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ATYPICAL HEMISPHERIC ASYMMETRY IN FETAL ALCOHOL SPECTRUM DISORDERS: A REVIEW OF THE EFFECTS OF PRENATAL ALCOHOL EXPOSURE ON LANGUAGE LATERALIZATION

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SUMMARY

Atypical lateralization is evident in developmental disorders, including autism spectrum disorders and dyslexia. Moreover, atypical lateralization is linked to language impairments: reduced or reversed lateralization is associated with poorer language outcomes. Fetal alcohol spectrum disorders (FASD) result from the deleterious effects of prenatal alcohol exposure on the brain, resulting in a range of physical, behavioural, and cognitive abnormalities, including language impairments. To date, little is known about lateralization in FASD. This review examines the effects of prenatal alcohol exposure on lateralization in FASD, seeking to determine the degree to which the language deficits associated with FASD can be attributed to aberrant cortical lateralization. The research reviewed indicates that the left temporo-parietal region is particularly vulnerable to prenatal alcohol exposure, causing atypicalities in structural and functional lateralization. As this region typically controls language processing, the data imply a direct link between atypical lateralization in FASD and language impairment. Knowledge of patterns of altered structural and functional lateralization in FASD has the potential to improve diagnostic efficacy and may facilitate the development of appropriate management and intervention programmes, improving outcomes for people with FASD.

Keywords: FAS, FASD, laterality, hemisphere, brain, temporal

INTRODUCTION

In western societies alcohol is widely used and generally socially well accepted (Holmila, Raitasalo & Kosola, 2013). However because alcohol readily crosses the placenta, alcohol ingested by a pregnant mother directly affects the developing fetus. Prenatal alcohol exposure is the leading preventable cause of birth defects and neurodevelopmental disorders (American Academy of Pediatrics, 2000), presenting a serious public health problem in all western countries (Leppo & Hecksher, 2011). Though the negative consequences of drinking during pregnancy have been known for centuries (e.g., "Beware, and drink no wine or strong drink … for lo, you shall conceive and bear a son", (Judges 13:4, 5)), a significant minority of pregnant women (7.6%) self-report consuming alcohol (Center for Disease Control and Prevention, 2012). As alcohol is a known teratogen, prenatal exposure may cause brain abnormalities and/or brain damage, leading to cognitive and behavioural problems postnatally. Jones and Smith (1973) introduced the term fetal alcohol syndrome (FAS) to describe the permanent birth defect syndrome that results from alcohol consumption during pregnancy. A diagnosis of FAS is based on: i) pre- and/or postnatal growth deficiencies, ii) a unique cluster of craniofacial anomalies, and iii) central nervous system (CNS) dysfunction and/or structural brain abnormalities.

EPIDEMIOLOGY

FAS affects 0.5 – 7 individuals per 1000 live births (National Center on Birth Defects and Developmental Disabilities, 2004; Niccols, 2007). However there are regional variations in prevalence, often linked to low socioeconomic status and societal trends for binge drinking and high alcohol consumption. For example, rates of FAS in a wine-growing area of South Africa are greater than 50 individuals per 1000 live births (May et al., 2000). Incidence increases in the children of chronic alcoholic mothers, with 25 individuals diagnosed with FAS per 1000 live births (Abel, 1988); in mothers who already have a child with FAS, the likelihood of subsequent offspring having FAS is extremely high (771 individuals per 1000; Huebert & Raftis, 1996).

Children with FAS typically exhibit intellectual impairments: IQs range from 20 – 120 (Mattson & Riley, 1998), with a mean of 60 – 65 (e.g., Streissguth et al., 1994). Consequently FAS represents the leading preventable cause of intellectual disability (Abel & Sokol, 1987). That said, it is important to note that not every child exposed to alcohol prenatally exhibits CNS dysfunction or brain abnormalities; equally, not every child who exhibits CNS dysfunction or brain abnormalities has FAS (Astley et al., 2009).

Recognising that even low levels of alcohol consumption during pregnancy can have a detrimental effect on the developing fetus, whilst not meeting the criteria for a diagnosis of FAS, the umbrella term Fetal Alcohol Spectrum Disorders (FASD) was introduced. Though not a medical diagnosis, FASD describes the range of outcomes resulting from alcohol consumption during pregnancy (Muk-

herjee et al., 2005). The damage resulting from prenatal alcohol exposure is highly variable, covering a spectrum of aberrations from a microcellular and neurochemical level (e.g., reduced choline; Astley et al., 2009) to broad structural abnormalities (e.g., cerebral dysgenesis; Roebuck et al., 1998, for review). Cognitive and behavioural sequelae are similarly variable, encompassing the full continuum from mild developmental delay to global developmental disability affecting both motor and cognitive domains. Prenatal alcohol exposure thus leads to a spectrum of disorders, with FAS representing the severe end of the continuum. FASD affects up to 4% of live births (Abel & Sokol, 1987; May et al., 2006; Sampson et al., 1997), and thus represents a common, preventable cause of birth defects and developmental disabilities.

Despite the prevalence of FASD, "very little is known regarding functional lateralization in FAS/FASD", (Domellöf et al., 2009, p.697). As atypical cortical lateralization is linked to a variety of developmental disorders, and is related to impairments in cognitive performance, this review examines the effects of prenatal alcohol exposure on the developing brain. It explores cerebral lateralization in FASD to shed light on the degree to which language deficits associated with FASD can be attributed to aberrant cortical lateralization. If atypical structural or functional lateralization can be established in FASD, this has the potential to improve diagnostic efficacy. Moreover, if atypical lateralization in FASD can be reliably linked to specific neuropsychological or cognitive deficits, this may facilitate the development of appropriate management and intervention programmes, improving outcomes for people with FASD.

IMPACT OF PRENATAL ALCOHOL EXPOSURE ON THE BRAIN

Whilst the economic costs of FASD are staggering, the most devastating consequences are evident in the brain. Prenatal alcohol exposure disturbs brain morphogenesis, resulting in a wide range of abnormalities and atypicalities at both micro- and macro-scopic levels (e.g., Norman et al., 2009). Microcephaly (small head for body size) is a hallmark feature of FAS, and is frequently accompanied by microencephaly (small brain for body size). Cerebral dysgenesis, sometimes resulting in fused frontal lobes (e.g., Coulter et al., 1993), and abnormal neural and glial migration, including leptomeningial heterotopias (see Clarren et al., 1978), are amongst the cortical changes seen in FAS. The cerebellum and brain stem may also be affected by dysgenesis (e.g., O'Hare et al., 2005), with changes ranging from hypoplasia to complete agenesis of the cerebellar vermis (e.g., Autti-Rämö et al., 2002; Wisniewski et al., 1983). Prenatal alcohol exposure also adversely influences the developmental of white matter tracts (e.g., Bjorkquist et al., 2010). This compromises the development of the corpus callosum, leading to abnormalities that range from thinning to partial or complete callosal agenesis (e.g., Riley et al., 1995). Such findings clearly indicate the broad and devastating consequences of prenatal alcohol exposure on the developing brain

(for review, please refer to: Guerri et al., 2009; Norman et al., 2009; Niccols, 2007; Roebuck et al., 1998; Riley & McGee, 2005).

IMPACT OF PRENATAL ALCOHOL EXPOSURE ON CEREBRAL LATERALIZATION

Given the breadth of changes in neuroanatomy evident in FASD, some researchers have suggested that there is no specific pattern of brain abnormality resulting from prenatal alcohol exposure (e.g., Clarren, 1986). However closer inspection is warranted. Atypical or abnormal cerebral lateralization is evident in many neurodevelopmental disorders (e.g., Lindell & Hudry, 2013; Moncrieff, 2010). Whilst there is a solid body of research examining the structural consequences of gestational alcohol consumption in FASD, studies examining cerebral lateralization and in particular, comparing the effects of prenatal alcohol exposure on the left and right hemispheres, are far less common. It is plausible that the overall loss of brain tissue (microencephaly) seen in FASD masks regionally-specific losses. Examination of hemispheric differences in FASD thus offers a potentially important opportunity to improve diagnostic precision, and shed light on the relationship between atypical cortical structure and cognitive outcomes in FASD.

Recognising that aberrant lateralization is a risk factor in a number of neurodevelopmental disorders, Sowell et al. (2008) examined left and right hemisphere cortical thickness in children with heavy prenatal alcohol exposure. They found a relative increase in thickness (up to 1.2mm) across bilateral temporal, bilateral inferior parietal, and right hemisphere frontal regions. As gray matter thins over the course of normal development, lower gray matter volume relative to brain size indexes enhanced cognitive performance in typically developing children (e.g., Sowell et al., 2001). Increased right hemisphere cortical thickness in FASD is consequently abnormal, suggesting problems in pruning and myelination processes.

Sowell et al.'s (2008) results are compatible with Sowell et al.'s (2002) previous report of reduced left orbito-frontal thickness, and increased right hemisphere gray matter volume, in FASD. Sowell et al. (2002) measured differences between children and adolescents with heavy prenatal alcohol exposure and typically developing controls. Beyond reduced average brain size in the FASD group, they found a specific reduction in the size of left anterior and orbital frontal cortex, indexing reduced growth. The left orbito-frontal region is crucial for behavioural inhibition; given that children with FASD have behavioural inhibition impairments (e.g., Rasmussen et al., 2013), reduced left hemisphere orbito-frontal volume appears directly linked to functional deficits in FASD.

Abnormalities in the left temporo-parietal cortex have also been noted. Sowell et al. (2001) examined brain structure in children and adolescents prenatally exposed to alcohol using 3D MRI. Compared with controls, the FASD group showed increased gray matter in the left hemisphere posterior temporo-parietal cortex.

Sowell et al.'s (2002) data similarly indicate atypical asymmetry: adolescents who were prenatally exposed to alcohol show greater symmetry in the posterior inferior temporal region than typically developing controls. As the perisylvian region is crucial for language processing (e.g., Catani & Jones, 2005), atypicalities in this region help account for the language deficits commonly observed in FASD.

Recent behavioural investigation also highlights atypical lateralization in children with FAS, using handedness to index laterality. As early brain damage adversely affects development of an established hand preference (Soper, & Satz, 1984), increased incidence of non-right handedness (i.e., either left or ambiguous handedness) is associated with neurodevelopmental disorders, including autism (see Lindell, & Hudry, 2013). Domellöf, et al. (2009) noted a higher incidence of left handedness in children with FAS (30.4%) in comparison with typically developing controls (18.4%); moreover, those FAS children who were right handed demonstrated a less strong hand preference than the right handed typically developing group, implying reduced lateralization. Janzen et al. (1995) also reported reduced hand preference in children with FAS (aged 3.5-5 years) in comparison with typically developing controls. As children do not typically establish a hand preference until the time they start school (Gudmundsson, 1993), the fact that children with FAS evidence decreased manual preference distinguishable from typically developing children well before such a preference is typically established points toward potential diagnostic utility.

IMPACT OF PRENATAL ALCOHOL EXPOSURE ON WHITE MATTER LATERALIZATION

Altered patterns of white matter structure are also evident in FASD (e.g., Archibald et al., 2001; Lebel et al., 2008). As white matter serves as a conduit for information transfer between different brain regions, changes in white matter structure compromise communication. The corpus callosum is particularly affected in FASD, with agenesis (absence) of the corpus callosum more common in FASD (7%) than in either the general population (0.3%) or other developmental disorders (2.3%; Jeret et al., 1986). Although callosal agenesis does not affect the majority of people with FASD, reduced callosal area is typical (e.g., Roebuck et al., 2002), with consequent impairments in interhemispheric information transfer and speed of processing.

For example, Lebel, et al. (2008) used diffusion tensor imaging (DTI) and fractional anisotropy (FA) (delineating white matter tracts and establishing white matter integrity respectively) to assess white matter tracts in children with FASD. Compared to typically developing controls, the FASD group evidenced white matter abnormalities in seven of the 10 tracts assessed. The largest differences were noted in the tracts connecting the temporal regions, a finding that has been reported by a number of other researchers (e.g., Sowell et al., 2002), highlighting highly significant reductions in white matter volume specific to the left parietal and temporal lobes (see also Sowell, et al., 2001). In the typically-developing

population white matter structures connecting the frontal, temporal and parietal lobes (e.g., arcuate fasciculus) show a strong left hemisphere asymmetry, with greater fibre density in the left than right hemisphere (e.g., Nucifora et al., 2005). As greater connectivity in the left temporo-parietal region facilitates normal language processing, this white matter reduction is a likely contributor to the language deficits evident in FASD.

SECTION SUMMARY

It is often lamented that "neuropathological studies have revealed no consistent alcohol-induced morphological alterations in the developing nervous system of infants with FAS" (Autti-Rämö et al., 2002, p.98). This reported lack of consistency is at least partially attributable to lack of an objective test for FAS. In addition, many previous investigations have failed to compare the consequences of prenatal alcohol consumption on the left and right hemispheres. For example, Astley et al. (2009) conducted a comprehensive investigation of an impressively large sample of children with an FAS diagnosis and children prenatally exposed to alcohol, combining structural and functional imaging techniques with a comprehensive neuropsychological and psychiatric battery. However the authors did not make comparisons between the left and right hemispheres. The research reviewed suggests that had such comparisons been drawn, more pronounced aberrations in left hemisphere structure and function would be evident.

In addition, variability in dosage and timing of prenatal exposure to alcohol in the different samples tested is a likely contributor. For example, Autti-Rämö, et al.'s (2002) sample of 17 children included five who were exposed to alcohol during the first trimester only, four exposed to alcohol during the first and second trimesters only, and eight exposed to alcohol throughout the gestation period. Other biological and environmental factors are also likely to influence the impact of prenatal alcohol exposure on the developing brain, including maternal age, genetic background, maternal nutrition, other maternal drug use, and socioeconomic status (Guerri et al., 2009).

Overall, studies that compare the effects of prenatal alcohol exposure on the left and right hemispheres of people with FASD indicate differential hemispheric effects. Whilst there is no question that the whole brain is affected, the left hemisphere is particularly susceptible to the deleterious influence of interuterine alcohol exposure. Research confirms a range of abnormalities, including atypical asymmetries in both gray (Sowell et al., 2001) and white matter in the left temporo-parietal region (Lebel et al., 2008). As such, it is clear that gestational alcohol ingestion adversely impacts cortical lateralization. It is important to note that the right hemisphere is also affected, with abnormally increased right frontal lobe thickness evident in FASD (Sowell et al., 2002; 2008), indicating problems in myelination and synaptic pruning. Thus the available data confirm the predicted atypical lateralization in FASD. The cognitive consequences of these lateralization abnormalities are now discussed.

CONSEQUENCES OF ATYPICAL LATERALIZATION IN FASD ON LANGUAGE PROCESSING

The majority of the studies indicate greater abnormality in the left than right hemisphere in FASD (e.g., Sowell et al., 2001, 2002; Riikonen et al., 1999). Although both sides of the brain are important for successful language processing, the left hemisphere's dominance is well established (e.g., Lindell, 2006). Thus, given the anatomical atypicalities noted, it is not surprising that the majority of people with FASD present with language problems consistent with the left hemisphere regions affected. Such deficits include speech impairments (e.g., Church et al., 1997), expressive and receptive grammar deficits (e.g., Carney, & Chermak, 1991), impairments in category and letter fluency (e.g., Kodituwakku et al., 2006), and impaired verbal learning (e.g., Sowell et al., 2007). Tasks that rely on the left tempo-parietal region are particularly affected, with children prenatally exposed to alcohol performing significantly worse than typically developing controls on measures of both word comprehension (Peabody Picture Vocabulary Test-Revised) and naming ability (Boston Naming Test; Mattson & Riley, 1998). Such findings indicate a direct relationship between structural atypicalities in left hemisphere regions and language impairments in FASD.

Just as research indicates that children with FASD exhibit reduced left hemisphere structural lateralization (e.g., Sowell et al., 2001, 2002), the brains of children with FASD show atypically lateralized functional activation when processing verbal stimuli. In one of the few studies to date that directly assesses the cognitive correlates of atypical lateralization, Sowell et al. (2007) examined functional MRI activation in children prenatally exposed to alcohol during a verbal paired associates learning task. Compared with the typically developing controls, children with prenatal alcohol exposure showed significantly less activation in the left medial and posterior temporal regions, and significantly more activation in the left and right dorsal prefrontal cortices. Given that Sowell et al. (2007) controlled for group differences in general memory ability, this atypical pattern of activation reflects language-related processing. During verbal learning the alcohol-exposed group showed greater activation than the control group in the dorsal prefrontal cortices, and less activation in the left temporal regions, suggesting that prenatal alcohol exposure has functionally deleterious effects on the peri-sylvian temporal structures that typically mediate verbal learning (e.g., encoding and retrieval of verbal information). People with FASD are consequently more reliant on frontal structures for the task. The fact that verbal learning performance is impaired in the FASD group confirms that increased engagement of the dorsolateral prefrontal cortices does not adequately compensate for the left parieto-temporal dysfunction resulting from prenatal alcohol exposure.

The abnormal increase in right dorsolateral prefrontal cortical thickness reported by Sowell et al. (2008) is also linked with poor language outcomes. Pre-

vious research confirms that thinner cortical thickness in the left frontal and parietal regions is associated with superior verbal abilities (e.g., Sowell et al., 2004): the cortex in these regions thins during typical development via activity-dependent pruning and myelination. However Sowell et al. (2008) found greater thickness in the right dorsolateral areas correlated with better verbal recall performance in people who were prenatally exposed to alcohol, in stark contrast with the typically developing controls. This implies that people prenatally exposed to alcohol rely on different brain regions for language processing, presumably because of the structural and connective abnormalities in the left hemisphere temporo-parietal areas that typically support language processing. However despite this compensatory activation, language performance in the FASD group was still significantly poorer than the control group, indicating that relying on atypical regions for language processing is not sufficient to overcome abnormalities in the left temporo-parietal regions.

Sowell et al.' s (2008) finding that increased, rather than decreased, cortical thickness in the right dorsolateral prefrontal region is correlated with better verbal recall performance in people prenatally exposed to alcohol is itself atypical; in typical development, thinner cortex is associated with better verbal recall performance (Sowell et al., 2004). As Sowell et al.'s (2008) study is the sole investigation to date that examines the relationship between cortical thickness and cognitive outcomes in people prenatally exposed to alcohol, further research is required to shed light on such brain-behavior relationships in FASD.

SECTION SUMMARY

Given the scarcity of research assessing structural lateralization in FASD, it is perhaps not surprising that there is a relative paucity of research directly examining the cognitive correlates of atypical lateralization in FASD. However, the research reviewed implies that such investigation is warranted, highlighting potential links between the abnormal structural lateralization and the common cognitive impairments noted in FASD. As Lebel et al. (2008) note, whilst the cognitive deficits evident in FASD indicate brain abnormality, "it may be overly simplistic to expect a one-to-one relationship between a single tract and a specific cognitive deficit", (p.1738). However, the research reviewed suggests that the structural atypicalities resulting from prenatal exposure to alcohol have a direct bearing on language outcomes.

As the left tempo-parietal region is crucial for language processing, and is atypically lateralized in FASD (Lebel, et al., 2008; Sowell et al., 2001, 2002), people who have been prenatally exposed to alcohol exhibit language impairments on tasks such as word comprehension and naming (Mattson, & Riley, 1998). In addition, the brains of children prenatally exposed to alcohol show significantly less activation in these typical language regions, presumably reflecting the structural abnormalities, and instead show greater activation in atypical regions (left and right dorsal prefrontal cortices) during verbal paired-associate learning (Sow-

ell et al., 2007). This reliance on an alternate brain region to subserve language processing in FASD may lead to abnormal patterns of cortical thickness, with Sowell et al. (2008) demonstrating that people who were prenatally exposed to alcohol have greater thickness in the right prefrontal dorsolateral area, correlating with better verbal recall performance; no such relationship was evident in typically-developing controls. As such, the research suggests that people who have been prenatally exposed to alcohol rely on different brain regions for language processing, with negative consequences for language performance.

CONCLUSIONS AND FUTURE DIRECTIONS

The development of cerebral asymmetries is adversely affected by prenatal exposure to alcohol, with FASD causing aberrations in both structural and functional asymmetry. People with FASD show atypical asymmetries in both gray (Sowell et al., 2001) and white matter in the left temporo-parietal region (Lebel et al., 2008), indicating that the left side of the brain is particularly vulnerable to maternal gestational alcohol consumption. As the left hemisphere is key to successful language processing, language impairments are evident: FASD causes deficits in tasks that rely on the left temporo-parietal region, including word comprehension and naming (Mattson, & Riley, 1998). Research confirms that children prenatally exposed to alcohol show less activation in the structurally anomalous left temporo-parietal area and instead rely on atypical dorsolateral frontal regions during verbal paired-associate learning (Sowell et al., 2007), leading to atypical cortical thickness in the right prefrontal dorsolateral area (Sowell et al., 2008). Yet despite engaging different regions to compensate for the left hemisphere's structural and metabolic abnormalities, language performance remains impaired, indicating that it is not sufficient to compensate for the atypical lateralization caused by prenatal alcohol exposure.

Whilst the literature examining structural and functional asymmetries in FASD is presently small, the research reviewed suggests that such investigations offer important possibilities. If the aberrant structural asymmetries noted in FASD are present at birth, the potential for earlier diagnosis and hence intervention implementation is clear. However distinguishing the cortical indices of FASD from those that characterise other neurodevelopmental disorders will require systematic investigation. One may speculate that a combination of increased left temporo-parietal gray matter (e.g., Sowell et al., 2001) and reduced left temporo-parietal white matter (e.g., Sowell et al., 2002) may distinguish probable FASD from other disorders (e.g., reduced fronto-temporal gray matter is evident in autism spectrum disorder; Lindell & Hudry, 2013), especially when accompanied by a confirmed family history indicating maternal gestational alcohol consumption. However research is needed to confirm this speculation and determine whether these atypicalities are evident prenatally.

Because the consequences of FASD are life long, treatments and interventions are required to address the challenges faced across the full range of the

developmental spectrum, from neonates to the elderly (refer to Chandrasena et al., 2009, for review). Given the white matter abnormalities and consequently reduced interhemispheric connectivity evident in people with FASD, interventions that seek to enhance neural connectivity appear prudent. For example, bimanual coordination interventions are often used to assist in rehabilitation following stroke (e.g., Rose & Winstein, 2005;) or following TBI if necessary (Chantsoulis et al. 2015), and would be potentially beneficial in the management of FASD as they target two deficits with one intervention. Such therapy has the potential to not only improve deficient bimanual coordination in FASD (e.g., Roebuck-Spencer et al., 2004), but may increase neural connectivity between the left and right hemispheres (i.e., corpus callosum), through a process of experience-based neural plasticity (Chrapusta et al. 2015; Pachalska et. al 2015).

Further studies examining the cognitive correlates of the structural lateralization abnormalities evident in FASD are also needed. To date few investigations have directly assessed the relationship between altered structural asymmetries and cognitive outcomes, presumably reflecting the fact that the literature examining lateralization in FASD is itself small. Such investigation is important: if atypicalities in structural or functional lateralization can be reliably linked to specific cognitive deficits, appropriate targeted intervention programmes can be developed. As Chandrasena et al. (2009) suggest, “interventions for individuals with FASD suffer universally from a serious lack of systematic development and evaluation”, (p.166). Given that FASD affects 0.33% to 4% of live births (Abel & Sokol, 1987; May et al., 2006), research in this area must be prioritised.

That said, one of the challenges in conducting research into FASD is the population under investigation. Some sampling bias is inevitable: children with severe psychiatric symptoms and/or severe behavioural disturbance are unlikely to participate. Consequently, even those studies that specifically seek to assess patients at the more severe end of the FASD spectrum are unlikely to be able to truly tap that population. One may speculate that if such patients were amenable to taking part, they may exhibit particularly pronounced deficits and aberrations in brain morphology, including aberrant lateralization.

The enormous social and economic burdens presented by FASD to the individual, their family, and society at large, mean that continued research efforts designed to systematically identify and manage FASD, and develop effective interventions, are imperative. Moreover, given that the disorders are 100% preventable, public awareness programmes, and interventions targeting high risk populations, are vital to reduce the incidence of FASD, preventing unnecessary disability and early mortality. This review suggests that investigation of lateralization in FASD has potentially important benefits: if structural atypicalities in hemispheric asymmetry are present at birth, and distinct from those evident in other neurobehavioral disorders, earlier diagnosis and intervention implementation would be facilitated. Thus researchers assessing brain structure and function in FASD should be encouraged to assess hemispheric differences as part of their investigations. Such simple comparisons could aid the development of identifiers

for FASD, increasing understanding of the neurocognitive phenotype of FASD, and potentially advancing diagnostic precision.

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