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Mental Health and Affect Regulation Impairment in Fetal Alcohol Spectrum Disorder (FASD): Results from the Canadian National FASD Database

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Abstract

Aims: Individuals with fetal alcohol spectrum disorder (FASD) frequently have challenges with regulating emotional arousal, or affect regulation (AR), and experience high rates of mental health disorders. This study examined children and adults with FASD to investigate the relationship between AR impairment and several mental health problems and diagnoses.

Methods: Data from the Canadian national FASD database was used for analysis. Seven mental health diagnoses, including attention-deficit/hyperactivity disorder, post-traumatic stress disorder, conduct disorder, attachment disorder, intellectual disability, and language disorder were examined. A history of suicidality was also examined. The prevalence of these mental health problems in individuals with and without AR impairment was compared.

Results: Individuals with FASD and AR impairment were significantly more likely to be diagnosed with conduct disorder (OR 4.8), attachment disorder (OR 6.1), or post-traumatic stress disorder (OR 8.1) when compared to those without AR impairment. They were also more likely to have a history of suicidality (OR 8.6). AR impairment was most commonly found in those with greater overall neurodevelopmental impairment. Having AR impairment was associated with receiving a diagnosis of FASD at a later age, but was not related to gender, intellectual disability, or language disorder.

Conclusion: AR impairment is strongly related to several mental health diagnoses in those with FASD and presents some promising possibilities for targeted early intervention.

Affect regulation (AR) concerns the ability to modulate emotional arousal such that an optimal level of engagement in the environment is fostered and an appropriate emotional response is given to

differing types of situations (Shields and Cicchetti, 1997). The concept of AR has been studied across a variety of contexts including normative populations and clinical samples (Konstantareas and

Stewart, 2006; Niedtfield *et al.*, 2010; Gyurk *et al.*, 2011). AR has been defined broadly as including experiential, behavioral and physiological reactivity (Samson *et al.*, 2015), and more narrowly as concerning only emotional lability (Shields and Cicchetti, 1997). The concept of AR has also been useful in describing dysfunction in areas such as autism spectrum disorder, borderline personality disorder and most recently fetal alcohol spectrum disorder (FASD).

FASD is the developmental disorder which can result from prenatal exposure to alcohol (Astley, 2004; Cook *et al.*, 2016; Hoyme *et al.*, 2016). It has a wide range of symptoms and outcomes including physical, cognitive, emotional, and behavioral impairments (Kodituwakku, 2007). The presentation of FASD can vary greatly depending on the timing, duration, quantity and frequency of maternal alcohol consumption, genetics, as well as other prenatal and post-natal events and exposures (Davis *et al.*, 2013). A recent World Health Organization population-based prevalence study estimated rates between 2% and 3% for FASD (Popova *et al.*, 2018).

In 2016, revised guidelines for the diagnosis of FASD were introduced in Canada (Cook *et al.*, 2016). Based on updated research findings from the previous 10 years and broad consultation with national and international experts, they made recommendations regarding screening women for alcohol use, multi-disciplinary diagnostic team composition, evaluation of prenatal alcohol exposure, medical/physical aspects and features of the disorder, and defining the required levels of brain dysfunction for diagnosis. Three or more neurodevelopmental domains of significant impairment were described as required for FASD diagnosis. These domains, which include, motor skills, neuroanatomy/neurophysiology, cognition, language, academic achievement, memory, attention, executive function, and adaptive behavior, were updated to include an additional domain for AR. In addition to Canada, several other countries have either adapted or adopted these guidelines for use in their own jurisdictions including Scotland (Scottish Intercollegiate Guidelines Network, 2019) and Australia (Bower and Elliott, 2016). The diagnostic criteria for FASD with Sentinel Facial Features (SFF) and FASD without SFF as well as the 'at risk' designation are described in Table 1.

Research support for the inclusion of the AR domain in FASD diagnosis comes from a variety of human studies as well as animal models of FASD. In human research, epidemiological studies have found very high levels of comorbidity between prenatal alcohol exposure and psychiatric problems, including mood and anxiety disorders (Streissguth and O'Malley, 2000; O'Connor *et al.*, 2002; Barr *et al.*, 2006; O'Connor and Paley, 2009; Pei *et al.*, 2011; Weyrauch *et al.*, 2017). Research on young children has also

reported that negative emotionality, irritability, sleep dysregulation, and the intensity of negative moods are evident very early and are some of the first observable signs of prenatal alcohol exposure in infants (O'Connor, 2001; Haley *et al.*, 2006; Alvik *et al.*, 2011). In addition to human studies, experiments with animals have also shown a direct link between prenatal alcohol exposure and increased neuroendocrine response to stress whereby prenatal alcohol exposure impacts the neuro-adaptive mechanisms that mediate the stress response. Through prenatal alcohol exposure, the hypothalamic-pituitary-adrenal axis is sensitized to stress, and this in turn leads an increased vulnerability to disorders associated with emotional dysregulation such as anxiety or depression (Hellemans *et al.*, 2008, 2010; Weinberg *et al.*, 2008; McLachlan *et al.*, 2016).

In the Canadian diagnostic guidelines, impairment in the domain of AR is defined as present when diagnostic criteria for one of several specified mood or anxiety disorders are met according to DSM-5 (APA, 2013) criteria. This includes: major depressive disorder (with recurrent episodes), persistent depressive disorder, disruptive mood dysregulation disorder, separation anxiety disorder, selective mutism, social anxiety disorder, panic disorder, agoraphobia, or generalized anxiety disorder. The AR domain is further specified to include individuals with a pervasive pattern of dysregulation, present for a significant period of time across the lifespan. It is not intended to include individuals who may be reacting to temporary, adverse situational challenges (e.g. new foster home placement; failure at school etc.) (Cook *et al.*, 2016). Advantages of using DSM-5 criteria for defining AR include having a well-described and defined, readily accessible, widely reviewed and accepted method of delineating AR impairments that encompasses two large areas of emotional reactivity commonly found in FASD (Pei *et al.*, 2011; Regier *et al.*, 2013). Disadvantages include the increased time and expertise needed to formally diagnose mood or anxiety disorders in FASD assessment, challenges with making such mental health diagnosis in younger children, and excluding AR-type impairments that might be present in other mental health disorders (e.g. intermittent explosive disorder, bipolar, personality disorders) (McLennan and Braunberger, 2017). Although operational definitions vary, the concept of impairment in emotional regulation has also been described in other FASD diagnostic systems including the Institute of Medicine guidelines (Hoyme *et al.*, 2016) and DSM-5's (APA, 2013) proposed 'neurobehavioral disorder associated with prenatal alcohol exposure'. The Institute of Medicine describes impairments in mood and behavior together, while the DSM-5 outlines challenges with mood lability, negative affect or irritability, and impulsivity or attention problems.

Table 1. Criteria for fetal alcohol spectrum disorder (FASD) diagnoses and the at-risk designation (Cook *et al.*, 2016)

FASD with Sentinel Facial Features

- Presence of all 3 sentinel facial features (short palpebral fissures, flat philtrum, thin upper lip); AND
- Prenatal alcohol exposure (PAE) confirmed or unknown; AND
- Impairment in 3 or more neurodevelopmental domains as follows: motor skills, neuroanatomy/neurophysiology, cognition, language, academic achievement, memory, attention, executive function, affect regulation, adaptive behavior/social skills/social communication

FASD without Sentinel Facial Features

- Impairment in 3 or more neurodevelopmental domains above; AND
- PAE confirmed at a level known to be associated with adverse effects

At-Risk for Neurodevelopmental Disorder and FASD - Associated with PAE

This is a designation (not a diagnosis) given when:

- There is confirmation of PAE at a level known to be associated with adverse effects; AND
- Neurodevelopmental impairment criteria above are not met; AND
- There are indications of neurodevelopmental disorder and reasons why results are inconclusive at time of assessment (e.g. individual was too young; incomplete assessment).

The objective of this study is to examine and describe how the domain of AR impairment in FASD might be related to a variety of mental health comorbidities in children and adults with prenatal alcohol exposure and FASD. Although there is significant evidence for the presence of AR impairment in FASD, there are few studies characterizing the presentation and attributes of individuals with this impairment.

METHODS

Ethical approval for this project and secondary data analysis was obtained from the University of Ottawa (#20160423-01H). Written informed consent was obtained from each participant before data was submitted to the project.

Data source

The individuals examined in this study are a subset of cases from the Canadian national FASD database. The database began in 2010 and is an ongoing repository of diagnostic information regarding FASD assessments and diagnoses made at 26 clinics in 9 provinces and territories across Canada. The project was designed to create a consistent set of data points, input at the clinic level via a secure online portal, and aggregated in a central location. Information collected includes patient exposures, comorbidities, and demographics; source of referral; results of neurodevelopmental assessments (e.g. medical, psychological, Language and OT assessments); final FASD diagnosis; and recommendations made following the assessment.

Records entered into the database conform to the 2016 Canadian diagnostic guidelines for FASD assessment. In the context of these guidelines, neurodevelopmental impairment within a functional domain is described as present when an individual achieves a score below the 3rd percentile on standardized tests or measures. A list of recommended measurement tools for each neurodevelopmental domain (e.g. psychological tests, caregiver questionnaires) is provided in an appendix to the Canadian guidelines and a recent survey of clinics contributing to the National database found most clinics to be using the recommended measures for their FASD assessments (Coons-Harding *et al.*, 2019). As noted in Table 1, three or more functional domains must be found impaired for a diagnosis of FASD to be made.

In addition to FASD diagnostic data, information regarding mental health diagnoses and a history of suicidality was input by clinics to the database for each individual assessed. The comorbid mental health diagnoses were defined based on categorizations representative of those used in the DSM-5 (APA, 2013) and were as follows: (1) intellectual disability; (2) language disorder; (3) attention-deficit disorder or attention-deficit/hyperactivity disorder; (3) attachment disorder; (4) conduct disorder; and (5) post-traumatic stress disorder (PTSD). Suicidality was defined as previous suicide attempts or suicidal ideation. Although suicidality is not a diagnosable disorder, it is a significant mental health challenge for individuals with FASD (Pei *et al.*, 2011) as well as a leading cause of death for this group (Thanh and Jonsson, 2016). For each comorbid diagnosis and reported history of suicidality, clinics indicated if the individual was assessed for the disorder or not, and if it was found to be present or absent. Assessment and diagnosis of comorbidities or suicidality could have taken place at the FASD clinic or the individual could have been assessed/ diagnosed prior to attending the FASD clinic.

A detailed description of the National database project, variables included, and the data collection procedures have been published previously (Clarren *et al.*, 2015).

Procedure

Eligibility criteria for this study included the following: (a) confirmed prenatal alcohol exposure; (b) diagnosis of FASD or prenatal alcohol exposure - at risk for FASD; (c) FASD diagnosis made between January 2015 and March 2018; (d) AR was assessed by a clinic and found to be present or absent (not missing); and (e) the age at diagnosis was 5 years or older. Five years was chosen as the minimum age based on a preliminary review of data which found there were no cases with confirmed AR impairment in a child under 5 years and most entries had either missing data or did not assess for AR. The date of 2015 was chosen because the new guidelines were widely available to clinics in 2015 the year prior to their formal publication. Four hundred and eighty individuals with confirmed prenatal alcohol exposure and a diagnosis of FASD or prenatal alcohol exposure-at risk for FASD were entered into the database from January 2015 to March 2018. Based on the criteria listed above, 145 cases were removed and a total of 335 individuals remained (see Fig. 1 for a

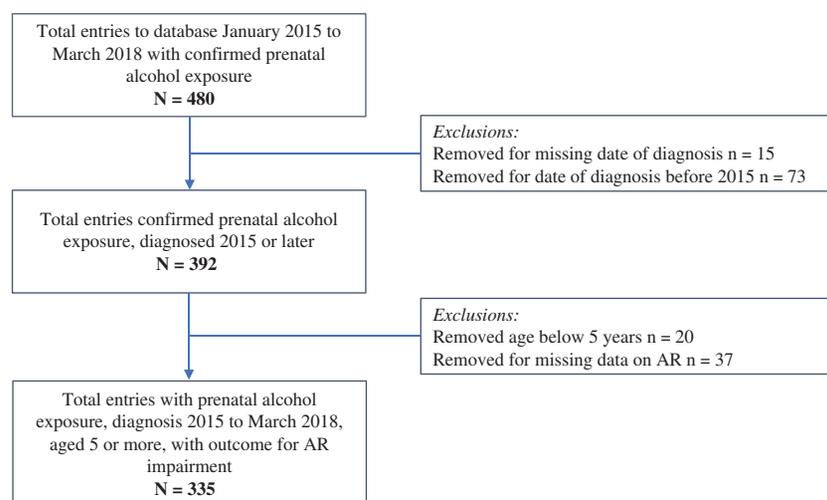


Fig. 1. Flowchart for inclusion in affect regulation (AR) and FASD study.

flowchart detailing this process). For the subset of 335 individuals analyzed, the following information was examined: demographics including age, gender and referral source; number of neurodevelopmental domains reported to be impaired in the context of FASD assessment; FASD diagnosis results; other comorbid mental health diagnoses present; and suicidality. Frequency distributions, one-way ANOVA, chi-square analysis, and odds ratios were calculated.

RESULTS

The age of individuals included in this study ranged from 5 years to 55 years, with a mean of 15.2 years. One hundred forty-four (43%) were female, 189 were male (56%) and two did not give a gender identity. For both groups, the most common source of referral was a social services agency or family members. More of the individuals with AR impairment were self-referred or referred by the legal system than persons without AR impairment. Overall, 136 (41%) were found to have AR impairment. Demographics for individuals with and without AR impairment are compared in Table 2.

Table 2. Demographics for individuals with affect regulation (AR) impairment ($n = 136$) and without ($n = 199$)

	Without AR N (%)	With AR N (%)
FASD Diagnosis		
FASD with SFF*	11 (5.5)	24 (18)
FASD without SFF	148 (74.5)	108 (79)
At Risk for FASD	40 (20)	4 (3)
Referral Source		
Social services	97 (48)	45 (33)
Family	59 (30)	32 (24)
Medical referral	21 (11)	18 (13)
Education system	15 (8)	9 (6)
Legal system	2 (1)	12 (9)
Self	2 (1)	11 (8)
Other	2 (1)	9 (7)
Gender		
Female	87 (44)	57 (43)
Male	111 (56)	78 (57)
IQ score		
70 or less	73 (37)	62 (46)
71-85	78 (39)	44 (32)
>85	37 (18)	26 (19)
Not calculated	11 (6)	4 (3)

*Sentinel Facial Features

No significant differences were found between those with AR impairment and those without for gender, $X^2(1, N = 333) = 0.10, P = 0.76$. Level of intellectual ability was divided into three IQ categories (<70; 71 to 85; >85) and compared for those with and without AR. Results found no significant difference between groups, $X^2(2, N = 320) = 2.57, P = 0.28$. Individuals with AR impairment were significantly older at the time of diagnosis compared to those without AR impairment, with a mean age of 19.1 years versus 12.5 years [$F(1, 334) = 43.1, P < 0.001$] respectively. Individuals with AR impairment were also diagnosed with significantly higher levels of overall neurodevelopmental impairment. Those with AR impairment had, on average 5.37 additional domains of neurodevelopmental impairment while those without AR had an average of 4.17 other domains impaired [$F(1, 333) = 28.72, P < 0.001$].

Odds ratios (OR) were calculated for 6 comorbid mental health diagnoses and a reported history of suicidality. The ORs presented indicate the likelihood that an attribute (e.g. a comorbid diagnosis, suicidality) is present in the AR impaired group. If the OR is less than or close to 1, there is lower risk or less likelihood that the attribute is present in the AR impaired group. Higher numbers indicate greater likelihood that the attribute is present in the AR impaired group. Table 3 presents results for all variables. Overall, individuals with AR impairment were at significantly higher risk for receiving a diagnosis of attachment disorder (OR 6.1), conduct disorder (OR 4.8), or PTSD (OR 8.1). They were also significantly more likely to have a history of suicidality (OR 8.6).

DISCUSSION

The objective of this paper was to examine AR impairment in FASD and how it might be related to various attributes and mental health diagnoses. Analysis of a subset of individuals from FASD clinics found that 41% of those with an FASD diagnosis or an 'at risk' designation had AR impairments. Previously published results (Clarren *et al.*, 2015) from this database found rates of impairment for most neurodevelopmental domains ranging from 32% to 63%, suggesting that AR is similarly common to other domains of impairment found in FASD. Results from this study also indicate that individuals with AR impairment are more likely to be older at the time of diagnosis and to have associated attachment disorders, PTSD, conduct disorders, and suicidality. The likelihood that AR impairment would be present was found to rise as the individuals' degree of overall neurodevelopmental impairment became greater.

Odds ratios for intellectual disability, language disorder, and attention-deficit/hyperactivity disorder were examined and not found to be significantly elevated for those with AR impairment.

Table 3. Odds ratios (OR) for individuals with affect regulation (AR) impairment to have each mental health comorbidity

Comorbidity	N*	Odds Ratio	95% Confidence Interval	p-value
Intellectual disability	251	0.9	0.5–1.6	0.91
Language disorder	221	0.6	0.3–1.1	0.15
ADHD**	273	1.4	0.8–2.4	0.22
Attachment disorder	162	6.1	2.4–15.3**	<0.001
Conduct disorder	145	4.8	1.9–12.1**	<0.001
PTSD***	122	8.1	2.5–25.2**	<0.001
Suicidality	154	8.6	3.8–19.6**	<0.001

*N is the number of individuals in the sample who were assessed for the disorder and found to either have it or not. It does not include those who were not assessed or whose data was missing. **Comorbid diagnoses where there is an elevated risk in those who have AR impairment. ***Attention-deficit/hyperactivity disorder. ****Post-traumatic stress disorder.

This suggests that factors such as low IQ and language problems do not appear to impede diagnostic teams evaluating and detecting AR impairment. Interestingly, even though depression is more commonly diagnosed in females from the general population (Angst *et al.*, 2002) in our study gender was not found to be associated with AR impairment. This is despite the fact that AR impairment is operationally defined here using DSM-5 criteria for mood and anxiety disorders, suggesting that AR impairments can be recognized across both males and females relatively equally.

Age at the time of FASD diagnosis for individuals found to have AR impairment was, on average, older than those without AR impairment. It has been noted in previous research that older age at diagnosis is a risk factor for more adverse outcomes (Streissguth *et al.*, 2004). It is possible that this difference in age between the groups might be due to challenges with assessing the AR domain in younger children. Older individuals come with longer histories available for review by diagnostic teams and these longer histories might make AR impairment more apparent (e.g. repeated episodes of depression or anxiety across many years). It may also be that identifying depression and/or anxiety is more difficult in younger children and/or clinicians may be more cautious about assigning a mental health diagnosis in younger individuals. As well, the assessment of AR in older individuals may be simpler than in young children because they can self-report symptoms and reflect more fully on issues such as guilt, concentration problems, or sleep issues. Diagnostic overshadowing may also be an issue in this age differential. Diagnostic overshadowing (Reiss *et al.*, 1982; Jones *et al.*, 2008) is the situation where healthcare professionals attribute symptoms to a mental health condition when another comorbid, often physical or developmental, issue is also present. In the context of FASD, individuals may receive diagnoses of attention-deficit disorder, conduct/oppositional defiant disorder, depression, anxiety, or PTSD prior to receiving an FASD diagnosis, and while these diagnoses are valid comorbidities, the contribution of FASD may go undiagnosed and unrecognized. This delay in FASD diagnosis or diagnostic overshadowing could be due to psychiatric and mental health services being more accessible and available than FASD diagnosis or because of possible stigma associated with giving/receiving a diagnosis of FASD. It is also possible that early service encounters for some individuals are for behavioral issues and FASD diagnosis is not considered. As well, for some cases the disclosure and/or confirmation of prenatal alcohol exposure are elusive at the time when other diagnoses are made.

Perhaps not unexpectedly, suicidality was found to be more frequent in those with AR impairment. This is not surprising given the definition of AR impairment used here is associated with depression which is an important factor in suicidal behavior. Additionally, many individuals with FASD have challenges with impulse control and executive functioning (Rasmussen *et al.*, 2008); attributes which also may place them at risk for suicidal behavior. The elevated presence of PTSD and attachment disorders in those with AR impairments may reflect the increased reactivity found in FASD coupled with the frequent traumas and adverse life circumstances these individuals often face. Not all individuals exposed to neglect, deprivation or trauma develop attachment disorders or PTSD, so it is possible that the elevated rate of these conditions in the AR impaired group indicates a predisposition to emotional dysregulation and increases the likelihood of having a more adverse reaction to any traumatic events experienced.

The associations between AR, attachment disorder, PTSD, and suicidality present a possible avenue for targeted intervention. If, as the research suggests (Alvik *et al.*, 2011), AR impairments can be

recognized early in children with prenatal alcohol exposure, effective coping strategies and environmental supports might be aimed at this particularly vulnerable group to decrease their risk during times of increased stress or challenge later in life. Because attachment disorders are typically diagnosed before the age of 5 years (APA, 2013), receiving this diagnosis within the context of prenatal alcohol exposure and FASD could be used as a signal for the need to introduce more intensive interventions in youth and adolescence to prevent suicidal risk. A similar logic could be applied to individuals with prenatal alcohol exposure and FASD following traumatic events or experiences. If AR impairment can be recognized and flagged, the individual might be referred for treatment aimed at preventing the development of PTSD symptoms (e.g. Berkowitz *et al.*, 2011) with the knowledge that they are particularly vulnerable to developing a stress related disorder.

There are several limitations to this study. First, the data examined is cross sectional in nature which means that inferences about causality cannot be made reliably. Second, although all clinics reported following the 2016 diagnostic guidelines which suggests uniformity in the definition of AR, there may be variation in how AR was assessed including some variation in assessment tools used and differing thresholds for identifying AR. Information regarding comorbid mental health diagnoses may also be effected by this type of variability across clinics. As noted earlier, comorbid diagnoses could have been made at the FASD clinic, reported by the individual or family member, or found through review of medical records. This variability may have limited the power of our analyses to detect some differences between groups. Finally, in situations where the AR domain was not assessed it is impossible to tell why it was not assessed (e.g. clinicians were not available to assess AR; they didn't feel it was relevant so did not assess for it; the individual refused to complete tests for AR, etc.).

CONCLUSIONS

In summary, AR impairment in FASD appears to be relatively common and is associated with several important mental health comorbidities. It is found more often in those presenting for diagnosis at an older age and is commonly found in more severely impaired individuals. In addition, assessing the AR domain presents some promising possibilities for interventions. Future research might work towards refining the AR domain and exploring additional criteria that might be added (e.g. reactive attachment disorder; bipolar disorders) as well as how the AR domain intersects with other diagnostic criteria such as the impaired self-regulation criteria in DSM-5's neurobehavioral disorder associated with prenatal alcohol exposure (APA, 2013). As well, future research might investigate the relationship between other prenatal exposures and AR (i.e. cannabis, opiates) as well as comparison of AR impairment in FASD with other neurodevelopmental disorders such as autism or cerebral palsy.

CONFLICT OF INTEREST STATEMENT

None declared.

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