in the adult brain: global aphasia ensues almost invariably. In contrast, left-hemispherectomized children are rarely globally aphasic. Although early studies based on clinical impression appeared to support the notion that the immature brain was protected from adverse language outcome by its inherent plasticity (see Vargha-Khadem, Issacs, Papeleloudi, Polkey, & Wilson, 1991 for a review), more recent studies have documented enduring language deficits in children undergoing this radical surgery (Brandt, Vining, Stark, Ansel, & Freeman, 1990; Stark & McGregor, 1997). However, these deficits are far less severe than those found in adults, particularly in children whose dominant hemisphere operations occurred early in life. Taylor (1991) notes that the optimum time for recovery of language ability likely ranges between the ages of 1 and 5 or 6. As is likely the case with regards to IQ, younger children or children whose neurological insult occurred early in life tend to have the best language outcomes after hemispherectomy (Vargha-Khadem et al, 1991; Mariotti,, Iuvone, Torrioli, & Silveri, 1998; Ogden, 1989). In the case of RE, disease effects, including intractable seizures originating in the affected hemisphere (Stark, Bleile, Vining, & Freeman, 1995) may hamper recovery of language in the healthy hemisphere. This tends to support the notion that recovery of language and other cognitive functions may be maximised by early surgery conducted soon after onset of RE.

Vargha-Khadem et al (1991) reported that one of their patients with onset of RE prior to age 2 had language deficits that were as severe as those of the left hemispherectomy patients, suggesting that very early disease onset may have a global effect on functioning. This is supported by findings of children with other types of lesions acquired prior to age 1 who typically show both reduced verbal and performance IQ, regardless of the laterality of the neurological insult (Kolb & Fantie, 1997).

Many studies outside of the hemispherectomy literature have noted that language functions tend to be preferentially preserved after disease or injury compromising the dominant hemisphere. However, there appears to be a cost to this re-organisation of functions. For children age 5 or less, there is typically a shift of language dominance to the right hemisphere, and language deficits are lessened; however, this shift is accompanied by reduced visual-spatial skills, a consequence thought to result from “crowding” in the remaining hemisphere (for a review, see Strauss, Satz, &

Wada, 1990, Satz, Strauss, Hunter, & Wada, 1994). In the case of children who underwent hemispherectomy for intractable seizures, other neurocognitive functions may also be compromised. In particular, Ogden (1989) posited that the isolated right hemisphere cannot develop normal calculation skills, verbal fluency, nonverbal memory, or higher cognitive visuospatial skills, and that consequently, these are less important for survival than are other skills such as language. Other skills such as spelling appear to depend exclusively on left hemisphere functioning, though the ability to spell non-word is impaired regardless of side of resection, suggesting that the phonological spelling route depends on both hemispheres (Ogden, 1996).

Memory

Few researchers have studied memory processes after hemispherectomy. This lack of research is likely due to the difficulty in obtaining valid memory scores in medically ill and low functioning children and to a dearth of standardized memory measures for children available to researchers and clinicians in the past. However, a few existing reports suggest that memory skills may be preserved in those whose disease process or operation occurred early in life. For example, Mariotti et al. (1998) reported normal verbal memory scores in a woman who had had a left hemispherectomy at age 3 for Sturge-Weber syndrome, suggesting that verbal memory can be taken over by the right hemisphere. Information on her visual memory capabilities was not reported. Evidence from other studies suggests that verbal memory may be less vulnerable to neurological insult and preferentially preserved over language in early left-hemisphere brain disease, possibly because bilateral damage is needed to fully render memory systems non-functional (Helmstaedter, Kurther, Linke & Elger, 1994). Interestingly, Honovar et al. (1992) found hippocampal sclerosis in the resected hemisphere of 6 of 10 hemispherectomy cases with RE, suggesting that lateralized memory deficits may be part of the clinical syndrome of RE prior to the surgery itself.

Visual-Spatial Skills

Apart from findings related to the “cost” of language preservation on other cognitive skills as outlined above, there exist few studies on the specific effects of hemispherectomy on visual-spatial skills after surgery in children. In particular, compared to studies examining language outcome, knowledge about the mechanisms of recovery and compensation of visual-spatial skills by the dominant hemisphere is scant. A handful of studies indicates that there are material-specific deficits after right-sided surgery, but that many children with left-sided surgery also have visual-spatial problems. For example, Brandt et al. (1990), in their small series of hemispherectomized children, report that right hemisphere patients demonstrated deficits in spatial learning that were not evident in left hemisphere patients. However, Stark et al. (1995) noted the presence of non-verbal deficits in both left and right hemispherectomized children, the majority of whom had RE. They attributed this to bilateral disease effects.

Attention and Executive Functioning

Findings from a small number of studies suggest that attentional and executive functioning may be more compromised with right-sided hemispherectomy. For example, Brandt et al. (1990) administered both an auditory and a visual continuous performance test (CPT) to five patients following hemispherectomy. The CPT is thought to measure aspects of attention and executive functioning, namely the ability to sustain attention over time and to inhibit impulsive responding. Right-hemispherectomized patients performed more poorly than left hemispherectomized patients on both CPTs in terms of omission and commission errors. However, the authors note that the left-hemisphere group was significantly older than the right hemisphere group, which confounds interpretation of these results. In addition, data from control children was not available. Other evidence supporting left-hemisphere advantage for attention/executive skills comes from a case study of another right-hemispherectomized patient who showed disinhibition on certain tasks compared to a matched child with left-hemispherectomy (Stark & McGregor, 1997). In contrast, conflicting findings were reported by Mariotti et al. (1998), who reported normal auditory attention and executive skills in a woman who underwent left hemispherectomy at age 3. Whether lesion timing and age at surgery interact in determining attention/executive outcome after hemispherectomy is unknown, though findings from the animal literature suggest that these issues may be crucial in determining functional outcome (see Kolb & Fantie, 1997).

Other Types of Cortical Resections

Although many centers offer other types of surgeries in addition to temporal lobectomy and hemispherectomy, almost no research has been published on the cognitive outcome of children receiving frontal lobe resections or resections to other cortical areas for relief of intractable seizures. Although cognitive outcome measures are restricted to IQ, one exception is a study by Gilliam et al. (1997). In this study, 21 children were assessed both pre- and post-operatively, including 10 children with surgeries in the frontal lobe. Two other children had parietal and occipital resections, respectively. Although the exact nature of the surgery conducted was not specified (i.e., focal resection vs. lobectomy) and results were not provided by surgery type, none of the patients with extra-temporal resections had reductions in IQ post-operatively. In addition, two of the children with frontal resections had an increase in IQ greater than 10 points following surgery. That there does not appear to be any other outcome studies on this population is unfortunate, given that a substantial number of children undergo resections involving the frontal lobe, as well as other cortical regions. Further research in this area is clearly needed.

Methological and Conceptual Issues

The findings reviewed above represent a crucial first step to furthering our understanding of the effects of epilepsy surgery in children. However, as noted by Strauss and Westerveld with regards to pediatric temporal lobectomy, many studies are plagued by methodological problems that make the delineation of cognitive risks and benefits of surgery difficult. These include small samples sizes, unclear outcome measures, omission of actual test data in some reports and use of retrospective ratings of cognitive functioning in others, heterogeneous outcome measures (including in the case of IQ, collapsing data across different measures and test versions), lack of appropriate control groups, differing post-operative intervals, and as mentioned above, lack of methodologically rigorous techniques to account for confounding factors in the evaluation of change. In some studies, mixed samples consisting of both adults and children also confound pediatric specific interpretations of findings (e.g., Brandt et al., 1990; Mizrahi et al., 1990). Although likely due to the rarity of these patients, there is a preponderance of case studies in the hemispherectomy literature, which also makes generalization of findings problematic. In addition, specific variables such as side of resection, hippocampal volume, and baseline memory level, known risk factors for memory loss in adults after temporal lobectomy (Chelune & Najm, in press), have not yet been systematically studied in groups of children large enough to yield replicable and robust findings.

From a methodological perspective, measuring cognitive abilities in children necessitates use of measures that (1) are adequately standardized across age groups, (2) are developmentally sensitive, and (3) allow repeat testing at different ages for the same child (Adams et al., 1990). These are not easy criteria to meet. As noted above, not all studies have used repeatable instruments with adequate standardization, or reported their results in a format that includes the measures and norms used. In addition, it is only in recent years that standardized batteries for children measuring cognitive skills other than intelligence and language have become available, a situation that in the past was a considerable obstacle for studies on outcome after surgery in children. For example, current batteries now enable a detailed analysis of memory skills, attention skills, and executive functioning in children over time. More findings on the functioning of surgically treated children in these cognitive domains are expected as these batteries become increasingly used in routine pre- and post-operative assessment.

One purpose of surgery is to reverse or at the very least arrest cognitive and behavioural deterioration without producing more morbidity than the disease itself (Brandt et al., 1990). Thus, with good seizure control, surgery can be seen as a way ensuring that a child maintains his or her standing relative to peers, even if actual increases on tests of cognitive functioning are not found post-surgery. Measuring the effects of surgery on cognitive development can be thus be accomplished in two ways: (1) assessing the level of performance after surgery compared to presurgical levels, and (2) tracking changes in the pattern of development compared to peers, including determination of regression, plateauing, or slowed developmental course over time. Although studies have attempted to measure the former, the latter has not yet been assessed in pediatric populations. This is another promising avenue for future research.

Summary and Conclusions

Based on the literature surveyed and the caveats noted above, the following preliminary conclusions are offered. Pediatric epilepsy surgery appears to be a procedure with few adverse effects on general intellectual abilities, regardless of presenting problem or surgery type. In children who are candidates for temporal lobectomy, risks and benefits approximate those of adult patients. These include increased risk of verbal memory deficits in dominant resections and increased risk for memory decline in those with higher pre-operative memory levels and in those without identified MTS. With regards to hemispherectomy, dominant-hemisphere surgery conducted between ages 1 and 5 is likely to minimize adverse language effects and may be preferable to later surgery in terms of preserving language abilities. Due to secondary effects of disease that may inhibit recovery of function in RE, minimizing the delay between diagnosis of RE and hemispherectomy appears wise. In general, the critical period for recovery of memory systems remains largely uncharted. However, it is possible that very early resections may confer lower risks of memory decline in children. The specific neurocognitive effects of focal surgeries such as frontal lobe resections also remain largely unknown in children with epilepsy, as does the longterm effects of surgery in the very young (i.e., prior to age 1). Our knowledge of attentional mechanisms and executive functioning in children undergoing epilepsy surgery remains inadequate.

The neuropsychology of pediatric epilepsy is an emerging field with significant potential for clarifying fundamental questions regarding recovery of function and the development and organization of cognitive abilities after surgical interventions in children. Recommendations for future research include further identification of specific risk factors associated with postsurgical decrements in cognitive functioning in children and further research on the developmental trajectory of cognitive skills in pediatric surgery patients.

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