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Learning from atypical development: A systematic review of executive functioning in children and adolescents with the 22q11.2 deletion syndrome

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ABSTRACT

In this systematic review, we investigate executive functioning (EF) in a selected population: children and adolescents with 22q11.2 Deletion Syndrome (22q11DS). Studying a selected subset of the population can inform our understanding of typical development by reducing the etiological variability associated with phenotypic expression of EF. In 22q11DS, EF deficits are, at least in part, the consequence of the deletion on chromosome 22. However, the expression of EF phenotype in 22q11DS varies and is possibly influenced by certain risk factors that occur at increased rates in this population. As such, 22q11DS allows us to study the impact of these factors on EF in the context of one underlying genetic etiology.

This review shows that inhibition and shifting are impaired in children with 22q11DS, while updating may be spared in childhood. Notably, EF deficits are found in this population after controlling for intellectual abilities, supporting the hypothesis that EF and intelligence do not reflect the same construct. Current evidence suggests that risk factors previously identified in the general population, such as congenital heart defects or low socioeconomic status, may not impact EF in a similar way in 22q11DS. In the process of demonstrating how studying the 22q11DS population can inform and advance our understanding of EF development, we identify gaps in the literature and highlight opportunities for future research.

Introduction

Executive functioning (EF[1]) refers to the higher-level cognitive mechanisms that regulate lower-level cognitive processes to

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[1] Abbreviations: 22q11DS = 22q11.2 Deletion Syndrome; CHD = Congenital Heart Defects; *COMT* = catechol-O-methyltransferase; EF = Executive Functioning; IQ = Intelligence Quotient; LBW = Low Birth Weight; PFC = Prefrontal Cortex; *PRODH* = proline dehydrogenase; RoB = Risk of Bias; SD = Standard Deviation; SES = Socioeconomic Status; TD = Typically Developing; WM = Working Memory.

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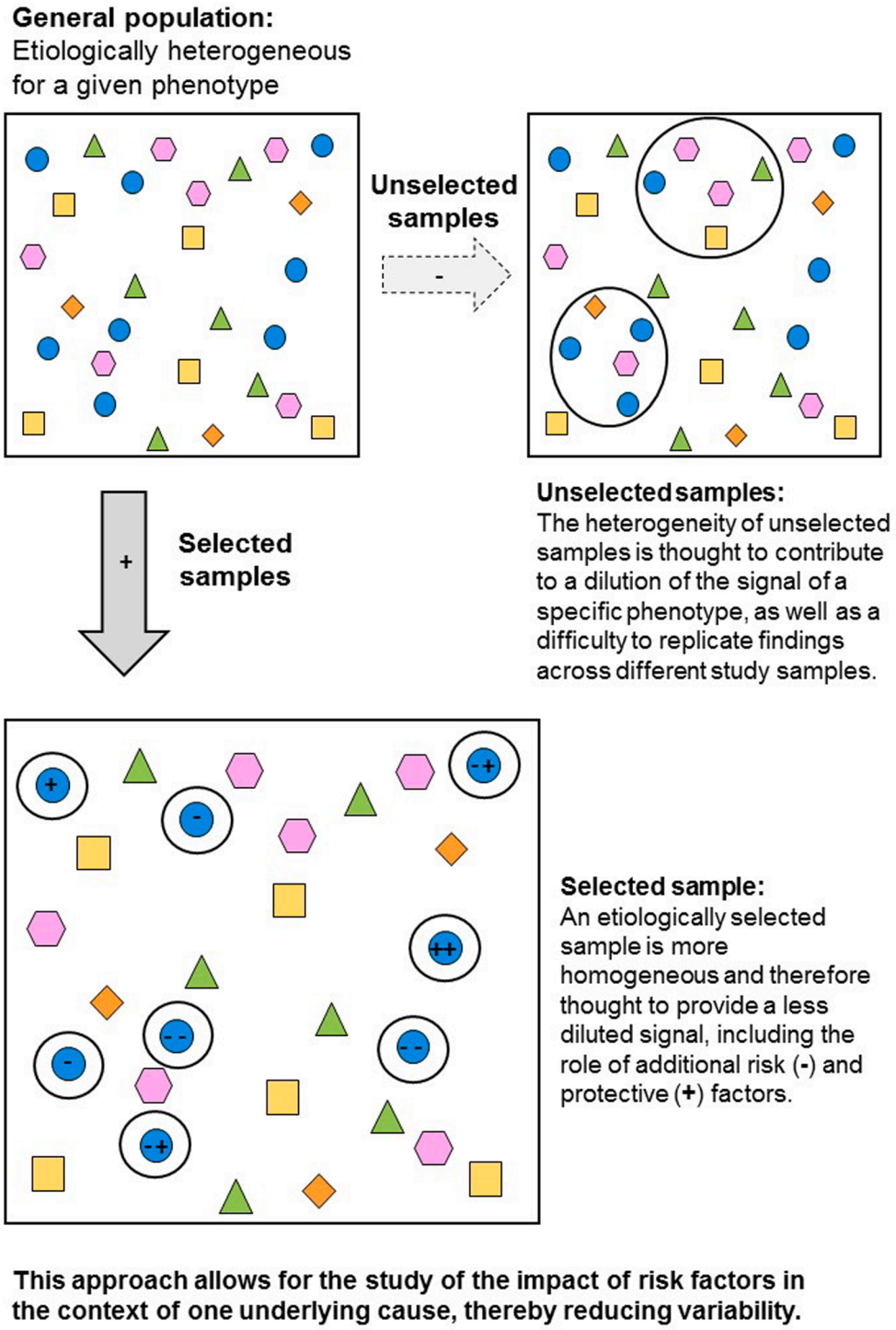

Fig. 1. Graphic depiction of the contribution of studying etiologically homogeneous groups for a given phenotype.

effectuate goal-oriented behavior (Friedman & Miyake, 2017). It is associated with many variables, including quality of life, mental and physical health (Diamond, 2013), and later outcomes, such as literacy and academic skills (Altemeier, Abbott, & Berninger, 2008; Nayfeld, Fuccillo, & Greenfield, 2013; Shaul & Schwartz, 2014; St Clair-Thompson & Gathercole, 2006). Although EF is frequently studied, knowledge concerning its developmental trajectory and putative risk factors is hampered by the variability in the general population. This variability not only exists as inter-individual differences in EF, but also in the heterogeneity of both endogenous (internal) and exogenous (external) variables contributing to these differences. Indeed, many different putative risk and protective

factors for impaired EF have been identified in the general population (e.g., Zysset et al., 2018). The complex interplay between some of these factors further impedes our ability to evaluate their individual contributions to EF development. The variability of underlying etiologies is a major challenge to studies in the general population and likely contributes to inconsistent findings in this field.

Research in individuals who share the same pathogenic genetic variant related to their EF deficits provides a unique opportunity to address this challenge. The expectation is that the reduced etiological heterogeneity may increase the strength of some of the associations that may be more difficult to observe in the general population where this signal is diluted due to a larger etiological heterogeneity (see Fig. 1). The aim of this systematic review is to gain a better understanding of specific EF deficits, their developmental trajectory, and underlying contributing factors in a selected population: children and adolescents with the 22q11.2 Deletion Syndrome.

The 22q11.2 Deletion Syndrome (22q11DS) is the most frequently occurring chromosomal microdeletion syndrome, with an estimated incidence of approximately 1 per 3000–6000 (McDonald-McGinn et al., 2015). It is caused by a hemizygous microdeletion on the long arm of chromosome 22 (Edelmann, Pandita, & Morrow, 1999; Morrow et al., 1995). Previously called velocardiofacial syndrome, the most common symptoms of 22q11DS include congenital heart disease and palatal abnormalities, but also immunodeficiency, endocrine abnormalities, and cognitive impairments, such as intellectual disability. Phenotypic expression, however, varies greatly among patients (McDonald-McGinn et al., 2015). Developmental delays are common, both physically (e.g., small stature) (Habel et al., 2012), and cognitive (e.g., delayed achievement of motor and language milestones) (McDonald-McGinn et al., 2015; Roizen et al., 2007). Moreover, individuals with 22q11DS have an increased risk for developing psychiatric problems, most prominently Attention Deficit Hyperactivity Disorder, Autism Spectrum Disorder, and schizophrenia (Fiksinski, Schneider, et al., 2018; McDonald-McGinn et al., 2015). These psychiatric disorders are all associated with EF deficits (Corbett et al., 2009; Happé et al., 2006; Lai et al., 2017; Knowles et al., 2015).

We add to previous work (Moberg et al., 2018) by providing a detailed EF profile and by reviewing the role of several factors impacting developmental EF performance in 22q11DS. Moberg et al. (2018) have shown widespread cognitive impairments, including EF deficits, in 22q11DS. In this population, EF deficits are, at the very least, partly due to this genetic variant, and thus more homogeneous in their etiology than EF deficits of individuals that are randomly selected from the general population (Fig. 1). Several putative risk factors for EF deficits occur at increased rates in the 22q11DS population. The unique characteristics of this specific population can advance theoretical debates, such as that on the division of EF domains and its developmental differentiation, or whether EF and general intelligence should be considered part of the same underlying (cognitive) construct.

Below, we first discuss theories on the division of EF and its development in the general population. Next, we describe the biological underpinnings of EF in the typical population, as well as in 22q11DS, followed by a discussion of both endogenous and exogenous risk factors for EF impairment. Lastly, we consider how studying selected populations can inform the debate on the relation between EF and intellectual abilities, before detailing the current study.

Executive functioning

Various models of EF have been proposed (e.g., Barkley, 1998; Friedman & Miyake, 2017; Lezak, 1995), but generally the concept is adopted as an umbrella term for higher-level cognitive functions used to manage lower-level cognitive processes to effectuate goal-oriented behavior (Friedman & Miyake, 2017). In the present study, we follow Miyake et al.'s (2000) proposal to divide EF into *inhibition*, *shifting*, and *updating*. Inhibition refers to the ability to suppress responses and ignore irrelevant information. Shifting refers to the ability to switch smoothly between tasks and mental states. Updating refers to the ability to monitor and manipulate the information stored in the working memory.

The subdivision of EF by Miyake et al. (2000) has mostly been validated in adults. In contrast, some studies argue that children's EF is undifferentiated and reflects a general competence at top-down control of behavior and cognition (Brydges et al., 2012; Hughes et al., 2009; Wiebe, Espy, & Charak, 2008; Wiebe et al., 2011; Willoughby, Wirth, & Blair, 2012). Other models of children's EF differentiate between two factors, including studies reporting an inhibition factor separate from an updating-shifting factor (Miller et al., 2012; Monette, Bigras, & Lafrenière, 2015; Usai et al., 2014), but also a separate updating and an inhibition-shifting factor (Lee, Bull, & Ho, 2013; van der Ven et al., 2013). The differentiation of executive functions may happen as late as early adolescence, as Xu et al. (2013) showed that even up to the age of 12 years a unitary EF model is a better fit than a multiple-factor model (but see Lee et al., 2013). Differentiation can be gradually seen in the developmental patterns of the different executive functions. Best and Miller (2010) describe that inhibition shows more rapid growth in childhood with slower gains during adolescence, while shifting shows a more protracted development. Working memory improves linearly throughout both childhood and adolescence. During development, children also become increasingly better in tasks that require the integration of these different functions (Davidson et al., 2006). Considering these developmental changes, we will distinguish between children and adolescents where possible in this review.

Biological foundation of EF

EF is argued to be influenced substantially by genetic variation (Friedman et al., 2011; Lee et al., 2012). Some have even argued that EF abilities can almost entirely be explained by genetic variance (Engelhardt et al., 2016; Friedman et al., 2008). Nevertheless, little is known about the specific genes implicated. Genome-wide association studies and polygenic scores derived from these studies show that these genetic associations are likely driven by numerous genes (Hatoum et al., 2020; Schork et al., 2019). Polygenic scores reflect the cumulative estimated effect of many different genetic variants on specific phenotypic traits. Associations of specific genetic variants with EF can strengthen research describing the full genetic architecture of EF, for example by contributing to these polygenic

scores (Wray et al., 2014).

At a cellular level, the biological underpinnings of EF development include maturation of synaptic functioning and certain neurotransmitter systems (e.g., dopamine) (Logue & Gould, 2014). Furthermore, neuronal migration, myelination, and pruning (i.e., synaptic elimination), as well as mitochondrial functioning are regarded essential to early neural development and subsequent cognitive development (Frye & Rossignol, 2012; Geary, 2018; Perone, Almy, & Zelazo, 2018). The neural substrates of EF are considered to be mostly located in the frontal cortex, specifically the prefrontal cortex (PFC), dorsolateral PFC, orbitofrontal cortex, and the anterior cingulate cortex (Alvarez & Emory, 2006). The PFC matures later than other cortical areas, developing up into late adolescence both structurally (Best, Miller & Jones, 2009; Gogtay et al., 2004; Sowell et al., 2003) and functionally (Casey, Galvan & Hare, 2005; Satterthwaite et al., 2013). On a structural level, white matter in the PFC appears to increase linearly throughout childhood, likely as a result of synaptogenesis (i.e., synapse formation), neuronal proliferation, and myelination, whereas gray matter has been reported to similarly increase *before* the onset of puberty, but to decline thereafter (Giedd et al., 1999; Gogtay et al., 2004), presumably as the result of synaptic pruning, apoptosis (i.e., programmed cell death), or an increase in intra-cortical gray matter (Paus, 2005). This structural development of the PFC is consistent with the protracted developmental trajectory reported for EF, as indicated by behavioral data.

Biological underpinnings of EF in 22q11DS

Evidently, children with 22q11DS differ from typically developing children in that they have a hemizygous (i.e., on one allele) deletion of up to 3-Mb encompassing up to 90 genes in band 11 of chromosome 22 (McDonald-McGinn et al., 2015; Edelmann et al., 1999; Morrow et al., 1995). Genes located in the 22q11.2 region, such as catechol-O-methyltransferase (*COMT*) and proline dehydrogenase (*PRODH*), contain different variants (i.e., polymorphisms). In the case of *COMT*, it primarily concerns the $Val^{158}Met$ (rs4680) variant, whereas for *PRODH* there are many different functional variants. These variants have been linked to cognitive performance in individuals without 22q11DS (e.g., Barnett et al., 2007; Li et al., 2008; Mier, Kirsch, & Meyer-Lindenberg, 2010; Moriguchi & Shinohara, 2018; but see Barnett, Scoriels, & Munafò, 2008). Moreover, individuals with 22q11DS thus only have one copy of genes located in the deleted region, creating unique opportunities to study genotype-phenotype interactions. The hemizygous deletion of genes such as *COMT*, *RANBP1*, and *PRODH* may affect the dopaminergic, GABAergic, and glutamatergic systems, thereby impacting the development and regulation of subsequent neural pathways (Kempf et al., 2008; Paronett et al., 2014; Sobin et al., 2004). It is likely that multiple genes within the 22q11.2 region may contribute to the EF profile of these children, but these relations appear to be largely unexplored. Similarly, knowledge concerning the role of genes in this region during different developmental stages is limited due to our incomplete understanding of expression patterns in the brain, and changes thereof during development.

Nonetheless, research has suggested that the 22q11.2 deletion may impact cortical development throughout various stages of development, starting with altered neuronal identity, aberrant neurogenesis (i.e., neuron formation) and neural migration patterns, and finally alterations in connectivity as a result of deficient mitochondrial functioning (resulting in lower energy production) (Li et al., 2019; Meechan et al., 2011). Indeed, aberrant trajectories of cortical development have been observed in individuals with 22q11DS (Nuninga et al., 2018; Ramanathan et al., 2017; Schaer et al., 2009), with increased cortical thinning during adolescence presumably due to disrupted synaptogenesis and pruning (Meechan et al., 2011; Schaer et al., 2009). This is corroborated by research showing reduced structural connectivity in networks associated with EF (Jonas et al., 2015; Padula et al., 2017; Scariati et al., 2016) and reduced activation of frontal areas in adults with 22q11DS during EF tasks (Harrell et al., 2017; Montojo et al., 2015).

Risk factors for EF impairment

EF development can be impacted by various factors throughout different phases of development. These factors can be both endogenous (child-internal) or exogenous (child-external) (e.g., Zysset et al., 2018) and with either protective or deleterious impacts on EF development. Many risk factors for EF impairment observed in the general population are more prevalent in the 22q11DS population, as will be detailed below. Investigating the effect of specific endogenous and exogenous factors on EF outcomes in 22q11DS provides an opportunity to reduce the variability caused by at least one of the many factors that might be at play: genetic variation. The specific genetic profile of these children can guide hypotheses on mechanisms crucial to EF development.

Endogenous risk factors for EF impairment

Endogenous risk factors for EF impairment are generally biological in origin and most likely impact EF by disrupting early cortical development. For example, variation of specific genes located in the 22q11.2 region have been associated with EF. Other endogenous factors that are frequently associated with EF impairment in the general population are premature birth, low birth weight, and congenital heart defects.

Meta-analyses have shown that children born preterm or with a very low birth weight (LBW) generally perform lower on measures of EF than children born term or with normal birthweight (Aarnoudse-Moens et al., 2009; Brydges et al., 2018; Mulder et al., 2009). On average, children born preterm or with LBW have smaller volumes of both gray and white matter (Davis, Buss, et al., 2011; De Kieviet et al., 2012). Preterm birth or LBW may be the result of an underlying genetic cause, which may also separately affect early brain growth. Additionally, both pre- or postnatal factors, such as nutritional deficiencies in utero or spending the first weeks of life in a Neonatal Intensive Care Unit, may be adverse to neural development. In Western countries, preterm birth occurs in around 9% of all births (Blencowe et al., 2012; Purisch & Gyamfi-Bannerman, 2017) and LBW in 7% of all births (Blencowe et al., 2019). In 22q11DS, a small but significantly heightened incidence of preterm birth (13–17%) and LBW (9–20.3%) has been observed (Kufert et al., 2016; Lima et al., 2010; Van et al., 2016).

In the general population, children with a Congenital Heart Defect (CHD) have poorer neurodevelopmental outcomes, including EF impairment (Mebius et al., 2017; Sterken et al., 2015). Their EF deficits may be the result of abnormal brain development. Infants with CHD are at risk for brain lesions, show delayed brain maturation, and have smaller total brain volumes (Khalil et al., 2014; Licht et al., 2009; Limperopoulos et al., 2010; Morton, Ishibashi, & Jonas, 2017; Watanabe et al., 2009). In these children, brain lesions in, and delayed maturation of brain regions subserving EF, may result from a complex interaction of various factors, such as abnormal cerebral blood flow in utero, reduced oxygen supply, or surgery-related factors (Peyvandi et al., 2019; Wernovsky & Licht, 2016). In 22q11DS, CHD prevalence rates are estimated to be as high as 75% (McDonald-McGinn et al., 2015). One study reported reductions of cortical thickness in various brain regions in individuals with 22q11DS and CHD as compared to those with 22q11DS and without CHD (Fountain et al., 2014). While these findings indicate a relation between CHD and cortical thickness, conclusive evidence in support of causality is not yet available. Plausible causal mechanisms include reduced oxygen supply which may be most pronounced at the borders of blood supply regions (i.e., watershed areas) and may have the largest impact on regions with the highest energy demand. This is supported by the beneficial effect that physical activity, which increases cerebral blood flow and oxygen saturation, seems to have on EF as reported in the general population (see section *Exogenous risk factors for EF impairment* below). However, these findings cannot rule out the possibility that the observed cortical abnormalities could also be the result of the deletion itself or be related to other medical issues common in 22q11DS (e.g., hypocalcemia or seizures). Indeed, a previous study by the same group reported a significant mean difference in total cerebral volume in 22q11DS (with and without CHD) compared to controls (without CHD) (Schaer et al., 2009). Furthermore, a meta-analysis has revealed widespread volumetric reductions in cortical matter in 22q11DS (Tan et al., 2009) but future studies are required to further elucidate the nature of this association. Based on the above, we argue research in 22q11DS can guide hypotheses on mechanisms crucial to EF development, such as the role of oxygen supply in mitochondrial functioning and subsequent neural development.

Exogenous risk factors for EF impairment

In addition to changes and disturbances of biological origin, exogenous factors can also impact EF. Some of the exogenous factors associated with EF impairment are stress, socioeconomic status, parenting behaviors, play, and exercise.

Early life stress has been argued to affect the development of the brain areas underlying EF (Pechtel & Pizzagalli, 2011). Excessive levels of cortisol (a hormone released in response to stress) can suppress physiological processes critical to early brain development, such as neuron and synaptogenesis, as well as lead to changes in neural development (atypical axon and dendrite development) (Conrad, 2008; Gould & Tanapat, 1999; Woolley, Gould, & McEwen, 1990). In the general population, heightened cortisol has been linked to poorer EF outcomes in early childhood (Blair et al., 2011; Wagner et al., 2016). However, certain demographic or familial factors may mitigate the effects of early life stress (Lopez et al., 2021). Children with 22q11DS and their parents may experience more stress due to the presence of severe medical issues, insecurity about the future, and challenges in finding appropriate healthcare and education (Goodwin, McCormack, & Campbell, 2017; Vo, McNeill, & Vogt, 2018). This might be further exacerbated by a biological predisposition for disrupted cortisol levels (van Duin et al., 2019; Sandini et al., 2020).

Demographic or familial factors, such as socioeconomic status (SES) or parenting style, are also suggested to impact the EF development in children (Kao et al., 2018; Rhoades et al., 2011). A meta-analysis shows that during development there is a stable small to medium effect of SES on EF in children, with lower SES associated with poorer EF performance (Lawson, Hook, & Farah, 2018). Factors such as parental scaffolding, stimulation, control, and responsiveness have been linked to better EF abilities in typically developing children (Blair, Raver, & Berry, 2014; Fay-Stammbach, Hawes, & Meredith, 2014; Hughes & Devine, 2019; Hammond et al., 2012). Additionally, more unstructured play time has been linked to stronger EF, presumably because it allows children to practice self-directed choice and planning skills (Barker et al., 2014). Parenting styles and the amount of structured time may differ between typically developing children and clinical populations. Chronic illness in children with additional stressors, such as behavioral or communication problems, has been shown to incite a more protective parenting style (Pinquart, 2013). There is currently no evidence that children with 22q11DS differ in SES from typically developing children, and research on parenting behaviors in parents of these children is scarce (Swillen, Moss, & Duijff, 2018).

Additionally, physical activity may have a positive impact on EF during childhood, supposedly by supporting physiological processes beneficial to EF development. This includes processes that are likely also affected by congenital heart defects, such as cerebral blood flow and oxygen saturation. Physical activity might furthermore benefit EF development due to the cognitive demands that accompany complex and goal-directed motor movements and exercise (Best, 2010; Chaddock et al., 2012). A randomized controlled trial with typically developing children showed that an intervention boosting physical activity improved EF performance (Hillman et al., 2014). Little is known about the physical activity of children with 22q11DS, but adolescents with 22q11DS report increased rates of fatigue and reduced activity (Vergaelen et al., 2017). Reduced activity might be a consequence of the presence of certain medical conditions, like CHD, but it may also further exacerbate the negative impact of such conditions on EF development in this vulnerable population.

Similarly, the role of factors like stress, parenting style, and unstructured time may also be affected by the presence of medical problems, such as CHD. Furthermore, many of these exogenous factors may also interact with endogenous factors (i.e., gene-environment interaction) (e.g., Chen et al., 2020). This underscores the complexity of the relation between such factors and EF outcomes.

Summary: EF risk factors and 22q11DS

Various risk factors associated with EF impairment in the general population, such as congenital heart defects (CHD) and stress, are clearly more prevalent in 22q11DS. Other risk factors, such as preterm birth, low birth weight, specific parenting styles, limited play

and physical activity are likely to be more prevalent, but limited research so far precludes robust conclusions. In the case of the effects of endogenous risk factors, studying 22q11DS can help us determine whether a common underlying genetic origin is responsible for atypical neural development, or whether downstream effects of the genetic defect might cause additional damage. For instance, pleiotropic effects of genetic variation associated with CHD may separately impact neural development (McQuillen & Miller, 2010; Nattel et al., 2017). If an underlying genetic mutation is responsible for both CHD and atypical neural development (leading to EF impairment), the secondary effects of CHD on EF abilities may be negligible in populations such as individuals with 22q11DS.

Association EF with intellectual abilities

It has been argued that EF and intellectual abilities are two sides of the same coin (e.g., Duncan et al., 1996), with some studies showing that EF functions can be fully incorporated into theories of general intelligence (Frischkorn, Schubert, & Hagemann, 2019; Jewsbury, Bowden, & Strauss, 2016). In contrast, others argue that EF and general intelligence are separate constructs (Ardila, Pineda, & Rosselli, 2000; Crinella & Yu, 1999). A correlation between Intelligence Quotient (IQ) and EF has been observed in typically developing children (Arffa, 2007; Ardila et al., 2000), although not unequivocally (Montoya-Arenas et al., 2018). Furthermore, while measures of intelligence and EF have been found to share some variance, EF also explains additional variance not captured by measures of intelligence (Davis, Pierson & Finch, 2011; Friedman et al., 2006). Likewise, Polderman et al. (2006) found that EF at age 5 appears to be a weak predictor for IQ at age 12. Thus, the constructs of intelligence and EF are correlated but there are distinct components to each of them.

As the evidence on typically developing children is mixed, evidence from children with atypical development, specifically those associated with intellectual disability, can be informative. Studying such populations may either reveal a double dissociation between EF and intelligence, supporting the idea that they are separate entities, or it may show that EF and IQ share a common underlying factor. If the latter is true, EF deficits in populations with intellectual impairment should disappear or at least weaken when controlling for IQ. The 22q11DS population lends itself well to this end as intellectual disability (IQ < 70) occurs in around 50% of children, with most having an IQ-score in the borderline range between 55 and 85 (McDonald-McGinn et al., 2015; De Smedt et al., 2007). Crucially, the IQ-scores of the 22q11DS population follow a normal distribution similar to the general population (Klaassen et al., 2016; Niklasson & Gillberg, 2010). Similar debates, such as that of the division of EF domains, could also be informed by observing specific populations, such as 22q11DS.

Current study

In summary, EF is a critical component of cognitive development, as it is associated with concurrent development of other cognitive functions and later outcomes, such as academic and psychosocial functioning. Beyond a direct (clinical) relevance to the population of individuals with 22q11DS, we suggest that findings reported here also have a broader value. It has been widely argued that 22q11DS can be taken as a model for the study of schizophrenia and its risk mechanisms (Gur et al., 2017; Insel, 2010). We propose that the same holds for other phenotypes, such as EF profile. As there are indications that EF is impaired in individuals with 22q11DS (e.g., Campbell et al., 2010; Moberg et al., 2018), understanding which factors, in addition to the deletion itself, impact EF abilities in this group, can further our understanding of underlying mechanisms.

This systematic review aims to comprehensively describe what is currently known about the specific EF profile of children and adolescents with 22q11DS. We will consider longitudinal studies or studies regarding the effect of age to provide insight into the developmental trajectory of EF in 22q11DS. Additionally, we focus on studies investigating the effect of various endogenous and exogenous risk factors, previously identified in the general population, on EF performance of children and adolescents with 22q11DS. This allows us to identify gaps in the literature and provide directions for future research. This can guide potential interventions for children with 22q11DS and support research in, and relevant to the general population.

Methods

This systematic review was conducted in adherence to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (Moher et al., 2009).

Search strategy

Title, abstract and keyword searches were conducted in PubMed, PsychInfo, and EMBASE in February 2020 using the search terms presented in Table 1. Due to the variability in terms used for both 22q11DS and EF, final search terms were selected based on whether they increased the number of hits in exploratory searches in PubMed. In these exploratory searches the 22q11DS and EF terms were not combined.

No limits were imposed on publication type, date, or language. The only limit imposed was the exclusion of articles published in PubMed in the EMBASE search to limit duplicates. In our search strings, the asterisk shortens the word to identify different endings, and MeSH terms (or equivalents) for 22q11DS were used when available.

Table 1
Search terms used in the query combining terms for 22q11DS with terms for EF.

22q11.2 deletion syndrome	AND	Executive functions
22q11* OR *22q11 OR del22q11* OR VCFS OR Velocardiofacial syndrome OR Velo-cardio-facial syndrome OR VCF syndrome OR DiGeorge syndrome OR Di-George syndrome OR Shprintzen syndrome OR Velocardiofacial OR Velo-cardio-facial OR DiGeorge OR Di-George OR Shprintzen OR CATCH22 OR catch 22 OR Sedlackova syndrome OR Takao syndrome OR Cayler cardiofacial syndrome OR Conotruncal Anomaly Face Syndrome		Executive funct* OR Executive control OR Executive dysfunc* OR Working memory OR Inhibition OR Attention* OR Cognitive flexibility OR Shifting OR Switching OR Prefrontal cognition

Note. For the exact queries per search engine, see Appendix A.

Study selection

In the first screening, titles and abstracts were independently checked by two authors each (EE, IS and/or TB) for reporting original data of behavioral methods in human subjects with 22q11DS. Any discordance was resolved by consensus. In the second screening, the remaining articles were assessed for eligibility to be included. The full text of the articles was examined for:

(1) mean age ($\leq$18 years);
(2) age range ($\leq$10 years) or the standard deviation (SD) of the mean age ($<$3.5) of the participants;
A maximum age range of 10 years was chosen to limit heterogeneity due to developmental differences in the participant sample. In studies that did not report the age range of their sample, the SD of the mean age of participants was used as an indication of the age range.

(3) sample size ($N \geq 15$);
A minimum sample size of fifteen was taken to ensure some ability to generalize given the heterogeneity within the 22q11DS population.

(4) reporting a genetically confirmed diagnosis of 22q11DS for all participants in the 22q11DS group;
(5) which task was used and whether this task is generally recognized as a task that validly gauges EF;
In order to be considered for this review, we required tasks to be commonly known for measuring EF. Alternatively, tasks were considered if the original authors of the study being screened, explained how the task they used measures one or more specific sub-components of EF and this explanation was in agreement with theories of EF. The current authors classified tasks into one of three EF domains, following the division by Miyake et al. (2000): inhibition, shifting, and updating (working memory; WM). Updating was further divided in verbal WM and visual(-spatial) WM (see Table 3). This classification did not consider the domain intended by the original authors.
- Tasks taken to measure verbal and/or visual(-spatial) WM were defined as tasks that require participants to keep the information active during an interfering task or to manipulate the input rather than just reproducing it (Baddeley, 1992). This means that for some tasks (e.g., Digit Span) only the *backward* condition is considered in this review. *Forward* conditions are thought to gauge short-term memory rather than WM. In a similar vein, only Trail Making Test (TMT) B, but not TMT A was considered to represent shifting.
- Both the verbal and the visual condition of the Self-Ordered Pointing Task were considered to represent visual WM, because the verbal condition also uses pictures, just ones that are easy to encode verbally. However, there is no way to check whether participants used a verbal strategy.
- Although frequently used to represent EF, verbal fluency and the Working Memory Index of the Wechsler Intelligence Scale for Children (WISC-WMI) are not discussed in the current review, because there is no consensus on what verbal fluency exactly measures (Shao et al., 2014; Stolwyk et al., 2015) and because the WISC-WMI is a composite score that combines both verbal and non-verbal WM measures in addition to short-term memory measures.

(6) whether the EF outcomes (e.g., mean score) were reported explicitly and not just in relation to other outcomes, and;
(7) whether there was a comparison with a control group, norm group, or a within-group comparison.

A comparison with a control group or norm scores or a comparison between two groups of participants with 22q11DS, was deemed necessary in order to interpret the results, since many neurocognitive measures do not produce outcomes that can be interpreted without context.

Studies were only classified as longitudinal if they reported EF outcomes for at least two time points.

The authors of the current study reviewed and discussed the articles. To limit possible bias, all studies were reviewed for potential overlap in study groups. In case of uncertainty, authors were contacted to verify whether there was overlap in the data reported in the paper. In case of confirmed or suspected overlap of data, the study with the lowest risk of bias and/or largest sample size was included.

Table 2
Risk of bias assessment checklist.

Risk of bias assessment for individual studies			
Control group?	Yes	No	
Cohort?	Longitudinal	Cross-sectional	
Study			
1. A clear research question and hypotheses;	−	−/+	+
Participants			
2. Clearly stated in- and exclusion criteria;	−	−/+	+
3. Comprehensive demographic data of the sample;	−	−/+	+
4. Cases and controls are selected from comparable populations;	−	−/+	+
5. Recruitment procedure is described (period, consecutive recruitment, non-response, etc.);	−	−/+	+
Data collection and analysis			
6. The study uses well defined, frequently used, and/or standardized measures (with norms or controls);	−	−/+	+
7. Confounds are identified and controlled for;	−	−/+	+
8. Adequate statistical analysis (e.g., correction for multiple testing);	−	−/+	+
Outcomes			
9. Confidence interval and effect sizes are reported;	−	−/+	+
10. All expected/pre-determined outcomes are included in the study descriptions;	−	−/+	+
If longitudinal:			
12. Time between measurements is long enough to see development/changes;	−	−/+	+
12. Cases and controls were included during the same time period;	−	−/+	+
13. Drop-out described or no participants lost.	−	−/+	+

Note. When a study did not report certain elements or did not perform certain procedures: −; if some information was reported but insufficiently: −/+; if adequately performed and/or reported: +.

Box 1
Data collected for analysis.

Data collected for analysis

Research institute 22q11DS group: Sample size, genetic confirmation, age (mean, SD, range)
Executive functions: EF domain as stated by the original article, EF domain as classified by the current authors, name of test(s)
Control group: Yes/no, and if yes, sample size, type of control group, age (mean, SD)
Longitudinal: Yes/no and if yes, how many measurement points and time between them
Other factors: Genetic variants, CHD, SES, prematurity, LBW, stress, parenting, play, physical activity, or IQ

Assessment of risk of bias

The risk of bias (RoB) assessment for all individual studies was performed by one author (EE) using the checklist below, see Table 2. A second author (FW) performed a secondary RoB assessment for eight of the studies (27.5%). Agreement was deemed satisfactory and in case of differing assessments, agreement was reached by consensus.

We created a risk of bias assessment tool based on various other risk-of-bias assessment tools, such as the RoBANS (Kim et al., 2013) and the Newcastle-Ottawa scale for assessing the quality of nonrandomized studies (Wells et al., 2000), but tailored to the specific characteristics of this field of study and the studies identified with the search. The reason for doing this was that many RoB assessment tools include criteria irrelevant to the studies in this review. Since one of the inclusion criteria for studies in this review is that cases are required to have a confirmed genetic diagnosis of 22q11DS, assessment of cases was not considered in the risk of bias assessment. Some criteria frequently assessed in risk-of-bias assessments were not considered here, because they applied to all or virtually none of the studies. These criteria are discussed in the results section of the risk of bias assessment. The last three items on the list are considered only if a study is longitudinal.

The final category was either a (1) high, (2) medium, or (3) low RoB. These categories were based on sample size and the overall result of the criteria specified in the checklist, although items varied in the weight ascribed to them. While studies with high or medium RoB provide valuable data, their conclusions should be considered with more caution compared to studies with low RoB.

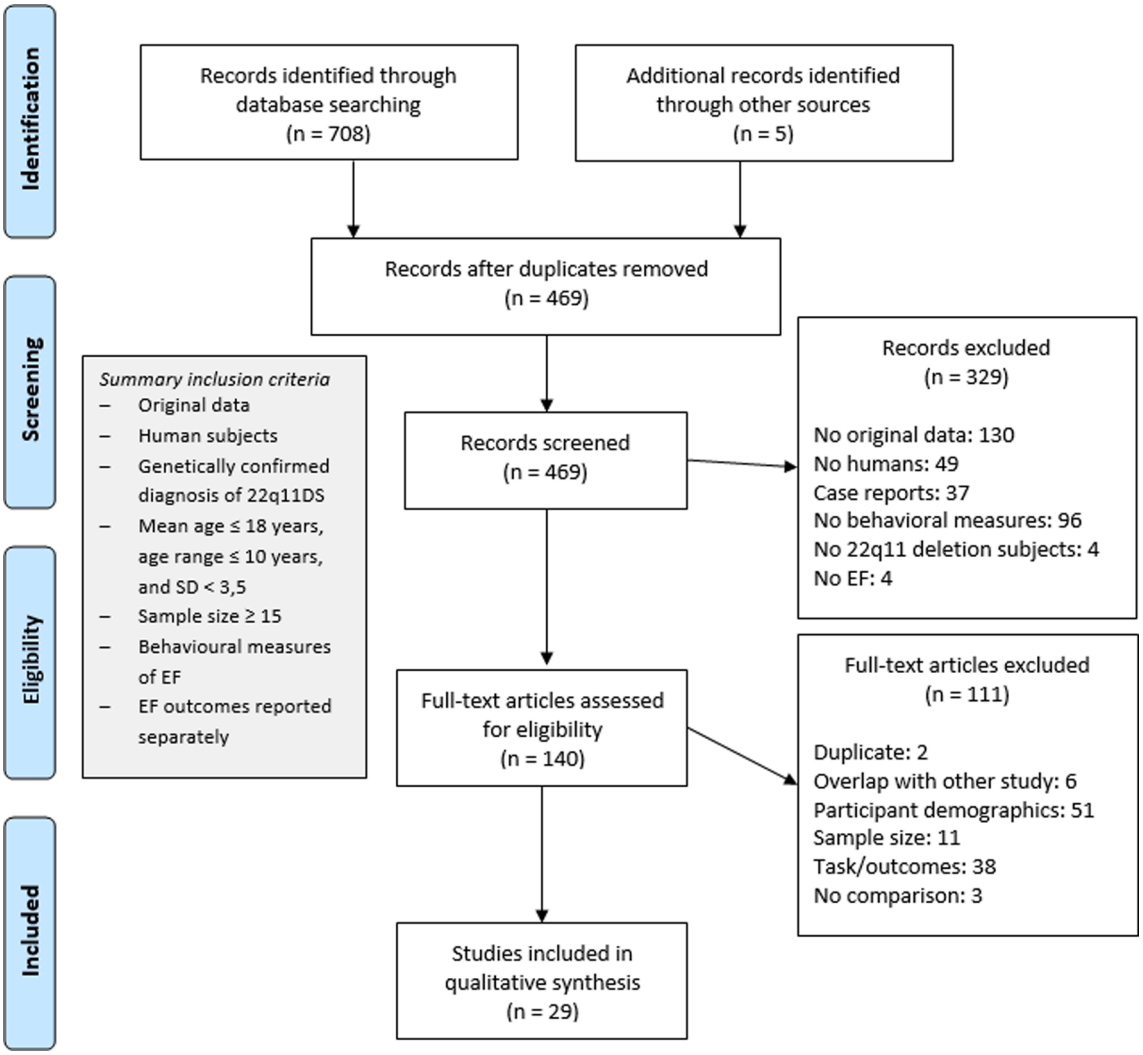

Fig. 2. Flow diagram of the systematic search and subsequent in- and exclusion (Moher et al., 2009).

Data collection and statistical analysis

Data was extracted based on a pre-developed extraction form (see Box 1). Note that some studies report both a comparison of their 22q11DS participants and controls/norms, and a comparison of groups within their 22q11DS sample. Additionally, various studies report on more than one task or report one task that spans multiple domains. If a study reports multiple tasks, each task is reported in the respective domain, whereas if one task spans multiple domains the outcomes are reported in the primary domain. The primary domain is determined based on the task itself and the reported outcome measures. Some studies report mixed outcomes with respect to different tasks or different outcome variables within one task, in which case both outcomes are reported. Some studies have overlap with other studies but are included nonetheless because they contain an additional analysis, data relevant for development, or because they provide (more detailed) information on factors associated with EF. These studies are not described or discussed in the results of individual studies per domain.

Results

Study selection

Our query returned 713 studies. After elimination of duplicates, the titles and abstracts of 469 studies were screened for original data of behavioral measures of cognition in human subjects with 22q11DS. A total of 140 studies met these inclusion criteria. The full texts of all these articles were available and these were screened for the secondary inclusion criteria. A total of 29 studies met the criteria for inclusion in this systematic review (see Fig. 2).

Table 3
Overview of the characterstics of the studies included for analysis.

	Author, Year	Sample size	Mean age (SD)	Age range	Task(s)	Domain	Control group? If so, *N*	Mean age (SD)	Outcome	RoB
1.	Bearden et al. (2004)	44	11.1 (3.2)	N.R.	DS, TMT B, VF, WISC-3 Arithematic	Broad EF	–		Met > Val	High
2.	Carmel et al. (2014)	32	8.06 (2.37)	N.R.	Flanker	Shifting	–		Met = Val Arg = Trp	Medium
		28	14.64 (1.73)	12–18	Flanker	Shifting	–		Met = Val Arg = Trp	
3.	De Sonneville et al. (2018)	58	13.48 (2.6)	9–18.5	AmstNT SSV	Inhibition	–		22q < TD error 22q = TD speed	Medium
					AmstNT SSV	Shifting			22q < TD 22q = TD 22q > TD	
					AmstNT MSL	Updating			22q < TD speed and error	
4.	Niklasson et al. (2005)	30	N.R.	7–13	Becker Go/No-Go	Inhibition	–		22q < TD	High
5.	Niklasson and Gillberg (2010)	30	N.R.	6–13	ToL	Inhibition	–		22q = TD	Medium
		22	N.R.	7–15	TMT B	Shifting	–		22q < TD	
6.	Shashi, Howard, et al. (2010)	40	9.53 (2.53)	7–16	CPT_IP, CPT_AX	Inhibition	–		Met = Val	High
					WCST	Shifting			Met > Val	
7.	Sobin, Kiley-Brabeck, Daniels, et al. (2005)	40	7.7 (2.4)	5.2–12.9	NEPSY Tower	Inhibition	–		22q = TD	Medium
					NEPSY AARS	Shifting			22q < TD	
8.	Stoddard et al. (2012)	53	N.R.	6–15	Flanker	Shifting	–		Met = Val	High
9.	Albert et al. (2018)	63	12.2 (2.3)	N.R.	ToL, GDS, Stroop	Inhibition	43	11.8 (2)	22q < TD 22q = TD	Low
					WCST	Shifting			22q < TD	
					DS, VSp	Updating			22q < TD	
10.	Antshel et al. (2017)	78	11.9 (2.1)	N.R.	CPT	Inhibition	50	12 (2)	22q < TD	Medium
					WCST	Shifting			22q < TD	
					VSp	Updating			22q < TD	
11.	Baker et al. (2005)	25	16.3 (2.1)	13.8–20.8	Sentence span task, Dot test	Updating	25	15.9 (3)	22q < TD TD > 22qMet, TD > 22qVal, 22qMet = 22qVal	High
12.	Bish et al. (2005)	18	9.17 (1.7)	7–14	Flanker	Shifting	16	9.58 (1.8)	22q < TD	High
13.	Brankaer et al. (2017)	25	9.83 (1.89)	6–12	DS, LSp	Updating	48	9.36 (1.75)	22q = TD	Low
14.	Campbell et al. (2015)	24	16.75 (3.14)	12–21	ToL	Inhibition	27	16.26 (3.65)	22q < TD	Medium
					2 experimental WM tasks	Updating			22q < TD	
15.	Cunningham et al. (2018)	70	11.2 (2.2)	6.2–14.87	CANTAB SOC	Inhibition	32	11.5 (2.1)	22q < TD	Low
					WCST	Shifting			22q < TD 22q = TD	
					CANTAB SWM	Updating			22q < TD	
16.	De Smedt et al. (2008)	25	9.8 (1.9)	N.R.	DS, LSp, Counting span	Updating	25	9.3 (1.7)	22q = TD	Low
17.	Kates et al. (2007)	17	N.R.	8–15	2-back non-spatial WM	Updating	20	N.R.	22q = TD	Medium
18	McCabe et al. (2014)	25	16.8 (2.9)	N.R.	ToL	Inhibition	30	16.5 (3.5)	22q < TD	Medium

(*continued on next page*)

Table 3 (*continued*)

	Author, Year	Sample size	Mean age (SD)	Age range	Task(s)	Domain	Control group? If so, *N*	Mean age (SD)	Outcome	RoB
19.	Sanders et al. (2017)	20	12.2 (2.4)	7–16	Shapes WM computer task	Updating	32	10.9 (2.5)	22q < TD	Medium
20.	Shapiro et al. (2014)	71	11.4 (2.5)	7–14	Stroop, Go/No-Go	Inhibition	52	10.6 (2.2)	22q < TD Met = Val + Met < Val	Medium
					WCST	Shifting			22q < TD Met = Val	
					SOPT	Updating			22q < TD Met = Val	
21.	Shashi, Keshavan, et al. (2010)	65	10.2 (2.6)	N.R.	CPT_IP, CPT_AX	Inhibition	52	10.4 (2.3)	22q < TD	Medium
					WCST	Shifting			22q < TD	
22.	Shashi et al. (2012)	66	10.5 (2.6)	N.R.	CPT_IP, CPT_AX	Inhibition	54	11 (2.3)	22q < TD	Medium
					WCST	Shifting			22q < TD	
23.	Sobin et al. (2004)	32	7.6 (1.6)	5–11.5	Flanker	Shifting	20	8.3 (2)	22q < TD	Medium
24.	Sobin, Kiley-Brabeck, & Karayiorgou (2005)	21	10.44 (2.59)	6–15.1	Flanker	Shifting	25	9.51 (1.98)	22q < TD	High
25.	Stoddard et al. (2011)	53	10.73 (2.02)	7–14	Flanker	Shifting	46	10.04 (2.38)	22q < TD	Medium
26.	Yi et al. (2014)	27	11.37 (2.24)	8–14	CNB	Broad EF	16 (CHD)	10.81 (1.28)	22q + CHD = 22q-CHD	Medium
							48 (TD)	N.R.	22q < TD	
27.	Antshel, Shprintzen, et al. (2010)	80	11.9 (2.2)	N.R.	CPT, ToL	Inhibition	73	12.2 (1.9)	TD_2 > TD_1 * 22q_2 = 22q_1 + 22q_2 > 22q_1	Medium
					WCST	Shifting			TD_2 = TD_1 22q_2 = 22q_1 + 22q_2 > 22q_1	
					VSp	Updating			TD_2 > TD_1 22q_2 > 22q_1	
28.	Chawner et al. (2017)	75	9.9 (2.4)	6 – N.R.	CANTAB SOC	Inhibition	33	10.6 (2)	Growth: 22q = TD	Low
					WCST	Shifting			Growth: 22q = TD	
					CANTAB SWM	Updating			Growth: 22q = TD	
29.	Hooper et al. (2013)	42	10.05 (2.49)	7–15.67	CPT_IP, CPT_AX	Inhibition	29	10.3 (1.74)	Growth: 22q > TD 22q = TD	Medium
					WCST	Shifting			Growth: 22q = TD	

Note. Studies are divided in studies without a control group (1–8), studies with a typically developing (TD) control group (9–26) and longitudinal studies (27–29). Within this division, studies are presented alphabetically. Outcomes are summarized per domain per study. Studies with outcome 22q < TD or 22q > TD found a significant difference between their 22q11DS group and the conrol group or norms on at least one task. Studies in the 22q = TD category did not report a significant difference between groups. Studies with mixed outcomes receive the labels of both outcomes. For studies that made a comparison within their 22q11DS sample based on genetic variants, abbreviations for these genetic variants were used (*COMT* Val^{158}Met: Val/Met and *PRODH* Arg^{185}Trp: Arg/Trp, see section *Genetic variation* in *Results*). For longitudinal studies, outcomes reflect the comparison between growth trajectories. An exception is the study by Antshel, Shprintzen, et al. (2010) which did not compare growth trajectories between groups. The labels for that study reflect the comparison between the first (_1) and the second (_2) timepoint for the 22q11DS and TD groups seperately.

Abbreviations: AmstNT = Amsterdam Neuropsychological Tasks, MSL = Memory Search Letters and SSV = Shifting Attentional Set Visual; ANT = Attention Network Task; CANTAB = Cambridge Neuropsychological Test Automated Battery, SOC = Stockings of Cambridge and SWM = Spatial Working Memory; CHD = Congenital Heart Defect; CNB = Penn Computerized Neurocognitive Battery; CPT = Continuous Performance Task, IP =

Identical Pairs and AX = A before X; DS = Digit Span; GDS = Gordon Diagnostic System; LSp = Listening span tasks; NEPSY = A Developmental NEuroPSYchological Assessment, AARS = Auditory Attention Response Set; N.R. = Not reported; RoB = Risk of Bias; SOPT = Self Ordered Pointing Task; TD = Typically Developing; TMT B = Trail Making Task version B; ToL = Tower of London (/Hanoi, or similar tasks); VF = Verbal fluency; VSp = Visual span task; WCST = Wisconsin Card Sorting Task; WISC-3 = Wechsler Intelligence Scale for Children 3; WM = Working memory

* Except for CPT commission errors for TD for which TD_2 = TD_1

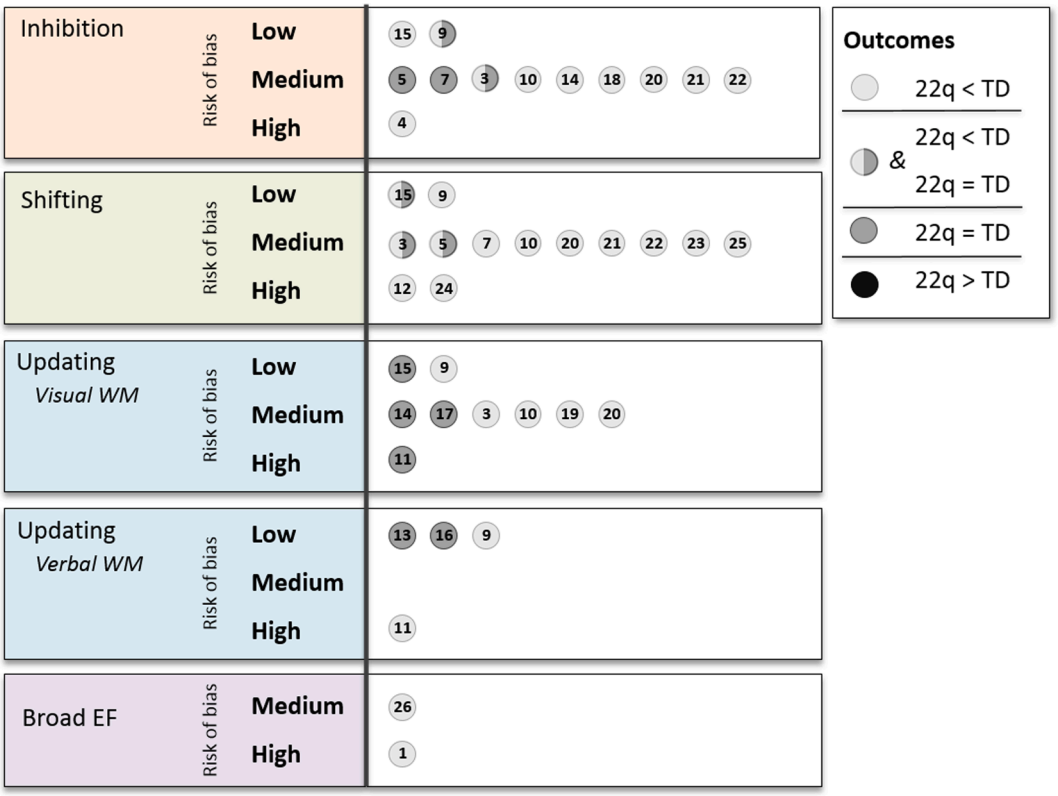

Fig. 3. Number of studies with certain outcomes per EF domain presented according to their RoB category. *Note*. Each circle represents one study (numbers correspond to those in Table 3) and the gray scale indicates the outcome. Circles with the two colors represent studies with mixed outcomes. Studies in the 22q < TD or 22q > TD category found a significant difference between groups on at least one task. Studies in the 22q = TD category did not report a significant difference between groups.

Study characteristics

The 29 studies included in this review reported on a total of 1274 participants with 22q11DS with a mean age of 11.3 (SD: 2.3) years (this excludes four studies that only reported age range). Overall, the average age range was 7.6 years as reported by 19 out of 29 studies (see Table 3). Following the age division of the World Health Organization (2017) guidelines, nine studies reported on children (mean age < 10), three reported on adolescents (mean age > 14), and 16 reported on a mix of children and adolescents (mean age > 10 and < 14). One study reported separately on a group of children and a group of adolescents. All included studies and an overview of their content is displayed in Table 3.

Twenty-one studies had a typically developing (TD) control group; two of these studies had an additional control group consisting of a different clinical sample (Turner Syndrome and CHD without 22q11DS). Seven studies made comparisons between two groups within their 22q11DS sample which are relevant for the current review. Three studies were longitudinal, all of which had a control group.

Methodological quality and/or risk of bias

Risk of bias in individual studies

We assessed seven studies as having a high risk of bias (RoB), thus providing more tentative evidence. Seventeen studies were assessed to have a medium risk of bias, and five studies were assessed to have a low risk of bias. None of the studies, except for one (Yi et al., 2014), actively checked contamination of their control group by inadvertently including cases as controls. However, given the low prevalence of the deletion and the high penetrance of associated phenotypes, the probability of contamination can be considered

nearing null. Only two studies reported a post-hoc power analysis (Shashi, Howard, et al., 2010; Sobin et al., 2004). See Table 3 for the RoB outcomes and Table 4 (Appendix B) for the full quality assessment.

Risk of bias across studies

The risk of bias of the cumulative evidence in the field may be affected by publication bias or selective reporting. In the case of studies reporting on clinical populations, such as 22q11DS, we would argue that publication bias is less likely, because null findings are typically also considered informative in these kinds of populations. Bias in the cumulative evidence presented here, most likely stems various ascertainment biases; for example, individuals recruited via clinical sites are more likely to have prominent phenotypical characteristics. Moreover, given that 22q11DS is a relatively rare disorder, studies may be recruiting participants from the same participant pool and/or reuse participants/data in different articles. Additionally, many studies do not report important demographic information, limiting our ability to confidently generalize these findings to the entire 22q11DS population.

Results of individual studies: EF performance per domain

None of the studies discussed here clearly differentiated between children and adolescents. Of the nine studies on children (mean age < 10), none had a maximum age below 11.5 years. Similarly, none of the four studies that reported on adolescents (mean age > 14) reported a minimum age of 14 years or higher[2]. Therefore, we decided to not discuss outcomes for children and adolescents separately. This does not preclude a discussion of age effects, however. We address these in the section *EF Development* below.

Results for all EF domains are presented in Fig. 3. To get a clear image of both the quantity and quality of evidence for a specific outcome, studies have been categorized by their respective risk of bias. As can be seen in Fig. 3, in most instances the control group or norm group outperformed the 22q11DS group. Updating is the only EF domain for which there is a more mixed distribution of outcomes. None of the studies reported that their 22q11DS sample outperformed the TD group.

Inhibition

Twelve studies had outcome measures that represent inhibition; eight of these had a control group. The three studies that did not have a TD group used normed tasks. There was one additional study (Shashi, Howard, et al., 2010) reporting on inhibition measures, but this study only made a within-22q11DS comparison between groups with different genetic variants (see section *Genetic variation* below).

Shifting

Thirteen studies reported outcomes classified as representing shifting; 10 of these had a control group. The three studies that did not have a TD group used normed tasks. Two additional studies (Carmel et al., 2014; Shashi, Howard, et al., 2010) reported on shifting measures by comparing different genetic variants within a 22q11DS sample.

Updating

Eleven studies investigated updating, of which two looked at verbal WM, seven at visuospatial WM, and two looked at both verbal and visuospatial WM. All studies had a control group.

Broad EF

Two studies looked at (composite) measures of broad EF. Both studies had a TD control group. Additionally, Bearden et al. (2004) compared two groups of 22q11DS with different genetic variants. The other study (Yi et al., 2014) had a control group of children with CHD without 22q11DS in addition to their TD group. This study also divided their 22q11DS sample into those with and those without CHD (see section *Congenital heart defects* below).

EF development

Longitudinal studies

All three longitudinal studies had two timepoints. The mean interval between time points was 3 years (range 2.7–3.5). A fourth longitudinal study (Antshel et al., 2017) only visualized longitudinal change graphically, without providing exact numbers, and was therefore not further considered in this section.

One study showed that the TD group demonstrated a larger increase in performance on a measure of shifting and one measure of inhibition, but not on another inhibition task (Hooper et al., 2013). Chawner et al. (2017) showed a developmental deficit for children with 22q11DS, meaning that they lag behind their peers, but appeared to develop at a similar rate. The difference between TD and 22q11DS (TD $>$ 22q) remained stable over time on tasks spanning all EF domains. The third study compared the difference between their first and second measurement outcomes for the 22q11DS group and the TD group separately, but they did not compare the longitudinal trajectories of both groups (Antshel, Shprintzen, et al., 2010). They found that children with 22q11DS improved significantly in their performance on a task measuring updating and one task measuring inhibition. No growth was observed on a

[2] It should be noted that Baker et al. (2005) reported a mean age of 16.3 (SD: 2.1) and an age range from 13.8 to 20.8 years

Fig. 4. Number of studies with certain outcomes comparing genetic variants within their 22q11DS sample presented according to their RoB category. *Note*. Each circle represents one study (numbers correspond to those in Table 3). The gray scale indicates the outcome. Studies with mixed outcomes are presented as circles with the colors of both outcomes. Studies in the *COMT* Met^{158} < Val^{158} / *PRODH* Arg^{185} < Trp^{185} or Met > Val / Arg > Trp category found a significant difference between groups on at least one outcome. Studies in the *COMT* Met^{158} = Val^{158} / *PRODH* Arg^{185} = Trp^{185} category did not report a significant difference between groups.

second inhibition task. The outcomes for shifting were mixed, with growth on one outcome measure, but not on another. The TD group showed significant growth on all outcomes except for the shifting task and one of the outcome measures of an inhibition task.

Cross-sectional studies with age as a covariate

Six studies took age as a covariate in their analyses. Three of these studies (De Smedt et al., 2008; De Sonneville et al., 2018; Shashi, Keshavan, et al., 2010) did not explicitly report the effect of age on the EF tasks within their 22q11DS sample. Of the remaining three studies, two studies showed that older children with 22q11DS do better than younger children with 22q11DS on a measure of shifting (Carmel et al., 2014; Stoddard, Beckett, & Simon, 2011). The third study by Shapiro et al. (2014) reported that older children with 22q11DS perform better on an updating task and had higher accuracy for a shifting task, but there was no effect of age on performance on either of the inhibition tasks. They did note that the absence of an effect of age for the inhibition tasks was caused by more variability in the older children with 22q11DS, where a subgroup of children performs similar to TD peers, but some do much worse. There was no clear difference in the mean age of participants between these three studies.

Summary EF development

In summary, the limited evidence from longitudinal studies suggests a developmental deficit, that is children with 22q11DS lag behind their peers, but appear to develop at a similar rate. The outcomes of cross-sectional studies were mixed, showing either positive correlations between EF and age, or no correlation. This is consistent with a developmental deficit.

Results of individual studies considering protective and risk factors

Genetic variation

Six studies investigated the effect of a common *COMT* polymorphism, *COMT* Val^{158}Met, which has been linked to cognitive outcomes in the general population (see section *Biological underpinnings of EF in 22q11DS* above). Five of these made comparisons within their 22q11DS sample only, but one study also compared the 22q11DS groups with a TD group (Baker et al., 2005). The outcomes of the studies classified by their respective risk of bias are presented in Fig. 4. Outcomes were mixed, but most evidence indicated there was no effect of this *COMT* variant on EF performance in children with 22q11DS. Baker et al. (2005) showed that a TD group performed better on measures of verbal WM than the 22q11DS Val^{158} carriers, but not the 22q11DS Met^{158} carriers. There was no difference between the 22q11DS Val^{158} carriers and 22q11DS Met^{158} carriers.

One study looked at different *PRODH* variants in their 22q11DS sample. Carmel et al. (2014) looked at the effect of the *PRODH* Arg^{185}Trp (rs4819756) polymorphism, and reported no differences on measures of inhibition between Arg^{185} and Trp^{185} carriers in 22q11DS. No other genotypic variation was investigated in any of the included studies.

Congenital heart defects

A single study investigated CHD as a factor in EF performance and compared children with 22q11DS with (22q + CHD) and without CHD (22q-CHD), children with CHD, but without 22q11DS (CHD-only) and typically developing children without CHD and 22q11DS (TD) (Yi et al., 2014: RoB medium). The 22q11DS groups did not differ from one another and had lower accuracy scores on measures of inhibition, shifting and updating than the TD and the CHD-only group. The latter two groups did not differ from each other. Authors noted that in the CHD-only group and 22q-CHD group factors such as type of CHD and surgery related factors could not be considered due to sample size.

Other potential moderators

Other risk factors, as addressed in the introduction, are preterm birth, low birth weight, stress, low socioeconomic status (SES), parenting styles, limited unstructured time, play, and physical activity.

The only study investigating SES as a factor in EF performance, found that within their 22q11DS sample there was no relation between parental SES and shifting or inhibition outcomes (Shashi, Keshavan, et al., 2010: RoB medium). There was a relation between SES and EF outcomes in their TD group. They reported that children with 22q11DS and TD controls did not differ on parental SES.

The only study that considered the effect of stress, as measured by salivary cortisol, in children with 22q11DS, reported no relation with WM performance (Sanders et al., 2017: RoB medium). The authors did note that children with 22q11DS had heightened cortisol levels compared to peers.

The other risk factors appear to not yet have been systematically investigated in relation to EF in the 22q11DS population.

Relation EF and intellectual abilities

Although many studies reported both IQ and EF data in 22q11DS, correlation analyses between the two were scarce. In most studies, both IQ and EF were used as independent predictors of other outcomes, such as social skills or psychopathology. Three studies investigated the relation between IQ and EF directly. Kates et al. (2007: RoB medium) found that there was no significant correlation between IQ scores and d-prime scores (representing accuracy) on their visual WM task ($r = 0.2$). De Sonneville et al. (2018: RoB medium) also reported no correlation between IQ scores and inhibition or shifting outcomes. However, contrary to Kates et al. (2007), they did observe a significant correlation between IQ and updating ($r = 0.24$). Lastly, Shapiro et al. (2014: RoB medium) reported that IQ did not predict overall task performance, suggesting that the EF impairments they observed were not fully explained by intellectual abilities.

Four studies controlled for IQ in their analyses of EF data. Three of those reported that their EF results remained significant after controlling for IQ (Antshel et al., 2017: RoB medium; Bearden et al., 2004: RoB high; De Sonneville et al., 2018), but the fourth reported that results were no longer significant (De Smedt et al., 2008: RoB low).

Discussion

In this systematic review, we investigated executive functioning (EF) in a selected population with a homogeneous etiology: children and adolescents with 22q11.2 Deletion Syndrome (22q11DS). Next to advancing knowledge of the cognitive phenotype associated with this syndrome, our review also informs our understanding of typical development by providing a focused context for the investigation of specific mechanisms and risk factors. In doing so, we identify gaps in the literature, highlight opportunities for future research, and discuss some clinical implications.

Our findings indicate frequent impairments in all domains of EF in individuals with 22q11DS, except for the subdomain updating. Evidence for updating is inconclusive but seems to suggest updating abilities might be a relative strength in childhood. While in the general population EF is affected by congenital heart defects (CHD) and genetic variation, tentative evidence shows these relations might be absent in 22q11DS. This sheds light on the specific mechanisms underlying EF development and how they can be disrupted. Furthermore, EF abilities in 22q11DS seem to be independent of intellectual abilities, supporting the theory that in the general population EF and intelligence are separate constructs. Below we will further discuss the implications of these results for our understanding of typical EF development.

EF profile and its developmental trajectory in 22q11DS

The current review yields substantial evidence that children and adolescents with 22q11DS have EF impairments in the domains of inhibition and shifting. On the other hand, evidence for deficits in updating, both visual and verbal working memory (WM), was mixed. The mixed evidence with respect to verbal WM impairment may be related to the reported Intelligence Quotient (IQ) decline, including verbal IQ, during childhood and early adolescence in individuals with 22q11DS (Duijff et al., 2013; Vorstman et al., 2015). Notably, the two studies that observed impaired verbal WM studied groups with a higher mean age (Albert et al., 2018; Baker et al., 2005), whereas the two that found no verbal WM impairment studied younger children (Brankaer et al., 2017; De Smedt et al., 2008). Conceivably, verbal WM might follow a trajectory comparable to that of verbal IQ in a subset of individuals with 22q11DS. Moreover, a recent study reports that updating may be more impaired in older individuals with 22q11DS (Morrison et al., 2020), suggesting the different EF domains may follow differing developmental trajectories and result in different end states.

Regarding the developmental trajectory of EF, limited evidence suggests a developmental deficit. Children with 22q11DS generally perform less well than typically developing peers, but this deficit appears to remain stable over time, indicating that they develop at a rate similar to peers. We could not draw conclusions about the development of separate EF domains due to the small number of longitudinal studies and the differences in measures and analyses that were reported. However, Maeder et al. (2016, not included due to large age range) found that children, adolescents, and young adults with 22q11DS differ in their developmental trajectory on measures of verbal WM from controls, whereas the developmental trajectory of inhibition appears similar. This, taken together with the findings of Morrison et al. (2020) described above, would suggest a developmental deficit is not present for all domains throughout development.

Future studies should investigate whether verbal WM is indeed relatively spared during childhood as compared to other EF domains in 22q11DS, and to what extent verbal WM is related to verbal IQ and its developmental trajectory. Furthermore, more research

is necessary to verify whether the separate EF domains in children with 22q11DS develop similarly to trajectories described in the typical population (Best & Miller, 2010). As suggested above, this may not be the case for inhibition and verbal WM. Differences in developmental trajectories between EF domains imply differentiation and might thus provide clues regarding the developmental progression of EF differentiation.

Risk factors for impaired EF in the context of 22q11DS

We considered endogenous and exogenous risk factors associated with EF in the general population, which are of particular relevance to, or are more prevalent in the 22q11DS population. Here we discuss some directions for future research based on the outcomes of this review.

Genetic variation

A few studies considered the effect of specific genetic variants on EF outcomes. The most frequently investigated genetic variant (*COMT* Val^{158}Met) has been associated with EF in the general population (e.g., Barnett et al., 2007; Moriguchi & Shinohara, 2018), although not unequivocally (e.g., Barnett, Scoriels, & Munafò, 2008; but Mier, Kirsch, & Meyer-Lindenberg, 2010). Similarly, the results of this review regarding the effect of this genetic variant on the EF performance of children with 22q11DS were mixed. Variants in another gene (*PRODH*) have been linked to changes in prefrontal-striatal brain circuits, impaired cognitive performance, and schizophrenia (Jacquet et al., 2002; Kempf et al., 2008; Raux et al., 2007). One study considered a single variant of this gene (*PRODH* Arg^{185}Trp) but observed no effect on EF in children with 22q11DS. These inconclusive findings so far mirror the observations of such genotype-phenotype associations in the general population (e.g., Mier et al., 2010), reflecting the complexity of the pathway from genes to behavioral expression. Future investigations can further elucidate this, amongst others by investigating the effects of other functional variants of genes in the 22q11.2 region and their interactions with other genes (Bender et al., 2005; Jonas, Montojo, & Bearden, 2014; Paterlini et al., 2005; Vorstman et al., 2009; De Koning et al., 2015). Although the effect of a single genetic variant on EF might be difficult to observe, these studies can elucidate which mechanisms and pathways are crucial to EF development. For example, 22q11DS also impacts genes implicated in mitochondrial functioning (Li et al., 2019; Meechan et al., 2011; Warren & Morrow, 2019), which has been linked to developmental disorders and cognitive impairments (El-Ansary, 2012; Fernandez et al., 2019). Future research can further our understanding of the exact role of mitochondrial functioning in cognitive outcomes. Furthermore, recently the cumulative effect of common genetic variants has been shown to modulate cognitive outcome (IQ) in the presence of the 22q11.2 deletion (Davies et al., 2020). Future studies could expand this approach to examine the polygenic contribution to the EF phenotype as well. Lastly, while it has been suggested that smaller deletions that are located in the middle or at the end of the region may lead to milder phenotypes (Rump et al., 2014; McDonald-McGinn et al., 2015), none of the included studies considered the possible effect of the type of 22q11DS deletion. Such studies could contribute to our knowledge of which genes should be in included in studies looking at the polygenic contributions to EF phenotype.

Congenital heart defects

The only study that considered congenital heart defects (CHD), found no effect on EF abilities in either the participants with or without 22q11DS, nor in those with or without CHD (Yi et al., 2014). The findings in their sample without 22q11DS differed from other studies in the general population, which have so far broadly supported an association between CHD and poorer cognitive outcomes, such as decreased EF performance or a lower IQ (Sterken et al., 2015). However, Yi et al.'s findings do appear to be in line with other research in individuals with 22q11DS that observed no effect of CHD on EF (Fountain et al., 2014, not included due to age range). Likewise, Zhao et al. (2018) found no effect of CHD on IQ in a sample of more than 1000 individuals with 22q11DS. This apparent absence of an effect of CHD in the 22q11DS population is further supported by previous studies that detected no effect on a variety of cognitive outcomes (Duijff et al., 2012; De Smedt et al., 2007; Gerdes et al., 1999; Niklasson & Gillberg, 2010; Swillen et al., 2005). The above seems to indicate that, at least for certain high impact genetic variants, the direct impact of this genetic variant on the brain and cognitive functioning exceeds the hypothesized impact of CHD. The potential relevance of these findings is that it should prompt a re-examination of the observed adverse neurodevelopmental trajectories in children with CHD. Possibly, in addition to the hypothesized assault of CHD on the developing brain, the genetic variant underlying the CHD could also directly impact neurodevelopment (McQuillen & Miller, 2010; Nattel et al., 2017). Indeed, a substantial proportion of genes associated with CHD in the general population are also associated with an increased risk of neurodevelopmental outcomes (e.g., Homsy et al., 2015). More specifically for 22q11DS, the gene *TBX1* is thought to be one of the main contributors to CHD but has also been linked to psychiatric phenotypes (Paylor et al., 2006). This would help to explain the observed concurrence of both phenotypes in some of these children.

Other risk factors: Socioeconomic status and stress

Only one study considered socioeconomic status (SES) but reported no effect of it on EF (Shashi, Keshavan, et al., 2010). This corresponds with other work showing no correlation between SES and EF measures in children with 22q11DS (Allen et al., 2014, not included due to age range). However, it contrasts with findings in the general population that suggest that the effect of SES on EF might be mediated by other factors in this population. Future research can elucidate the exact mechanisms underlying the relation between EF and SES.

Tentative evidence from a single study (Sanders et al., 2017) showed heightened cortisol levels, as an indicator for stress, but this did not correlate with EF performance. Again, this raises the question whether the impact of the deletion exceeds the impact of other factors. Jacobson, Bursch, and Lajiness-O'Neill (2016, not included due to task type) also reported heightened cortisol in children with

22q11DS, but in their study there was a significant relation with memory and attention. However, in adults with 22q11DS reduced cortisol levels have been reported, likely as the result of chronic overactivation of the hypothalamic–pituitary–adrenal axis (van Duin et al., 2019). More research into the effect of stress on EF in 22q11DS is warranted, especially as this population is suggested to be more vulnerable to consequences of stress due to pituitary dysmaturation (Sandini et al., 2020). Such investigations can also further guide theories on the effect of stress on neural pathways subserving (early) cognitive development.

Relation EF and intellectual abilities

Most evidence suggests that EF deficits in children with 22q11DS are not (fully) explained by their intellectual abilities. This is further supported by studies in individuals with 22q11DS that reported that their EF results remained significant after controlling for IQ (Lewandowski et al., 2007, not included due to overlap; Maeder et al., 2016). Studies in other clinical populations also show a dissociation between EF and intellectual abilities. For example, despite an average to high IQ, EF impairments have been reported in individuals with Attention Deficit Hyperactivity Disorder (Antshel, Faraone, et al., 2010; Brown, Reichel, & Quinlan, 2009; Schuck & Crinella, 2005). Similar observations have been made in children with high-functioning Autism Spectrum Disorder (Lai et al., 2017). Our results are in line with these findings showing that executive dysfunction can occur irrespective of level of intellectual abilities.

These results support the hypothesis that EF and IQ are separate cognitive constructs, as has been previously argued for typically developing children (Ardila, Pineda, & Rosselli, 2000; Crinella & Yu, 1999). Nonetheless, in typically developing children, IQ and EF are not completely independent, and are in fact correlated with one another (Arffa, 2007; Ardila et al., 2000). The current findings seem to indicate this correlation is weak in children with 22q11DS, although this may in part be due to little power. Future research should address this and is required to draw robust conclusions.

Clinical implications

This systematic review shows that EF impairments are commonly found in children and adolescents with 22q11DS. The knowledge that updating might be relatively preserved during childhood may be important to clinical practice. Relatively stronger verbal WM during childhood may cause children with 22q11DS to appear more competent than they are, increasing the likelihood of creating an imbalance between environmental demands and the child's abilities, heightening the risk for psychiatric problems (Fiksinski, Schneider, et al., 2018). Additionally, relatively preserved (verbal) WM in childhood, might provide an entry for interventions that can help improve later outcomes. Similar to the general population, EF abilities in 22q11DS have been shown to predict later outcomes, such as adaptive functioning and psychopathology (Albert et al., 2018; Fiksinski, Breetvelt et al., 2018; Hamsho et al., 2017). Future research should investigate the development and effectiveness of interventions aimed at strengthening EF (e.g., Kirk, Gray, Riby, & Cornish, 2015) and explore whether such interventions could be beneficial to both children with 22q11DS, but also to other children predisposed to psychiatric illness.

Additionally, clinicians might benefit from the identification of other risk factors for EF impairment in the 22q11DS population, as risk factors previously identified in the general population, such as CHD and low SES, do not appear to have the same impact in this population.

Gaps in the literature and opportunities for future research

Our review identified several gaps in the current literature, thereby revealing opportunities for future studies. Firstly, studies considering various potential risk factors, both endogenous and exogenous, for EF impairment in 22q11DS are scarce. Risk factors associated with EF deficits, like CHD, stress, and low SES, have been investigated, but only by a small number of studies. Factors such as preterm birth, low birth weight, parenting styles, limited unstructured time, play, and physical activity have not at all been investigated in any of the included studies, even though many of these factors are, or may be more prevalent in 22q11DS (see section *Endogenous* - and *Exogenous risk factors for EF impairment* in *Introduction*). As we argued in the introduction, the 22q11DS population thus provides an opportunity to reduce variability in the study of these factors. Similarly, studies investigating the developmental differentiation of EF in 22q11DS are scarce. Therefore, it is currently unclear if and how developmental EF differentiation differs from typical development. Studies looking at this could help validate models of EF development.

Secondly, while 22q11DS studies are likely hampered by various ascertainment biases, many of the currently available studies frequently do not report important characteristics of their study cohort (e.g., IQ, CHD, SES, etc.), making it difficult to assess whether they report on representative subsamples. Considering that sample sizes in some studies of the 22q11DS population are understandably small, the reliability of outcomes would benefit from further reduced heterogeneity within these samples (e.g., age range, phenotypic characteristics, etc.). Large cohort or population studies reporting the prevalence and severity of various symptoms should provide an unbiased characterization of the 22q11DS population. Conclusions concerning EF development in 22q11DS and the effect of age were limited by the relatively high mean age at inclusion and the wide age ranges characterizing most study samples. Studies investigating EF in early childhood (<6 years of age) were absent precluding any insight into early cognitive development. More longitudinal studies covering the entire developmental period are essential for describing developmental trajectories. Longitudinal studies starting at preschool age could show whether EF impairments are present from an early age on and whether similar associations with an increased risk for psychiatric disorders can be observed (Vorstman et al., 2015). This could further support research on predictors of schizophrenia in the general population, for which the 22q11DS population can be taken as a model (Fiksinski, Breetvelt et al., 2018; Gur et al., 2017; Insel, 2010).

Strengths and limitations

We used predefined criteria for classifying which EF task measured which EF domain, independent of the classification in the original study. This reduces variability in our results by eliminating differences due to terminology and provides a clear image of what is being compared. The intricate nature of EF complicates consistent and reliable assessment. As for all cognitive functions, behavioral indices of EF are indirect and require interpretation by researchers (Paap & Sawi, 2016). Moreover, tasks meant to measure EF are frequently unable to measure only a single EF domain without interference of the other domains. This, in addition to the large variety of tasks used, makes it difficult to draw reliable and generalizable conclusions about the different EF domains in any population, including 22q11DS. By broadly grouping tasks and only including studies using tasks that are widely considered to measure EF, we have tried to diminish the effect of this to the best of our abilities.

This review focused on children and adolescents for which we used inclusionary restrictions with regard to mean age, age range, and sample size. Although the specifics of these restrictions are based on a reasonable rationale (see section *Study selection*), other choices could also be justified. However, given the variability in this population, we argue that the selected criteria ensure generalizability to the entire 22q11DS population and strengthen conclusions by reducing variability. Nonetheless, the selected upper age limit did limit our ability to review the full developmental trajectory into adulthood. With more data becoming available in the older age groups, this is important to examine in future work. The findings and outcomes discussed here could be further supplemented with biomarkers such as brain imaging or gene expression studies, which were also not considered in this review.

Despite the limitations described above, the current review identifies relative strengths (verbal WM) and weaknesses in EF for children with 22q11DS. This review also finds tentative evidence in this population for a decreased or absent effect of certain risk factors for impaired EF, like congenital heart defects and low socioeconomic status. Our findings suggest that the developmental trajectory of updating may differ to some extent from that of inhibition and switching. More research is needed to confirm this and to determine whether this is due to differences in the mechanisms underlying these EF domains. Lastly, our findings support studies in typically developing children that suggest that EF and intelligence are correlated but distinct cognitive constructs.

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CRediT authorship contribution statement

Emma Everaert: Conceptualization, Formal analysis, Investigation, Validation, Visualization, Writing - original draft, Writing - review & editing. **Tessel Boerma:** Conceptualization, Validation, Writing - original draft, Writing - review & editing. **Iris Selten:** Validation, Writing - review & editing. **Jacob Vorstman:** Visualization, Writing - review & editing. **Frank Wijnen:** Conceptualization, Funding acquisition, Validation, Writing - review & editing.

Declaration of Competing Interest

J.V. serves as a consultant for NoBias Therapeutics. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Exact search queries per search engine

Pubmed

((22q11 deletion syndrome[mh]) OR (22q11*[Title/Abstract] OR *22q11[Title/Abstract] OR del22q11*[Title/Abstract] OR VCFS [Title/Abstract] OR Velocardiofacial syndrome[Title/Abstract] OR Velo-cardio-facial syndrome[Title/Abstract] OR VCF syndrome [Title/Abstract] OR DiGeorge syndrome[Title/Abstract] OR Di-George syndrome[Title/Abstract] OR Shprintzen syndrome[Title/Abstract] OR Velocardiofacial[Title/Abstract] OR Velo-cardio-facial[Title/Abstract] OR DiGeorge[Title/Abstract] OR Di-George [Title/Abstract] OR Shprintzen[Title/Abstract] OR CATCH22[Title/Abstract] OR catch 22[Title/Abstract] OR Sedlackova syndrome[Title/Abstract] OR Takao syndrome[Title/Abstract] OR Cayler cardiofacial syndrome[Title/Abstract] OR Conotruncal Anomaly Face Syndrome[Title/Abstract])) AND (Executive funct* [Title/Abstract] OR Executive control[Title/Abstract] OR Executive dysfunc*[Title/Abstract] OR Working memory[Title/Abstract] OR Inhibition[Title/Abstract] OR Attention*[Title/Abstract] OR Cognitive flexibility[Title/Abstract] OR Shifting[Title/Abstract] OR Switching[Title/Abstract] OR Prefrontal cognition[Title/Abstract])

OVID psychinfo

((22q11* or *22q11 or del22q11* or VCFS or Velocardiofacial syndrome or Velo-cardio-facial syndrome or VCF syndrome or DiGeorge syndrome or Di-George syndrome or Shprintzen syndrome or Velocardiofacial or Velo-cardio-facial or DiGeorge or Di-George or Shprintzen or CATCH22 or catch 22 or Sedlackova syndrome or Takao syndrome or Cayler cardiofacial syndrome or Conotruncal Anomaly Face Syndrome) and (Executive funct* or Executive control or Executive dysfunc* or Working memory or Inhibition or Attention* or Cognitive flexibility or Shifting or Switching or Prefrontal cognition)).ab

Table 4
Full risk of bias assessment of studies included in the analysis.

Study				*Aim*	*Participants*				*Data collection and analysis*			*Outcomes*		*If longitudinal:*			
	Controls?	Longitudinal?	N 22q11DS	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	Risk of Bias
Albert et al. (2018)	Yes	No	63	+	+	−/+	+	−/+	+	−/+	−/+	−/+	+	n.a.	n.a.	n.a.	**Low**
Antshel et al. (2010)[a]	Yes	Yes	80	−/+	−	−	+	−	+	−/+	−/+	−/+	−/+	+	−	+	**Medium**
Antshel et al. (2017)	Yes	No	78	+	−/+	−	−/+	−/+	+	−	−/+	−	−/+	n.a.	n.a.	n.a.	**Medium**
Baker et al. (2005)	Yes	No	25	+	−/+	−	−	−/+	−/+	−/+	−/+	−/+	−/+	n.a.	n.a.	n.a.	**High**
Bearden et al. (2004)	No	No	44	−/+	−	−	n.a.	−	+	+	−/+	−	+	n.a.	n.a.	n.a.	**High**
Bish et al. (2005)	Yes	No	18	+	−	−	−	−	+	−	−	−	+	n.a.	n.a.	n.a.	**High**
Brankaer et al. (2017)	Yes	No	25	+	+	+	+	−/+	+	+	−/+	−/+	+	n.a.	n.a.	n.a.	**Low**
Campbell et al. (2015)	Yes	No	24	+	+	−/+	+	−	−/+	−/+	−/+	−	+	n.a.	n.a.	n.a.	**Medium**
Carmel et al. (2014)	No	No	60	+	−	−/+	n.a.	−	+	−/+	−/+	−	+	n.a.	n.a.	n.a.	**Medium**
Chawner et al. (2017)	Yes	Yes	75	+	+	−	+	+	+	−/+	+	−/+	+	-/+	+	+	**Low**
Cunningham et al. (2018)	Yes	No	70	+	+	+	+	−/+	+	+	−/+	−/+	+	n.a.	n.a.	n.a.	**Low**
De Smedt et al. (2008)	Yes	No	25	+	+	−/+	+	−/+	+	+	−/+	−/+	+	n.a.	n.a.	n.a.	**Low**
de Sonneville et al. (2018)	No	No	58	+	−	−/+	n.a.	−/+	+	+	−/+	−/+	+	n.a.	n.a.	n.a.	**Medium**
Hooper et al. (2013)	Yes	Yes	42	−/+	−/+	+	+	−/+	+	−/+	+	−/+	+	+	−	−	**Medium**
Kates et al. (2007)	Yes	No	17	+	+	−	−/+	−/+	−/+	+	−/+	−/+	+	n.a.	n.a.	n.a.	**Medium**
McCabe et al. (2014)	Yes	No	25	+	+	−	−/+	−/+	−/+	−/+	−/+	−	+	n.a.	n.a.	n.a.	**Medium**
Niklasson et al. (2005)	No	No	30*	−/+	+	−/+	n.a.	−	+	−	−	−	+	n.a.	n.a.	n.a.	**High**
Niklasson and Gillberg (2010)	No	No	30	−/+	−	−/+	n.a.	−/+	+	+	+	+	−/+	n.a.	n.a.	n.a.	**Medium**
Sanders et al. (2017)	Yes	No	20	+	+	−/+	−/+	−/+	−	−/+	+	−/+	+	n.a.	n.a.	n.a.	**Medium**
Shapiro et al. (2014)	Yes	No	71	+	+	−/+	−	−	−/+	+	−/+	−	+	n.a.	n.a.	n.a.	**Medium**
Shashi, Howard, et al. (2010)	No	No	40	−/+	−	−	−/+	−	+	−	−	−	−	n.a.	n.a.	n.a.	**High**
Shashi, Keshavan, et al. (2010)	Yes	No	65	+	−	−/+	+	−/+	+	+	+	−/+	+	n.a.	n.a.	n.a.	**Medium**
Shashi et al. (2012)	Yes	No	66	+	−/+	−/+	+	−	+	−	−	−/+	+	n.a.	n.a.	n.a.	**Medium**
Sobin et al. (2004)	Yes	No	32	+	−/+	−	+	−	+	−/+	−/+	−	+	n.a.	n.a.	n.a.	**Medium**
Sobin et al. (2005)[b]	Yes	No	21	+	−/+	−	+	−	+	−	−/+	−	+	n.a.	n.a.	n.a.	**High**
Sobin et al. (2005)[c]	No	No	40	+	−/+	+	n.a.	−/+	+	−	−/+	n.a.	+	n.a.	n.a.	n.a.	**Medium**
Stoddard et al. (2011)	Yes	No	60	+	−	−	−	−	+	−/+	+	−/+	+	n.a.	n.a.	n.a.	**Medium**
Stoddard et al. (2012)	No	No**	53	−/+	−	−	−/+	−	+	−	−/+	−	+	n.a.	n.a.	n.a.	**High**
Yi et al. (2014)	Yes	No	54	+	+	+	+	−/+	+	+	−/+	−/+	+	n.a.	n.a.	n.a.	**Medium**

Note. Numbers or RoB items correspond to assessment criteria described in Table 2. Legend: − = no or very limited information; −/+ = some information, but incomplete/not sufficiently detailed; + = information present and sufficiently detailed/qualitatively good; n.a. = not applicable.

* for Tower of London; $n = 22$ for Trail Making Test B

** There are controls, but they have not been genotyped for *COMT* and this paper is only considered for its outcomes regarding genetic variance.

[a] Antshel, Shprintzen, et al. (2010)

[b] Sobin, Kiley-Brabeck, Daniels, et al. (2005)

[c] Sobin, Kiley-Brabeck, & Karayiorgou (2005)

EMBASE

([article]/lim OR [article in press]/lim) AND ('22q11*':ti,ab,kw OR 'del22q11*':ti,ab,kw OR 'vcfs':ti,ab,kw OR 'velocardiofacial syndrome':ti,ab,kw OR 'velo-cardio-facial syndrome':ti,ab,kw OR 'vcf syndrome':ti,ab,kw OR 'digeorge syndrome':ti,ab,kw OR 'di-georgе syndrome':ti,ab,kw OR 'shprintzen syndrome':ti,ab,kw OR 'velocardiofacial':ti,ab,kw OR 'velo-cardio-facial':ti,ab,kw OR 'digeorge':ti,ab,kw OR 'di-george':ti,ab,kw OR 'shprintzen':ti,ab,kw OR 'catch22':ti,ab,kw OR 'catch 22':ti,ab,kw OR 'sedlackova syndrome':ti,ab,kw OR 'takao syndrome':ti,ab,kw OR 'cayler cardiofacial syndrome':ti,ab,kw OR 'conotruncal anomaly face syndrome':ti,ab,kw OR 'chromosome deletion 22q11'/exp) AND ('executive funct*':ti,ab,kw OR 'executive control':ti,ab,kw OR 'executive dysfunc*':ti,ab,kw OR 'working memory':ti,ab,kw OR 'inhibition':ti,ab,kw OR 'attention*':ti,ab,kw OR 'cognitive flexibility':ti,ab,kw OR 'shifting':ti,ab,kw OR 'switching':ti,ab,kw OR 'prefrontal cognition':ti,ab,kw) NOT ([medline]/lim AND [embase]/lim)

Appendix B. Full risk of bias assessment

Table 4

References

*Studies included in the analysis are marked with an asterisk **

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