Title registration for a systematic review: Psychological interventions for improving executive functions in children with Fetal Alcohol Spectrum Disorder (FASD)

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Title of the review

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Background

Prenatal Alcohol Exposure (PAE) is associated with profound and lifelong disability. The umbrella term Fetal Alcohol Spectrum Disorder (FASD) describes a spectrum of impairments resulting from the deleterious effects of PAE (Chudley et al., 2005). Historically, the spectrum comprised four disorders: Fetal Alcohol Syndrome (FAS), Partial FAS (pFAS), Alcohol-Related Neurodevelopmental Disorder (ARND) and Alcohol-Related Birth Defects (ARBD; Lange, Rovet, Rehm & Popova, 2017). All four disorders share PAE as their etiological base and all but ARBD result in neurological deficits (ARBD comprising physical defects). While information on prevalence rates remains a significant challenge (Roozen et al. 2016), estimates have been as high as 5% in general population studies in the US (May et al., 2014; May et al., 2018). Understanding how to support children with a diagnosis of FASD is particularly important given the condition has been linked to a range of poor outcomes, including increased contact with the justice system, substance misuse (Burd, Fast, Conry & Williams, 2010), anti-social and delinquent behaviour, learning disabilities, externalising and aggressive behaviour, as well as a range of other adaptive functioning and mental health problems (Rasmussen, Andrew, Zwaigenbaum, & Tough, 2008).

There is evidence that a core deficit underpinning many of these adverse outcomes is impairment in executive functions (EFs) (Khoury, Milligan & Girard, 2015). EFs are higher-order mental processes which allow individuals to deploy attention strategically, hold and manipulate goal-relevant information and consciously enforce goal-directed behaviour (Diamond, 2013; Baggetta & Alexander, 2016). According to Diamond, EFs comprise three core abilities; (i) inhibitory control – the ability to inhibit prepotent responses of attention, behaviour, thoughts and/or emotions in favour of what is appropriate or necessary; (ii) working memory – the ability to hold information in mind and manipulate it in goal-directed ways; (iii) cognitive flexibility – the ability to solve problems using different perspectives or rules as they arise. Different combinations of these core EFs produce a range of higher-order manifestations, including reasoning, problem-solving, planning and directing attention (Diamond, 2013).

Children with FASD have frequently shown impairment compared to typically developing children across a wide range of both core EFs and higher order manifestations (Rasmussen, 2005). Deficits have been found on cognitive inhibition, verbal and nonverbal fluency (Schonfeld, Mattson, Lang, Delis, & Riley, 2001), use of attentional strategies, planning (Green et al., 2009), visual attention, spatial working memory (Rasmussen, Soleimani & Pei, 2011), behavioural inhibition, the ability to form complex concepts and cognitive flexibility (Rasmussen et al. 2013). Research also suggests that EF impairments are often more severe

than would be suggested by IQ deficits alone (Connor, Sampson, Bookstein, Barr, & Streissguth, 2000).

Importantly, these deficits may underlie a number of poor outcomes associated with FASD. Broadly, poor EF has been linked to attention deficit hyperactivity disorder (ADHD; Diamond, 2005), autism (Geurts, Verte, Oosterlaan, Roeyers, & Sergeant, 2004), obesity (Crescioni et al., 2011), lower quality of life (Davis, Marra, Najafzadeh & Liu-Ambrose, 2010), poorer school readiness (Blair & Razza, 2017), poorer school performance (Borella, Carretti, & Pelegrina, 2010), financial problems, criminal behaviour, and substance misuse (Moffit et al., 2011). Consequently, addressing EF deficits in FASD populations may offer an important opportunity to significantly improve both individual and societal outcomes.

As the literature has developed around the cognitive impairments associated with PAE, interest has grown in trialling interventions to improve outcomes, with a growing number that focus on EF (see Reid et al., 2015, for a narrative review of these studies). One program that has been evaluated across three studies is the Alert program. Originally designed to help children with learning disabilities to utilise a number of self-regulation strategies (Williams & Shellenberger, 1996), the first randomised controlled trial of the program in children with FASD was conducted by Wells, Chasnoff, Schmidt, Telford, and Schwartz (2012). Children were randomly allocated to receive Alert or a no-treatment control group. Executive function outcomes were measured using the Behaviour Rating Inventory of Executive Function (BRIEF) (Gioia, Isquith, Guy & Kenworthy, 2000), a questionnaire completed by caregivers that assesses executive function behaviours at home and school. Children were also given the Robert's Apperception Test for Children (RATC) (Worchel, 1987), which assessed the children's emotional problem solving abilities.

Nash et al. (2015) also conducted a randomised controlled trial in which children were assigned to the ALERT program or delayed treatment control group. Executive function outcomes were assessed using a variety of methods. A battery of tests was administered to children, including EF subtests of the Developmental Neuropsychological Assessment (2nd edition) (NEPSY-II) (Korkman, Kirk, & Kemp, 2007), the Test of Everyday Attention for Children (TEA-Ch) (Manly, Robertson, Anderson, & Nimmo-smith, 1999) and the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Robins et al., 1994), and parents completed the BRIEF. Similarly, the Alert program was evaluated by Soh et al. (2015) in which children with FASD were randomly allocated to either an immediate-treatment or delayed control treatment group, with typically developing children serving as controls. Executive function capability was measured using EF subtests from the NEPSY-II, and behavioural ratings collected using the BRIEF, and brain imaging techniques were used to map concurrent changes to brain structure. Most recently, Coles, Kable, Taddeo, & Strickland (2018) conducted a small pilot using a metacognitive development program (GoFar) to support behaviour change in children with confirmed PAE. The program used the FAR metacognitive strategy**,** teaching the three steps of focus (F), act (A) and reflect (R). Children and caregivers were randomized to either (i) the GoFar program (ii) Faceland – an alternative program designed to improve facial expression recognition or (iii) an inactive control group. Executive function outcomes were assessed using the Tests of Variables of

Attention (TOVA) (Greenberg & Waldmant, 1993), NEPSY-II subtests, and behavioural measures of EF were assessed using the BRIEF.

While recent years has seen an increase in studies assessing interventions designed to improve EF functioning in children with FASD, a critical gap in the literature is the absence of an updated, comprehensive systematic review and meta-analysis in the area. Given the severely compromised outcomes associated with EF deficits, and the frequency of EF impairment in children with FASD, a rigorous synthesis of the effectiveness of available interventions offers great value to practitioners, individuals with FASD and their families.

Policy relevance

Governments across the developed world have a range of initiatives aimed at preventing FASD through increased public awareness of the effects of PAE and by the development of clearer diagnostic processes (e.g., Astley & Clarren, 2000; Bower and Elliot, 2016; Chudley et al., 2005). This review supports major initiatives and policy as outlined in key government documents. For example, the Australian Government's Commonwealth Action Plan (Australian Government, 2014) seeks to "manage the impact of a diagnosis of FASD on the individual and the family to ensure the child and the family are supported through and after the diagnostic process" (Australian Government, 2014, pp. 3). Similarly, the Canadian Government's FASD Framework for Action sets out an objective of "meeting the needs of individuals with FASD, their families and communities" (Public Health Agency of Canada, 2005, pp. 9). This includes improving outcomes and helping individuals to reach their full developmental potential. In the US, the National Task Force on Fetal Alcohol Syndrome (US Department of Health and Human Services, 2009) sets out the objectives of intensifying research initiatives around FASD, and promoting comprehensive continuums of care for individuals with FASD. This review will provide strong evidence regarding the utility of interventions in that aim to improve EFs in children with a FASD diagnosis. This evidence will allow practitioners and policy-makers to make informed choices regarding treatment and pathways of care, ultimately driving better outcomes and improving supports as set out in the various government policy agendas.

Objectives

The current review has two aims: (i) systematically gather and synthesise published and unpublished impact evaluations of psychological interventions aimed at improving the executive functioning of FASD children; (ii) data permitting, the review will also provide the first meta-analysis on the effectiveness of interventions used in FASD populations, with a sole focus on the EF domain of functioning.

Existing reviews of treatment interventions

A number of recent systematic reviews have been published in the areas of FASD prevalence (Roozen et al., 2016; Popova et al., 2017), comorbidity (Popova et al., 2016), and assessing interventions aimed at treatment (Peadon, Rhys-Jones, Bower, & Elliott, 2009; Reid et al., 2015). The most recent review by Reid et al. (2015) provided a synthesis of effectiveness of treatment interventions for FASD that comprised both an assessment of methodological quality of FASD intervention studies and adopted a lifespan perspective. Included interventions targeted parenting skills, self-regulation and attentional control, mathematics skills, non-verbal reasoning, and reading comprehension. Although the final corpus of studies were not able to be meta-analysed, individual study results suggest modest but consistent gains in executive functions across most studies retrieved. The review also illustrated improvements resulting from interventions targeting mathematics, social skills and parenting skills.

A limitation of Reid et al.'s review is the lack of quantitative synthesis of effect sizes. By providing a meta-analysis in parallel to the review, more precise conclusions can be provided regarding the overall efficacy of interventions that address a core deficit in children with FASD. Reid et al. (2015) were unable to undertake a meta-analysis due to the high variability in the nature of interventions. While this approach is useful in providing initial evidence of potential improvement across all FASD deficits, it is limited in its potential to provide more detailed analysis of the nature of plasticity within specific domains. The current study will overcome this limitation by narrowing focus to a single domain of functioning known to be of chief importance in FASD (EF), and only including psychological training and educational interventions. Further, Reid et al.'s literature search covered only papers published up to November 2015. The current study therefore seeks to provide a systematic update to this review and conduct a meta-analysis.

A systematic review protocol has also recently been published by Singal et al. (2018) aiming to review effectiveness of interventions in FASD populations. The review intends to include meta-analysis; however, it aims to evaluate any outcome pertaining to children's physical and mental health as well as cognitive, behavioural and social skills. With such broad inclusion criteria, limitations may be placed on the ability of authors to perform meta-analysis. By focusing on one domain of functioning (EF) and just two types of interventions common in FASD research, this review seeks to provide a more targeted synthesis of available literature. It is hoped this will provide the basis for stronger conclusions regarding the utility of interventions in FASD populations.

Interventions

The review will include training and educational psychological interventions that aim to improve any domain of executive functioning in children. This will include studies that include pharmacological interventions in combination with training and/or educational interventions. These may need to be analysed as a subgroup of studies. As per Diamond

(2013), executive functioning is defined as any measure of: (i) inhibitory control, (ii) working memory, (iii) cognitive flexibility, (iv) reasoning, (v) problem-solving, (vi) planning, and (vii) attention. Described below are two broad categories of psychosocial interventions commonly used to enhance EFs.

Training interventions

Training interventions are the intentional teaching of skills and knowledge aimed at restoring or improving cognitive functions and are generally administered by a qualified practitioner. These interventions can be delivered face-to-face (Loomes, Rasmussen, Pei, Manji, & Andrew, 2008), or as computerised training (Holmes et al., 2010). Tasks often aim to improve skills by offering practice of specific abilities unique to EF domains (Holmes et al., 2010).

Much contemporary cognitive training is administered digitally, typically using a computer, laptop or tablet to deliver training to participants. Computerised training is usually presented in the form of games and tasks, designed to hold interest and challenge EF abilities, and often involves working through levels of difficulty (Holmes et al., 2010). Thus, a core strength of computerised training is the capacity to automatically adjust for ability level, allowing for continual optimisation of training impact (Klingberg et al., 2005). Most programs also include motivational aspects such as scoring, personal best records, and rewards following completion (Holmes et al., 2010).

Computerised training has shown success in improving EF across a range of populations (Diamond & Lee, 2011). This form of intervention has been used to facilitate working memory in a range of children, including pre-schoolers (Bergman et al., 2011), intellectual under-performers (Holmes, Gathercole, & Dunning, 2009), and children diagnosed with ADHD (Holmes et al., 2010). Recently, Kerns, MacSween, Vander Wekken & Gruppuso (2010) used computerised interventions to improve attentional capability in children diagnosed with FASD. Non-computerised cognitive training has also been used by Loomes et al. (2008), who employed cognitive rehearsal training aimed at improving working memory in children with FASD.

Educational interventions

These interventions can either supplement pre-existing curricula, or be stand-alone educational programs (Diamond & Lee, 2011). A key objective of these programs is to promote skills necessary to optimal child development in real-world environments (Riggs, Greenberg, Kusché, & Pentz, 2006). Programs often incorporate enjoyable activities (e.g. dramatic play) with tasks that facilitate, test and aid EFs such as attention, memory or inhibition in everyday situations (Diamond et al., 2007). In addition to EFs, some programs also include a focus on broader developmental challenges, such as emotional literacy, empathy, friendship and communication skills (Webster-Stratton, & Reid, 2004).

A great strength of these interventions lies in the incorporation of training with real-world contexts, ultimately driving the external validity of treatment effects. For example, Riggs et

al. (2006) administered the Promoting Alternative Thinking Strategies (PATH) program aimed at improving classroom behaviour through improvements in EF.

Population

While the specifics of the different diagnostic systems have varied over time, all include as criteria for diagnosis some variation of facial/physical dysmorphology and/or confirmed PAE and/or multiple neurobehavioural deficits. According to the most recent Australian guidelines, if evidence of impairment is present but insufficient for diagnosis, or the individual is too young for comprehensive assessment, individuals may be considered 'at risk of FASD' (Bower & Elliot, 2016). As such, eligibility for inclusion requires (i) a formal diagnosis of FAS, FASD, pFASD, ARND or 'at risk of FASD' using any the following diagnostic systems: The Institute of Medicine Diagnostic system (Hoyme et al., 2005), The Washington 4-Digit Code (Astley & Clarren, 2000), The Canadian Guidelines (Chudley et al., 2005) or the Australian Guidelines (Bower & Elliot, 2016); or (ii) classified as having FAS based on facial dysmorphology alone; or (iii) confirmed or suspected prenatal alcohol exposure (light, moderate or heavy dosages).

For the purpose of the review, children will be aged between 3 and 16 years. This lower age range has been selected as it is possible to measure executive functions at this age, and as mentioned in the absence of physical features a diagnosis of "at risk for FASD" can be given in younger children (Bower and Elliot, 2016). Children solely with an ARBD diagnosis will not be included, as this condition is not known to result in neurological deficits. The sample will include children from anywhere in the world. It is likely that variability exists among different countries/cultures which may produce differences in diagnosis. As such, clear, formal diagnostic criteria will be used for inclusion. Where included studies do not use one of the four formal diagnostic criteria mentioned above (i.e. participants included based solely on confirmed PAE or facial dysmorphology) they will be analysed separately, allowing for comparison with studies using formal diagnosis.

Outcomes

The review will include outcomes pertaining to the measurement of EF as defined by Diamond (2013). Core measures of EF will be included in the review, as well as any higher-order manifestations arising from combinations of core EF abilities (e.g., reasoning, problem solving, planning, attention etc.). Studies will be included if the outcome data is gathered using either standardised measures, behavioural observation, or reported by others (e.g. parent/teacher). Based on Diamond (2013), the following types of outcomes (not exhaustive) will be included in the review:

- Inhibitory control
- Working memory
- Cognitive flexibility

- Reasoning
- Problem-solving
- Planning
- Attention

Study designs

The proposed review will include studies that utilise experimental and rigorous quasi-experimental research designs. Whilst single group designs that measure outcomes prior to and after interventions are considered highly subject to bias, in emerging areas of intervention research these studies can provide useful information about the breadth of interventions available and preliminary indications of effectiveness. As such, studies of this design will be included in this review; however, will be synthesised separately from experimental and rigorous quasi-experimental studies.

Eligible study designs are as follows:

- Randomised controlled trials
- Quasi-experimental designs where participants are allocated to groups by some other method than randomisation (e.g., allocation by pre-existing differences and compared, such as FASD diagnosed children vs. typically developing children)
- Single pre/post designs (to be synthesised separately)

Studies will be considered eligible if the evaluation utilises a placebo, treatment-as-usual, alternative treatment, no treatment, waitlist control or comparison condition. Studies that include pharmacological interventions as alternative treatment conditions will be included. Intervention settings to be included in the review will be medical/psychological clinics, schools or home-therapy settings. To be included in a meta-analysis, studies will need to report sufficient data for the calculation of effect sizes. Where insufficient information is included in final papers, authors will be contacted and sufficient data sought.

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Roles and responsibilities

The review team offers comprehensive coverage of the required skills and experience to successfully produce this review. Joseph Betts (lead reviewer) has experience leading on a range of analytic projects as a statistician for central government (United Kingdom – Department for Business Innovation and Skills). Joseph is currently employed at the University of Queensland as a research assistant, aiding in the screening and coding stages of a systematic review project (managed by co-author Elizabeth Eggins). Joseph's PhD research is focused on exploring new mechanisms of early detection and treatment in FASD populations, and will receive ongoing support from Professor Sharon Dawe as his primary supervisor. Sharon Dawe is a Professor of Clinical Psychology and has a strong background in research pertaining to parental substance use and child/family functioning. Professor Dawe has made significant contributions in research, policy and practice areas. As part of a larger review team based at the University of Queensland, Elizabeth Eggins has co-authored and managed a range of research projects grounded in systematic review methodology, including Campbell Collaboration and industry funded systematic reviews and scoping or qualitative research that uses systematic search, screening and coding techniques. Doctor Doug Shelton is a registered Paediatrician who specialises in community health and child development. Doctor Shelton's special interest area is FASD, for which he has received accolades for investigating the production of a comprehensive assessment and intervention service of children with FASD. Doctor Haydn Till is a registered psychologist and endorsed Clinical Neuropsychologist with clinical and research experience across the age spectrum. His PhD was a systematic review and meta-effect size analysis of cognition research in cardiac surgery. He currently holds the position of Clinical Associate Professor of Neuropsychology and sub-investigator on genetic and clinical drug trials for dementia with the Queensland University of Technology. He currently leads the neuropsychological services of the Child Development Service at Gold Coast Health and supervises the clinical assessments conducted by the FASD clinics.

Review tasks will be distributed as such:

- Content: Dawe, Betts, Shelton, Till
- Systematic review methods: Betts, Eggins
- Statistical analysis: Betts, Eggins, Till, Harnett
- Information retrieval: Betts, Eggins, Dawe

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Potential conflicts of interest

Professor Sharon Dawe and Paul Harnett are co-founders and have been involved in the evaluation of the Parents under Pressure (PuP) program. PuP is a parenting program designed to improve outcomes (including executive function) in high-risk, substance misusing families, and would therefore qualify for inclusion as an eligible intervention. Both Sharon and Paul have co-authored a recent systematic review on interventions for improving outcomes in FASD (Reid et al., 2015). To minimise potential bias, other authors will screen and code any papers co-authored by Professor Dawe or Paul Harnett.

Preliminary timeframe

- Date you plan to submit a draft protocol: October 2018
- Date you plan to submit a draft review: October 2019