

# Brain imaging and fetal alcohol spectrum disorders

Christie L. McGee<sup>(a)</sup> and Edward P. Riley<sup>(b)</sup>

<sup>(a)</sup>Joint Doctoral Program in Clinical Psychology, San Diego State University, San Diego (CA), USA

<sup>(b)</sup>Department of Psychology and Center for Behavioral Teratology San Diego State University, San Diego (CA), USA

**Summary.** Over thirty years of research has revealed that prenatal exposure to alcohol has a devastating impact on the structure and function of the developing central nervous system. Imaging studies over the past ten years have improved our understanding of the structural alterations related to prenatal alcohol exposure and provided researchers with potential hypotheses for brain-behavior relationships. Structural alterations associated with prenatal alcohol exposure have been found in overall brain size, shape, and symmetry, along with regional decreases in white and gray matter. In addition, abnormalities have been noted in specific structures such as the cerebellum, basal ganglia, and corpus callosum. This review demonstrates that specific areas of the brain may be more vulnerable to prenatal exposure to alcohol.

*Key words:* fetal alcohol syndrome, imaging, prenatal alcohol exposure, brain.

**Riassunto** (*Diagnostica per immagini e sindrome fetoalcolica*). Oltre trent'anni di ricerca hanno dimostrato che l'esposizione prenatale ad alcol ha un effetto devastante sulla struttura e funzione del sistema nervoso centrale in via di sviluppo. La diagnostica per immagini negli ultimi dieci anni ha molto migliorato la comprensione delle alterazioni strutturali legate all'esposizione prenatale all'alcol e ha fornito agli studiosi nuove ipotesi di relazione tra sviluppo cerebrale e comportamento. Le alterazioni strutturali alcol-relate riguardano dimensione, forma e simmetria del cervello, e diminuzioni della materia bianca e grigia. Inoltre, sono state trovate anomalie in strutture specifiche quali cervelletto e corpo calloso. Questo lavoro dimostra che specifiche aree del cervello possono essere più vulnerabili all'esposizione prenatale all'alcol.

*Parole chiave:* sindrome fetoalcolica, diagnostica per immagini, esposizione prenatale ad alcol, cervello.

## INTRODUCTION

The teratogenic effects of alcohol on the developing brain have been known for over thirty years [1-3]. During this period, a host of neuropsychological and behavioral deficits associated with prenatal alcohol exposure have been identified and have helped to increase awareness of this public health concern. Although a limited number of autopsy studies have been completed, it was not until the utilization of imaging techniques during the last ten years that the opportunity to view the range of structural effects resulting from prenatal alcohol exposure on the living brain has been available.

Perhaps the most widely recognized consequence of prenatal alcohol exposure is fetal alcohol syndrome (FAS). FAS is a major public health concern wherever women consume alcohol and the overall prevalence in the United States is estimated to be between 0.5 and 2.0 per 1000 births [4]. It is diagnosed based on a characteristic pattern of facial abnormalities, pre- and/or postnatal growth deficiency, and central nervous system (CNS) dysfunction. Facial alterations typically seen in individuals with FAS include short palpebral fissures, thin vermilion of the upper lip, and smooth philtrum. CNS dysfunction can be evidenced

by functional and/or structural alterations depending on the specific diagnostic criteria used [5, 6]. Common functional impairments include deficits in overall intellectual ability, problem solving, language, social skills, and motor functioning. Structural alterations, the focus of this article, can be determined by brain imaging or at autopsy, or a proxy such as head circumference or neurological signs may be used.

However, FAS is not the only consequence of prenatal alcohol exposure. Recently, the National Organization on Fetal Alcohol Syndrome coined the term fetal alcohol spectrum disorders (FASD) to describe the full range of effects resulting from prenatal exposure to alcohol. These effects range from FAS on the most severe end to subtle physical, cognitive, or behavioral effects. When considering the full range of effects, prevalence estimates of FASD are approximately 1 in 100 [7]. Various moderating factors have been proposed that may account for the variability of outcomes resulting from prenatal alcohol exposure. Some of these factors include genetic variation, timing and amount of alcohol consumed, nutrition, maternal age, socioeconomic status, and family and community resources [4]. FASD was not intended to be a diagnostic term, but serves to unify diagnostic labels such as

alcohol related neurodevelopmental disorder, alcohol related birth defects, and FAS as belonging to the same spectrum. FAS is sometimes referred to as dysmorphic FASD due to the presence of diagnostic facial features, whereas individuals on the remainder of the spectrum are nondysmorphic, or lack the constellation of characteristic facial features. Numerous studies have shown that individuals with prenatal exposure to alcohol, with or without facial dysmorphism, perform similarly on a number of neuropsychological and behavioral measures [8]. Thus, it is not unreasonable to expect similar patterns of structural brain alterations.

Autopsy studies have revealed heterogeneous findings in individuals with FASD including gross microcephaly, cellular disorganization, migration errors, microdysplasia, and anomalies to such structures as the corpus callosum and cerebellum. These findings have been reviewed elsewhere [9], and therefore the focus of this review will be on evidence of structural alterations found in imaging studies. Imaging technologies offer the ability to examine structural brain damage in the living brain, and thus are more representative and generalizable to the larger population of individuals prenatally exposed to alcohol. These imaging techniques utilize differences in biological tissue density (*i.e.*, bone, gray matter, white matter) and produce data that can be reconstructed into visual images. In a research setting, these images can be analyzed quantitatively using specialized software packages and group differences can be compared.

This review will begin by describing structural alterations to the cerebrum followed by more specialized structures such as the cerebellum, corpus callosum, basal ganglia, and hippocampus. Each section will progress from identifying more global findings to more detailed and specific structural alterations. When appropriate, brain-behavior relationships will be discussed, and comparisons to other developmental disorders will be explored.

### CEREBRUM AND WHOLE BRAIN ANALYSES

Imaging studies have consistently found size reductions in the cranial vault in individuals with prenatal alcohol exposure [10-20]. According to one study, adolescents with alcohol exposure had an average volume reduction of 12% compared to controls [19]. Findings of reduced brain size are not surprising given head circumference measurements indicating microcephaly below the 10<sup>th</sup> centile in many FAS cases. In addition to gross reductions in brain size, several studies with decent sample sizes have demonstrated significant overall gray and white matter reductions in individuals with prenatal alcohol exposure [10, 15]. When reductions in brain size were taken into account, white matter was disproportionately reduced and was more severe than gray matter hypoplasia [10]. In other words, relative to overall brain volume, individuals with histories of heavy prenatal exposure may have too much relative gray matter and not enough white matter [15].

More detailed analyses have been conducted to determine if brain reductions are diffuse or more specific in

nature. Volumetric reductions have been found in the parietal, frontal, and temporal lobes [16]. However, when overall brain size was considered, only the parietal lobe was disproportionately reduced [10, 16]. This disproportionate reduction indicates that brain tissue in individuals prenatally exposed to alcohol is not uniformly affected, but rather specific areas may be more vulnerable to insult. White and gray matter volumes have also been examined for each lobe, and both white and gray matter were disproportionately reduced in the parietal lobe [10]. When examined separately in comparison with controls, individuals in the alcohol exposed group without a FAS diagnosis tended to show a similar pattern of reductions, but comparisons did not reach significance [10]. Upon visual inspection of group means, the nondysmorphic group was generally intermediate to the FAS group and controls. These findings suggest that individuals without dysmorphic facial features show a similar pattern of alterations, but may be less severely affected than individuals with FAS.

Based on the disproportionate reductions found previously, voxel-based morphometric analyses have been conducted with individuals with prenatal alcohol exposure to examine regional alterations in brain tissue. Voxel-based morphometry allows the whole brain to be analyzed at once without the delineation of specific regions required in volumetric analyses. It also permits the examination of brain regions without clear gyral or structural boundaries and regional alterations that may be obscured with more global volumetric measurements can be identified with this approach. Analyses were conducted examining group differences for gray and white matter separately [15]. For the gray matter analysis, significant differences in tissue composition were found between groups for 17 clusters, with the largest occurring in the left posterior temporo-parietal region. The exposed group exhibited increases in gray matter for all clusters where the control group tended to have cerebral spinal fluid (CSF) or white matter. Similarly, the exposed group showed significant decreases in white matter for 25 clusters where voxels tended to segment as gray matter or CSF in controls. The largest region of white matter reduction corresponded with gray matter findings. In other words, alcohol exposed subjects tended to have increased gray matter and decreased white matter in the left posterior temporo-parietal region. In addition, separate analyses revealed similar patterns for both dysmorphic and nondysmorphic individuals with histories of prenatal exposure to alcohol. The number of significant clusters was greater and individual clusters tended to be larger for the group with FAS, whereas nondysmorphic individuals exhibited less robust clusters [15].

In concordance with the voxel-based findings, a separate study [16] found a 15% increase in gray matter density bilaterally in the inferior parietal and perisylvian cortex. These findings were robust when overall brain size was controlled, indicating a disproportionate increase in gray matter in this region. Evidence of increased gray matter likely reflects white matter

reductions in this region, although this was not directly measured in this study. In addition to volumetric and density measures, this study conducted regional shape analyses by calculating distances from the center of the brain for over 65 000 points on the brain surface. This measurement allows for the examination of regional differences in local brain growth and when taken together illustrates alterations to brain shape. Compared to controls, alcohol exposed subjects exhibited bilateral reductions in brain extent in inferior parietal and perisylvian cortex, independent of overall brain size. Brain growth and gray matter density have been shown to be inversely related [21]. In other words, decreases in local brain growth should be related to increases in gray matter density. Consistent with this relationship, increased gray matter density and reduced white matter density have been demonstrated with individuals with prenatal exposure to alcohol in the same region of reduced local brain growth [10, 15]. Thus, brains of individuals prenatally exposed to alcohol tend to be smaller and narrower in the inferior parietal and perisylvian areas than non-exposed individuals. This study also found reduced local brain growth in the anterior and orbitofrontal cortex, specifically in the left hemisphere. The orbitofrontal cortex is proposed to be involved in socially mediated behavior and emotion-related executive skills, and alterations in this region are consistent with reports of executive deficits and difficulties with social functioning seen in individuals with prenatal alcohol exposure [22].

Based on findings of disproportionate reductions in the left hemisphere [15], asymmetry patterns were examined in adolescents with prenatal exposure to alcohol [23]. From surface based analyses, both typically developing individuals and alcohol exposed subjects showed prominent asymmetry in the perisylvian region in which inferior parietal and superior temporal cortices were shifted backward in the left relative to the right hemisphere. However, when gray matter density asymmetry was examined, alcohol-exposed subjects lacked the prominent right greater than left asymmetry seen in the posterior inferior temporal lobe in controls. This region coincides with areas primarily involved in language and object/face recognition (Brodmann areas 21, 22, 37), which may be impaired in individuals with prenatal exposure to alcohol [24]. No other differences in asymmetry were found between alcohol exposed subjects and controls. This study provides additional evidence that specific areas of the brain are more vulnerable to teratogenic insult from alcohol.

Before concluding this section, one functional study has found specific alterations in metabolic activity that are consistent with structural findings discussed above [25]. Metabolic activity serves as a measure for brain functioning in that increased metabolic rate within a specific region indicates more neural activity. Compared to data from non-exposed children, children with FAS exhibited decreases in cerebral blood flow in the left parieto-occipital region. The authors speculated that altered functioning in this region is related to difficulties that children with

FAS have with arithmetic and speech. Additionally, children with FAS exhibited hyperperfusion, or increased uptake of the radiotracer, in the right frontal lobe compared to the left, a finding which could be related to the attention deficits commonly seen in this population. In comparison, similar studies with children with attention deficit hyperactivity disorders (ADHD) have found patterns of decreased uptake in portions of the left frontal lobe [26-28].

In summary, brains of individuals prenatally exposed to alcohol are reduced in size and show narrowing in the inferior parietal and perisylvian region. Increases in gray matter density and corresponding reductions in white matter likely contribute to narrowing in this region. In addition, reduced local brain growth has been demonstrated in the area of the frontal lobe believed to be responsible for socially mediated behavior. Finally, findings of altered functional activity have been found in areas corresponding to structural alterations. It has been proposed that white matter hypoplasia may be a result of abnormal myelination. Both frontal and parietal lobes, areas shown to be affected by prenatal alcohol exposure, continue to mature into early adulthood in association with late myelination [10]. Abnormal myelin deposition could prevent normal growth and thinning, which could result in reductions in synaptic density [16]. In addition, abnormal glial cell functioning, apoptotic regulation, and errors in proliferation and differentiation of new cells may have contributed to brain alterations seen in individuals with histories of prenatal alcohol exposure [15].

## CEREBELLUM

The cerebellum is a highly convoluted region of the brain that is largely involved in the coordination of movement and motor learning. Volumetric reductions of the cerebellum have been found in several studies with individuals prenatally exposed to alcohol [10-13, 25]. In comparison with controls, individuals with FAS exhibited significant gray and white matter reductions in the cerebellum. However, when total brain size was taken into account, neither gray or white matter was disproportionately reduced in volume.

The cerebellum consists of two hemispheres, divided by connecting tissue called the cerebellar vermis. Hypoplasia of the vermis has been found in a number of individuals with FAS [11]. In a quantitative study [29], alcohol-exposed subjects showed disproportionate reductions in the anterior portion of the vermis (lobules I-V), whereas mean area measurements of other regions were nearly identical to controls. In addition, the pattern of disproportionate vermal reduction is distinct from other developmental disorders. For example, reduction in lobules VI and VIII were found in individuals with autism [30], whereas increases were noted in lobules VI and VIII in individuals with Williams syndrome [31]. In addition, disproportionate reductions of vermal lobules VIII to X have been found in ADHD [32]. Thus it appears that some portions of the cerebellum are more vulnerable to prenatal

exposure to alcohol and these regions are distinct from alterations seen in other developmental disorders.

Cerebellar alterations may explain some of the neuropsychological impairments often seen in children prenatally exposed to alcohol. The cerebellum is most often linked to motor coordination and quantitative studies have demonstrated balance impairments in alcohol-exposed individuals [33, 34]. Although historically the cerebellum has been linked to motor coordination and learning, accumulating evidence has also supported its involvement in attentional processes [32, 35-38]. Thus, alterations to the cerebellum may also account for some of the attention problems often observed in children with histories of prenatal exposure to alcohol [39-42].

### CORPUS CALLOSUM

The corpus callosum is a tract of fibers that connects the two cerebral hemispheres and forms the roof of the lateral ventricles. Development of this structure begins relatively early, beginning between the sixth and eighth gestational weeks. A definite corpus callosum is formed by weeks 12-13 and continues to grow in the caudal direction for the next 5-7 weeks. Although the corpus callosum is fully formed, additional axons continue to pass through this structure to form connections with the other hemisphere up until the third decade of life.

Alterations of the corpus callosum are among the most frequently cited brain abnormalities in imaging studies with individuals with prenatal alcohol exposure. At the most extreme end, a number of studies have found agenesis, or complete absence of the corpus callosum in children and adolescents who were prenatally exposed to alcohol [12, 17, 18, 43, 44]. Riley *et al.* reported an incidence rate of 6.8% of agenesis of the corpus callosum in their larger sample of alcohol-exposed children [43], and FAS has been proposed to be one of the leading causes of this rare condition [45]. This rate is considerably higher than the general population rate of 0.3% and even the rate of 2.3% in developmentally disabled populations. In addition to complete agenesis, others have noted less severe alterations such as marked thinning, hypoplasia, or partial agenesis, which often occur in more posterior regions [11, 12, 17-20, 25, 44, 46]. As was noted above, the corpus callosum forms the roof of the lateral ventricles, and thus it is not surprising that ventricular and other midline abnormalities commonly coincide with such marked alterations of the corpus callosum.

However, the majority of individuals with prenatal alcohol exposure do not exhibit such severe alterations in callosal morphology. Several studies have conducted quantitative studies to determine if more subtle alterations are common in individuals with prenatal alcohol exposure. Overall, the corpus callosum of alcohol-exposed subjects has been found to be significantly smaller in area and length than controls [11, 19, 43]. However, once total brain volume was added as a predictor, the area of the corpus callosum in exposed subjects was

not significantly reduced compared to controls [19]. Although the overall structure is not disproportionately reduced in area, disproportionate reductions in regions of the corpus callosum have been found, most notably in the most posterior region corresponding to the splenium [19, 43]. In addition, similar alterations in callosal morphology have been reported in cases of attention deficit-hyperactivity disorder [47-49].

In addition to area reductions, alterations in shape and location of the corpus callosum have been found in individuals with prenatal alcohol exposure [19]. Specifically, the posterior region of the corpus callosum (*i.e.*, splenium) was shown to be displaced approximately 7 mm in the inferior and anterior direction. In contrast, no evidence of displacement was found in the anterior or posterior commissures, suggesting the specificity of damage to the corpus callosum. Similar to the whole-brain analyses described above, when dysmorphic and nondysmorphic groups were separated, the nondysmorphic group showed a similar but not statistically significant pattern of callosal alterations as the FAS and alcohol group as a whole. In addition to examining alterations to brain structure, this study assessed the relationship between callosal displacement and verbal learning. Anterior-posterior displacement was found to be a significant predictor of verbal learning for the exposed group. Specifically, individuals with more anterior displacement demonstrated more impaired verbal learning. Anterior displacement was general rather than region specific and was a better predictor of verbal learning than verbal intelligence. Thus, these findings suggest a somewhat specific relationship between callosal displacement and verbal learning rather than reflecting overall cognitive impairment. In addition, although not directly assessed, alterations to the corpus callosum are proposed to underlie the variable and inaccurate performance of children with prenatal alcohol exposure on a task of bimanual coordination [50].

An independent group of researchers studying a large prospectively identified sample has generally found no difference in the average size or shape of the corpus callosum when comparing alcohol-exposed individuals with controls [51, 52]. However, they found that individuals with prenatal exposure to alcohol have excess variability of callosal shape. Consistent with these findings, the authors [51] examined the data from Riley *et al.* and noted that the coefficients of variation for all sub-regions of the corpus callosum in exposed subjects were significantly larger than controls. Excess variation may be a result of the timing and levels of exposure during the development of the corpus callosum, which could have resulted in a number of patterns deviating from normal variation. Based on this excess variability, a classification algorithm was created that accurately classified subjects (alcohol-exposed *vs* not) with high sensitivity (100 out of 117) and specificity (49 out of 60) [52]. Bookstein *et al.* argue that by focusing on variances rather than mean differences more sensitive and clinically useful data can be obtained to discriminate alco-

hol-exposed individuals from non-exposed controls, which may result in a useful diagnostic tool.

In addition, this group assessed the relationship between callosal variation and neuropsychological performance [53]. In exposed individuals, excess shape variation was associated with two distinct profiles of cognitive impairment. A relatively thick callosum was associated with executive function deficits whereas a relatively thin callosum was related to motor deficits. The thicker corpus callosum was found not to extend as far into the frontal lobes as the thinner callosum. This may reflect abnormalities of the white matter fibers that connect the frontal lobes through this region of the corpus callosum and may result in the observed executive deficits. The authors propose that motor impairments seen in individuals with thinner callosa may be related to a loss of some white matter pathways projecting from the parietal sensory inputs, caudate nucleus, and cerebellum through the corpus callosum to motor and premotor centers. As identified in this review, abnormalities in the parietal lobe, caudate, and cerebellum have been described in individuals with prenatal alcohol exposure.

In summary, alterations of the corpus callosum have been frequently cited in imaging studies with individuals with prenatal alcohol exposure. In addition to gross abnormalities such as agenesis that are visible upon inspection, more subtle alterations have been found from quantitative studies. More subtle alterations of the corpus callosum include disproportionate area reductions especially in the most posterior region, excess variability in shape, and anterior and inferior displacement. Furthermore, alterations were related to impaired neuropsychological performance in several domains including verbal learning, executive functioning, and motor skill. In addition to the hypotheses described above, callosal dysmorphology may be due to arrested growth at the time of exposure or delayed continued development after the initial insult [19]. Several mechanisms may account for altered prenatal development including disruption of the glial facilitated migration of cells and errors in apoptosis [18]. As identified above, callosal morphological changes are consistent with alterations seen in other areas such as the caudate, cerebellum, and the perisylvian region as well as with observed neuropsychological impairments [15, 19, 53].

### BASAL GANGLIA

The basal ganglia are a group of subcortical nuclei including the caudate, nucleus accumbens, putamen, and globus pallidus. The putamen and globus pallidus are often grouped and referred to as the lenticular nucleus. Collectively, the basal ganglia are often considered to control voluntary motor function. However, as with many of the structures described in this review, the basal ganglia maintain many connections with other regions of the brain and may be involved in other critical functions such as executive functioning, motivation, and social behavior. Smaller case studies with

individuals with prenatal exposure to alcohol found disproportionate reductions in the volume of the basal ganglia [12-14]. However, when overall brain size was taken into account only disproportionate reductions were evident in the caudate [12, 14] with gray matter being disproportionately affected [12]. The volume of the lenticular nucleus was relatively spared [14]. A larger study found similar results with a disproportionate reduction of the caudate and relative sparing of the lenticular nucleus and nucleus accumbens [10]. In addition to structural alterations noted in the caudate, a functional study with adolescents with prenatal alcohol exposure found significant reductions in metabolic activity in the thalamus, the caudate heads, and the right portion of the caudate-putamen body [46]. Overall, research suggests that the caudate may be specifically affected both structurally and functionally by prenatal exposure to alcohol, which may be related to functional impairments observed in this population.

### HIPPOCAMPUS / AMYGDALA

The hippocampus and the amygdala are components of the limbic system and are generally considered to be involved in the formation of long term memories and emotion respectively. These structures maintain connections with each other as well as receive projections from other areas of the brain. Few imaging studies with individuals with prenatal alcohol exposure have noted alterations to the hippocampus, and those that have found abnormalities generally have reported on a few individuals with gross alterations [11, 44]. However, one study with a small sample of individuals with FAS noted significant differences in the asymmetry of the hippocampus with the right larger than the left [25]. In contrast, Archibald *et al.* found that the hippocampus was relatively spared when the whole brain volume was taken into account [10]. So far, studies have consistently found relative sparing of the amygdala [10, 13, 25].

### CONCLUSIONS

Prenatal alcohol exposure has been shown to have effects on brain development. This review has illustrated that specific portions of the brain are more vulnerable to the teratogenic insult of alcohol. While brains of individuals prenatally exposed to alcohol tend to be smaller in size, portions of the parietal and temporal lobes near the perisylvian region have been found to be disproportionately affected, exhibiting narrowing and decreases in white matter. In addition to these robust findings, some structural and functional abnormalities have been noted in the frontal lobe. Specific disproportionate alterations to the cerebellar vermis, corpus callosum, and caudate have been found in a number of studies. Such specific alterations were not expected based on the heterogeneity of autopsy findings. However, cases that reach autopsy may not be representative of the larger population affected by prenatal alcohol exposure. That is, these cases may represent the most severe end of the spectrum. Thus, imaging

studies are able to study a larger more representative portion of individuals with prenatal alcohol exposure and therefore have shown more consistent results.

Brain imaging is still a relatively young technique and advancements in acquiring and analyzing images are continually being made. Thirteen years have passed since the first report of brain imaging with two children with FAS [12]. Since that time, additional studies have provided a clearer understanding of the structural impact of prenatal alcohol exposure. However, much is still to be learned. Many of the findings have yet to be replicated with independent samples. Due to the extensive cost and time involved in imaging studies, sample sizes are typically small. Therefore there is a considerable chance for bias, which speaks to the need for replication. Future studies should continue applying newly developed analytic techniques such as the surface-based analyses described above. Additional imaging techniques such as diffusion tensor imaging may prove to be illustrative of structural damage resulting from prenatal alcohol exposure. Furthermore, few functional imaging studies have been conducted with individuals with prenatal alcohol exposure. Although we have evidence of specific structural brain alterations, knowledge of the location of functional anomalies will aid in interpreting structural and behavioral findings. A few studies reported above have directly examined brain-behavior relationships for specific brain alterations. Future studies should continue

to directly assess brain-behavior relationships rather than draw parallels from the literature base and neuropsychological theory. This is especially important for prenatal alcohol exposure and other developmental disorders because the developing brain may have a drastically different pattern of functional organization than the adult brain. Hopefully improvements in developmental neuropsychological theory will allow for more precise interpretations and provide additional hypotheses for brain-behavior relationships.

In conclusion, brain imaging has improved our understanding of alcohol's effects on brain structure during development and has demonstrated that not all areas of the brain are equally vulnerable. In addition to summarizing the existing literature on brain imaging and prenatal alcohol exposure, this review has attempted to draw some preliminary conclusions on brain-behavior relationships. Future studies will further clarify both the structural and functional effects of prenatal alcohol exposure on the developing brain. With this knowledge, recognition of brain alterations can be integrated with behavioral and neuropsychological findings to better understand the teratogenic effects of alcohol on the whole person and develop improved interventions.

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