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Developmental variability in children and adolescents with Down syndrome

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CONTENTS

ABSTRACT (English version)

Down syndrome (DS) is characterized by a marked inter-individual variability. The syndrome has been amply described as a whole over the years, but reviewing the existing literature reveals considerable individual differences (e.g., Karmiloff-Smith et al., 2016). These differences emerge on both the global and the domain-specific levels, with an Intellectual Quotient (IQ) ranging from mild to severe (e.g., Määttä et al., 2006; Vianello, 2006), with high standard deviations and a wide range of scores in various domains (e.g., Daunhauer et al., 2014; Winders et al., 2019). The present PhD dissertation begins with a discussion of the heterogeneity in DS (Chapter 1), which also provides an overview on the cognitive, adaptive and motor development of individuals with DS. This sets the stage for the main body of the research, which aimed to elucidate the variability seen in DS, exploring it from different angles: from the timing of developmental milestones to the developmental and cognitive profiles identifiable at different ages; from the influence of concomitant conditions on the development of individuals with DS to the variables that can affect their developmental trajectories.

Examining when typically-developing (TD) and clinical populations reach certain developmental milestones facilitates the planning of intervention for the latter, and the early detection of any risk of comorbidities. The normative timing for TD children to acquire cognitive and communication skills has been established, but little is known about what happens in children with DS. The aims of Study I (Chapter 2) were therefore: (1) to provide foundational information on when infants with DS acquire cognitive and communication skills; and (2) to facilitate the early identification of infants at risk of concomitant developmental delays. Seventy-four infants with DS (age range: 4-18 months) completed the Bayley Scales of Infant Development-III (BSID-III), and individual items from the cognitive and communication scales were selected for analysis. Parents provided information about their child's developmental and family history. The percentages of the infants acquiring each skill was calculated within two-month age bands. For those failing to acquire a given skill within each age band, the rates of prematurity, heart defects, corrective heart surgery, and significant illness were

calculated as well. This study generated useful information for the purpose of developing a timetable for the cognitive and language development of infants with DS.

As they grow up, individuals with DS are generally predisposed to a pattern of relative developmental strengths and challenges, but a great deal of within-syndrome heterogeneity is also apparent. This prompted Study II (Chapter 3), which aimed: (1) to explore the overall developmental profile of infants with DS; (2) to examine whether any heterogeneity is detectable already during infancy; and (3) to identify any associations with various health-related and environmental factors that might influence early skills acquisition. Fifty-four infants with DS (age range: 3-17 months) completed the BSID-III. Parents provided information on their developmental and family history. Scores obtained on the five BSID-III scales were analyzed to ascertain the developmental profile of the sample as a whole, and to identify any different profiles using a clustering approach. Associations with chronological age, prematurity, medical problems, therapies, and mothers' education level were also explored. At group level, expressive communication emerged as a relative strength in these infants, and gross motor skills as a weakness. Two different developmental profiles emerged, one more and the other less advanced developmentally, with infants in the first group younger than those in the second.

Heterogeneity in individuals with DS was then further explored in Study III (Chapter 4), shifting the focus to childhood and adolescence. The goals of this third study were: (1) to explore the cognitive profile of children and adolescents with DS; (2) to examine whether their inter-individual variability could be classified in terms of subgroups with different cognitive profiles; and (3) to investigate the association between cognitive profile(s) and developmental milestones, medical conditions, and parents' education levels. Seventy-two children/adolescents with DS from 7 to 16 years old were assessed with the Wechsler Preschool and Primary Scale of Intelligence – III. Age-equivalent scores were adopted, and Verbal and Non-Verbal indexes were obtained for each participant. These scores were first analyzed to explore the cognitive profile of the group as a whole, then used for a cluster analysis. The study group's overall profile revealed similar scores in the verbal and non-verbal

domains, while cluster analysis identified three different profiles, labelled as “Non-Verbal”, “Verbal” and “Homogeneous”. The first subgroup had the lowest scores and the typical DS profile (i.e., they were weaker on verbal and stronger on non-verbal processing); the second had intermediate scores and fared better on verbal than on non-verbal tasks; and the third, with the highest scores, fared equally well in the verbal and non-verbal domains. These three subgroups did not differ in terms of chronological age. Environmental variables seemed to have had a role in shaping the Verbal and Homogeneous profiles.

General conclusions drawn from the main findings of the three studies, and their clinical implications are discussed in the last chapter (Chapter 5) of this dissertation.

Investigating heterogeneity in individuals with DS offers crucial insight on the strengths and weaknesses of their clinical profile, thus enabling more specific and targeted interventions. There is still space for further research, however. It would be worth conducting a longitudinal investigation to pinpoint the variables associated with a given profile and developmental trajectory. This dissertation was an effort to raise and clarify some points, but other questions remain to be answered.

ABSTRACT (Italian version)

La sindrome di Down (SD) è caratterizzata da una marcata variabilità interindividuale. La sindrome è stata ampiamente descritta nel suo complesso nel corso degli anni, ma una revisione della letteratura esistente ha rivelato notevoli differenze individuali (ad esempio Karmiloff-Smith et al., 2016). Queste differenze emergono sia a livello globale che a livello dominio specifico, con un Quoziente Intellettivo (QI) che va da lieve a grave (ad esempio, Määttä et al., 2006; Vianello, 2006), deviazioni standard elevate e un ampio intervallo di punteggi nei vari domini (ad esempio, Daunhauer et al., 2014; Winders et al., 2019). La presente tesi di dottorato ha inizio con una panoramica sullo sviluppo cognitivo, adattivo e motorio degli individui con DS e sugli aspetti di variabilità (Capitolo 1). Questo pone le basi per il corpo principale della ricerca, che mira a chiarire la variabilità osservata nella SD, esplorandola da diverse angolazioni: dall'età di acquisizione delle tappe dello sviluppo ai profili di sviluppo e cognitivi identificabili a diverse età; dall'influenza di condizioni concomitanti sullo sviluppo in individui con SD alle variabili che possono influenzare le loro traiettorie di sviluppo.

Esaminare quando individui a sviluppo tipico e atipico raggiungono determinate tappe di sviluppo facilita la pianificazione dell'intervento per questi ultimi e l'individuazione precoce di fattori in comorbidità. Sono già state delineate tabelle normative per l'acquisizione delle abilità cognitive e comunicative nello sviluppo tipico, ma meno si sa su ciò che accade nei bambini con SD. Gli obiettivi dello Studio I (Capitolo 2) sono quindi: (1) fornire informazioni fondamentali su quando i bambini con SD acquisiscono abilità cognitive e comunicative; e (2) facilitare l'identificazione precoce dei bambini a rischio di comorbidità. Settantaquattro bambini con SD (con un'età compresa tra i 4 e i 18 mesi) hanno completato la Bayley Scales of Infant Development-III (BSID-III), e singoli item delle scale cognitiva e di comunicazione sono stati selezionati per l'analisi. Inoltre, i genitori hanno fornito informazioni sullo sviluppo del loro bambino e sulla storia familiare. Le percentuali dei bambini che hanno acquisito ogni abilità sono state calcolate all'interno di fasce d'età di due mesi. Per coloro che hanno dimostrato di non aver acquisito una determinata abilità, sono stati calcolati anche i tassi di prematurità, difetti cardiaci, interventi chirurgici cardiaci correttivi e malattie significative. Questo

studio ha permesso di ottenere informazioni utili allo scopo di determinare i momenti per le tappe dello sviluppo cognitivo e linguistico dei bambini con SD.

Crescendo, gli individui con SD hanno un profilo di sviluppo caratterizzato da punti di relativa forza e debolezza, ma è anche evidente una grande eterogeneità all'interno della sindrome. Questa nozione ha dato luce allo Studio II (Capitolo 3), che mira a: (1) esplorare il profilo di sviluppo in bambini con SD durante l'infanzia; (2) esaminare se l'eterogeneità è rilevabile già durante questo periodo; e (3) identificare il ruolo di vari fattori ambientali e relativi alla salute che potrebbero influenzare l'acquisizione delle prime abilità. Cinquantaquattro bambini con SD (con un'età compresa tra i 3 e i 17 mesi) hanno completato la BSID-III, mentre i genitori hanno fornito informazioni sulla loro storia di sviluppo e familiare. I punteggi ottenuti nelle cinque scale BSID-III sono stati analizzati per esplorare il profilo di sviluppo di tutto il gruppo e, tramite un'analisi dei cluster, un'eventuale presenza di profili di sviluppo differenti. Sono state anche esplorate le associazioni con l'età cronologica, la prematurità, i problemi medici, le terapie e il livello di istruzione delle madri. A livello di gruppo, la comunicazione espressiva è emersa come un punto di forza relativo, e le abilità grosso-motorie come una debolezza. Sono emersi inoltre due diversi profili di sviluppo: uno caratterizzato da punteggi di sviluppo più alti, l'altro più bassi, e con i bambini del primo gruppo più piccoli di quelli del secondo.

L'eterogeneità negli individui con SD è stata poi ulteriormente esplorata nello Studio III (Capitolo 4), spostando l'attenzione su bambini più grandi e adolescenti. Gli obiettivi di questo terzo studio sono: (1) esplorare il profilo cognitivo di bambini e adolescenti con SD; (2) esaminare se la loro variabilità interindividuale possa essere classificata in termini di sottogruppi con diversi profili cognitivi; e (3) indagare l'associazione tra profilo cognitivo e tappe dello sviluppo, condizioni mediche e livelli di istruzione dei genitori. Settantadue bambini/adolescenti con SD dai 7 ai 16 anni sono stati valutati con la Wechsler Preschool and Primary Scale of Intelligence - III. Sono stati adottati punteggi età equivalente e, per ogni partecipante, sono stati ottenuti un indice verbale e uno non verbale. Questi punteggi sono stati prima analizzati per esplorare il profilo cognitivo del gruppo nel suo complesso,

poi utilizzati per un'analisi dei cluster. Il profilo complessivo del gruppo ha rivelato punteggi simili nei domini verbali e non verbali, mentre l'analisi dei cluster ha identificato tre diversi profili, etichettati come "Non-Verbale", "Verbale" e "Omogeneo". Il primo sottogruppo aveva i punteggi più bassi e il profilo tipico della SD (più deboli sul verbale rispetto al non verbale); il secondo presentava punteggi intermedi e con punteggi migliori nei compiti verbali rispetto ai non verbali; e il terzo, con i punteggi più alti, mostrava punteggi simili nei due domini. Questi tre sottogruppi non differivano in termini di età cronologica e le variabili ambientali sembrano aver avuto un ruolo nel determinare i profili verbali e omogenei.

Le conclusioni generali tratte dai risultati principali dei tre studi e le loro implicazioni cliniche sono discusse nell'ultimo capitolo (Capitolo 5) di questa tesi.

Indagare l'eterogeneità in individui con SD offre una visione importante sui punti di forza e di debolezza del loro profilo di sviluppo e cognitivo, permettendo così interventi più specifici e mirati. Tuttavia, c'è ancora spazio per ulteriori ricerche, dove sarebbe interessante condurre un'indagine longitudinale per individuare le variabili associate a un determinato profilo e a una certa traiettoria di sviluppo. Tuttavia, nonostante la presente tesi sia stata un tentativo nel sollevare e chiarire alcuni punti, molte altre domande rimangono ancora senza risposta.

CHAPTER 1

DEFINING DOWN SYNDROME

1.1 Genetic causes and types of trisomy 21

Down syndrome (DS) is the most common neurogenetic syndrome linked to intellectual disability, affecting approximately 1 in every 800 live births (Bull et al., 2020). It stems from a full trisomy of chromosome 21 in most cases (90-95%), while the remainder are due to either mosaicism for chromosome 21 (2-4%) or an inherited structural rearrangement leading to partial trisomy of most of its content (2-4%) (Papavassiliou et al., 2015; Patterson, 2009). Trisomy 21 (or "free," "full" or "primary" trisomy 21) results from the failure of normal chromosome segregation during meiosis (meiotic nondisjunction) leading to the production of a gamete containing two copies of chromosome 21, rather than a single copy as in normal meiosis. Although this can occur during the formation of the egg or the sperm, it is usually of maternal origin, occurring primarily during the first meiotic division in the maturing oocyte; primary trisomy 21 is of paternal origin in less than 10% of cases (Antonarakis, 1998). Mosaicism leads to some cells of the body having trisomy 21, while others have a normal chromosomal arrangement. This can occur in one of two ways: when a normal zygote with 46 chromosomes undergoes an early mitotic error after fertilization, resulting in some cells with trisomy 21; or when an early mitotic error allows some cells in a DS embryo with trisomy 21 to revert to a normal karyotype (Papavassiliou et al., 2015). There are also some cases due to chromosomal rearrangements involving the long arm of chromosome 21 (21q) and resulting in a partial trisomy for chromosome 21. Most of these rearrangements are Robertsonian translocations between chromosome 21 and another acrocentric chromosome (usually chromosome 14), but sometimes within chromosome 21 itself (Flores-Ramírez et al., 2015). In short, most cases of DS are not inherited, but the result of mistakes in cell division during the development of the egg, sperm or embryo. While

maternal meiotic nondisjunction events are the main cause of DS (accounting for about 88% of cases), various risk factors have been suggested over time, including folate metabolism (Coppedè, 2015) and dietary, lifestyle, environmental, occupational, genetic, and epigenetic factors (Cocchi et al., 2010; Coppedè, 2016; Morris et al., 2005). There is still no clear model capable of explaining the birth of a child with DS, however. The only factor now known to increase the probability of having a child with DS is maternal age (Cocchi et al., 2010; Morris et al., 2005).

1.2 Signs and symptoms

The clinical manifestations of DS include several dysmorphic features and a delayed psychomotor development (Roizen & Patterson, 2003; Weijerman & De Winter, 2010). Neonatal signs include small ears, brachycephaly, a flat face, epicanthic folds, a flat nasal bridge, a small mouth with a large protruding tongue, a short neck with a bulge of fat at the back, broad hands, a transverse line in the palm of the hand ("Simian fold"), a gap between the first and second toes ("sandal gap"), hypotonia and hyper-flexibility (Roizen & Patterson, 2003; Weijerman & De Winter, 2010). Congenital heart defects (CHDs), hearing loss and ophthalmological problems have also been recorded. Around one in every two (44–58%) newborn with DS has CHDs. Hearing loss is found in 38-78% of DS individuals. Vision disorders are equally common (38-80%), and include strabismus, nystagmus, cataracts, refractive errors and glaucoma. Other clinical issues include: sleep disorders (in more than 50% of cases); respiratory disorders (in up to 36%); congenital defects of the gastrointestinal tract (4-10%); disorders of the endocrine (28-40%) and urinary (3%) tracts; bone and muscle disorders (up to 30%); and dermatological problems (up to 39%) (Weijerman & De Winter, 2010).

1.3 The cognitive profile in Down Syndrome

Along with the typical medical and clinical features, DS is also associated with intellectual disability. Intellectual functioning is assessed with standardized tests that have to be appropriate for the

respondents' age and culture. These assessment tools give us an estimate of the individual's intellectual quotient (IQ). Scores indicate a respondent's position vis-à-vis the typically-developing (TD) population of the same chronological age (CA) and are usually expressed on a distribution with a mean of 100 and a standard deviation of 15. Individuals with DS have an IQ that can vary from mildly to severely impaired, and generally ranges between 25 and 70 (Dykens et al., 2006). It has also been found to decline with increasing CA (Vianello, 2006), a change that can be explained in terms of a slower rate of development in individuals with DS (Couzens et al., 2011) compared with their TD peers, which widens the gap between them as they grow older (Glue & Patterson, 2009). This is confirmed by the fact that, although IQ declines with age, mental age and raw test scores continue to rise (Vianello, 2012). The wide range of IQ scores found in individuals with DS underscores the variability seen in this population (Määttä et al., 2006; Vianello, 2012).

Moving to specific domains of functioning, individuals with DS are characterized by a particular cognitive and behavioral profile. They tend to have relatively strong non-verbal skills and social functioning. There are more obvious problems with speech and language (with greater difficulties in expressive than in receptive language), memory span (especially auditory verbal memory), executive functions, and some aspects of motor functioning (Abbeduto et al., 2007; Chapman & Hesketh, 2000; Fidler, 2005; Lanfranchi et al., 2010). They vary considerably on these aspects, however, just as they do on IQ. Karmiloff-Smith et al. (2016) made the point that DS has mainly been described at group level for many years, giving the erroneous impression that individuals with DS form a homogeneous group, whereas a review of the existing literature reveals ample individual differences on many levels (i.e., genetic, cellular, neural, cognitive and behavioral). It is important to envisage the DS population as heterogeneous because this means that changes may occur on different levels (and influence other levels differently), and it is therefore necessary to consider tailored interventions. This particular aspect is discussed towards the end of this chapter, after a presentation of the findings relating to the single developmental domains.

1.2.1 Language

Receptive vocabulary is often seen as a relative strength in individuals with DS, while their expressive vocabulary tends to be poor by comparison (Chapman, 1997), and also compared with TD children matched on non-verbal mental age (Næss et al., 2011). That said, it seems that the depth of their receptive vocabulary (how well words are known) is weaker than in TD peers matched on breadth of receptive vocabulary (Laws et al., 2015). As regards their expressive language, infants with DS communicate through gestures, vocalizations, facial expressions and other movements just like TD infants between 12 and 18 months old, but then they continue to do so for longer (Kaat-van den Os et al., 2017; Zampini & D'Odorico, 2011). There is some evidence of strengths in gestural communication, while the onset of canonical babbling (consonant–vowel combinations) is delayed in infants with DS, and continues into the second year of life (Roberts et al., 2007). Their first words come late too, between 18 and 36 months old on average (Laws & Bishop, 2003; Levy et al., 2013). Word production increases with developmental age in DS, as in TD children, and individual variability tends to increase with developmental age. At developmental ages of 18, 24 and 30 months, children with DS reportedly produce significantly fewer words than TD children matched on a cognitive level (Zampini & D'Odorico, 2012). Then the vocabulary spurt (i.e., a rapid increase in the rate at which young children learn new words, which occurs at around 18 months old in TD children) does not always happen in children with DS: researchers have found that some of them have a vocabulary spurt, while others have a gradual pattern of new word acquisition (Kaat-van den Os et al., 2017). A vocabulary spurt may occur much later, at around 30 months old, or even when DS children are 5 or 6 years old (Caselli et al., 1997). As for the more complex aspects of language, the acquisition and use of syntax and grammar rules appear to be severely impaired in DS, as is the phonological component of speech (Abbeduto et al., 2007).

In short, DS is characterized by a language competence profile characterized by more or less severe impairments. Considering DS children's overall functioning, their phonology, grammar and syntax

are weak, while their intentional use of communication and gestures, learning of a simple vocabulary, and social use of communication generally seem to be in line with their mental age.

1.2.2 Visuo-spatial abilities

Visuo-spatial abilities are used to process visual information that involves spatial relations, and individuals with DS are known to have generally better visuo-spatial than verbal abilities (Chapman & Hesketh, 2000; Silverman, 2007). Findings may vary, however, depending on which particular ability is examined, as visuo-spatial abilities include a whole set of different skills. This is well illustrated in a review by Yang at al. (2014), who distinguished between: visuo-spatial memory (the ability to retrieve information about objects, or features of objects, in relation to each other in space, and to retrieve the locations of objects); visuo-spatial construction (the ability to see parts of an object and then reconstruct the original object based on interpretations of the parts); mental rotation (turning 2D and 3D objects in the mind's eye); and closure (combining different pieces of information into larger wholes, and separating larger wholes into smaller parts). The review showed that individuals with DS perform less well than TD children matched (or controlled) for general cognitive functioning in recalling locations and closure, while the results for mental rotation and visuo-spatial construction were less consistent. As regards the recall of locations, researchers have examined visuo-spatial working memory (the ability to retain and process visuo-spatial information): participants with DS performed less well than controls matched for mental age in recalling simultaneously-presented spatial information, but not when it was presented sequentially (Lanfranchi et al., 2009). Studies on closure abilities suggested a worse performance in individuals with DS than in TD children matched for equivalent age (Cornish et al., 1999; Vicari et al., 2006). As for mental rotation, that Meneghetti et al. (2018) analyzed in individuals with DS matched with TD children on mental age, the former proved less accurate than the latter (Meneghetti et al., 2018). Previous studies on the same construct had obtained somewhat different results, however (Hinnell & Virji-Babul, 2004; Vicari et al., 2006).

Hinnell and Virji-Babul (2004) found that DS and TD groups matched for mental age did not differ significantly in response times, but did differ in accuracy. Vicari et al. (2006) reported finding no significant differences between individuals with DS and TD children matched on mental age administered a mental rotation task. Finally, as concerns visuo-spatial construction abilities, some studies produced evidence of impairments in this area (Cornish et al., 1999), while others found the performance of individuals with DS in line with that of TD children matched for mental age (Lee et al., 2010). In short, although visuo-spatial abilities are considered a relative strength of individuals with DS, this is only partly true, depending on the particular skill considered.

1.2.3 Executive functions

Executive functions (EFs) is an umbrella term describing a set of higher-order cognitive processes that are important for completing goals (Stuss & Benson, 1984; Zelazo et al., 1997). Several abilities have been classified as EFs, including working memory, shifting, planning and organisation, cognitive flexibility, monitoring and emotional control (Friedman et al., 2006; Pennington & Ozonoff, 1996). Several studies suggest impairments in individuals with DS, with respect to their mental age, in a number of EFs, such as verbal and visuospatial working memory, the verbal component of inhibition, shifting and planning skills, and sustained attention (Borella et al., 2013; Carney et al., 2013; Costanzo et al., 2013; Lanfranchi et al., 2010). In particular, when Lanfranchi et al. (2010) administered a battery of tasks measuring EFs to adolescents with DS and a TD group matched for mental age, the group with DS performed significantly worse on tasks assessing inhibition, shifting, working memory and sustained attention, thus suggesting a broad impairment that went beyond their general level of development. Borella et al. (2013) conducted a similar study on individuals with DS between 10 and 19 years old, who were compared with TD individuals matched for cognitive level, finding deficits in verbal working memory and inhibition. When the cognitive processes relating to inhibition were analyzed (i.e. prepotent response inhibition, response

to distracter inhibition, and resistance to proactive interference), they were all found impaired. Different results emerged from a study by Carney et al. (2013) on individuals with DS and TD children: after controlling for the effect of chronological and mental age, the former were most impaired in executive-loaded working memory and verbal set shifting, whereas no differences emerged in inhibition or fluency tasks. The reason for these discrepancies might stem from the type of task used to assess EFs. Although a given task may be designed to assess a specific EF domain, it might involve other abilities too (such as verbal or visuo-spatial abilities), and this could give rise to results differing between studies. The Behavior Rating Inventory of Executive Function, BRIEF (Gioia et al., 2000) has been widely used in studies on DS to avoid the drawbacks of laboratory testing. Studies adopting this tool have found relative strengths in emotional control and shifting, and weaknesses in working memory (Loveall et al., 2017). While this is true of preschool children, the situation differs slightly in school-age children with DS, whose strengths appear to be emotional control and organisation of materials, while their weakest areas concern working memory, monitoring, planning/organisation, and shifting (Brooks et al., 2015; Daunhauer et al., 2014; Lee et al., 2011, 2015; Loveall et al., 2017). In other words, the picture remains fairly stable over time, with emotional control and working memory remaining a strength and a weakness, respectively, while shifting and planning/organisation abilities change over time.

1.4 Adaptive behavior in Down syndrome

The term adaptive behavior describes an individual's functioning (in the sense of conceptual, practical and social skills) deployed in developmentally appropriate everyday activities (Schalock et al., 210). Conceptual skills involve both receptive and expressive language, reading, writing, math reasoning, and understanding the concepts of time and money. Social skills include awareness of others' thoughts and feelings, friendship skills, the ability to obey social rules, and social judgment. Practical skills concern personal care, task-related sense of responsibility, money management, and work task

organization (Schalock et al., 2010). Adaptive behavior is an essential factor in the diagnosis of intellectual disability, just as important as intellectual functioning (Tassé et al., 2016). It is adaptive functioning that defines the severity of a condition and the level of support required (American Psychiatric Association, 2013). In DS, difficulties emerge already in the first year of life (Will et al., 2018), with standard scores declining further as the child grows older (Spiridigliozzi et al., 2019; Will et al., 2018). This means that their adaptive behavior is acquired at a slower rate than in TD children, not that it is not acquired at all (Van Duijn et al., 2010). In fact, young children with DS have trouble keeping pace in all areas of adaptive functioning, and the trend of their adaptive behavior decelerates as they grow up. The most pronounced discrepancies between DS and TD concern motor and communication skills (Will et al., 2018). Preschool-aged children with DS show relative strengths in socialisation, and weaknesses in communication and motor skills (Dykens et al., 2006; Spiridigliozzi et al., 2019; Will et al., 2018) and this profile remains fairly stable over time, although the picture seems to be more varied in toddlers, while the profile is flatter in 12-year-olds (Van Duijn et al., 2010). This profile seems to persist through adolescence and young adulthood, before a decline in communication skills sets in beyond the age of 22 (Spiridigliozzi et al., 2019).

1.5 Motor functioning in Down syndrome

Motor functioning includes gross and fine motor abilities. The former are a set of skills deriving from the coordination of muscles, bones and nerves to perform ample hand, arm and leg movements, and to move the body in space. The latter stem from the coordination of muscles, bones and nerves to perform small, accurate movements (Alesi & Pepi, 2018). Both are acquired by infants and children with DS in much the same order as in their TD peers, but usually at significantly older ages (Winders, 1997). Studies on the acquisition of gross motor skills in DS indicate that, on average, they can control their heads at 6 months old (Kim et al., 2017), and they learn to sit at between 8.5 and 15.2 months of age (Kim et al., 2017; Tudella et al., 2011; Vicari, 2006; Winders et al., 2019). They are creeping

(moving with their tummies still on the floor) by 10.4 to 17.9 months old, and learn to crawl between 13.1 to 23.1 months of age. They learn cruising between 15.1 to 29.5, and start walking between 19.7 to 36.3 months old (Kim et al., 2017; Winders et al., 2019). As for their fine motor development, they can generally: use a raking grasp when picking up small items by 9-12 months of age; transfer an object from one hand to the other at 12-18 months; deliberately drop an object into an open container at 22-36 months; and use a pincer grasp with their index or middle fingers at 22-66 months old (Frank & Esbensen, 2015). Their motor functioning delays might be explained by central nervous system maturation disorders and an atypical cerebrum size, and/or by biomechanical factors. Concerning the former, the regions in the central nervous system involved in motor planning (the pre-frontal lobe) and programming (the cerebellum and basal ganglia) are known to be characterized by a weak neural growth in terms of dendritic proliferation and myelination of the cortical and subcortical areas, and the smaller cerebellum impairs posture and the sensory system (Ábrahám et al., 2012; Battaglia et al., 2008). As for the biomechanical factors, a role has been suggested for muscle weakness and hypotonicity, joint hypermobility and ligament laxity (Galli et al., 2008; Rigoldi et al., 2012). As individuals with DS grow older, studies on their gross motor skills have shown that: as concerns locomotion, they are relatively good at running and sliding skills, and weaker on jumping forward; in object controlling tasks, they fare better with catching a ball than with bouncing a ball (de Castro Ferracioli et al., 2014; Malak et al., 2013). Children with DS have proved more capable in ball and running tasks than in terms of balance, posture or motor planning (Marchal et al., 2016; Vicari, 2006). When Abd and El (2016) considered the fine motor skills of 8- to 10-year-old children with DS, their performance was poor by comparison with their TD peers in all four aspects: fine motor precision (precise finger and hand movements, as in drawing, folding paper, and cutting with scissors), fine motor integration, manual dexterity, and upper limb coordination. The children with DS were weakest on fine motor precision and relatively strong in terms of upper limb coordination (Abd & El, 2016).

1.6 Variability in Down syndrome

Although a profile of this syndrome has been established in the literature, DS is also characterized by a considerable degree of inter-individual variability, apparent on various genetic, cellular, neural, cognitive, behavioral and environmental levels. This emerges clearly from a paper by Karmiloff-Smith et al. (2016). On the genetic level, variability lies in the type of mutation: the most common cause of DS is full trisonomy, but partial trisonomy or mosaicism may be involved (Korbel et al., 2009; Papavassiliou et al., 2015). On the cellular level, there have been reports of an accumulation of hyperphosphorylated tau protein (a hallmark of Alzheimer's disease), and it has been found randomly distributed at the genome level (Shi et al., 2012). On the neural level, prenatal brain size in cases of DS is relatively normal only until about 20-24 weeks of gestation, after which individual differences in fetal brain development emerge (Guihard-Costa et al., 2006; Schmidt-Sidor et al., 1990). In some cases, these differences involve a smaller volume of the hippocampus, cerebellum, and occipital-frontal areas during fetal life. In others, there is initially a more or less normal dendritic formation and arborization, followed by a stagnation in the developmental process, with dendrites no longer increasing in either number or complexity. At birth, the brains of many newborn with DS already have a reduced dendritic arborization and fewer synapses – a feature that probably contributes to the limited functional brain connectivity found in many newborns with DS (Imai et al., 2014). All these genetic, cellular and neural differences might be relevant to the heterogeneity seen in individuals with DS, but cognitive and behavioral factors may well have an important part to play too. The IQ of individuals with DS varies considerably, with impairments ranging from mild to severe (Costanzo et al., 2013; Liogier d'Ardhuy et al., 2015; Määttä et al., 2006; Vianello, 2006). Liogier d'Ardhuy et al. (2015) used the Leiter-R to assess individuals with DS between 12 and 30 years old. The IQ ranged from 36 to 80 in those aged 12 to 18, and from 36 to 65 in those between 18 and 30 years old. When Määttä et al. (2006) considered a sample of individuals with DS aged 0-66 years, they found that intellectual disability was mild (IQ 50-69) in 19%, moderate (IQ 35-49) in 30%, severe (IQ 20-34) in 33%, and profound (IQ <20) in 18% of cases. Costanzo et al. (2013) assessed 8- to 21-year-old

participants with the Stanford Binet test, finding their IQ in the range of 36-83. Apart from their IQ, individuals with DS also vary in other domains. When compared with a TD group matched for chronological or mental age, or with individuals who had other neurodevelopmental disorders (such as Williams syndrome or autism) based on standard deviations, the individuals with DS showed at least twice as much within-group variability as that of the other groups (e.g., Daunhauer et al., 2014; Lanfranchi et al., 2010). Looking at milestones acquisition, studies again established a marked variability. To give an example, the range of ages when gross motor milestones were acquired varied from 8 to 15 months, depending on the skill - with the more complex skills showing a greater variability (e.g., Kim et al., 2017; Winders et al., 2019). This aspect is discussed in depth in Chapter 2. To date, few studies have explored heterogeneity in the developmental skill acquisition profiles of infants with DS. Fidler et al. (2019) examined a sample of infants in terms of their exploratory behavior profiles, and whether these were associated with different Bayley scores. They found differences in the exploratory behavior of infants with DS, which were associated with different cognitive profiles. Two exploratory behavior profiles emerged, one more active and the other more passive (the infants respectively spending more or less time exploring objects), which were associated with higher and lower Bayley scores, respectively. This aspect is discussed in depth in Chapter 3. Moving into childhood and adolescence, several studies examined the overall cognitive functioning of children with DS using a complex measure with separate verbal and non-verbal indexes. This revealed a more varied picture than might have been expected: some children had the typical DS profile of relatively stronger non-verbal than verbal abilities; for others the opposite applied; and some obtained similar scores in the two domains. In particular, one study exploring the cognitive profiles of children with DS (Tsao & Kindelberg, 2009) found that they could be characterized by individual differences. The authors applied a clustering procedure to the children's performance in verbal and nonverbal reasoning, which revealed four different subgroups, each featuring different patterns of abilities. One subgroup obtained similar scores in verbal and nonverbal tests; one performed poorly in all tests, but particularly badly on the verbal measures; one scored significantly

higher in the verbal tests; and one scored higher in the nonverbal tests. Such heterogeneity in children and adolescents with DS is further discussed in Chapter 4.

This raises an interesting question: where does this variability come from? There may be different degrees of individual and environmental factors involved. Regarding the part played by individual factors, we need to consider the differences at genetic, cellular and neuronal level that might lead to different outcomes. As for the influence of environmental factors, the type of environment and the stimuli provided have an important role as well. Focusing on IQ, its variability might have a biological explanation, but factors such as a poor or rich environment, and the availability of cognitive stimulation and interventions for the child are important too (Vianello, 2012). Couzens et al. (2011) suggested that individuals with DS whose mothers were better educated scored higher in the Stanford-Binet test (Couzens et al., 2011). Tsao and Kindelberg (2009) investigated the cognitive profiles of individuals with DS who had all been exposed to positive developmental conditions, and argued that the differences seen in their profiles might relate to the quality of early intervention and parenting. Variability in outcomes among infants with DS may also be explained by other factors, such as prematurity, health problems or obstructive sleep apnea. Premature birth affects the acquisition of developmental skills in the general population (Msall & Tremont, 2002; Rose et al., 2008), and therefore may have an impact on infants with DS as well (Fidler et al., 2019). Medical conditions are known to have a role in cognition in DS. For instance, CHDs seem to account for a portion of the variability in their language impairment (Aoki et al., 2018; Visootsak et al., 2013), although their effects on neurodevelopmental outcomes seem to be stronger in toddlerhood, while later in childhood and adolescence are not as apparent (Alsaied et al., 2016). In addition, a history of surgery has been associated with delays in their cognitive (van Trotsenburg et al., 2006) and motor development (Kim et al., 2017). Obstructive sleep apnea has also been linked to impaired executive functioning and a low verbal IQ (Edgin et al., 2015).

1.7 General aim of the present dissertation

The purpose of this chapter is to introduce the idea that, although the literature has described a specific DS profile, individuals with this syndrome can vary considerably – and the aim of this dissertation is to shed more light on this variability. Doing so would not only improve our understanding of the syndrome, but would also provide important information on how to plan tailored interventions. The diversity observed in DS is discussed from different aspects, in terms of developmental milestones, cognitive profiles, and other potentially associated variables. The specific aims of each chapter are presented below.

1.8 Overview of the chapters

Variability in individuals with DS is first explored in terms of their acquisition of developmental milestones. **Chapter 2** describes studies conducted on the topic, with an emphasis on the heterogeneity of milestones acquisition in DS. Delving into these studies made it clear that there are currently no comprehensive characterizations of infants with DS in terms of their cognition and acquisition of language milestones, although there are reports more broadly dealing with their communication skills in the first years of life. Chapter 2 consequently presents a study (Study I) that aimed to fill this gap. In particular, the goals of the study were to: provide foundational information regarding the timing of cognitive and communication skill acquisition in infants with DS; and to facilitate the early identification of the risk of other concomitant conditions. This study was conducted during a period spent at the Colorado State University. It involved 74 infants with DS (age range: 4-18 months) administered the Bayley Scales of Infant Development-III (BSID-III). Parents provided information regarding their child's developmental and family history. Individual items from the cognitive and communication scales were selected for analysis, and the percentage of infants acquiring each skill was calculated within 2-month age bands. For infants not acquiring a given skill within each age band, the rates of prematurity, heart problems, surgery, and significant illness were

calculated to obtain information on variables that might be associated with failure to reach certain milestones. With information of this nature, assessments of early development in infants with DS can be based on a given child's performance vis-à-vis that of their peers with DS, thus enabling assessors to establish promptly which of them is developing early, appropriately for their age or late relative to others with DS, and to refer them for targeted intervention.

Having outlined the heterogeneous picture of milestones acquisition in DS, **Chapter 3** explores this variability in terms of developmental profiles in infants with DS. Another study (Study II) is presented that aimed to examine these developmental profiles, whether any variability during infancy is detectable across different domains of functioning (cognition, communication, motor composites), and the role of various health-related and environmental factors (i.e., prematurity, medical problems, therapies administered and parents' education levels) that might contribute to early skills acquisition. Like Study I, this study was also conducted at the Colorado State University, and involved 54 infants with DS (age range: 3-17 months) who completed the BSID-III. Their parents provided information regarding their developmental and family history. A cluster analysis was run to explore the developmental profiles and the impact of prematurity, medical problems, therapies, and parents' education levels was then investigated. This study generated foundational information on the variable picture of DS in infancy, affording a better understanding of the early developmental presentation associated with DS that can help to orient early intervention planning. Knowing that within-syndrome variability is detectable so early in life would suggest the need for more tailored interventions that target a given individual's profile.

Chapter 4 goes on to explore the heterogeneity of DS in children and adolescents. The main goal of a third study (Study III) was to define and explore the cognitive profiles of a group of 72 children and adolescents with DS, from 7 to 16 years old, who were assessed with the Wechsler Preschool and Primary Scale of Intelligence – III. A verbal and a non-verbal index were obtained, and entered in a cluster analysis to see if any characteristic profiles came to light. Here again, the impact of prematurity, medical problems, therapies, and parents' education was taken into account. Although

this study was only exploratory, its findings support the possibility of different cognitive profiles in DS that need to be taken into account in order to propose targeted interventions for children and their families. Such interventions need to be informed by an understanding of the emerging profile of a given individual with DS, enabling practitioners to focus on each child's strengths and thereby counter their weaknesses.

Chapter 5 summarizes the main findings of each study (described in Chapters 2-4), describing their strengths and limits, and mentioning questions that remain to be answered and suggestions for further research. The clinical implications of these studies are also discussed.

CHAPTER 2

ACQUISITION OF COGNITIVE AND COMMUNICATION MILESTONES IN INFANTS WITH DOWN SYNDROME (STUDY I)

2.1 Introduction

The first years of development are crucial for lifelong learning and development. As explained by Scharf in his paper (2016), where developmental milestones are defined in TD, it is important to understand normal development because it helps clinicians to recognize delayed development. In addition, early identification of developmental delays allows to plan early interventions. However, if developmental milestones have been widely described in TD, fewer studies aimed to define them in DS. It is known that the cognitive delays associated with DS can be detected early in life (Fidler 2005) and that children with DS generally reach developmental milestones in the same order as their TD peers, but at later chronological ages (Tudella et al. 2011). The rate at which cognitive growth occurs in individuals with DS is thought to decrease over time, and thus, the rate at which they develop new skills becomes increasingly slower throughout development (Zigler & Hodapp, 1991). The slower rate is due to genetic, neurodevelopmental, and other biomedical influences (e.g., premature birth, sleep dysregulation), and also environmental factors, such as the presence or absence of intervention experiences or the level of caregiver responsivity (Karmiloff-Smith et al. 2016; Pelleri et al. 2016; Van Hooste & Maes 2003).

The timing and onset of motor milestones have been a more active area of study in DS compared to the cognitive and communication domains (Tudella et al. 2011; Winders et al., 2019). Tudella and colleagues (2011) reported that prior to the age of 7 months, infants with DS in their sample were delayed by 1 month relative to typical infants but, after the 7th month, the degree of delay increased. However, all infants in the Tudella et al.'s study received intervention, which may have impacted and accelerated milestone acquisition. Studies of gross-motor skill acquisition in DS report that, on

average, head control is achieved at 6 months, rolling emerges between 5 and 11 months, sitting between 7 and 15, creeping between 10 and 24, crawling between 11 to 30 months, cruising between 12 to 29, standing alone later than the 12th month, and walking between 16 to 48 months (Horovitz & Matson, 2011; Kim et al. 2017; Tudella et al. 2011; Vianello, 2006, Vicari 2006; Winders et al. 2019). The studies that reported gross-motor milestones acquisition are reported in Table 2.1. The studies have been listed in chronological order of publication and data regarding the onset of each milestone are reported considering the information described in the studies. In Table 2.1 the average age of attainment for each skill for TD is reported as well (Sharf et al., 2016).

Table 2.1 Gross-motor milestones acquisition

Authors	Date	Head control	Rolling	Sitting	Creeping	Crawling	Cruising	Standing alone	Walking
Vianello	2006	5 months Range: 3-9	5 months Range: 3-9			16 months Range: 11-30		18 months Range: 13-36	20 months Range: 16-48
Vicari	2006		Range: 5-6.4	Range: 8.5-11.7		Range: 12.2-17.3			Range: 15-74
Horovitz & Matson	2011					M=12.59 SD=4.22			M=19.82 SD=4.85
Tudella et al.	2011	9 months		11 months				Not reached by 12 months	
Kim et al.	2017	M=6.1 SD=2.6	M=8.8 SD= 3.1	M=11.9 SD=3.3	M=13.9 SD=3.5	M=18.1 SD=5.0	M=22.3 SD=7.2		M=28.0 SD=8.3
Winders et al.	2019		M=6.5 SD= 1.6	M=10.3 SD= 3.1	M=17.9 SD= 6.7		M=18.4 SD= 5.9		M=26 SD= 8.4
TD		2 months	4-5 months	7 months	8 months	9 months	10 months	11 months	12 months

Note: M=Mean; SD=Standard Deviation

With regard to fine-motor development, on average, the onset of the use a raking grasp when picking up small items mostly occurs between 9 and 12 months, transfer an object from one hand to the other between 12 and 18 months, intentionally drop and release an object into an open container between 22 and 36 months, and utilising a pincer grasp with either their index or middle fingers between 22 and 66 months (Frank & Esbensen 2015). The same skills are acquired between 6 and 12 months in TD (Sharf et al., 2016). As it is clear from the wide age range estimates for motor milestones, there

is a high degree of variability in skill acquisition and, importantly, heterogeneity is present in developmental trajectories (Cardoso et al. 2015; Tudella et al. 2011).

Moving from the motor to the cognitive and communication domains, up to date, there are fewer characterizations of milestone acquisition in infants with DS.

Considering cognition, to our knowledge, there are no published studies that have been conducted with the aim to define and report a schedule of cognitive development as it is in TD (see Scharf et al., 2016 as an example), although Vianello (2006) did report in his book the acquisition of some cognitive milestones based on his research work. These milestones were reported considering the sensorimotor stage of the Piaget's theory of cognitive development and their timing of acquisition was reported as follows: grab an object by opening an hand (problem solving) at 10 months, find a partially hidden object (object permanence) at 11, pull something to obtain object (problem solving) at 15, build a tower with two blocks (spatial relations) at 28 and puts objects in a cup and tips them over to get them out (spatial relations) at 29.

Differently from cognition, there is a clearer delineation of milestones in the communication domain, although most of the studies describe communication in DS more broadly during the first years of life (Berglund et al., 2001; Laws & Bishop 2003; Levy & Eilam 2013; Oliver & Buckley, 1994; Roberts, 2007; Kaatvan den Os et al. 2017; Zampini & D'Odorico 2011). Some studies suggest that infants with DS tend to communicate through gestures, vocalizations, facial expressions and other movements as TD infants do between 12 and 18 months, but for a longer period (Kaatvan den Os et al. 2017; Zampini & D'Odorico 2011). There is some evidence for strengths in gestural communication, while the onset of canonical babbling (consonant–vowel combinations) is delayed and continues into the second year of life (Roberts et al. 2007). Acquisition of first words tends to be delayed too, appearing, on average, between 18 and 38 months (Laws and Bishop 2003; Oliver & Buckley, 1994), the vocabulary explosion at 30 months and two words phrases around 37 months (Oliver & Buckley, 1994). Word production increases with developmental age in DS, as commonly occurs in TD, and its individual variability tends to increase with developmental age. However,

children with DS at developmental ages of 18, 24, and 30 months produce significantly fewer words than TD children matched on a cognitive level (Zampini & d'Odorico 2012).

Table 2.2 reports the studies that have defined some developmental milestones in communication development. The studies have been listed in chronological order of publication and data regarding the onset of each milestone are reported considering the information described in the studies (e.g., mean, standard deviations, range). Table 2.2 also reports the average age of attainment for each skill in TD (Sharf et al., 2016).

Table 2.2 communication milestones acquisition

	Date	Babbling	First words	Vocabulary explosion	Two words sentence
Oliver and Buckley	1994		M=27.3 Range: 19-38	M=30 Range: 28-32	M=36.9 Range: 25.52
Berglund et al.	2001		Range: 12-24		
Laws & Bishop	2003		Range: 18-36		
Vianello	2006		Range: 22-26		Range: 36-48
Roberts	2007	Delayed, continues into the 2nd year of life			
Horovitz &Matson	2011		M=13.16 SD=4.21		
Zampini and D'Odorico	2011			36 months	
Kaatvan den Os et al.	2017			M=26.9 SD=2.6 Range: 23-31	
TD		6 months	12 months	18 months	20 months

Note: M=Mean; SD=Standard Deviation

As it emerges from all these studies investigating different domains, there is variability in reaching developmental milestones. Several factors might play a role on this, both from the individual and environmental level (Karmiloff-Smith et al., 2016), where genetic, cellular and neural aspects interact with the type of environment.

In addition, relevant to the present study, children with DS are at elevated risk for various comorbidities that impact physiology (e.g., hypotonia, ligamentous laxity; Hickey et al. 2012; Weijerman and de Winter 2010) and significant psychiatric comorbidities (e.g., autism spectrum disorder, attention deficit and hyperactivity disorder, Bull, 2011; Oxelgren et al. 2017). Moreover,

prematurity appears to be associated with cognitive development delays (Fidler et al. 2019), but, in other research no significant effect has been found (Aoki et al. 2018). CHDs account for variation in language delay (Aoki et al., 2018; Visootsak et al. 2013), however, associations between heart defects and cognition are inconsistent (Visootsak et al., 2011; Visootsak et al., 2016). Additionally, it is important to note that surgery history has been associated with poorer cognitive (Van Trotsenburg et al. 2006) and motor development (Hyo et al. 2017) in children with DS, but not all studies find significant effects (Rosser et al. 2018).

2.2 Overview of the current study

Motor milestones have been widely described in DS, while fewer studies report the timing of early cognitive and communication milestones. However, a careful delineation of the modal onset of critical cognitive and communication-related milestones in DS can contribute to a more informed, precision approach to intervention planning during the earliest stages of development, and can address ongoing questions regarding the timing and sequencing of early cognitive and communication development in subgroups of children with ID.

The purpose of this study is to address the gap in our knowledge related to early cognitive and communication skills acquisition in infants with DS, utilizing items from the Bayley Scales of Infant and Toddler Development Third Edition (BSID-III; Bayley 2006). The importance of delineating milestones in DS is well described in Winders et al. (2019), where the authors note that a developmental schedule with norms for development in DS is necessary to allow medical professionals to make appropriate referrals, plan targeted intervention, and answer the questions of parents regarding their children's developmental milestones. Without a developmental schedule that provides norms for development in DS, medical professionals are limited in their ability to contextualize the developmental presentation of a particular child with DS, and whether he/she shows similar, fewer, or more pronounced delays in comparison with his or her peers with DS. In addition,

given the presence and the importance of co-occurring medical conditions during development (e.g Aoki et al., 2018; Hyo et al., 2017; Vissostak et al., 2011), their presence is explored, in order to provide information on their relevance in milestones acquisition. Findings from this study would be helpful for paediatricians, family practitioners, and early intervention providers who would obtain essential information that can contribute to a more targeted, precise approach to early treatment and intervention.

This study has been conducted during my period abroad at the Colorado State University (US), under the supervision of Professor Deborah Fidler.

2.3 Method

2.3.1 Participants

Participants included 74 infants with DS, between the ages of 4 and 18 months, from the US. Group characteristics are reported in Table 2.3.

Table 2.3 Participant Characteristics (n=74)

	Mean (SD) or %	n
Sex (% male)	51.4	38
Infant chronological age (months)	10.04 (3.98)	
Race (%)		
White	81.1	60
Asian	2.7	2
Black or African American	2.7	2
More than one race	8.1	6
Unknown/not reported	5.4	4
Ethnicity (%)		
Hispanic or Latino	23	17
Non-Hispanic	66.2	49
Unknown/not reported	10.1	8
Maternal age (years)	35.41 (5.96)	
Maternal education (% college degree or higher)	64.9	48
Paternal age (years)	36.82 (6.69)	
Paternal education (% college degree or higher)	56.8	42
DS type (%)		

Trisomy 21	94.6	70
Mosaicism	1.4	1
Translocation	2.7	2
Unknown	1.4	1
Prematurity (%)	40.5	30
Heart defect (%)	43.2	32
Corrective surgery (%)	23	17
Significant illness (%)	6.8	5

2.3.2 Materials

Child developmental and family history

Caregivers completed a questionnaire that provided information regarding their age, education level and ethnicity. Caregivers reported on their infant's sex, prematurity status, and the presence and correction of CHDs. Regarding prematurity status, parents were asked whether their child was born prematurely and if so, at how many weeks of gestation. However, no information was provided for parents regarding the number of weeks gestation that defined prematurity. CHDs and corrective surgery were queried by asking whether their child had any diagnosed heart defects (without specification of specific examples and if a corrective surgery took place). The questionnaire also included a dichotomous question (yes/no) regarding any history of any significant illness (e.g., pneumonia), and an open-ended question asking parents to elaborate on the nature of the illness, if one was reported. To provide information regarding DS, caregivers also were asked to report their child's current diagnosis, whether they were diagnosed with trisomy 21, translocation, or mosaicism, the method of diagnosis, and the date of diagnosis.

The Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III; Bayley, 2006)

All infant participants completed the BSID-III, a standardized assessment of cognition, receptive communication, expressive communication, fine motor, and gross motor development for young children ages 1–42 months (Bayley, 2006). Assessments were approximately 40 min in duration and were administered by an advanced doctoral-level graduate student. Infants were supported in the lap of their caregiver, seated on the floor, or positioned on a blanket, depending on the infant's needs.

This measure has been standardized with a sample of 1700 children in the United States and has high internal consistency (.86–.93) and test–retest reliability (.80–.87; Bayley 2006). Adequate concurrent validity has been shown between the Wechsler Preschool and Primary Scale of Intelligence-Third Edition and the BSID-III cognitive and language scales (.71–.83), and the Preschool Language Scale-Fourth Edition and the BSID-III communication scales (.51–.71; Bayley 2006). Given that the data collection was conducted in the US, the American version of the scale was adopted.

For this study, key items were selected from the cognitive, receptive, and expressive communication scale. All the selected items, with a brief explanation, are presented in Table 2.4. The reasons for these choices are presented after the table.

Table 2.4 BSID-III items

Skill	Item	Description
Cognitive Scale		
Shifts Attention	10	The experimenter holds a bell in one hand and a rattle in the other. Child's eye move from one object to another in response to sound or movement of objects.
Prefers novel object	13	Child looks longer at ball than block in both presentations.
Explore object	16	Child attends to sight, sound, or feel of object by shaking, mouthing or other activity.
Persistent Reach	21	With an object in front of the child, the child persistently reaches for it.
Pull cloth to obtain object	28	Child pulls washcloth purposely toward him/her to obtain object.
Searches for missing object	34	Child looks into empty cup for blocks that were removed
Finds hidden object	40	Child finds bracelet by looking first under correct washcloth when hidden on both left and right side
Receptive Communication Scale		
Responds to a person's voice	5	Child clearly responds to the person's voice
Responds to name	9	Child turns head when his/her name is called, but he/she does not respond to unfamiliar name.
Interrupts activity	10	Child looks up and briefly pauses during play when his/her name is called
Recognizes 2 familiar words	11	Child responds differentially to at least two familiar words.
Responds to no-no	12	Child stop reaching for object in response to no-no.
Attends to others play routine	13	Child maintains attention and enjoy interacting with the examiner in a play routine for at least 60 seconds.
Responds to request for social routine	14	Child responds in an appropriate manner to at least one spoken request.
Identifies object series: 1 correct	15	Child correctly identifies at least one object between those presented.

Identifies object in the environment	16	Child correctly identifies at least one object named by the experimenter.
Identifies picture series: 1 correct	17	Child correctly identifies at least one picture.
Expressive Communication Scale		
Vocalizes mood	3	Child produces vocalizations that express at least one mood.
Social vocalizing or laughing	5	Child vocalizes or laughs in response to speaker's attention.
2 vowel sounds	6	Child vocalizes at least two different, distinct vowel sounds.
Gets attention	7	Child tries to get attention from the others.
2 consonant sounds	8	Child vocalizes at least two different, distinct consonant sounds.
Uses gestures	9	Child uses at least one gesture to make wants known.
Consonant-vowel combination:1 combination	10	Child imitates at least one repetitive consonant-vowel combination.
Participates in play routine	11	Child actively participates in at least one play routine.
Consonant-vowel combination:4 combination	13	Child imitates at least four repetitive consonant-vowel combinations.
Uses 1 word approximation	14	Child produces at least 1 word approximation.
Direct attention of other	15	Child points to or shows at least one object.
Imitates word	16	Child imitates at least one word, even if imitation consists of vowels only.
Initiates play interaction	17	Child imitates at least one interaction for play.
Name object series: 1 object	20	Child correctly names at least one object.

These items were selected for several reasons. In some cases, selected items were early representation of key cognitive and communicative dimensions (e.g., precursors of executive function, early social responsivity) that have been discussed extensively in the literature on DS or in the broader pediatric literature. In other cases, items were selected because they represented informative incremental change within a pivotal area of development, such as early vocalization, which would be of potential benefit and utility to care providers and interventionists. Item selection was also informed by existing literature on milestone acquisition in preterm infants (e.g., Scharf et al., 2016). However, these BSID-III items were chosen not only considering major milestones, but also taking into account potential risk factors for co-occurring conditions, such as Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD). For example, as shown in many studies (e.g., Deconinck et al. 2013; Osterling & Dawson, 1994; Ozonoff et al. 2010; Zwaigenbaum et al. 2009), decreased social responsiveness, lack of response to the parents' voices and to name, absence of intention to play and interact, and absence of social smile are early indicators of risk for ASD in the general pediatric

population. These early indices from research on early ASD risk map onto specific BSID-III items. Items such as "Responds to a person's voice" and "Responds to name" map on to social responsiveness and responsivity to name, which it is known to be impaired in ASD (Nadig et al., 2007), while "Attends to others play routine", "Responds to request for social routine", "Participates in play routine", "Direct attention of other" and "Initiates play interaction" are useful for assessing the intention to play and interact. Similarly, "Social vocalizing or laughing" maps on to the presence of social smiling. Other BSID-III items were selected because of their possible utility as potential predictors for co-occurring ADHD. Children at familial risk for ADHD demonstrate lower levels of interest, such as shorter duration of orienting to and manipulation of objects at 7 months, and lower levels of shifting attention at 7 months and 1 year of age (Auerbach et al. 2008). These dimensions are captured in items such as "Shift attention" and "Explore object" on the BSID-III. Reduced inhibitory control is associated with ADHD (Gagne et al. 2011), and the "Respond to no-no" item can be used as a first indicator of inhibition. A delay in speech and language is reported in infants with a future development of ADHD (Gurevitz et al. 2012), therefore, the items grouped in the vocalization category are useful to investigate. Items grouped by category are reported in Table 2.5.

Table 2.5: BSID-III items grouped by dimension

	Task	Scale
Early Cognitive Regulation	Shift attention	Cognitive
	Prefers novel object	
	Explore object	
	Persistent Reach	
Early Mental Representation	Pull cloth to obtain object	Cognitive
	Searches for missing object	
	Finds hidden object	
Early Intersubjectivity	Responds to a person's voice	Receptive
	Responds to name	
	Interrupts activity	
	Attends to others play routine	
	Responds to request for social routine	
	Social vocalizing or laughing	Expressive
	Gets attention	
	Participates in play routine	
	Direct attention of other	
	Initiates play interaction	

Vocabulary Mapping	Recognizes 2 familiar words Responds to no-no Identifies object series: 1 correct Identifies object in the environment Identifies picture series: 1 correct	Receptive
Gestures	Uses gestures	Expressive
Vocalization	Vocalizes mood 2 vowel sounds 2 consonant sounds Consonant-vowel combination:1 combination Consonant-vowel combination:4 combination Uses 1 word approximation Imitates word Name object series: 1 object	Expressive

2.3.3 Procedure

Data were collected under Institutional Review Board (IRB) approval at Colorado State University. Parents of infant participants provided written consent prior to the completion of any study measures. Participant recruitment took place in metropolitan areas in the South, Midwest, and Mountain West of the US and Canada through regional DS associations, clinics and support groups. Participating organizations posted information regarding this study via social media and through mailings.

2.3.4 Analysis Plan

Descriptive statistics were performed for each of the selected cognitive and communication items. The proportion of children within each age band who had attained each skill was calculated.

Considering the pace of skill acquisition during infancy, and with the goal to give the most detailed description of development, proportions were calculated for 2-month age intervals. This approach is similar to the approach taken by Frank and Esbensen (2015). Moreover, descriptive statistics were reported regarding the presence of prematurity, heart defect, surgery and significant illness within those infants that did not master the skills. Data were analysed by the statistical package R (R Core Team, 2020).

2.4 Results

Skills acquisition

The proportion of infants who acquired each skill within each 2 months age band are reported in Table 2.6 for the Cognitive Scale, Table 2.7 for the Receptive Communication Scale and in Table 2.8 for the Expressive Communication Scale. A "representative achievement" age-band was designated when 75% of infants assessed at a particular age had mastered the skill, as per Frank and Esbensen (2015).

Representative Achievements in Cognition. An examination of Table 2.6 suggests that infants with DS follow a relatively similar order of skill acquisition to that which was designated by the BSID-III Cognitive domain. Overall, the sample appears to be slightly delayed in the acquisition of most of these first-year milestones. The earliest skills mastered included shifting attention, preferring novel object, and exploration, with over 75% of infants having achieved this milestone by 4 months. Somewhat more pronounced delays were observed for tasks that involve action planning, including persistent reaching behaviour and pulling a cloth to obtain an object and mental representation of objects such as searching for missing objects. Similarly, finding a hidden object (which requires mental representation) does not seem to be mastered in the age range considered in this study (Table 2.6). Overall, these findings suggest some modest delays in early cognitive skill acquisition for the majority of infants, with more pronounced difficulties as motor and representational demands increase for task items.

Table 2.6: Cognitive Scale

Age range (mos) n	4-5.9 14		6-7.9 14		8-9.9 7		10-11.9 12		12-13.9 10		14-15.9 12		16-18 5	
Skill	%	n	%	n	%	n	%	n	%	n	%	n	%	n
Shift attention	100	14	100	14	100	7	100	12	100	10	100	12	100	5
Prefers novel object	78.6	11	71.4	10	100	7	91.7	11	100	10	100	12	100	5

Explore object	100	14	100	14	100	7	100	12	90	9	100	12	100	5
Persistent Reach	57.1	8	71.4	10	100	7	83.3	10	100	10	100	12	100	5
Pull cloth to obtain object	0	0	7.1	1	42.9	3	75	9	80	8	83.3	10	100	5
Searches for missing object	0	0	0	0	14.3	1	16.7	2	80	8	83.3	10	100	5
Finds hidden object	0	0	0	0	0	0	0	0	10	1	16.7	2	40	2

Representative Achievements in Communication. Table 2.7 reports the percentage of infants in each age band who mastered each receptive communication skill. In this cohort, early competencies appeared to be present in the ability to respond to a person's voice. More cognitively demanding skills, such as responding to name and recognizing 2 familiar words, appeared to be mildly delayed in the age of representative achievement, with most infants having acquired these skills by 14-15 months. However, receptive communication that involves additional regulation skills, such as responding to no-no and attending a play routine, appear to emerge after 18 months, as these skills were not acquired by all the participants in the oldest age band in this sample. Finally, responding to a request for a social routine and word identification seem to be achieved later than 18 months (Table 2.7).

Table 2.7: Receptive Communication Scale

Age range (mos)	4-5.9		6-7.9		8-9.9		10-11.9		12-13.9		14-15.9		16-18	
N	14		14		7		12		10		12		5	
Skill	%	n	%	n	%	n	%	N	%	n	%	n	%	n
Responds to a person's voice	92.9	13	100	14	100	7	91.7	11	100	10	100	12	100	5
Responds to name	7.1	1	14.3	2	28.6	2	8.3	1	50	5	75	9	100	5
Interrupts activity	0	0	7.1	1	42.9	3	25	3	60	6	75	9	80	4
Recognizes 2 familiar words	0	0	0	0	14.3	1	16.7	2	40	4	75	9	100	5
Responds to no-no	0	0	0	0	0	0	8.3	1	30	3	66.7	8	80	4
Attends to others play routine	0	0	0	0	0	0	16.7	2	40	4	75	9	60	3
Responds to request for social routine	0	0	0	0	0	0	0	0	0	0	25	3	40	2
Identifies object series: 1 correct	0	0	0	0	0	0	0	0	0	0	16.7	2	20	1
Identifies object in the environment	0	0	0	0	0	0	0	0	0	0	8.3	1	0	0
Identifies picture series: 1 correct	0	0	0	0	0	0	0	0	0	0	8.3	1	0	0

Table 2.8 reports the age of representative achievement for early expressive communication milestones. An examination of this table in contrast to Tables 2.6 and 2.7 suggests that the acquisition of expressive communication milestones is collectively most pronounced in terms of delay. In the present sample, producing vocalization that expresses at least one mood was, in general, acquired early in infancy, and social smiling or vocalizing appeared to be achieved at 6 months. However, in terms of prelinguistic vocalizing, only vowel sounds were mostly present at 12 months, and they seem to have consolidated by 14 months, when consonant sounds were present in most of the sample. At the same age-range (14-15 months), the combination of vowel and consonant sounds appeared to be acquired by most of the children, although only one combination was produced. More combinations of vowel-consonant, word imitation, and word production seemed to appear later in development (after 18 months).

Table 2.8: Expressive Communication Scale

Age range (mos)	4-5.9		6-7.9		8-9.9		10-11.9		12-13.9		14-15.9		16-18	
N	14		14		7		12		10		12		5	
Skill	%	n	%	n	%	n	%	n	%	n	%	n	%	n
Vocalizes mood	100	14	100	14	100	7	100	12	100	10	100	12	100	5
Social vocalizing or laughing	71.4	10	78.6	11	100	7	83.3	10	80	8	100	12	100	5
2 vowel sounds	42.9	6	64.3	9	85.7	6	66.7	8	80	8	100	12	100	5
Gets attention	35.7	5	64.3	9	100	7	66.7	8	70	7	100	12	100	5
2 consonant sounds					71.4	5	58.3	7	70	7	91.7	11	60	3
Uses gestures	7.1	1			57.1	4	41.7	5	50	5	83.3	10	80	4
Consonant-vowel combination:1 combination	7.1	1	7.1	1	42.9	3	50	6	60	6	91.7	11	60	3
Participates in play routine	0	0	0	0	14.3	1	16.7	2	50	5	83.3	10	60	3
Consonant-vowel combination:4 combination	0	0	0	0	0	0	0	0	20	2	50	6	60	3
Uses 1 word approximation	0	0	0	0	0	0	0	0	30	3	25	3	60	3
Direct attention of other	0	0	0	0	0	0	0	0	10	1	50	6	60	3
Imitates word	0	0	0	0	0	0					25	3	60	3
Initiates play interaction	0	0	0	0	0	0	8.3	1	20	2	25	3	20	1
Name object series: 1 object	0	0	0	0	0	0								

Health-related variables and BSID-III scores

For each task, a closer examination was conducted to explore possible sources of more pronounced delay among infants who had not yet mastered the skill in question. Within those, percentages of prematurity, presence of heart defect, surgery and significant illness are reported in Table 2.9. Among infants who did not master a given skill, some were reported with more than one condition, while others did not present any additional condition. Based on the distribution of percentages, prematurity and heart defect were the most prevalent variables among participants who had not yet mastered a given skill.

Table 2.9 percentages of prematurity, presence of heart defect, surgery and significant illness within infants that did not master the skill

Task	Not mastered skill % (n) infants	Prematurity % yes (n)	Heart defect % yes (n)	Surgery % yes (n)	Significant illness % yes (n)
Cognition					
Shift attention	0				
Prefers novel object	10.8 (8)	50 (4)	62.5 (5)	0	0
Explore object	1.4 (1)	100 (1)	0	0	0
Persistent Reach	16.2 (12)	50 (6)	58.3 (7)	8.3 (1)	0
Pull cloth to obtain object	51.4 (38)	36.8 (14)	39.5 (15)	10.5 (4)	2.6 (1)
Searches for missing object	64.9 (48)	39.5 (19)	37.5 (18)	12.5 (6)	8.3 (4)
Finds hidden object	93.2 (69)	42 (29)	43.5 (30)	21.7 (15)	7.2 (5)
Receptive Communication					
Responds to a person's voice	2.7 (2)	50 (1)	100 (2)	0	0
Responds to name	66.2 (49)	44.9 (22)	44.9 (22)	18.4 (9)	8.2 (4)
Interrupts activity	64.9 (48)	41.7 (20)	41.7 (20)	14.6 (7)	8.3 (4)
Recognizes 2 familiar words	70.3 (52)	42.3 (22)	42.3 (22)	13.5 (7)	7.7 (4)
Responds to no-no	77 (57)	43.9 (25)	38.6 (22)	14 (8)	8.8 (5)
Attends to others play routine	74.3 (55)	41.8 (23)	41.8 (23)	14.5(8)	9.1 (5)
Responds to request for social routine	93.2 (69)	42 (29)	42 (29)	21.7 (15)	7.2 (5)
Identifies object series: 1 correct	95.9 (71)	42.3 (30)	43.7 (31)	22.5 (16)	7 (5)
Identifies object in the environment	98.6 (73)	41.1 (30)	43.8 (32)	23.2 (17)	6.8 (5)
Identifies picture series: 1 correct	98.6 (73)	41.1 (30)	43.8 (32)	23.3 (17)	6.8 (5)
Expressive Communication					
Vocalizes mood	0				
Social vocalizing or laughing	14.9 (11)	45.5 (5)	54.5 (6)	9.1 (1)	9.1 (1)
2 vowel sounds	28.4 (21)	57.1 (12)	38.1 (8)	4.8 (1)	4.8 (1)

Gets attention	29.7 (22)	54.5 (12)	40.9 (9)	9.1 (2)	0
2 consonant sounds	55.4 (41)	43.9 (18)	43.9 (18)	9.8 (4)	2.4 (1)
Uses gestures	60.8 (45)	44.4 (20)	40 (18)	8.9 (4)	4.4 (2)
Consonant-vowel combination:1 combination	58.1 (43)	46.5 (20)	44.2 (19)	11.6 (5)	7 (3)
Participates in play routine	71.6 (53)	43.4 (23)	37.7 (20)	13.2 (7)	7.5 (4)
Consonant-vowel combination:4 combination	85.1 (63)	41.3 (26)	19 (12)	7.9 (5)	43.1 (28)
Uses 1 word approximation	87.8 (65)	43.1 (28)	43.1 (28)	21.5 (14)	6.2 4)
Direct attention of other	86.5 (64)	42.2 (27)	40.6 (26)	18.8 (12)	7.8 (5)
Imitates word	91.9 (68)	42.6 (29)	42.6 (29)	20.6 (14)	7.4 (5)
Initiates play interaction	90.5 (67)	41.8 (28)	41.8 (28)	20.9 (14)	7.5 (5)
Name object series: 1 object	100 (74)	40.5 (30)	43.2 (32)	23 (17)	6.8 (5)

2.5 Discussion

The timing of early cognitive and communication milestone acquisition in TD children has been well characterised by developmental scientists, but little information is available regarding these skills in infants with DS. The existing literature on early milestones in DS focuses exclusively on motor development, but the timing of cognitive and communication skill acquisition in this population has a great deal of clinical relevance for health care providers and interventionists as well.

The present study contributes to the development of a schedule of cognitive and communication development for infants with DS, as it allows for comparison of the development of an individual child with DS with that of his or her counterparts who also have DS. Observing developmental patterns in DS is informative and provides useful information on the development in relation to the syndrome, without being restricted to the notion that the development is delayed when compared to a TD child (Burack et al., 1988; Cicchetti & Ganiban, 1990; Cicchetti & Pogge-Hesse,1982). These data allow health care professionals and educators to access a reference for evaluating cognition and language of a child with DS, similar to that which is available for children who develop typically (Scharf et al. 2016). With this information, professionals can readily identify children who fall outside of the norm, enabling early referral for targeted intervention.

In order to help professionals in this work, Table 2.10 provides a summary of the age band where most infants with DS are expected to have achieved each milestone, with additional adjusted information for infants with heart defects and infants born prematurely. In other words, this table, meant to be readily accessible to clinicians, summarizes the age bands for the representative achievement (75-100%, as per Frank and Esbensen, 2015.) Additional clinically-relevant information is provided with the reporting of the developmental progression of infants with prematurity and heart defects along with those who do not. Hence, a clinician providing care for a child with DS and co-occurring heart defects, or a child with DS who is born prematurely, will be able to examine these tables for useful comparison and evaluation. To further help clinicians, data on TD are reported as well considering what is required for each single item (Scharf et al., 2016). Lastly, the results may also be useful information to provide to parents as means to establish a set of expectations regarding their infant's development. However, given the modest sample size, and the cross-sectional nature of these data, cautious interpretation of these findings is needed. In addition, considering corrective heart surgery and significant illness, the sample size was not sufficient to provide a comprehensive account of infants who had these two conditions.

Table 2.10 Representative achievement (75-100%) for each item in the whole group (n=74), in the group of children who were premature (n=31) and in the group of infants with heart defect (n=33). Mean age of achievement is reported for TD as well.

	Total sample	Prematurity group	Heart defect group	TD
Cognitive scale				
Shift attention	4-5.9	4-5.9	4-5.9	2 months
Prefers novel object	4-9.9	4-9.9	6-13.9	4 months
Explore object	4-5.9	4-5.9	4-5.9	4 months
Persistent Reach	6-13.9	8-13.9	8-9.9	4 months
Pull cloth to obtain object	10-18	10-15.9	12-13.9	9 months
Searches for missing object	12-18	12-15.9	12-13.9	8 months
Finds hidden object	NA	NA	NA	10 months
Receptive communication				
Responds to a person's voice	4-7.9	4-7.9	4-7.9	4 months
Responds to name	14-18	14-after 18 months	14- after 18 months	5 months

Interrupts activity	14-18	14-after 18 months	14- after 18 months	6 months
Recognizes 2 familiar words	14-18	14-15.9	14- after 18 months	7 months
Responds to no-no	16-18	NA	14- after 18 months	6 months
Attends to others play routine	14-after 18 months	NA	14- after 18 months	7 months
Responds to request for social routine	NA	NA	NA	8 months
Identifies object series: 1 correct	NA	NA	NA	10 months
Identifies object in the environment	NA	NA	NA	10 months
Identifies picture series: 1 correct	NA	NA	NA	10 months
Expressive communication				
Vocalizes mood	4-5.9	4-5.9	4-5.9	2 months
Social vocalizing or laughing	6-15.9	4-55.9	6-7.9	3 months
2 vowel sounds	8-15.9	14-15.9	8-9.9	4 months
Gets attention	8-15.9	14-15.9	8-9.9	4 months
2 consonant sounds	14-after 18 months	14-after 18 months	14-after 18	4 months
Uses gestures	14-after 18 months	14-15.9	14-15.9	5 months
Consonant-vowel combination:1 combination	14-after 18 months	14- after 18 months	14-15.9	6 months
Participates in play routine	14-after 18 months	14- after 18 months	14-15.9	7 months
Consonant-vowel combination:4 combination	NA	NA	NA	8 months
Uses 1 word approximation	NA	NA	NA	10 months
Direct attention of other	NA	NA	NA	12 months
Imitates word	NA	NA	NA	13 months
Initiates play interaction	NA	NA	NA	13 months
Name object series: 1 object	NA	NA	NA	14 months

NA= not achieved in this sample

Milestone acquisition. From these data, it appears that the most pronounced delays were observed in communication, while performance on cognitive scale items was mostly similar to that observed in TD development. TD infants have the ability to shift attention, prefer novel objects, explore objects

and persistent reach by 4 months (Scharf et al. 2016), similar to the performance observed in this DS sample (with the exception of persistent reaching, which appeared to be mastered in the age range of 8-9.9 months). Searching for a missing object is acquired at 8 months in TD infants, but 4 months later in DS; similarly, finding a hidden object emerges at 12 months in TD (Scharf et al. 2016), but after 18 months in the DS sample. It might be possible that, as shown by Tudella and colleague (2011) for motor development, development in early infancy (e.g., at 4-5 months) is slightly delayed in DS relative to TD infants (1 month delay), but, as they grow older, the delay in development increases in relation to the typical infants. In contrast to the cognition findings, delays in communication were clearly observable early in infancy in this sample. Responding to a person's voice appears to be acquired by 4 months, which is in line with TD. However, from that point, the difference in receptive language acquisition rate diverges for infants with DS. On average, TD infants respond to their name at 4-5 months (Mandel et al. 1995), "no-no" at 6 months, and requests for social routines and objects by 12 months (Menyuk et al. 1995). In contrast, the present sample of infants with DS showed that they respond to their name between 14-16 months, "no-no" between 16-18 months, and requests for social routines and objects by 18 months. A similar pattern was observed for expressive communication, where first milestones were visible by 4 months for infants with DS (such as vocalizing mood and social vocalizing/laughing), but then the delay became more evident. TD infants move from cooing to babbling at 4-6 months, to using gestures to communicate and uttering first word approximations by approximately 8-10 months (Goldin-Meadow, 2009). Around the 12th month, they are able to say some words (Bernhardt et al. 2007; Majorano & D'Odorico 2011; Saaristo-Helin et al. 2011). In contrast, the present sample of infants with DS had mastered gestures as well as first vowel-consonant combinations at 14-16 months for the most part, and they uttered first words after 18 months, which is in line with previous studies on language development in DS (Kaatvan den Os et al. 2017; Zampini & D'Odorico, 2011).

The aim of this comparison is not to underscore the delays in comparison to the TD population, but to show the rate of development in different areas, in order to provide clinicians with general idea of

the developmental presentation of infants with DS as a group. Information of this nature makes it possible to compare infants with DS to their peers with the same condition, enables early identification of advanced, age-appropriate or delayed development, and will facilitate early detection of risk for co-occurring conditions and early referrals for targeted early intervention.

Implications

Delineating cognitive and communication milestones in DS also may facilitate the detection of early risk factors for a child's development. In particular, the BSID-III items considered in this paper are potentially informative indicators of risk for specific conditions, such as ASD and ADHD.

ASD is characterised by impairments in social interaction and communication along with repetitive, restricted, and stereotyped behaviours, interests, and activities (American Psychiatric Association 2013). The prevalence of ASD in DS has been found to range between 20% and 40% (DiGuiseppi et al. 2010; Oxelgren et al. 2017). Researchers show that symptoms of social disability become more apparent at approximately 12 months of age (Rogers 2009). Moreover, about 50% of parents of children with ASD report having concerns before 12 months of age, and many more report they recognise abnormalities between 12 and 24 months (Deconinck et al. 2013). Symptoms observed in the first year of life cover different aspects of the child's development, such as behaviour, language, interactions with others and play. Atypical object exploration and repetitive behaviours are also registered (Kim & Lord 2010; Ozonoff et al. 2008), as well as delays in language and nonverbal communication (Landa & Garrett-Mayer 2006; Paul et al. 2011). Poor eye contact and lack of response to the parents' voices and to name or attempts to play and interact is registered, together with extreme temperament and behaviour (such as irritability or passivity) and absence of social smile (Deconinck et al. 2013). In the BSID-III manual (Bayley 2006), it is reported that the Communication subscales include a number of items reflective of social development. Several items investigate the child's attention to people, how the child responds to their name, reacts when interrupted in play, and understands inhibitory words. A child's failure to look up or orient to his or her own name, or to respond to speech directed to him or her early in life, marks an indicator associated with a later

diagnosis of ASD (Zwaigenbaum et al. 2005). Hence, given all of these aspects, the BSID-III items considered in this paper could be as early risk indices for ASD.

Furthermore, BSID-III items can also be used to consider precursors to ADHD, a disorder characterised by attention deficits and hyperactivity and impulsivity symptoms. Challenges with attention and hyperactivity have been found in approximately 40% of school-age children with DS (Ekstein et al. 2011; Oxelgren et al. 2017). In particular, it is possible to examine underlying executive functions (EFs) related and recognised to be areas of challenge among individuals ADHD. EFs refer to the cognitive regulatory processes necessary for goal-directed behaviour (i.e. inhibitory control, working memory/updating and set-shifting) and appear to be impoverished in children with ADHD compared with their peers (Frazier et al. 2004; Doyle, 2006; Ozonoff et al. 2008), with difficulties detectable in early development (Barkley 1997), even as young as 7 months of age (Auerbach et al. 2004). In DS, attention and hyperactivity symptoms during very early development are less well understood. Therefore, given this potential comorbidity, practitioners may examine item level performance on the BSID-III cognitive domain to determine whether assessment for ADHD is warranted.

Importance of early diagnosis

Early diagnosis is a necessary prerequisite for early intervention, and early intervention offers an important window of opportunity to impact developmental trajectories in neurogenetic disorders. In order to develop treatments that will ameliorate the effects of neurogenetic diagnoses on development, a comprehensive understanding of early phenotypic profiles is critical (Edgin et al. 2015). In addition, it is important to compare children with DS with other children with DS. For example, there are studies showing that toddlers with ASD evince significantly greater delays in developmental milestones when compared to other atypically developing toddlers. In the same way, this reasoning can be applied to the DS population: if a child with DS shows greater delays on some milestones when compared to his/her peers, risk for ASD might be present. Once again, this shows the importance of knowing when milestones emerge in DS (Keen et al. 2010; Leaf et al. 2010; Matson

et al. 2010). The tables reported in these papers could help in this process because they express the developmental goal as percentages of acquisition in a certain age range.

Association with biomedical conditions

There was also the interest in understanding the presence of medical events (prematurity, CHD, heart surgery, significant illness) among those infants who did not master specific cognitive and communication items. Based on inspection of the presence of these cooccurring conditions, prematurity and heart defect were not only the most prevalent in all the sample but also most prevalent among infants who did not master a given skill (around 45%). Infants who had heart surgery or significant illnesses accounted for 10-20% of those who were unable to master various tasks. Moreover, it does not seem to be a difference between domains and within the same domain, with the exception of significant illness, which is frequently present in those children that did not produce four consonant-vowel combinations. Prematurity, heart defect, heart surgery and significant illness are known to impact cognitive outcomes in the general population (Bhutta et al. 2002; Karsdorp et al. 2006; Mahle 2001; Noble et al. 2015) and appear to play a role in DS as well.

These biomedical risk findings echo those that have been reported in other cohorts of children with DS. In regard to DS, the effects of prematurity are not well understood. In some studies, prematurity appears to be associated to cognitive development delays (Fidler et al. 2019) but, in other research no significant effect has been found (Aoki et al. 2018). CHDs account for variation in language delay, although this has not been always confirmed (Aoki et al., 2018; Visootsak et al. 2013, 2018) and it seems there is a developmental trend of its effects on neurodevelopmental outcomes (Alsaied et al., 2016). Additionally, it is important to note that surgery history is associated with poorer cognitive (Van Trotsenburg et al. 2006) and motor development (Hyo et al. 2017) in children with DS, but not all studies find significant effects (Rosser et al. 2018).

2.6. Future directions and conclusions

There are several limitations to this study, despite the adherence to important guidelines in previously published work (Frank and Esbsensen 2015). First, the data reported are cross-sectional, and not longitudinal, which prohibits a more detailed account of the precise timing of skill acquisition for each individual infant. Future work should track developmental milestones longitudinally on a month-by-month basis in order to define an even more precise accounting of developmental trajectories.

Furthermore, as already mentioned above, these data are derived from a somewhat modest sample size, and therefore, careful interpretation is needed. Future work should seek to define a more detailed trajectory and should extend the age range to explore when subsequent cognitive and language milestones are acquired later in development.

This study provides foundational information regarding cognitive and communication skill acquisition during infancy in DS. With information of this nature, early development in individual infants with DS can be assessed based on the child's performance relative to other peers with DS, enabling early identification of advanced, age appropriate or delayed development relative to others with DS, and allowing for appropriate referrals for targeted intervention.

CHAPTER 3

EARLY DEVELOPMENTAL PROFILES IN INFANTS WITH DOWN SYNDROME: HETEROGENEITY AND CHANGE OVER TIME (STUDY II)

3.1 Introduction

Numerous studies have found that individuals with DS are at high risk for specific cognitive and behavioral outcomes. The behavioral phenotype was described in the first chapter of this work. Here I recall some of the main aspects to frame the study presented in the present chapter. The behavioral phenotype in DS includes a higher risk of language and verbal memory challenges, and a relatively lower risk of impairments in nonverbal abilities and implicit memory (Davis, 2008; Grieco et al., 2015 2015; Silverman, 2007). Children with DS also show specific strengths and weaknesses in adaptive functioning, their communication skills generally proving more impaired than their daily living skills and socialization (Fidler et al., 2009; Griffith, et al., 2010; van Duijn et al., 2010). Strengths and weaknesses are established considering individuals' MA, not their CA.

Some facets of the developmental profile seen in DS have been well characterized, but it is important to bear in mind that phenotypic outcomes emerge over time and vary with CA (Chapman & Hesketh, 2000; Grieco et al., 2015; Patterson, et al., 2013; Silverman, 2007; Vicari, 2006). There is also a phenotypic heterogeneity among individuals with DS (Jobling, 1998; Tsao & Kindelberger, 2009), possibly related to the severity of their intellectual disability (Patterson et al., 2013) and any concomitant conditions, such as autism or ADHD (Bull, 2011; Oxelgren et al. 2017). Identifying and understanding the nature of within-DS heterogeneity is likely to provide much-needed information to support the planning and implementation of educational interventions.

While DS has been extensively described at group level, there has recently been growing interest in examining within-syndrome variability, with new calls for a better understanding of the sources of individual differences in several domains (genetic, cellular, neural or cognitive) (Karmiloff-Smith et

al., 2016). Taking the example of cognition, most studies considered individuals with DS by comparison with TD individuals matched for chronological or mental age, or with individuals who had other neurodevelopmental disorders such as Williams syndrome or autism (e.g., Annaz et al. 2009, Lee et al. 2010). Across these comparisons, variability between different individuals with DS was at least twice as great as it was with other groups taken for comparison, particularly in studies that focused on IQ, language, attention, and memory (Karmiloff-Smith et al., 2016).

Few studies as yet have explored heterogeneity in the acquisition of developmental skills among infants with DS. One, conducted by Fidler et al. (2019), found that infants with DS vary in their exploratory behavior, which is associated with various cognitive abilities: more time spent exploring objects correlated with higher cognitive scores, for instance. The authors emphasized the variability, examining the factors that contributed to developmental outcomes. Other studies examined predictors of later functioning in infants (e.g. Marchal et al., 2016), usually focusing on variability by examining longitudinal outcome predictors (e.g. Roberts et al., 2007; Tudella et al., 2011).

Variability in outcomes among infants with DS may be explained by several factors, such as prematurity, health problems, and parents' education level. Premature birth affects developmental skill acquisition in the general population (Msall & Tremont, 2002; Rose et al., 2008), and presumably in infants with DS too (Fidler et al., 2019). Medical conditions are known to affect cognition in DS. CHDs, for example, seem to account for a portion of variation in their language delay (Aoki et al., 2018; Visootsak et al., 2013), although the relation with the cognitive domain has not always been confirmed (e.g., Lee et al., 2020; Startin et al., 2020) and seems to vary with age (Alsaied et al., 2016). A history of surgery is related to cognitive (Van Trotsenburg et al., 2006) and motor development in individuals with DS too (Hyo et al., 2017). Mothers with higher education levels are also associated with individuals with DS scoring higher on the Stanford-Binet scales (Couzens et al., 2012).

3.2 Overview of the study

Almost all individuals with DS have relative strengths and weaknesses throughout their lives, though they vary considerably from one individual to another (Karmiloff-Smith et al., 2016). The aim of the study described in this chapter was to examine the developmental profile of infants with DS. The focus was on whether any heterogeneity can be detected across domains of functioning (cognition, communication, motor composites) during infancy, and the role of various health-related and environmental factors (i.e., prematurity, medical problems, use of therapies, and parents' education level) that may contribute to early skill acquisition.

Examining the profiles of infants with DS can offer insight on the early stages of the syndrome and on within-group heterogeneity. It can also help characterize the association between infant cognition and development in general. A better understanding of the early signs of DS can also inform prompt intervention programs tailored more specifically to a given infant's personal strengths and vulnerabilities.

The study described here was conducted during a period abroad at the Colorado State University (US), under the supervision of Professor Deborah Fidler.

3.3 Method

3.3.1 Participants

The study involved 54 infants with DS, between the ages of 3 and 17 months, from the US. Their characteristics are listed in Table 1. The prematurity rate in this sample (slightly more than one in three infants) is comparable with that of previous studies (e.g., Fidler et al., 2019), as is the rate of CHDs (~50%; Coppedè, 2015; Freeman et al., 1998) and significant illness (~10%; Bull et al., 2011). The distribution of the infants by ethnicity is in line with that of the North American population.

Table 3.1 Participants' characteristics (n=54)

	Mean (SD) or %	n
Sex (% male)	50.0	27
Infant's chronological age (months)	9.38 (3.91)	
Race (%)		
White	83.2	45
Asian	3.7	2
Black or African American	1.9	1
More than one race	7.4	4
Unknown / not reported	3.7	2
Ethnicity (%)		
Hispanic or Latino	18.5	10
Non-Hispanic	72.2	39
Unknown / not reported	9.3	5
Mother's age (years)	34.81 (6.10)	
Mother's education (% college degree or higher)	61.1	33
Father's age (years)	36.14 (6.48)	
Father's education (% college degree or higher)	57.4	31
Type of DS (%)		
Trisomy 21	92.6	50
Mosaicism	3.7	2
Translocation	3.7	2
Prematurity (%)	38.9	21
Heart defect (%)	44.4	24
Corrective surgery (%)	20.4	11
Significant illness (%)	7.4	4

3.3.2 Measures

The Bayley Scales of Infant and Toddler Development-Third Edition

All infants were administered the Bayley-III (BSID-III), a standardized assessment of cognition, receptive communication, expressive communication, and fine and gross motor development for children aged 1-42 months (Bayley, 2006). This measure has been standardized with a sample of 1700 children in the United States. It has a high internal consistency (.86–.93) and test-retest reliability (.80–.87; Bayley 2006). An adequate concurrent validity has been demonstrated between the Wechsler Preschool and Primary Scale of Intelligence-Third Edition and the BSID-III cognitive

and language scales (.71–.83), and between the Preschool Language Scale-Fourth Edition and the Bayley-III communication scales (.51–.71; Bayley 2006). Scaled scores (M=10; SD=3) were used in the analyses. The American version of the scale was adopted as the data were collected in the US. Assessments took approximately one hour and were administered by an advanced doctoral-level graduate student. Infants were supported in their caregivers' laps, seated on the floor, or placed on a blanket, depending on the infants' needs.

Infants' developmental and family history

Caregivers completed a questionnaire that provided information regarding their age, education level, income, and ethnicity. Caregivers also reported on their infant's sex, and any prematurity and medical conditions. The medical conditions investigated were: CHDs (e.g., atrioventricular canal defect), surgery, and significant illness (e.g., respiratory syncytial virus).

As regards DS, caregivers were also asked to report whether their child was diagnosed with trisomy 21 (non-disjunction), translocation or mosaicism, the diagnostic method used, and the date of their diagnosis. Parents also provided information about the types of therapy the infants received.

3.3.3 Procedure

Data were collected with the approval of the Institutional Review Board (IRB) at Colorado State University. All parents gave their written consent before any study measures were undertaken. Participants were recruited in metropolitan areas in the South, Mid-West, and Mountain West of the US and Canada, through regional DS associations, clinics and support groups. Participating organizations posted information regarding this study via social media and through mailings.

3.3.4 Analysis plan

The analysis plan included the following goals: (1) to explore the infants' overall developmental profile; (2) to establish whether different developmental profiles were detectable; and (3) to investigate the variables associated with such profiles.

First of all, descriptive statistics were obtained using the BSID-III Scales, and an ANOVA was run to explore the infants' overall developmental profile. Then a cluster analysis was run, considering the five BSID-III scales, to identify any subgroups with different developmental profiles. Cluster analysis is an exploratory statistical method used to identify naturally-occurring groups or patterns of responses on a given set of measures or scales. The infants were empirically grouped according to their relative similarity on the various measures (Henry et al., 2005). Standardized scores were used, so there was no need to control for CA. The agglomeration method was applied because the Agglomerative Coefficient (AC) indicated that Ward's method was the one capable of identifying stronger clustering structures (AC "average": 0.77; AC "single": 0.60; AC "complete": 0.87; AC "Ward": 0.93; where values closer to 1 suggest a more balanced clustering structure, while values closer to 0 suggest less well formed clusters). The "NbClust" package in R was used to validate the results of a clustering analysis. This package provides an exhaustive list of validity indices for estimating the number of clusters in a dataset (Charrad et al., 2015), enabling a comparison of the clusters resulting from the hierarchical cluster analysis with the 30 fit indices. To further confirm the results, the "tidyLPA" package in R was used to check the fit statistics on models with one to four profiles. The Bayesian Information Criterion (BIC; Schwartz, 1978), the entropy value, and the bootstrapped likelihood ratio test (BLRT) were considered. Lower BIC values indicate a better fit. The entropy value gives an indication of a model's classification quality, with values ranging from 0 to 1. Higher values indicate a better quality (Celeux & Soromenho, 1996), and values greater than 0.80 are generally considered adequate (Jung & Wickrama, 2008). The BLRT compares the improvement in fit between neighboring class models (i.e., a model with k profiles compared with a

model with k-1 profiles) and generates a p value useful for establishing whether there is a statistically significant improvement in fit when one more class is included.

A repeated-measures ANOVA was run to explore the profiles between and within clusters, with Cluster as the between-subjects factor and Scale as the within-subjects factor. When the assumption of sphericity was violated in the ANOVA, the Greenhouse-Geisser adjustment was applied to the *p*-values (reported as $p_{[gg]}$). Post-hoc t-tests were two-tailed and the *p*-values were corrected for multiple comparisons using Bonferroni's method (i.e., alpha divided by the number of comparisons). Cohen's d was calculated to ascertain the magnitude of the difference between the clusters at each session. Bayes factors (BF_{10}) were used to express the probability of the data, given H1 relative to H0 (i.e., values larger than 1 are in favor of H1, and values smaller than 1 are in favor of H0). The cut-off for the BFs are: "anecdotal" (BF < 3); "moderate" (BF > 3); "strong" (BF > 10); "very strong" (BF > 30); and "extreme" (BF > 100) (Jeffreys, 1961). A t-test was run to control for differences in CA between the groups. A chi-squared test was run to test the association with other variables as the concomitant medical conditions (heart defect, heart surgery and significant illness) were dichotomous variables (present vs not present), and so were the parents' education level (≤ high school vs > high school), and the therapies administered (yes vs no). All analyses were run using R (R Core Team, 2020).

3.4. Results

3.4.1 Defining the developmental profile of the sample as a whole

Descriptive statistics for each BSID-III Scale are provided in Table 3.2.

Table 3.2 Descriptive statistics for the whole sample, with the mean (standard deviation) of the scaled scores.

	Total sample (n=54) M (SD) [min-max]
Cognitive	6.33 (2.94) [1-14]
Receptive communication	6.02 (2.57) [2-14]
Expressive communication	7.20 (2.54) [2-12]

Fine motor	6.00 (2.45) [1-13]
Gross motor	4.69 (3.09) [1-13]

Note: scaled scores have a mean of 10 and standard deviation of 3

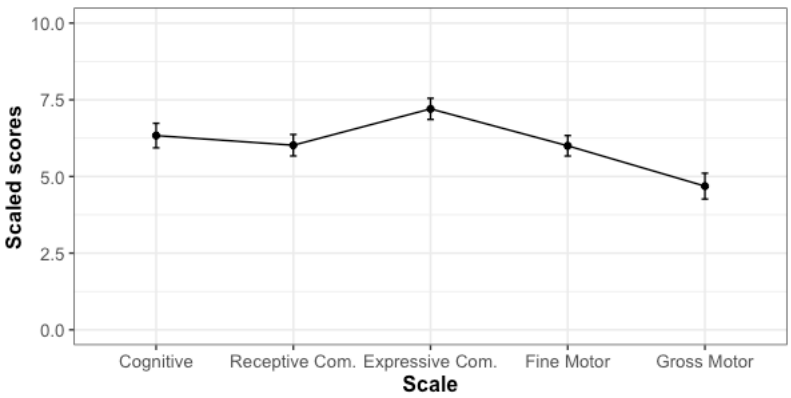
The profile of the sample as a whole was investigated by running an ANOVA. An effect of Scale emerged, $F(3.13, 165.91)=15.15$, $p_{[gg]}<.001$, $\eta_p^2=0.22$, $BF_{10}=1.46X10^8$, suggesting heterogeneity in the profile. Table 3.3 shows the results of subsequent post-hoc analyses, adjusted using Bonferroni's correction, with the alpha level adjusted to 0.005 (i.e., .05/10).

Table 3.3 Post-hoc analyses – effect of Scale

		t	p	d	BF_{10}
Cognitive	Receptive communication	1.00	0.32	0.14	0.24
	Expressive communication	-2.50	0.02	0.34	2.52
	Fine motor	1.38	0.17	0.18	0.36
	Gross motor	4.51	<.001	0.61	$5.69X10^2$
Receptive communication	Expressive communication	-5.11	<.001	0.70	$3.91x10^3$
	Fine motor	0.06	0.95	0.008	0.15
	Gross motor	3.75	<.001	0.51	5.65x10
Expressive communication	Fine motor	3.80	<.001	0.52	6.78x10
	Gross motor	6.86	<.001	0.93	$1.63x10^6$
Fine motor	Gross motor	-3.26	<.001	0.44	1.53x10

The analyses showed that scores were higher for Expressive communication than for almost all the other scales (except for the Cognitive scale), and Gross motor scores were lower than all the others. The profile of the sample as a whole is graphically represented in Figure 3.1.

Figure 3.1 Developmental profile of the sample as a whole



3.4.2 Identifying any different developmental profiles

Hierarchical cluster analysis using Ward's method and Euclidean distances resulted in the following indices: 5 proposed two as the best number of clusters, 11 proposed three, and 7 proposed four. Then models with from one to four profiles were run on the LPA, which showed that the model with three profiles provided the best overall fit for the data, confirming the hypothesis of heterogeneity in the developmental profiles of the sample of infants with DS. The results are presented in Table 3.4.

Table 3.4: Comparison of overall model fit statistics for latent profiles with 1–4 profiles

	Overall model fit			
	1 profile	2 profile	3 profile	4 profile
BIC	1338.97	1269.67	1231.97	1237.19
Entropy		0.89	0.97	0.98
BLRT (p value)		0.01	0.01	0.06

Although the lowest BIC was seen in the 3-profile solution, the highest entropy in the 4-profile solution, and the best BLRT values (indicating improvements over the previous models) emerged for the 2- and 3-profile solutions, the 2-profile model was ultimately chosen. This choice was done for the following reasons: it had an adequate classification quality (Entropy >0.80); the BLRT value showed an improvement over the 1-profile model; and the profile breakdown was more reasonable than in the 3-profile model (where participants were grouped with 22 in the first profile, 5 in the second, and 27 in the third). The 2-profile model contained 27 participants in each group, and the groups were labelled as a *Less Developmentally Advanced Profile* and a *More Developmentally Advanced Profile.* The choice of this solution was also supported by previous analyses on the same data[1]. Table 3.5 shows descriptive statistics for the two profiles in the 5 BSID-III Scales.

[1] These data were collected at the Colorado State University and analyzed to identify any heterogeneity in the infants' developmental profiles, and explore whether these early developmental profiles changed over 6 months. Latent profile and latent transition analyses were conducted using Mplus, which confirmed the 2-profile solution at both the baseline and after 6 months (the paper reporting these analyses is currently under review). The same procedure was adopted here, consistently with the method used in Study 3 (Chapter 4).

Table 3.5: Descriptive statistics with the mean (standard deviation) of the scaled scores for the two profiles.

	Less Developmentally Advanced Profile (n=27) M(DS) [min-max]	More Developmentally Advanced Profile (n=27) M(DS) [min-max]
Cognitive	4.77 (2.25) [1-8]	7.89 (2.86) [2-14]
Receptive communication	4.44 (1.65) [2-7]	7.59 (2.37) [3-14]
Expressive communication	5.81 (2.40) [2-9]	8.59 (1.85) [4-12]
Fine motor	4.85 (2.03) [1-8]	7.15 (2.32) [2-13]
Gross motor	2.11 (1.19) [1-4]	7.26 (2.07) [4-13]

Note: scaled scores have a mean of 10 and standard deviation of 3

Comparison between clusters – ANOVA

An ANOVA run with Cluster as the between-subjects factor and Scale as the within-subjects factor revealed a significant effect of Cluster, $F(1,52)=61.22$, $p<.001$, $\eta_p^2=0.54$, $BF_{10}=3.57x10^7$, infants with the *More Developmentally Advanced Profile* scoring higher than those with the *Less Developmentally Advanced Profile*. The Cluster x Scale interaction was also significant, $F(3.26,169.68)=6.02$, $p_{[gg]}<.001$, $\eta_p^2=0.10$, $BF_{10}=8.22x10^7$, so post-hoc analyses were run (Table 3.6 and 3.7). Adopting Bonferroni's correction, the alpha levels were adjusted to .025 (i.e., .05/2) for comparisons between groups, and to 0.005 (i.e., .05/10) for comparisons between the Verbal and Non-Verbal Index within the two groups.

Table 3.6 Post-hoc analyses: Cluster X Scale – between-group comparison

	Less Developmentally Advanced Profile vs More Developmentally Advanced Profile			
	t	P	d	BF_{10}
Cognitive	-4.56	<.001	0.73	$5.99x10^2$
Receptive communication	-5.66	<.001	0.74	$1.92x10^4$
Expressive communication	-4.76	<.001	0.65	$1.13x10^3$
Fine motor	-3.87	<.001	0.54	8.53x10
Gross motor	-11.22	<.001	1.21	$2.30X10^{12}$

Between-group comparisons showed that infants with the *More Developmentally Advanced Profile* scored higher than those with the *Less Developmentally Advanced Profile* on all the scales.

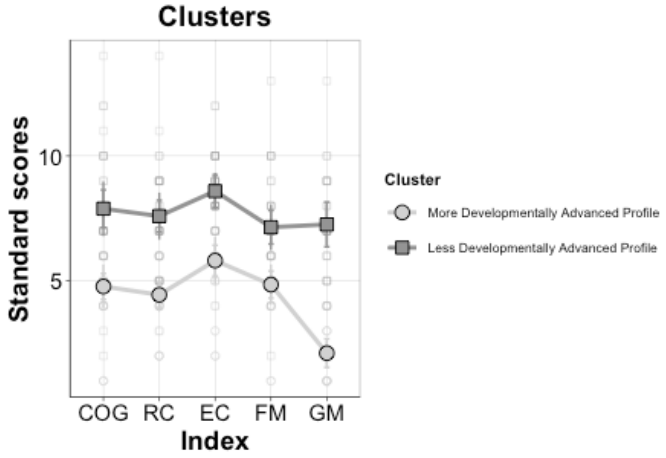
Table 3.7 Post-hoc analyses: Cluster X Scale – within-group comparison

		Less Developmentally Advanced Profile				More Developmentally Advanced Profile			
		t	P	d	BF_{10}	t	p	d	BF_{10}
Cognitive	Receptive communication	0.86	0.40	0.10	0.28	0.59	0.56	0.09	0.24
	Expressive communication	-2.46	0.02	0.32	2.52	-1.26	0.21	0.22	0. 41
	Fine motor	-0.27	0.79	0.02	0.21	1.90	0.06	0.23	0.96
	Gross motor	7.14	<.001	0.82	$1.10x10^5$	1.10	0.27	0.19	0.35
Receptive communication	Expressive communication	-4.46	<.001	0.42	$1,96x10^2$	-2.86	0.008	0.31	5.46
	Fine motor	-1.04	0.31	0.13	0.33	0.99	0.33	0.13	0.32
	Gross motor	6.31	<.001	0.72	$1.61x10^4$	0.60	0.55	0.10	0.24
Expressive communication	Fine motor	2.18	0.04	0.30	1.53	3.16	0.004	0.44	10.23
	Gross motor	8.83	<.001	1.13	$4.46x10^6$	2.59	0.015	0.41	3.23
Fine motor	Gross motor	7.22	<.001	0.84	$1.32x10^5$	-0.18	0.85	0.03	0.21

In the within-group comparisons, the infants with the *Less Developmentally Advanced Profile* scored lower on the Gross motor scale than on all the other scales, and higher on Expressive communication than on Receptive communication. The infants with the *More Developmentally Advanced Profile* showed no significant differences between the scales.

The two groups are graphically represented in Figure 3.2.

Figure 3.2 Developmental profiles of the two groups



Note: COG=Cognitive; RC=Receptive Communication; EC=Expressive Communication; FM=Fine motor; GM=Gross motor

When a t-test was run to see if the two groups were similar in terms of CA, a difference emerged (t=5.45, p<.001, d=1.48), as the infants with the *Less Developmentally Advanced Profile* were older (M=11.75, SD=3.23) than those with the *More Developmentally Advanced Profile* (M=7.05, SD=3.07).

3.4.3 The association with medical problems, parents' education and therapies

Table 3.8 shows details regarding prematurity, medical problems, parents' education and therapies for the infants in the two clusters, with the chi-squared test on the associations between variables and groups.

Table 3.8 Descriptive statistics and X^2 test for prematurity, medical problems, parents' education, and use of therapies

	Less Developmentally Advanced Profile	More Developmentally Advanced Profile	X^2	p
Prematurity % yes (n)	48%(10)	52%(11)	0.07	0.78
Medical problems				
Heart defect % yes (n)	58% (14)	42% (10)	1.20	0.27
Heart surgery % yes (n)	82% (9)	18% (2)	5.59	0.02
Significant illness % yes (n)	100% (4)	0% (0)	4.32	0.04
Parents' education level				
Mother's education % college degree or higher (n)	59% (19)	41% (13)	2.76	0.10

Father's education % college degree or higher (n)	52% (16)	48% (15)	0.07	0.78
Therapies				
Speech therapy	60% (15)	40% (10)	1.86	0.17
Physiotherapy	64% (25)	36% (14)	11.17	<.001
Occupational therapy	56% (19)	44% (15)	1.27	0.26

The chi-squared test revealed no associations between the two profiles and prematurity or heart defects, while associations were found with heart surgery and significant illness, the infants with the *Less Developmentally Advanced Profile* having higher percentages of these variables. Parents' education levels were not associated with the profiles. As for any treatments, no association emerged for speech or occupational therapies, while more infants with the *Less Developmentally Advanced Profile* have been administered physiotherapy.

3.5 Discussion

The primary aim of the study described in this chapter was to explore the developmental profile of infants with DS. A heterogeneous picture emerged, with their expressive communication relatively strong, and their gross motor abilities relatively weak. That their expressive communication should be found a relative strength might seem to contrast with the literature reporting difficulties with speech and language in children with DS, and more with expressive than with receptive language. The focus here, however, was on communication, not language (which is a more complex process), and the apparent discrepancy might be explained by the fact that communication in infancy is still largely non-verbal and prelinguistic; it is only later on that it becomes more structured, and consequently more difficult to learn.

A second aim of the study was to see whether a heterogeneous developmental profile was detectable in DS, already in infancy. The role of various factors that may contribute to early skill acquisition, such as prematurity, medical problems, therapies, and parents' education level, was also explored.

Profiles in DS

The study findings indicated that infants with DS tended to have one of two main profiles across the developmental domains of cognition, communication, and motor skill development. The *Less Developmentally Advanced Profile* was more heterogeneous: scores were lower than in the other profile across all domains, but relatively high scaled scores were seen for expressive communication and relatively low scores for gross motor skills; cognition, receptive communication and fine motor skill levels tended to be similar, scoring lower than expressive communication and higher than gross motor skills. The scores in the *More Developmentally Advanced Profile* were higher overall, and more homogeneous. The present study adds to the evidence of variability in the developmental profiles of children with DS that some authors have recently highlighted (e.g., Couzens et al., 2012; Karmiloff-Smith et al., 2016; Patterson et al., 2013), prompting investigations in infants with DS (Fidler et al., 2019). The Fidler et al. study (2019) focused on within-syndrome variability in the exploratory behavior of infants with DS, and whether different presentations of exploratory behavior were associated with different developmental skills. Two profiles of exploratory behavior were observable, one more active and one more passive, and the former was associated with significantly higher age-equivalent scores on the BSID-III Cognitive, Communication, and Motor scales than the latter. Converging with these results, also the present study identified two profiles, one showing a greater developmental competence than the other. Looking at their descriptive statistics (since no information on the magnitude of the within-group differences between the scales was available), however, the age-equivalent scores were lower for communication than in the other domains, and fine and gross motor skills obtained similar scores, so these two profiles do not coincide with the *Less* and *More Developmentally Advanced Profiles* identified in the study discussed here.

The CA differed between the two clusters identified in the present study, the infants with the *Less Advanced Profile* being older. That younger children should have higher developmental scores is in line with reports in the literature indicating that, while the mental age of children with DS increases over time, their standard scores tend to decline. This would explain the widening gap between DS and TD children over time, due to the slower development of individuals with DS (Vianello, 2012).

Variables associated with infant profiles in DS

When the associations between the clusters and prematurity, medical problems, parents' education and any therapies administered to the infants with DS were explored, prematurity revealed no such association. This is consistent with the work done by Aoki et al. (2018), and contrasts with the findings of Fidler et al. (2019). The former study also found that CHDs accounted for variations in language delay. Here again, this was not confirmed in the present sample, or in the study by Startin et al. (2020). Heart surgery and significant illness did show an association with the clusters identified in the present study. The former result is in line with previous reports of a history of surgery being associated with a more impaired cognitive and motor development in children with DS (Hyo et al. 2017; Van Trotsenburg et al. 2006). The higher proportions of heart surgery and significant illness in the cluster with the *Less Advanced Profile* might be because this group was also older, however. Parents' education levels revealed no associations with our clusters, whereas Couzens et al. (2012) found that mothers with a better formal education were associated with higher scores on the Stanford-Binet tasks in their offspring with DS. This apparent discrepancy might be an effect of age too, as participants in Couzens's study were older than those in the present study. This association may be more readily detectable later on, as a child's strengths and weaknesses become more pronounced, and their cumulative effects more measurable. As for the association between physiotherapy and our clusters, more infants with the *Less Advanced Profile* had received such treatment. Here too, this could be merely an effect of time as the children in this cluster were older and consequently more likely to have started this type of therapy.

The lack of any association for prematurity, parents' education, speech therapy and physiotherapy does not imply that these variables have no impact on the development of an infant with DS. Such associations might only become apparent later in life when the children are faced with more complex tasks. The duration, severity and intensity of the effects of these variables (not considered in this

study) could also influence a child's development. It is also important to bear in mind that such variables do not take effect separately, but interact in shaping a child's development.

It is important to understand the variability in the developmental profiles of children with DS, characterize it early in their lives, and be aware of the variables involved. Shedding light on these issues is of interest not only in research but also in the clinical setting, as it can promote tailored, early interventions and guidance. Planning more specific interventions may positively influence developmental trajectories, and thereby improve the quality of life for individuals with DS.

3.6 Future directions and conclusions

Longitudinal research on how individuals with DS develop poses challenges, as participant recruitment demands outreach and engagement with various stakeholders across a number of DS communities. The findings presented in this study shed light on the early heterogeneity observable among infants with DS, but a larger sample would need to be examined in future research. It would have been useful to reassess the children at subsequent time points to monitor the developmental trajectories associated with the two profiles identified. Our infants were also assessed in different settings (at home, at the university laboratory, in child-friendly spaces in hotels), and this may have contributed a degree of variability to their performance. In addition, considering the importance of the socio-economic status on development (e.g., Arango et al., 2018), it would be important to involve this measure in future studies.

This study provides foundational information on the variability in the developmental profiles of infants with DS. Knowing that within-syndrome variability is detectable early in life may facilitate the planning of early, tailored intervention to target the needs of a given individual. Being aware of which variables have a role enables more focused interventions. Our findings show that biomedical risks are an important factor, meaning that children with concomitant medical problems may need more or different types of support - such as providing parents with specific information and services

regarding their child's medical condition and developmental needs. The novel findings reported here on the heterogeneous developmental profiles detectable in infants with DS contribute to the larger effort to improve early treatments that capitalize on this population's early neuroplasticity. Future work should aim to translate these findings into ways to promote healthy and adaptive outcomes for individuals with DS throughout their lives.

CHAPTER 4

COGNITIVE PROFILES IN CHILDREN AND ADOLESCENTS WITH DOWN SYNDROME (STUDY III)

4.1 Introduction

As explained in the previous chapters, a specific cognitive profile has been associated with the syndrome, individuals with DS being most likely to have more pronounced language and verbal memory challenges, and relatively stronger non-verbal abilities and implicit memory skills (Grieco et al., 2015; Silverman; 2007). Delving into studies that assessed the overall cognitive functioning of children with DS using a complex measure with a separate verbal and non-verbal index reveals a more varied picture, however. Some studies documented the typical profile with greater non-verbal than verbal abilities, such as Lanfranchi et al. (2009), Duarte et al. (2011), Breslin et al. (2014). For example, Lanfranchi and colleagues (2009) investigated working memory in a sample of children/adolescents with DS aged 8-19. When the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) was administered to ascertain their cognitive level, they scored higher on non-verbal (M=61, SD=10.4) than on verbal abilities (M=51.1, SD=6.5). Similar results were reported by Duarte and colleagues (2011), using the versions of the Wechsler scales for older individuals (the Wechsler Intelligence Scale for Children, WISC, and Wechsler Adult Intelligence Scale, WAIS): their sample with DS aged 7-18 had a Verbal IQ of 52.6 (SD=7.3) and an Executive IQ of 55.2 (SD=9.7). Neither of these studies focused on exploring the cognitive profile in DS, however, so no direct comparisons between the indexes were performed. In their study on a group of 7- to 12-year-olds with DS, Breslin et al. (2014) distinguished between those with and without obstructive sleep apnea (OSA). Assessed with the Kaufman Brief Intelligence Test (KBIT-2), the descriptive statistic showed the typical DS profile in the children with OSA, with a verbal IQ of 45.11 (SD=8.83) and a non-verbal IQ of 48.53 (SD=9.92), while those without OSA scored slightly higher on verbal IQ (M=54.42, SD=11.54) than on non-verbal IQ (M=52.67, SD=13.55). The typical DS profile, with

better non-verbal than verbal skills, also emerged in the majority of studies focusing on working memory (e.g., Schworer et al., 2021, Vicari et al., 2004). Other studies revealed higher scores for verbal than for non-verbal processing (Pezzuti et al., 2018; Evans and Ulijarevic, 2018, Sabat et al., 2020). To give an example, when Pezzuti et al. (2018) analyzed the intellectual profile of children and adolescents with DS (aged 7-16 years) using the WISC-IV, their findings suggested a more variable profile in DS. The highest scores were recorded in the Verbal Comprehension Index (M=42.70, SD=17.71), with intermediate scores in the Perceptual Reasoning (M=38.87, SD=16.57) and Processing Speed (M=37.53, SD=11.91) indexes, and the lowest scores for Working Memory (M=31.31, SD=17.21). Strengths and weaknesses sometimes emerged within a given index as well. In the Verbal Comprehension subtests, respondents fared better in the Similarities task, and less well in the Vocabulary and Comprehension tasks. In the subtests measuring Processing Speed, a relative strength emerged in the Block Design task. The participants' verbal and non-verbal performance was comparable in the subtests generating the other two indexes. Similarly, Evans and Uljarevic (2018) found that children and adolescents with DS tended, at both 7 and 15 years of age, to have a higher verbal than nonverbal IQ when assessed with the Stanford-Binet Intelligence Scale - 4th edition. In particular, the group of children showed a verbal IQ of 58.21 (SD=10.61) and a non-verbal IQ of 53.23 (SD=8.06), while the group of adolescents had a verbal IQ of 49.09 (SD=6.58) and a non-verbal IQ of 47.27, (SD=9.57). Higher scores in the verbal domain also emerged in a study by Sabat et al. (2020), who examined a sample of adolescents with DS (aged 12-18 years) using the WISC or WAIS. Here again, their verbal IQ (M=48.36, SD=5.94) was higher than their non-verbal IQ (M=46.28, SD=3.79), though the researchers did not define the magnitude of this difference because the cognitive assessment was done to describe the sample, not to answer their research questions. Then there is a third set of studies describing a homogeneous cognitive profile in individuals with DS. For instance, Cebula et al. (2017) used the WPPSI to assess a group of children/adolescents with DS (aged 9-18 years), and found that their verbal and non-verbal mental age scores were much the same (M=4.07, SD=7.2 and M=4.48, SD=7.0 respectively).

In short, some studies confirm the typical profile of DS, some show an opposite picture, and some delineate a balanced cognitive profile, hence the high variability seen in individuals with this syndrome. As Karmiloff-Smith and colleagues (2016) underscored, the wide range of individual differences at every descriptive level (genetic, cellular, neural, cognitive, behavioral, and environmental) would help to explain the diverse cognitive profiles encountered in DS (e.g., Couzens, et al., 2004; Karmiloff-Smith et al., 2016; Tsao & Kindelberger, 2009; Vianello, 2006). When they considered cognitive and behavioral scores, Karmiloff-Smith and colleagues (2016) found the standard deviation in groups with DS higher than in TD samples (e.g., Vicari, et al., 2006), and the range of scores was wide (e.g., Dykens et al., 2000; Zampini & D'Odorico, 2009). To shed more light on cognitive interindividual variability in DS, Tsao and Kindelberg (2009) assessed 88 children aged from 5.11 to 11.8 years, using the Differential Scales of Intellectual Efficiency, which is a measure of verbal and non-verbal reasoning abilities. Verbal performance was assessed in terms of vocabulary (picture naming), knowledge (acquired in the course of everyday life or at school), and social comprehension (social adaptive behaviors, with questions based on comprehension of interpersonal relations). Non-verbal performance was assessed on classification (finding a principle of similarity between two familiar objects), categorical analysis (arranging geometric forms by shape, color and dimension), and practical adaptation (embedding test). The results confirmed a high interindividual variability, and a clustering approach led to four cognitive profiles being identified, each featuring a particular pattern of abilities. Four different sub-groups emerged: one (n=22) characterized by similar scores on verbal and non-verbal tests; a second (n=24) performed poorly in all subtests, but especially in verbal ones; a third (n=22) scored significantly higher in verbal subtests; and a fourth (n=20) scored higher in non-verbal subtests. This variability might be attributable to individual and environmental factors having an impact on a child's development. Some such factors could be medical conditions, developmental milestones and parents' education levels. Medical conditions have been shown to influence cognition in DS: CHDs seem to account for a portion of the variance in the severity of language impairments (Aoki et al., 2018; Visootsak et al., 2013), and a history of gastrointestinal

surgery has been associated with this diagnostic group's cognitive (Van Trotsenburg et al., 2006) and motor development (Hyo et al., 2017). Another factor concerns when individuals with DS reach certain developmental milestones can be charted vis-à-vis their acquisition of earlier stages of development. It has been demonstrated that the delay with which individuals with DS reach these milestones is linked to their subsequent cognitive and language development (e.g., Fidler et al., 2019; Locatelli et al., 2021; Lynch et al, 1995; Yamauchi, 2019). Motor milestones have been found related to successive cognitive and language development (Yamauchi et al., 2019), and communication milestones to language development (Lynch et al., 1995). Finally, parents' education is also an important factor contributing to children's development. Just as research on typical development identified a strong association between the mothers' education and their children's cognitive development (Reardon, 2018), this also applied to DS: individuals with DS whose mothers had a better education scored higher in the Stanford-Binet tasks (Couzens et al.,2012).

4.2 Overview of the current study

Bearing in mind the previous literature, this study aims to shed more light on the cognitive profile of children and adolescents with DS, also considering interindividual variability. In particular, the aims are to:

1) explore the cognitive profile of a sample of individuals with DS. Based on their reportedly greater strength in non-verbal than in verbal skills, they generally might be expected to score better in the non-verbal domain, and less well on verbal processing. That said, other profiles could be envisaged, and a broader and more varied picture, in the light of previous research conducted using cognitive assessment batteries;
2) examine whether interindividual variability in this sample could be classified in terms of subgroups of participants with different cognitive profiles. Given the diverse findings of studies on the cognitive profile of DS, and the variability observed by Tsao and Kindelberg

(2009), it would be expected to identify some individuals with the classical cognitive profile (better non-verbal than verbal skills), but also subgroups of children with other profiles;

3) investigate the association between cognitive profile and other variables, such as medical conditions (CHDs, a history of heart surgery, OSA), the timing of milestone acquisition, and parents' education level. If any subgroups were to emerge, it would be expected these variables to be associated with them. In particular, it is hypothesized that a greater prevalence of medical problems, a later acquisition of developmental milestones, and less well-educated parents would be associated with a worse overall cognitive profile.

It is important to explore all these aspects because a better understanding of the different cognitive facets of DS could lead to more effective intervention programs, more specifically tailored to a given individual's strengths and vulnerabilities.

4.3 Method

4.3.1 Participants

The study concerned 72 children and adolescents with DS (males, n=41). Their mean CA in months was 134.38 (SD=31.24, min=85.00 and max=195.00). Participants were recruited during their annual visit to the Neonatology Unit at St. Orsola-Malpighi Polyclinic in Bologna (Italy). The inclusion criteria were a diagnosis of DS with homogeneous or mosaic trisomy 21, and a CA ranging between 7 and 16 years. All participants were attending mainstream schools.

4.3.2 Measures

Cognitive assessment

All participants were assessed with the Wechsler Preschool and Primary Scale of Intelligence – III, WPPSI-III (WPPSI-III, Wechsler 1997), a standardized method for measuring cognitive development

for preschoolers and young children (aged from 2.6 to 7.3 years). Although the WPPSI-III was designed for young children, it was used here to avoid any floor effect and because it was considered more in line with the supposed mental age of our sample. This approach has already been adopted in previous studies (e.g., Antonaros et al., 2020, 2021; Tsao & Kindelberg, 2009). The WPPSI-III has two versions, one for younger children (from 2.6 to 3.11 years old), and the other for older children (from 4 to 7.3 years of age). The former was used in the present study to ensure that all the children and adolescents could understand and complete the tasks. There are 5 subtests: Receptive Vocabulary, Picture Naming, Information, Block Design and Object Assembly. In Receptive Vocabulary (which assesses receptive language), respondents are asked to look at a group of four pictures, and to point to the one the examiner names aloud. In Picture Naming (designed to measure expressive vocabulary), they have to name pictures shown one at a time in a stimulus booklet. In the Information subtest (for assessing a child's ability to acquire, retain, and retrieve general factual knowledge), respondents are asked questions testing their general knowledge. The Block Design subtest (which measures the ability to analyze and synthesize abstract visual stimuli, and to form non-verbal concepts) involves participants having to reproduce models with a set of blocks. Finally, there is Object Assembly (which assesses visual-perceptual regulation, and the ability to analyze and synthesize an abstract design), where participants are shown pieces of a puzzle in a standard arrangement and asked to fit the pieces together to form a given figure. The scores obtained in the subtests are used to calculate a Verbal Index (which includes Receptive Vocabulary, Picture Naming and Information), and a Non-Verbal Index (comprising Block Design and Object Assembly). A Total Index can be calculated as well. Using a test standardized for younger children prevented us from considering standard scores, so age-equivalent (AE) scores were used instead, following a procedure suggested by Toffalini et al. (2019).

Participants' developmental history

Caregivers provided family background and information on their children's development, including any medical conditions, when they reached the main milestones, and whether they attended any intervention programs. For the purposes of the present study, we considered the age when they reached specific milestones (sitting, babbling, walking, and first words), medical conditions (heart problems, a history of heart surgery and OSA), and parents' education level.

4.3.3 Procedure

The data considered here were collected as part of a broader project exploring the correlation between genotype and phenotype in DS. All participants were attending the Day Hospital at the Neonatology Unit, Sant'Orsola-Malpighi Polyclinic, Bologna, and the study was proposed at a routine annual follow-up for cases of DS. Written consent was obtained from participants' parents/caregivers. Then the children and adolescents were assessed at the Department of Developmental Psychology at the University of Padova. The assessment sessions lasted approximately 90 minutes. Participants were recruited between November 2017 and February 2020. The present study was approved by the independent Ethics Committee at the St. Orsola-Malpighi Polyclinic and University Hospital (Bologna, Italy) and it was performed in accordance with the Declaration of Helsinki.

4.3.4 Analysis plan

To explore participants' overall cognitive profile, descriptive statistical analyses were conducted on the WPPSI indexes and subtests, then two ANOVAs were run on the scores obtained, one for the indexes, and the other for the subtests.

To identify any subgroups with different cognitive profiles, a cluster analysis was run using the WPPSI Verbal and Non-Verbal Indexes. Cluster analysis is an exploratory statistical method used to identify naturally-occurring groups or patterns of responses in a given set of measures or scales. Participants were empirically sorted into groups based on their relative similarities to one another on

the measures considered (Henry et al., 2005). AE scores for the two indexes were partialized for CA, and their residuals were used in the analyses. The residuals then underwent hierarchical cluster analysis, using squared Euclidean distances to distinguish the clusters. The agglomeration method was used because the Agglomerative Coefficient (AC) indicated that Ward's method was the one capable of identifying the strongest clustering structures ("average" AC 0.89; "single" AC 0.68; "complete" AC 0.95; "Ward" AC 0.97; where values closer to 1 suggest a more balanced clustering structure, and those closer to 0 suggest less well-formed clusters). The "NbClust" package in R was used to validate the results of clustering analysis. Since this package provides an exhaustive list of validity indices for estimating the number of clusters in a data set (Charrad, et al., 2015), it was possible to compare the clusters resulting from the hierarchical cluster analysis with 30 fit indices. A majority rule approach was considered to facilitate the choice of clusters in the real data sets (Charrad et al., 2015). To further confirm the results, the "tidyLPA" package in R was used to check the fit statistics on models with one to four clusters. The Bayesian Information Criterion (BIC) (BIC; Schwartz, 1978), the Entropy value, and the Bootstrapped Likelihood Ratio Test (BLRT) were considered. When the BIC is applied, lower values indicate a better fit. The Entropy value gives an indication of a model's classification quality, with values ranging from 0 to 1; higher values indicate a better classification quality (Celeux & Soromenho, 1996), and values above 0.80 are generally assumed to indicate an adequate classification quality (Jung & Wickrama, 2008). The BLRT compares the improvements in fit between neighboring class models (i.e., a model with k clusters to a model with k-1 clusters), generating a p value that is useful for establishing whether including one more class leads to a statistically significant improvement in the fit.

Two repeated-measures ANOVAs were used to explore the profiles between and within clusters, one considering the indexes, the other considering the subtests, with Cluster as the between-subjects factor and Index/Subtest as within-subject factors.

When the assumption of sphericity was violated in the ANOVAs, the Greenhouse-Geisser adjustment was applied to p values (reported as $p_{[gg]}$). Post-hoc t-tests were two-tailed and the p values were

corrected for multiple comparisons using the Bonferroni method (i.e., the value of alpha divided by the number of comparisons). Cohen's d was calculated to ascertain the magnitude of the difference between the clusters at each session. We also report Bayes factors (BF_{10}) expressing the probability of the data, given H1 relative to H0 (i.e., values larger than 1 are in favor of H1, and those smaller than 1 are in favor of H0). The cut-offs for the BFs are: "anecdotal" (BF < 3), "moderate" (BF > 3), "strong" (BF > 10), "very strong" (BF > 30), or "extreme" (BF > 100) (Jeffreys, 1961). ANOVAs were run with AE scores partialized for CA, and their residuals were used. These analyses were also run on AE scores with CA as the control variable to see for any differences emerged. The results led to the same conclusion, so those with the residuals are reported for consistency with the cluster analysis where these scores were used.

Finally, to test the association with other variables, the chi-squared test was run for categorical variables, and correlations for continuous variables. Since the three medical conditions considered were dichotomous variables (present vs absent), and so was parents' education level (≤ high school vs > higher education), the chi-squared test was conducted in these cases, while correlations were run for age on reaching milestones.

Analyses were run using R (R Core Team, 2020).

4.4 Results

4.4.1 Defining the cognitive profile of the sample as a whole

Descriptive statistics for each subtest and for the Verbal, Non-Verbal and Total indexes are given in Table 4.1.

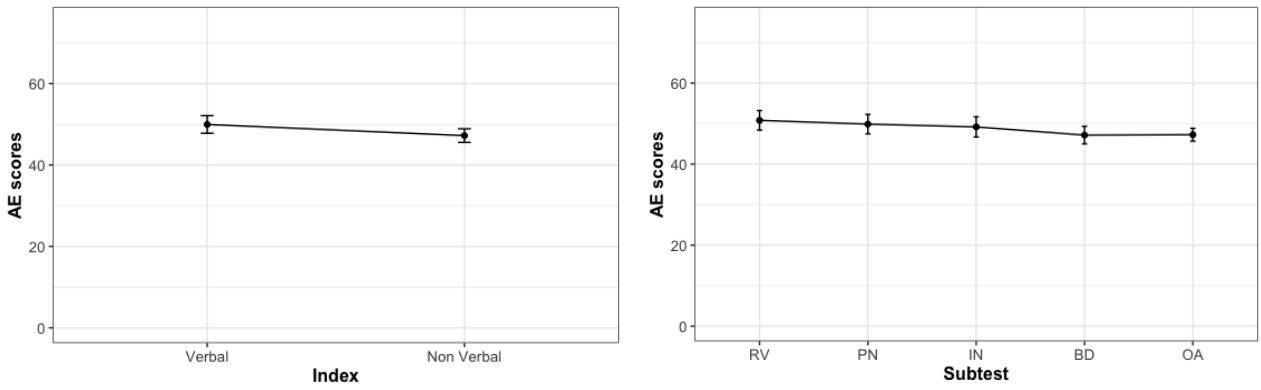
Table 4.1: Descriptive statistics for the sample as a whole (AE scores)

	Whole sample (n=72) *M (SD)*
Verbal Index	49.95 (18.33)
Receptive Vocabulary	50.80 (20.52)
Picture Naming	49.87 (20.43)
Information	49.18 (21.21)

Non-Verbal Index	47.21 (14.11)
Block Design	47.16 (18.44)
Object Assembly	47.25 (13.41)
Total Index	48.85 (18.26)

The profile of the sample as a whole was investigated by running two ANOVAs, one with Index as the within-subject factor, the other with Subtest as the within-subject factor. No effect of Index (p=1.000, η_p^2<0.001, BF_{10}=0.17) or Subtest emerged ($p_{[gg]}$=1.000, η_p^2<0.001, BF_{10}=0.006), suggesting a flat cognitive profile. The standard deviations were high, however, suggesting a marked interindividual variability. The profile of the sample as a whole is graphically represented in Figure 4.1, where Indexes and Subtests are considered separately.

Figure 4.1: Cognitive profile of the sample as a whole, considering indexes and subtests



Note: RV=Receptive Vocabulary, PN= Picture Naming, IN= Information, BD= Block Design, OA=Object Assembly.

4.4.2 Identifying clusters

Hierarchical cluster analysis using Ward's method and Euclidean distances resulted in the following indexes: 9 indexes pointed to two as the best number of clusters, while 10 indicated three, and 4 suggested four. Taking the majority rule approach, the best number of clusters was three (C1, C2, C3).

To confirm as much, models with one to four clusters were run on the latent profiles analysis, which revealed that the 3-cluster solution provided the best overall model fit for the data, confirming the

assumption of a heterogeneous developmental picture within the sample of children/adolescents with DS that could be identified with the aid of mixture modelling. The results are presented in Table 4.2.

Table 4.2: Comparison of overall model fit statistics for latent profiles analysis considering 1–4 clusters

	Overall model fit			
	1 cluster	2 clusters	3 clusters	4 clusters
BIC	1204.59	1204.15	1204.34	1214.58
Entropy		0.55	0.85	0.87
BLRT (p value)		0.02	0.03	0.28

Though the 3-cluster solution did not have the lowest BIC, it did have a better entropy value than the 2-cluster solution. On examining the BLRT findings it emerged that the 3-cluster model showed a better fit than the 2-cluster model, and there was no additional improvement in the fit with the 4-cluster model.

Although residuals were adopted in the analyses, descriptive statistics are reported for AE scores as they are more readily interpretable (Table 4.3). The three groups of participants were labeled as follows: C1, the *Verbal Profile* group (scoring higher on verbal than non-verbal skills); C2, the *Non-Verbal Profile* group (scoring higher on non-verbal processing); and C3, the *Homogeneous Profile* group (with similar verbal and non-verbal abilities). The three groups were similar in terms of the numbers of participants in each one.

Table 4.3: Descriptive statistics for the three clusters (AE scores)

	Verbal Profile (n=29) *M (SD)*	Non-Verbal Profile (n=22) *M (SD)*	Homogeneous Profile (n=21) *M (SD)*
Verbal Index	55.80 (10.59)	29.36 (11.02)	63.44 (14.20)
Receptive Vocabulary	55.64 (17.11)	33.00 (14.57)	62.78 (18.14)
Picture Naming	56.37 (13.45)	27.66 (14.36)	64.14 (13.92)
Information	55.38 (14.10)	27.42 (16.07)	63.41 (16.08)
Non-Verbal Index	41.11 (9.38)	40.11 (11.06)	63.06 (9.06)
Block Design	42.77 (15.59)	36.86 (15.48)	64.01 (13.15)
Object Assembly	39.45 (8.87)	43.36 (9.56)	62.11 (9.76)
Total Index	49.92 (8.47)	33.66 (8.34)	63.28 (11.03)
Chronological age	133.65 (31.17)	134.18 (34.52)	135.57 (29.16)

No significant differences emerged between the three groups in terms of CA ($p>.05$, $BF_{10}=0.12$).

Comparison between clusters - Verbal and Non-Verbal Indexes

The results of the repeated-measures ANOVA with Index as the within-subject variable are given in Table 4.4, and graphically represented in Figure 4.2.

A significant effect of Cluster emerged ($F(2,69)=89.51$, $p<.001$, $\eta_p^2=0.72$, $BF_{10}=1.03x10^{14}$), and subsequent post-hoc analyses showed that the *Homogeneous Profile* group's scores were higher than the *Verbal Profile* group ($t=7.07$, $p<.001$, $d=0.85$, $BF_{10}=3.77x10^{7}$) or the *Non-Verbal Profile* group ($t=11.81$, $p<.001$, $d=1.57$, $BF_{10}=1.72x10^{16}$). The *Non-Verbal Profile* group had lower scores than the *Verbal Profile* group ($t=-6.20$, $p<.001$, $d=0.83$, $BF_{10}=1.52x10^{7}$). No main effect of Index was found. The Cluster x Index interaction was significant ($F(2,69)=26.93$, $p<.001$, $\eta_p^2=0.44$ $BF_{10}=1.14x10^{23}$), so post-hoc analyses were run (Table 4.4). Using Bonferroni's correction, we adjusted the alpha levels to .016 (i.e., .05/3) for the comparisons between groups, and to 0.025 (i.e., .05/2) for the comparisons between Verbal and Non-Verbal Indexes within the three groups.

Table 4.4: Post-hoc analyses, Cluster x Index

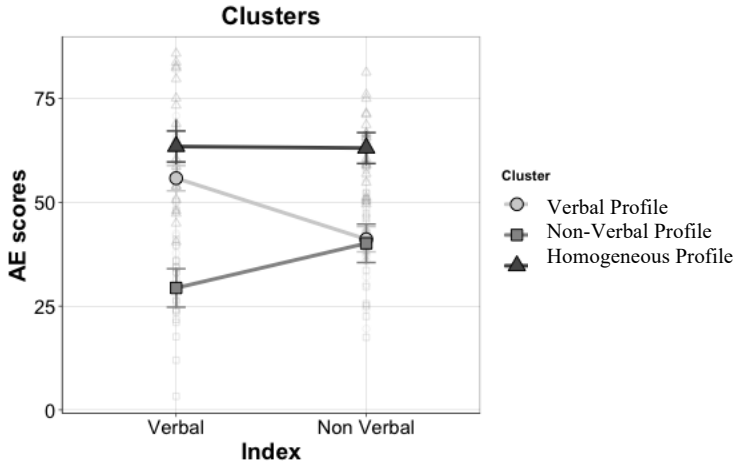
	Between-subjects Comparison			Within-subject Comparison		
	Verbal Profile vs Non-Verbal Profile	Verbal Profile vs Homogeneous Profile	Non-Verbal Profile vs Homogeneous Profile	Verbal Profile	Non-Verbal Profile	Homogeneous Profile
Verbal Index	$t=10.96$ $p<.001$ $d=1.19$ $BF_{10}=9.53x10^{13}$	$t=-2.29$ $p=0.03$ $d=0.32$ $BF_{10}=3.17$	$t=-9.88$ $p<.001$ $d=1.40$ $BF_{10}=3.03x10^{19}$	$t=5.83$ $p<.001$ $d=0.61$ $BF_{10}=6.69x10^{3}$	$t=-4.36$ $p<.001$ $d=0.60$ $BF_{10}=1.12x10^{2}$	$t=-0.94$ $p=0.36$ $d=0.10$ $BF_{10}=0.34$
Non-Verbal Index	$t=0.41$ $p=0.70$ $d=0.05$ $BF_{10}=0.30$	$t=-8.13$ $p=<.001$ $d=0.96$ $BF_{10}=2.89x10^{10}$	$t=-10.44$ $p<.001$ $d=0.94$ $BF_{10}=2.89x10^{7}$			

Considering the within-subject comparisons, the *Verbal Profile* group had significantly higher scores in the Verbal Index (M=55.80) than in the Non-Verbal Index (M=41.11); vice versa, the *Non-Verbal*

Profile group scored significantly higher in the Non-Verbal Index (M=40.11) than in the Verbal Index (M=29.36); and for the *Homogeneous Profile* group there was no significant difference between the Verbal and Non-Verbal Indexes (M=63.44 and M=63.06, respectively).

The between-subjects comparisons showed that: the *Verbal Profile* group scored significantly higher than the *Non-Verbal Profile* group in the Verbal Index (M=55.80 and M=29.36, respectively); the *Non-Verbal Profile* group scored significantly lower than the *Homogeneous Profile* group in both the Verbal Index (M=63.44 and M=29.36, respectively) and the Non-Verbal Index (M=63.06 and M=40.11, respectively); and the *Homogeneous Profile* group scored higher than the *Verbal Profile* group in the Non-Verbal Index (M=63.06 and M=41.11, respectively).

Figure 4.2



Comparison between clusters - WPPSI subtests

The second repeated-measures ANOVA was run to examine the profiles by single subtest. The results are given in Tables 4.5 and 4.6, and graphically represented in Figure 4.3.

There was an effect of Cluster ($F(2,69)=90.03$, $p<.001$, $\eta_p^2=0.72$, $BF_{10}=1.68x10^{17}$), and subsequent post-hoc analyses showed that the *Homogeneous Profile* group scored higher than the *Verbal Profile* group ($t=7.64$, $p<.001$, $d=0.75$, $BF_{10}=1.95x10^{14}$) or the *Non-Verbal Profile* group ($t=15.44$, $p<.001$, $d=1.58$, $BF_{10}=8.87x10^{32}$). The *Verbal Profile* group scored higher than the *Non-Verbal Profile* group ($t=9.02$, $p<.001$, $d=0.95$, $BF_{10}=9.74x10^{9}$). There was no main effect of Subtest. A Cluster x Subtest

interaction emerged ($F(8,276)=9.58$, $p<.001$, $\eta_p^2=0.21$, $BF_{10}=1.53x10^9$), so post-hoc analyses were run (see Table 4.5 for between-subjects comparisons, and Table 4.6 for within-subject comparisons). Using Bonferroni's correction, we adjusted the alpha levels to .016 (i.e., .05/3) for comparisons between groups, and to 0.005 (i.e., .05/10) for comparisons between subtests within the three groups.

Table 4.5: Post-hoc analyses, Subtest x Index – between-subjects comparison

	Between-subjects Comparison		
	Verbal Profile vs Non-Verbal Profile	Verbal Profile vs Homogeneous Profile	Non-Verbal Profile vs Homogeneous Profile
Verbal Index			
Receptive Vocabulary	$t=5.99$ $p<.001$ $d=0.73$ $BF_{10}=3.70x10^4$	$t=-1.48$ $p=0.15$ $d=0.21$ $BF_{10}=0.73$	$t=-6.45$ $p<.001$ $d=0.88$ $BF_{10}=1.16x10^5$
Picture Naming	$t=8.11$ $p<.001$ $d=0.93$ $BF_{10}=9.35x10^7$	$t=-2.10$ $p=0.04$ $d=0.24$ $BF_{10}=1.80$	$t=-9.04$ $p<.001$ $d=1.07$ $BF_{10}=2.22x10^8$
Information	$t=7.01$ $p<.001$ $d=0.91$ $BF_{10}=1.82x10^6$	$t=-1.84$ $p=0.07$ $d=0.25$ $BF_{10}=1.20$	$t=-7.83$ $p<.001$ $d=1.07$ $BF_{10}=6.53\ x10^6$
Non-Verbal Index			
Block Design	$t=1.46$ $p=0.15$ $d=0.18$ $BF_{10}=0.69$	$t=-5.95$ $p<.001$ $d=0.68$ $BF_{10}=2.29x10^4$	$t=-6.54$ $p<.001$ $d=0.81$ $BF_{10}=1.18x10^5$
Object Assembly	$t=-1.50$ $p=0.14$ $d=0.13$ $BF_{10}=0.71$	$t=-9.25$ $p<.001$ $d=0.72$ $BF_{10}=9.60\ x10^8$	$t=-7.10$ $p<.001$ $d=0.56$ $BF_{10}=6.98x105$

Between-subjects comparisons showed that the *Verbal Profile* group scored higher than the *Non-Verbal Profile* group in all the subtests contributing to the Verbal Index. No differences emerged for the Non-Verbal Index subtests. The *Verbal Profile* group had lower scores than the *Homogeneous Profile* group in all the Non-Verbal Index subtests, while the *Non-Verbal Profile* group scored lower than the *Homogeneous Profile* group in the subtests contributing to both indexes.

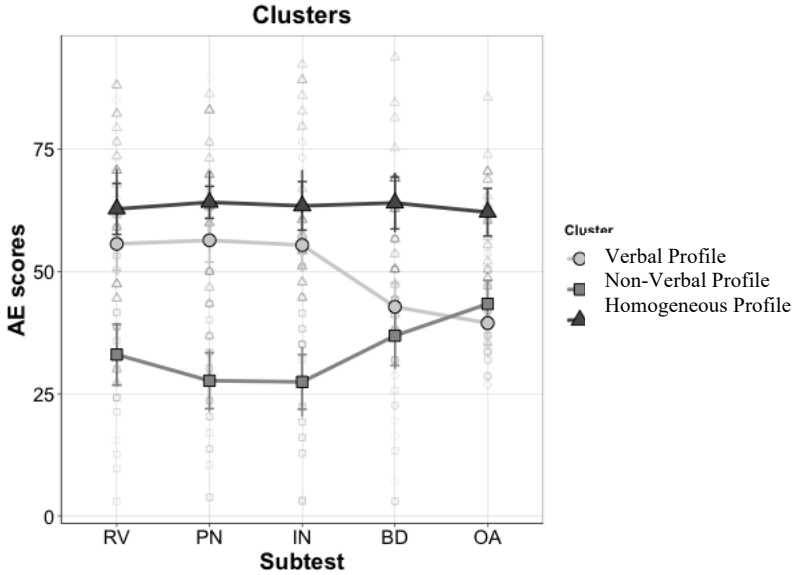
Table 4.6: Post-hoc analyses, Subtest x Index – within-subject comparisons

		Within-subject Comparison		
		Verbal Profile	Non-Verbal Profile	Homogeneous Profile
Receptive Vocabulary	Picture Naming	t=-0.50 p=0.62 d=0.06 BF_{10}=0.22	t=1.11 p=0.28 d=0.14 BF_{10}=0.39	t=-0.77 p=0.45 d=0.08 BF_{10}=0.30
	Information	t=-0.36 p=0.72 d=0.05 BF_{10}=0.21	t=0.99 p=0.33 d=0.13 BF_{10}=0.36	t=-0.78 p=0.44 d=0.08 BF_{10}=0.30
	Block Design	t=2.48 p=0.02 d=0.36 BF_{10}=2.60	t=-1.76 p=0.09 d=0.25 BF_{10}=0.83	t=-1.36 p=0.19 d=0.16 BF_{10}=0.51
	Object Assembly	t=4.32 p<.001 d=0.48 BF_{10}=1.56x10^2	t =-3.62 p=0.001 d =0.45 BF_{10}=23.74	t=-0.81 p=0.43 d=0.10 BF_{10}=0.30
Picture Naming	Information	t=0.10 p=0.92 d=0.01 BF_{10}=0.20	t =-0.13 p =0.90 d =0.01 BF_{10}=0.22	t=0.005 p=1.00 d=0.001 BF_{10}=0.23
	Block Design	t=3.59 p=0.001 d=0.42 BF_{10}=27.41	t=-2.55 p=0.02 d=0.39 BF_{10}=2.97	t=-1.03 p=0.31 d=0.08 BF_{10}=0.36
	Object Assembly	t=4.52 p<.001 d=0.54 BF_{10}=2.55x10^2	t =-5.39 p <.001 d =0.60 BF_{10}=9.96x10^2	t=-0.23 p=0.82 d=0.02 BF_{10}=0.24
Information	Block Design	t=3.26 p=0.003 d=0.41 BF_{10}=13.19	t=-2.82 p=0.01 d=0.39 BF_{10}=4.89	t=-0.61 p=0.55 d=0.06 BF_{10}=0.27
	Object Assembly	t=4.79 p<.001 d=0.53 BF_{10}=4.97x10^2	t=-4.53 p<.001 d=1.46 BF_{10}=1.61x10^2	t=-0.21 p=0.83 d=0.02 BF_{10}=0.23
Block Design	Object Assembly	t=1.17 p=0.25 d=0.11 BF_{10}=0.36	t=-2.24 p=0.04 d=0.21 BF_{10}=1.73	t=0.59 p=0.56 d=0.06 BF_{10}=0.27

In the within-subject comparisons, the *Verbal Profile* group scored lower on Object Assembly than in any of the other Verbal Index subtests, and lower on Block Design than on Picture Naming or Information. The *Non-Verbal Profile* group scored higher on Object Assembly than on any of the

other Verbal Index subtests. The *Homogeneous Profile* group showed no significant differences between the subtests.

Figure 4.3



Note: RV=Receptive Vocabulary, PN= Picture Naming, IN= Information, BD= Block Design, OA=Object Assembly.

4.4.3 The role of medical problems and mothers' education

Considering medical problems, the percentages of individuals with heart problems, a history of heart surgery and OSA are given in Table 4.7.

Table 4.7: Prevalence of medical conditions in each group

	Verbal (N=29)	Non-Verbal (N=22)	Homogeneous (N=21)	Whole sample N
Heart problems % yes (n)	37% (15)	30% (12)	32% (13)	40
Prior heart surgery % yes (n)	30% (6)	40% (8)	30% (6)	20
OSA % yes (n)	29% (5)	29% (5)	42% (7)	17

The chi-squared test revealed no associations between any of these medical conditions and group ($p<.05$).

A chi-squared test exploring the association between parents' education levels and group revealed no association between parents' education level and the groups (Table 4.8).

Table 4.8: Prevalence of parents having an education level higher than high school

	Verbal	Non-Verbal	Homogeneous	Whole group N
Mothers' education > high school % (n)	43 (14)	27 (9)	30 (10)	33
Fathers' education > high school % (n)	42 (11)	27 (7)	31 (8)	26

4.4.4 The role of developmental milestones

As for the developmental milestones, descriptive statistics for each group are given in Table 4.9, with the results of the ANOVAs comparing the three groups on each milestone.

Table 4.9: Descriptive statistics for age (in months) when developmental milestones were reached, and results of the comparisons between the groups

Group	Verbal	Non-Verbal	Homogeneous			
Sitting				F	p	η_p^2
n	26	20	18			
M (DS) [min-max]	8.83 (2.80) [5.5-14]	12.38 (11.74) [6-60]	8.94 (2.61) [5-13]	1.75	0.18	0.05
Babbling						
n	24	20	16			
M (DS) [min-max]	15.96 (6.12) [6-30]	21.25 (16.62) [5-78]	11.03 (3.55) [6-20]	4.22	0.02	0.13
Walking						
n	27	22	21			
M (DS) [min-max]	24.11 (5.54) [13-36]	27.41 (13.40) [12-72]	23.01 (5.01) [14-36]	1.48	0.24	0.04
First words						
n	26	22	21			
M (DS) [min-max]	27.54 (16.72) [12-96]	31.36 (13.85) [7-66]	24.71 (11.46) [10-60]	1.16	0.32	0.03

The descriptive statistics show that the *Non-Verbal Profile* group reached each milestone later than the other two groups, although the difference was only significant for babbling ($F(2,57)=4.22$, $p=0.02$, $\eta_p^2=0.13$), where the *Non-Verbal Profile* group reached this milestone later than the *Homogeneous Profile* group ($t=2.89$, $p=0.02$, $d=0.81$). All milestones were then correlated with the total WPPSI

score: sitting, babbling, walking, and first words correlated negatively and moderately with the global score in the *Non-Verbal Profile* group. All the correlations are given in Table 4.10.

Table 4.10: Correlations between developmental milestones and WPPSI global score in each group

	Verbal	Non-Verbal	Homogeneous
Sitting	0.028	-0.652**	0.035
Babbling	-0.151	-0.675**	-0.233
Walking	-0.222	-0.572*	0.060
First words	-0.242	-0.385	-0.108

Note: ***<.001, **<.01, *<.05

4.5 Discussion

This study explored the cognitive profile of DS, focusing on clarifying its interindividual variability. Looking at the cognitive profile of this sample as a whole suggested a homogeneous picture, with no differences between participants' verbal and non-verbal abilities. This differs somewhat from the "classical" cognitive profile hitherto described in individuals with DS, according to which they have relatively stronger non-verbal than verbal skills. The profile of this sample was not only homogeneous in terms of their verbal and non-verbal skills, but also when subtests were considered separately. It is noteworthy that participants' expressive and receptive vocabulary (measured with the Picture Naming and Receptive Vocabulary tasks, respectively) did not differ, in contrast with previous reports (e.g., Ypsilanti et al., 2005).

That said, a marked interindividual variability emerged within the present sample as a whole, revealing three subgroups of much the same size with different cognitive profiles. In fact, only one group of 21 participants showed similar verbal and non-verbal skills (the *Homogeneous Profile* group), and obtained higher global cognitive scores than the other two subgroups. A second group of 22 participants showed the classical profile (the *Non-verbal Profile* group), with lower scores in the verbal than in the non-verbal domain. This group of participants showed the lowest cognitive level.

A third group of 29 children (the *Verbal Profile* group) obtained better results in the verbal domain (with scores as high as in the *Homogeneous Profile* group) than in the non-verbal one (their scores being similar to those of the *Non-Verbal Profile* group). These results explain the marked interindividual variability identified both within groups and between different studies, suggesting that it would be better to assume that individuals with DS can express not just one, but multiple different cognitive profiles. One of the three subgroups (the *Non-Verbal Profile* group) had the features of the classical profile widely described in the literature, with more difficulties in the verbal domain and a better performance in non-verbal processing. Some previous studies had also found evidence of a profile characterized by better verbal than nonverbal scores (e.g., Pezzuti et al., Sabat, 2020), however, while others had reported finding similar scores in the two domains (e.g., Cebula, 2017). Further analyses conducted at subtest level generally indicated homogeneity between subtests referring to the same index.

Findings from the present study tend to be in line with the report from Tsao and Kindelberg (2006) on the only study that previously explored the possible existence of different cognitive profiles in DS. Focusing on childhood, they identified four profiles, three of which correspond to those emerging in the present study. Their group with similar scores for verbal and non-verbal processing coincides with the *Homogeneous Profile* group, with one exception: whereas the scores obtained in the subtests of the two indexes were much the same in our group, they saw a drastically worse score in one subtest (Classification, which was part of the Non-Verbal Index). Their second group scored better in non-verbal subtests, like the *Non-Verbal Profile* group. Their third group obtained significantly higher scores in verbal subtests, like the *Verbal Profile* group. No cluster corresponding to their fourth group was found, which featured verbal scores close to the mean, and lower than non-verbal scores. This difference might be due to the tasks used to assess verbal and non-verbal skills, as some were similar (e.g., their "Vocabulary" task corresponded to our "Picture Naming" task), while others differed (e.g., none of the tasks we administered resembled their "Social comprehension" task). Another possible

explanation would concern environmental variables that might have shaped participants' cognitive profiles differently.

Three variables potentially influencing the sample's different cognitive profiles were examined. Medical conditions showed no association with the different profiles, although CHDs are known to alter blood oxygenation, which affects brain development (Baburamani et al., 2019), and OSA can impair consolidation processes during sleep (Edgin et al., 2015). Parents' education levels were also unassociated with the different profiles, although this variable is known to modulate the cognitive level of individuals with DS (Evans & Uljarevic, 2018; Price et al., 2007). Regarding the third variable considered in this study, age on reaching developmental milestones, the *Non-Verbal Profile* group reached each milestone (and babbling in particular) at an older age than the other two groups, and it was the only group in which global cognitive scores correlated with age on reaching milestones. Since the *Non-Verbal Profile* group had the "classical profile" and the lowest global task performance scores, and reached developmental milestones later in life, it might be surmised that this was the group in which individual factors (e.g., at the genetic, cellular and neural level) had the most impact on the individuals' cognitive profile. Alternatively, the higher scores obtained in the verbal domain by the *Verbal Profile* group or in both domains by the *Homogeneous Profile* group might be more related to environmemntal factors, such as an enriched home environment, early therapeutic intervention and/or other environmental variables that intervene during development. It has been widely suggested that the type of environment influences children's cognitive development, with a "poor" environment leading to a "loss" of several IQ points, while a "rich", stimulating environment and appropriate intervention can raise a child's IQ score (e.g., Vianello, 2012). These are mere speculations, of course, that would need to be tested in future studies.

None of the above-mentioned factors are independent of each other; they interact continuously, contributing to the variability seen in individuals with DS. From early infancy, individual and environmental factors interact and influence a child's development in subtle ways (e.g., Fidler et al., 2019). Early experiences are thought to initiate "developmental cascades" (Masten & Cicchetti, 2010)

that, though difficult to monitor, shape the way infants respond to their environment. It is not that genes create an individual, and then this individual is influenced by the environment; there are multi-directional interactions constantly underway between the environment, the genetic material, and the individual (Masten & Cicchetti, 2010). Taking a multi-level approach and considering the variability at each level, we are therefore bound to find many factors influencing the DS phenotype.

4.6. Future directions and conclusions

While the present study contributes important information on the cognitive heterogeneity of children and adolescents with DS, it has some limitations that should be borne in mind. First, as is generally the case in neurogenetic syndrome research, the sample size is smaller than would be ideal for cluster analysis. It would be useful to replicate our findings in a larger sample, and to consider more variables (e.g., the quality of therapies, the characteristics of home environments, the socio-economic status) to enable an external validation of the clusters. In addition, future studies might aim to clarify which factors have a major role in shaping the cognitive variability involved in this syndrome.

Finally, although the present study was only exploratory, these findings induce to recommend taking the possibility of different cognitive profiles in DS into account in order to propose targeted interventions for children and their families. Such interventions need to be informed by an understanding of the emerging profile of a given individual with DS, enabling practitioners to focus on their strengths and thereby counter their weaknesses.

CHAPTER 5
GENERAL DISCUSSION

Since delving into the literature has shown that individuals with DS can vary considerably in terms of their development, the aim of this dissertation was to shed more light on this issue. The variability seen in DS was examined from different angles, in terms of developmental milestones, cognitive profiles, and other potentially-associated variables. The main findings are presented below.

5.1 Main findings

Pointing, waving "bye bye", understanding "no", crawling and taking the first steps are just some of the developmental milestones that children acquire in the first years of life. Their acquisition follows a predictable order and timing in TD infants and children, whose later developmental skills build on those already learned. The situation is slightly different for individuals with DS, who generally reach developmental milestones in the same order as their TD peers, but at later chronological ages (Tudella et al. 2011). Considering that the timing and onset of motor milestones have been a more fruitful area of study in DS compared to the cognitive and communication domains (Tudella et al. 2011; Winders et al., 2019), and that it is important to compare the development of an individual child with DS with that of his or her counterparts who also have DS, Study I (Chapter 2) was conducted to obtain foundational information on when infants with DS acquire cognitive and communication skills. The results indicate that the skills observable in the infants with DS in the very first months of life were more similar to those seen in their TD counterparts, while the discrepancy between them increased as they grow older. In terms of cognition, the earliest skills mastered (by 4 months old) included shifting attention, preferring a novel object, and exploring. Somewhat more pronounced delays were seen for tasks that involved action planning (persistent reaching, pulling a cloth to obtain an object) and mental representation of objects (searching for missing objects, finding a hidden object). Comparing patterns of development in DS with those of TD children revealed modest delays in the acquisition of early cognitive skills for most infants with DS, while their difficulties became greater

as the motor and representational demands increased. Moving from cognition to receptive communication, infants with DS showed early competences (responding to a person's voice), while the acquisition of more demanding skills (responding to their name and recognizing two familiar words) appeared to be mildly delayed. When more regulatory skills were required (responding to "No, no" and attending a play routine), their difficulties became more apparent. As for expressive communication, infants with DS were producing vocalizations that expressed at least one mood and social smiling by 4-6 months old, but their delay in acquiring more demanding skills became gradually more evident.

The order in which developmental milestones were acquired by the sample of infants with DS considered here seemed to follow that of the BSID-III. In other words, it was much the same as is generally seen in TD infants. This would seem to support the hypothesis of a universal sequence of development (Zigler & Hodapp, 1991), and confirm that milestones are reached by infants with DS in the same order as in TD children. The former master these skills later in life, however, and the more the skills become demanding, the greater the delay in children with DS, in both the cognitive and the communication domains. Their slower rate of development could derive from genetic, neurodevelopmental and other biomedical influences (e.g., premature birth, sleep dysregulation), and also from environmental factors, such as any interventions to support children with DS or the responsiveness of their caregivers (Karmiloff-Smith et al. 2016; Pelleri et al. 2016; Van Hooste & Maes 2003). Some of the factors known to have a potential influence on a child's development (i.e., prematurity, heart defects, heart surgery, and significant illness) were considered in Study I. It emerged that prematurity and heart defects were not only the most prevalent factors in the group as a whole, but also the most prevalent among the infants failing to master a given skill (around 45%). Notably, on comparing infants with no such issues with those born prematurely or with a heart defect, the latter showed a wider range of times to reach milestones than the former, which would confirm the impact of these variables on their development. That said, the range of times was wide among all the infants, with or without such issues, so it is likely that the timing of milestone acquisition varies

considerably anyway, possibly exacerbated by prematurity or heart defects, for instance. Previous studies on DS also reported a wide range of cognitive scores (e.g., Dykens et al., 2000; Zampini & D'Odorico, 2009), as well as higher standard deviations in groups with DS than in TD samples (e.g., Vicari et al., 2006; Dykens et al., 2000; Zampini & D'Odorico, 2009). Such heterogeneity has been observed not only in terms of scores, but also in developmental and cognitive profiles, which were explored in Studies II (Chapter 3) and III (Chapter 4). In fact, individuals with DS are generally thought most likely to have more pronounced language and verbal memory impairments, and relatively stronger non-verbal abilities and implicit memory skills (Grieco et al., 2015; Silverman; 2007), but diving into the literature reveals a different picture. At present, few studies have explored heterogeneity in profiles of developmental skill acquisition among infants with DS. Among the few examinations of this topic is the finding that infants with DS vary in their exploratory behaviour, which is associated with different cognitive abilities: those spending more time exploring objects had higher developmental scores (Fidler et al., 2019). The presence of different developmental profiles in infants with DS was confirmed in Study II (Chapter 3). Two groups emerged, one with higher standard scores and a more homogeneous performance on cognitive, communication and motor scales, the other with lower standard scores and a more heterogeneous profile. CA was emerged to be different in the two groups (and possibly capable of explaining) as the group with lower scores was older than the group with higher scores. This is in line with the literature on DS reporting that standard cognitive scores decrease with increasing age (Vianello, 2006). In addition, heart surgery, significant illness and having received physiotherapy were found to influence these profiles, and to be associated with lower developmental scores. This might be an effect of age, however, as older infants were included in the group considered.

Moving from infancy to childhood, there have been more studies on the variable cognitive picture seen in DS. Tsao and Kindelberg (2009) explored the topic of cognitive profiles using a clustering procedure. This approach enabled them to identify four cognitive profiles: in one, individuals obtained similar scores on verbal and non-verbal tests; in another, they performed poorly in all

subtests, and especially in verbal ones; in a third, they scored significantly better in verbal subtests; and in a fourth, they scored higher in non-verbal subtests. A similar pattern emerged in other studies, suggesting three cognitive profiles: one with greater non-verbal than verbal abilities (e.g., Breslin et al. 2014; Lanfranchi et al., 2009; Duarte et al., 2011), one with higher scores for verbal than for non-verbal processing (e.g., Pezzuti et al., 2018; Evans and Ulijarevic, 2018, Sabat et al., 2020), and with homogeneous scores in the two domains (e.g., Cebula et al., 2017). No direct comparisons were drawn in most cases, however, as this was not the aim of the studies. Study III (Chapter 4) thus explored the cognitive profiles of a group of children and adolescents with DS, focusing on whether inter-individual variability in the sample could be classified in terms of subgroups with different cognitive profiles. A homogeneous picture emerged in the group as a whole, with no differences between participants' verbal and non-verbal abilities. There were three subgroups with different cognitive profiles, however. One had much the same verbal and non-verbal skills, and obtained higher overall AE cognitive scores than the other two subgroups. A second subgroup had the classical profile, with lower scores in the verbal than in the non-verbal domain, and this subgroup scored lowest on cognitive tasks. A third subgroup obtained better results in the verbal than in the non-verbal domain. These findings suggest that it would be wise to assume that individuals with DS can express not just one, but several different cognitive profiles. In addition to contributing to what we know about DS, the marked inter-individual variability that emerged in Study III is also of interest in the clinical setting. This aspect is discussed below. It is noteworthy that, when developmental milestones were considered (i.e., sitting, babbling, walking and first word pronunciation), the subgroup with the "classical profile", and the lowest global cognitive scores, reached these milestones later in life, presumably because individual factors (at the genetic, cellular and neural level) had the greatest impact on these individuals' cognitive profiles. Alternatively, the other two subgroups' higher scores might be due to an enriched home environment and/or early therapeutic interventions. It has often been suggested that the type of home environment influences children's cognitive development, with a "poor" environment leading to a "loss" of several IQ points, while a "rich", stimulating environment

and appropriate intervention can raise a child's IQ (e.g., Vianello, 2012). Unlike the case of Study II, the three subgroups in Study III did not differ in terms of CA, so also other variables were at work in influencing their development. CA seems to play a major role in early development, while its effect is modulated by other factors as the child grows older.

To summarize, Studies I, II and III showed that there is variability in DS that is apparent from the timing of individuals' acquisition of developmental milestones and the existence of different developmental/cognitive profiles. This variability emerges early in life and, although CA initially seems to have an important role, more individual and family factors might influence a child's later development.

5.2 Study limitations and suggestion for future research

While the findings of these studies provide foundational information regarding the acquisition of cognitive and communication skills during infancy in DS, and contribute important information on the developmental and cognitive heterogeneity of infants, children and adolescents with DS, there are some limitations that should be borne in mind.

The data reported are cross-sectional, not longitudinal, which makes it impossible to obtain a more detailed picture of the precise timing of each infant's skill acquisition or their developmental patterns over time. Future work should track their development longitudinally to obtain a more accurate account of the developmental trajectories involved. The data also come from a sample of modest size, so the findings should be interpreted with caution. A larger sample size in future work would be recommended. Studies II and III adopted a clustering approach, and the results obtained with such an exploratory method need to be confirmed by further studies investigating associated variables.

5.3 Clinical implications

Setting cognitive and communication milestones helps clinicians gain a general idea of the developmental progress of infants with DS as a group. Information of this nature enables infants with

DS to be compared with their peers with the same syndrome, helps to identify cases of advanced, age-appropriate or delayed development, and facilitates the early detection of any risk of concomitant conditions, prompting early referrals for early targeted intervention. Delineating such milestones in DS may also make it easier to detect early risk factors for a child's development. In fact, some of the BSID-III items considered in Study I are potentially informative indicators of the risk of specific conditions, such as ASD and ADHD. Examples are: "Responds to a person's voice" and "Responds to name", which map on to social responsiveness – a trait known to be impaired in ASD (Nadig et al., 2007); or "Attends to others' play routine", "Responds to request for social routine", "Participates in play routine", "Directs attention of other", and "Initiates play interaction", which are useful for assessing a child's intention to play and interact. Similarly, "Social vocalizing or laughing" maps on to the presence of social smiling. In the case of ADHD, the items "Shifts attention", "Explores objects" and "Responds to No, no" can be used as indicators. In other words, the BSID-III items considered in this study could serve as early indicators of the risk of ASD and ADHD when a child with DS shows a delay in acquiring these skills by comparison with their DS peers. For instance, there are studies showing that toddlers with ASD experience significantly greater delays in reaching developmental milestones than other atypically-developing toddlers. The same reasoning could be applied to the DS population: if a child with DS is slower to reach some milestones than their peers, this may indicate a risk of ASD. Early diagnosis is a prerequisite for early intervention, and early intervention creates an important window of opportunity for influencing developmental trajectories in neurogenetic disorders.

As Studies II and III pointed to different developmental and cognitive profiles in DS, work with these individuals needs to be tailored to a given child's characteristics. If clinicians are aware of the varied picture encountered in DS, they might have a better idea of what to expect, and be more precise in their interventions, using strategies appropriate for a given child. Knowing each child's strengths and weaknesses tells us not only where work is needed, but also what strategies to use. For example, if a child does relatively well in verbal processing, then the verbal channel can be used to strengthen their

other skills, whereas a child having difficulty with receptive and expressive language would benefit more from using non-verbal strategies. It is important to intervene as early as possible in a child's development in order to work on a more plastic brain and succeed in modifying their developmental trajectories. The efficacy of any intervention depends partly on its quantity and duration, and even more on the quality of the educational environment. Good-quality and personalized programs are the best choice, delivered in a cooperative environment where different figures (parents, teachers, other professionals) join forces.

Alongside the heterogeneity identified in DS, Studies II and III also provide some other information important to the clinical practitioner: as the children grow older, more environmental factors (i.e., a "poor" and a "rich" environment) might play a part in determining their variability. The "Wilson effect" (Bouchard, 2013) states that environmental influences on cognition are more pronounced when individuals are younger, and that genetic effects play a larger effect later in life. This effect was drawn considering studies on TD individuals, however. It is important to bear this in mind because: first, individuals with DS might be more exposed to environmental stimuli (e.g., interventions); secondly, considering that environmental influence seems to count less from the age of 10 years old for TD individuals, their developmental level is not comparable with that of individuals with DS. Therefore, although genes play a role on development, the effect of the environment is important as well because it underscores how a "rich" environment positively affects the individual's development. Creating a rich environment does not mean providing lots of stimuli; it means providing the right amount of stimulation, working on the proximal learning zone (Vygotskij, 1978). In other words, it is important to establish a few objectives for each child, which should regard skills in the proximal learning zone. It is only after these skills have been acquired that new goals can be set.

To conclude, investigating variability in individuals with DS is a highly complex issue because many factors play a part and interact, continuously shaping a child's development. It is consequently difficult to establish the precise reasons for this variability, though there is room for more research to replicate the findings of the present studies and shed more light on the important variables. The

present dissertation was an effort to raise and clarify some aspects, but other questions remain to be answered.

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