An analytical approach to visuospatial cognition: What can neurodevelopmental disorders tell us about developmental pathways?

Annette as a mentor, a collaborator and a friend

I first met Annette in October 1998 when I was three weeks into my PhD, at a national convention held by the Williams Syndrome Foundation, UK. Having spent those first three weeks reading a lot of her papers, I was very much in awe of her. I had several questions to ask her, and whilst I was daunted to be introduced to Annette, I was delighted that she gave her time so generously to someone at such an early stage in their career. I was equally awe-struck, when she spent the evening dancing like the best of us at the Williams syndrome disco. On that one day, I witnessed Annette's generosity of character and her enthusiasm for fun, which I was to see many times over the subsequent years.

Beyond my PhD I began to collaborate with Annette. She helped me to get that coveted first grant, and agreed to give a keynote speech at the first conference that I organised. My most cherished memories are of the year that we spent co-editing a book together (Farran & Karmiloff-Smith, 2012). The book began life as a book on Williams syndrome (WS), with Annette as one of the contributors. Annette (rightly!) pointed out that I'd simply gathered my friends together to write chapters, and that it needed a theoretical focus. I asked Annette to come on board as a co-editor (she later told me that she had broken her vow to never write an edited book). Annette's suggestions were invaluable. We used Williams syndrome as a case study to demonstrate neuroconstructivist principles, a theoretical focus which gave the book a broader purpose. The intense collaboration was absolutely enthralling. I witnessed Annette's brilliance in her ideas, and the sheer speed at which she could write fabulously insightful pieces of work. The book was 'born' in the same month as my first daughter. Annette asked me to weigh the book, and she put together a slide for her talks announcing the birth of both book and baby, along with their birthweights and names. She was not only an immensely intelligent woman, but she had a brilliant sense of humour! Annette may no longer be with us, but she still guides us in many ways. Whilst those of us who were lucky to have known Annette, strive to mentor like her, and can only hope to achieve Annette's sense of style, this book is about her impact on the academic world. With this in mind, in the sections below, I use quotes from Annette's papers to illustrate

neuroconstructivist principles predominantly from within my domain of expertise, visuospatial cognition.

The neuroconstructivist approach explains development as a dynamic process which occurs within the context of genetic, neural, biological and environmental constraints on the developing brain. In this way, domain specificity emerges over developmental time through repeated pairings of domain-relevant brain areas (i.e., areas best suited to processing certain kinds of input) to specific sensory input, via interactions with other multilevel processes (genetic, environmental). Annette first applied neuroconstructivist principles to neurodevelopmental disorders in her seminal paper, "Development itself is the key to understanding developmental disorders" (Karmiloff-Smith, 1998). Among other principles, she explained how genetic differences are most likely to impact low-level cognitive outcomes, rather than specific domains. Syndrome-specific cognitive phenotypes, therefore, result from the cascading effects of this genetic impact (among other inputs) across different domains as development occurs. This importance placed on the developmental process is a central tenet to the principles listed below.

Visuospatial Cognition

Visuospatial cognition refers to the ability to perceive and interact with our visual world. For example, being able to individuate objects, to perceive the location and shape of objects and to understand the relationships between them. It provides us with skills such as the ability to read a map, to search for an object in a visual array (e.g., finding your coat on a coat rack), and to draw and interpret diagrams and pictures. Visuospatial ability also applies to large scale knowledge. That is, we use visuospatial ability to navigate to work and back, to reorient when we get lost and to know when to get off the bus. Here I will provide examples from my own data and others, of neuroconstructivism within the domain of visuospatial cognition, each example inspired by quotes from Annette's papers. To pay homage to much of the work that Annette and I collaborated on, I will predominantly use examples from individuals with WS.

Static vs. Dynamic Approaches to Neurodevelopmental Disorders

"…the roots of development are often critical for understanding the dynamic trajectory"

(Karmiloff-Smith, 2009).

Early studies of neurodevelopmental disorders discussed the brain of individuals with neurodevelopmental disorders as having parts intact and parts impaired. This assumes that brain-behaviour associations are pre-determined and does not take into account input from genetic, developmental or environmental factors, i.e., it ignores neuroplasticity. Annette (e.g., Karmiloff-Smith, 2009) highlighted that the brain is not a static unchanging structure, but that it is self-organising and developmentally responsive to interactions across multiple levels. For example, children exposed to more parental spatial language, develop stronger spatial language and better spatial abilities (Pruden, Levine & Huttenlocher, 2011).

Annette was keen to emphasise that precursors or antecedents to later development provide a window to understanding interacting developmental processes. In her research she demonstrated that the deficit in number processing in WS, relates to atypical early attentional processes (Karmiloff-Smith et al., 2012), and that in WS, in contrast to typical development (Bates et al., 1979), joint attention is not a precursor to the emergence of first words (Laing et al., 2002).

A current example of the dynamic approach to understanding development, is the strong interest in determining early markers of later impairment which is being investigated via prospective longitudinal studies of infants at risk of a behaviourally defined disorder such as Autism (see Jones, Gliga, Bedford, Charman & Johnson, 2014). These studies have discovered, for example, that early deficits in attention disengagement and an atypical neural response to shifts in eye gaze are associated with a later diagnosis of Autism (Elsabbagh et al., 2013; 2013; also see Bedford et al., 2017). We are also currently experiencing an explosion of research into early motor behaviour as a predictor of later development. A longitudinal association between early motor abilities and later expressive language has been documented in both typical and atypical development (Iverson, 2010; Leonard & Hill, 2015), whilst atypical motor development at 6 months is another early predictor of later Autism status (LeBarton & Landa, 2019; also see Bedford, Pickles & Lord. 2016). This cascading influence of early motor development extends beyond the language domain. Clearfield (2004), for example, report that,

in typical development, the onset of crawling and walking marks step changes in the development of spatial cognition (see Newcombe, 2019 for further examples)

The above "roots of development" enable a better understanding of typical development, as well as the developmental trajectory that leads to the emergence of a specific phenotype. With reference to the relationship between motor and language skills, for example, it is considered that this reflects a developmental pathway in which a growth in motor skill increases children's ability to explore objects, which in turn supports their ability to learn about the properties of objects and to engage others in play and thus language experiences (LeBarton & Landa, 2019). Subtle differences in this early development, can have a cascading impact on later development, hence why poor motor development predicts disruption in later expressive language development. Relatedly, interventions that are targeted at these early markers, as opposed to the domain of impairment, have the potential to have downstream impact on phenotypic outcomes (e.g., Jones et al., 2017). Furthermore, for behaviourally defined disorders such as autism, these early markers provide an opportunity to detect risk of later diagnosis (Bedford et al., 2017).

In my lab, we are currently investigating whether the spatial deficit in WS has its origins, at least in part, in the impaired development of motor abilities in this group. This stems from knowledge of the association between motor and spatial development discussed above (Clearfield, 2004). Our initial investigations, which relied on retrospective reports of the emergence of motor milestones in WS, demonstrated that motor milestones were substantially delayed in WS, and that large-scale spatial abilities in adulthood were impaired in WS. These two deficits, however, did not show an association (Farran et al., 2018). Motor milestone measures are relatively course, and a long retrospective element can decrease the reliability of these measures; the next steps in this programme of research is to follow infants with WS longitudinally to prospectively document motor milestone achievement and motor quality, and to determine their impact on the development of spatial cognition. Annette often said that there wasn't enough research into infants with WS. She was a collaborator on the study above, and she would have been delighted to know that we're developing this research in this way. In view of the association between motor ability and expressive language, we also plan to determine the broader impact of early motor deficits in WS, such as the predictive relationship with later expressive

language. Given that joint attention (which, although predominantly social, has a motor element) is not predictive of the emergence of language in WS (Laing et al., 2002), it is possible that the relationship between motor and language domains is not fixed, but that language can develop via alternative developmental pathways. The extent to which alternative pathways are fully compensatory, however, has implications for intervention design.

The future of the dynamic approach to neurodevelopmental disorders.

Individual differences in cross-sectional data do not always reflect longitudinal developmental processes (Purser, Thomas, Farran, Karmiloff-Smith & Van Herwegen, 2019; although see Jarrold, Baddeley, Hewes & Philips, 2001), thus longitudinal data is important if we are to truly understand the dynamics of development. Over the next decade, longitudinal studies will reveal the importance of early sensory, attentional and motor development (as well as other factors) on later development. There are now many prospective longitudinal studies of children at risk of diagnosis of behaviourally defined disorders (examples from the Centre for Brain and Cognitive Development [CBCD], Birkbeck, where Annette worked are: The British Autism Study of Infant Siblings [BASIS]; and Studying Autism and ADHD Risks [STAARS]). These programmes enable us to understand the infant start-state and, vitally, to document the developmental processes which lead to the phenotypic characteristics of that disorder. However, there are few longitudinal studies of genetically diagnosed disorders. Paradoxically, in contrast to "at risk" groups, for genetic disorders a confirmatory diagnosis can be made before the behavioural phenotype fully emerges. Until recently, the rarity of genetically defined disorders has provided a stumbling block. The LonDownS consortium (https://www.ucl.ac.uk/london-down-syndrome-consortium/) is one of the first truly multi-level, developmental investigations into Down Syndrome (DS). Annette lead the infant strand of this research collaboration, and while she was not able to see the fruition of her work, this longitudinal cohort of infants and toddlers with DS, in concert with the other strands of the LonDownS consortium (an adult strand, genetics, cellular modelling and mouse modelling), really paves the way for understanding multi-level dynamic development in DS. It truly is a project which "takes development seriously" (Karmiloff-Smith, 1998).

Whilst large longitudinal data is expensive to generate, at a minimum as researchers, we should work collaboratively to agree common protocols of background or baseline tasks that will feature in all testing batteries across multiple labs. This would enable pooling of data across labs in a cost effective manner, and over time will generate longitudinal datasets. Indeed, in response to the lack of longitudinal research with individuals with WS, a number of researchers in the UK have formed the Williams Syndrome Development (WISDom) group. We have pooled together our data (including Annette's) from individuals with WS, across decades of research, with plans to collate and collect further data. Preliminary analyses have demonstrated that cross-sectional development of verbal and non-verbal ability does not necessarily mirror that observed longitudinally (Purser, Thomas, Farran, Karmiloff-Smith & Van Herwegen, 2019). This emphasises the impact of individual differences when working with cross-sectional data. Further research using this dataset will enable us to better understand the *longitudinal* cross-domain dynamics of development in WS. This will help to determine which cascading developmental trajectories observed in the typical population are fixed, and which aspects of development can emerge via alternative developmental pathways, akin to the example of joint attention and language above.

Cross-domain associations

"Do … systems start out prespecified in the infant brain, already dissociated into separate subsystems, or do these subsystems emerge over time through early cross-domain interactions as different brain circuits progressively specialized for different … functions?" (Karmiloff-Smith et al., 2012)

The brain is not modular at the infant start-state. Optimum development involves extensive interaction across domains. Many of the developmental cascades discussed in the section above are demonstrations of cross-domain interactions (e.g., cross-domain interactions between motor and language domains). For neurodevelopmental disorder populations, cross-domain interaction can also be influenced by their phenotypic cognitive profile. A relative strength in their cognitive profile can

be used to bootstrap an area of weakness, whilst a relative weakness can negatively impact the development of subdomains of an area of strength.

Individuals with WS demonstrate an uneven cognitive profile within which visuospatial cognition is poor relative to verbal abilities. In WS, whilst visuospatial cognition has scarcely been investigated in infancy (Farran, Brown, Cole, Houston-Price & Karmiloff-Smith, 2007), there is clear evidence of cross-domain developmental interactions between the visuospatial domain and other domains from data from child and adult participants. For example, for inhibition tasks, number tasks and working memory, stronger performance is observed in WS when a verbal strategy can be applied, than when the task is reliant on visuospatial processing (Atkinson et al., 2003; Ansari et al., 2003; Jarrold et al., 1999).

A well-documented cross-domain interaction in typical development is the ability to represent visual images verbally, which Bruner (1966) describes as a shift from an iconic to a symbolic representation which occurs at about 6 years. This is supported by the working memory literature; from a similar age, children begin to verbally rehears visual information (Baddeley et al., 1998). In my research we have shown that individuals with WS can employ a verbal coding strategy during simple spatial navigation tasks (Farran et al., 2010; 2012_a), in a manner akin to the verbal rehearsal of visuospatial information documented above. Whilst this does not reflect an atypical strategy, it demonstrates that spatial performance can be augmented in WS via compensation from verbal ability, a relative strength within the WS cognitive profile.

Within the domain of number, Ansari et al. (2003) measured the cardinality principle in children with WS. This principle refers to knowledge that the total number of objects in a set is the same as the last number in the counting sequence of those objects, and emerges at about 3 years in typically developing (TD) children (Wynn, 1990). Ansari et al. (2003) compared the performance of children with WS (aged 6-11 years) with that of TD children (aged 2-5 years) on two measures of cardinality. The two groups performed at the same level for both tasks, and showed similar progression with task difficulty (i.e., numbers 1 to 3 were easier than numbers 4 to 6). However, correlational analyses demonstrated an association between verbal ability and task performance for the WS group, but between visuospatial ability and task performance for the TD group. Thus, although the performance

of the two groups initially looked the same, by considering the contributions of verbal and visuospatial abilities it is possible to conjecture that the development of cardinality does not proceed along a typical developmental trajectory in WS. That is, in WS, poor visuospatial ability is compensated for by their comparatively stronger verbal abilities. Ansari et al. (2003) also point out that verbal abilities are not able to completely compensate; performance was below their verbal mental age. This suggests that visuospatial deficits (and possibly other constraints such as attention; Karmiloff-Smith et al., 2012) remain a constraint on performance because of the visuospatial demands of the task.

The developmental trajectory approach can also reveal cross-domain interactions (Thomas et al., 2009). This approach involves building task-specific cross-sectional developmental trajectories via regression analyses of the predictive power of potential pre-requisite mechanisms (e.g., spatial ability, verbal ability, attention, memory) against an outcome measure of interest. If development has proceeded in an atypical manner for the atypical group, developmental trajectory analysis might reveal the presence of a compensatory mechanism, or a limiting factor on development. We have used this approach to explore the contributing mechanisms to large-scale spatial navigation in DS and WS (e.g., Farran et al., 2012$_b$; Farran et al., 2015; Purser et al., 2014). Annette was always very enthusiastic about my navigation research. I think this was for two reasons. First, there is cross-species relevance - one of Annette's infamous studies, which often appeared on her slides, was her ball pool Morris water maze (a task that has been extensively used to study navigation in rodents), which she used with toddlers with WS and partial deletion patients. Second, due to the real-world application of navigation research. Annette took care to spend time with the families of the participants that she worked with, and provided advice and help to countless families (as many of us have continued to do so). Research with a direct application to the families, therefore, had strong appeal.

Using developmental trajectory analysis in our navigation research, we determined that the ability to learn a route from A to B (route knowledge; Siegal & White, 1975) in a virtual environment was related to non-verbal ability (as measured by the Ravens Coloured Progressive Matrices, Raven,

1993) for individuals with WS, individuals with DS and TD children, but that group differences were revealed with respect to input from attentional mechanisms and long-term memory (Purser et al., 2014). For the DS and WS groups, poorer inhibition was associated with making more route learning errors, whilst for the TD group, sustained attention was a better predictor of route learning ability. Furthermore, long-term memory was a strong contributor to route learning in the DS and TD groups, but not the WS group. Thus, whilst large-scale navigation is broadly considered as a spatial task, it is impacted by different attentional mechanisms in atypical development (in this case DS and WS), compared to typical development. This might relate to strengths and weaknesses for each group; for both DS and WS group, inhibition is weak, particularly so for WS (Carney et al., 2013). Thus, we deemed poor inhibition to be a limiting factor to the development of large-scale navigation in these groups. In contrast, for the TD group, the inhibition demands (e.g., inhibiting turning down an incorrect path, and inhibiting attending to non-unique landmarks such as streetlights) of the task did not challenge their ability to learn the route. These analyses, therefore, revealed important mechanistic cross-domain differences across syndromes in how a task is completed.

The future of cross-domain associations

Cross-domain interactions occur as part of typical and atypical developmental trajectories. Equally, task completion is influenced by an individual's strengths and weaknesses. Where a phenotypic cognitive profile is uneven, as in many groups with neurodevelopmental disorders, we have observed that tasks are completed in an atypical manner, by compensating for areas of weakness using areas of relative strengths. This is further evidence of the self-structuring nature of development. However, a current weakness in the majority of neurodevelopmental disorder research, are the small sample sizes. Thus, where the statistical techniques that are used with data from typical developing children now take a more mechanistic or process-based approach (i.e., they determine what the underlying processes are that drive performance in an outcome measure), this is not so easy in neurodevelopmental research. Because of the difficulty achieving sufficient power, much of the research with neurodevelopmental disorder groups relies on analyses of group means and group differences. Multiple regression and mediation analyses, as examples, enable one to determine the

relative contribution of a range of potential contributing mechanisms to performance and thus would pinpoint cross-domain interactions at a fine-grained level. One way to accomplish strong group numbers is to run multicentre studies. The EU-AIMS (https://www.eu-aims.eu/) and AIMS 2 TRIALS (https://www.aims-2-trials.eu/) studies of autism is are examples of this within neurodevelopmental disorder research.

Associations can be as informative as dissociations

"…researchers need to recall that similar behavioral outcomes may stem from very different cognitive/brain causes…" (Karmiloff-Smith, 2009).

The cross-domain interactions described above provide insight into the use of compensatory strategies in neurodevelopmental disorders. I advocate an analytical approach to understanding task performance. An understanding of why and how a particular level of performance is achieved can uncover dissociations, where performance might otherwise have been described as typical or simply delayed. Techniques such as eye-tracking, error analysis, and determining input from underlying mechanistic processes are examples of such an analytical approach. Jo Camp, in her PhD (Camp, 2013), employed the Tower of London task (TOL: Shallice, 1982) as a measure of planning ability with individuals with WS, individuals with Down syndrome and TD children. In this task, the participant is presented with three different coloured beads on three pegs of different heights. They are shown a goal state and asked to rearrange the beads one at a time to reach the goal configuration of beads. Camp (2013) demonstrated that despite similar overall TOL scores (a composite score comprised of: errors; rule violations; and number of moves made) across the groups, this was driven by different behaviour. The WS group produced more absolute errors than the TD group (this included perceptual errors and reaching the maximum number of twenty moves without reaching the solution). The increased number of perceptual errors is indicative of the limitations in WS in visuospatial perception. The DS group, in contrast, lost points by violating the rules of the task. Equally, whilst the TD and WS group demonstrated a relationship between TOL performance and planning ability, this was only evident for the easier trials in the DS group, suggesting a lack of

engagement with the task once it became difficult. This suggests that poor performance on this task, for the WS group, was a reflection of both poor planning and poor visuospatial cognition; their phenotypic visuospatial deficit limited performance on this task for this group in a manner that was not evident for the DS and TD groups.

Face processing is another area in which an analytical approach can reveal atypical processing despite seemingly typical performance. Early studies of face processing in WS employed standardised face processing tasks such as the Benton Facial Perception Test (BFPT: Benton, Sivan, Hamsher, Varney, Spreen, 1983) to reveal performance in the normal range for people with WS (e.g., Bellugi, Sabo & Vaid, 1988). However, these tasks lack the sensitivity required to detect subtle atypicalities in processing. In the typical population, a holistic/configural strategy is employed to process faces, e.g., processing the whole face or the spatial distance between the eyes and nose (Young et al., 1997). Where studies have taken a more analytical approach, evidence suggests that individuals with WS do not process faces in a typical manner, but rely on featural information, i.e., the individual components of a face (eyes, nose, mouth) to recognize faces (Deruelle et al., 1999). Annette and her team investigated configural processing capabilities in WS in depth (Karmiloff-Smith et al., 2004). Across a series of studies, they demonstrated that individuals with WS are less sensitive to configural information than TD children and adults, and show an atypical developmental trajectory for configural information. Instead, individuals with WS are reliant on a featural face processing strategy (where a task allows) to process faces.

We have recently shown that the featural processing strategy employed to process face identity also extends to face expression processing in WS (Ewing, Farran, Karmiloff-Smith & Smith, 2017). This collaboration was borne out of one of Michael Thomas' and Annette's DNL lab meetings. When I came to London, I received a fantastic welcome from Michael and Annette, and absolutely relished the weekly DNL meeting. Marie Smith presented the innovative "bubbles" technique (Gosselin & Schyns, 2001) at one of these meetings; we went on to use this technique in WS. Using this technique, on each trial, a face is visible through randomly presented circular apertures or "bubbles". The participant uses the information visible through the bubbles to make their judgement. In this study, participants were asked to judge facial expression from a partially concealed face. Hence, we were

able to determine the specific information from each face that was used to make the facial expression judgement. Our results showed that the WS group required the same number and size of bubbles as 11-year-old TD children but that they rely on a less integrated set of visual information to categorise facial expressions than either TD adults or TD children, i.e. a relatively more featural processing style. This ability to achieve a similar level of performance to controls, via an alternative processing route is consistent with the results mentioned above in the context of face identity processing. Face processing, therefore, represents an elegant example of associations being as informative as dissociations. One further example within this domain, for which I have fond memories of Annette, relates to the impaired social interaction observed in both WS and Autism. This is nicely described by Debbie Riby in our book (Riby, 2012). When editing the book, I wrote 'editor summaries' at the end of each chapter, and an absolute favourite sentence of Annette's was the idea that "…whilst *decreased* attention to faces in Autism can be detrimental to social interaction, in WS *increased* attention to faces can have the same effect." (Farran & Karmiloff-Smith, 2012).

The Raven's Coloured Progressive Matrices (RCPM; Raven, 1993) and Raven's Standard Progressive Matrices (RSPM; Raven, 1976) are commonly used measure of non-verbal reasoning, which are often used with individuals with neurodevelopmental disorders. This is based on the assumption that these tasks measure the same processes and constructs as in the typical population. This assumption has been tested in WS, DS and Autism (Facon & Nuchadee, 2010; Soulieres et al., 2009; Van Herwegen, Farran & Annaz, 2011). For both WS and DS, the proportion of each error type resembled that observed in typical development, and the developmental changes in the kinds of error types and the difficulty level of items were both typical in both groups. This demonstrated that the underlying mechanisms that support performance on this task in these groups, do not differ from typical development. This is an example where an analytical approach has enabled us to validate an association as a true association which reflects common strategy use across these groups. In contrast, for individuals with Autism, for whom a relative strength in performance is observed on the RSPM task, performance differs at the neural level, compared to TD controls. Performance in Autism is associated with increased activation in left occipital areas and decreased activation in medial posterior parietal and left lateral prefrontal areas. This is interpreted as reflecting a stronger reliance on visual

processing, and reduced reliance on working memory (Soulieres et al., 2009) relative to TDs. Thus, for this group, the RSPM is tapping into underlying processes in an atypical manner, which should be taken into account when using this measure, particularly when used as a measure by which to match participant groups. These are important findings given the frequent use of these tasks with these groups.

The example above regarding RSPM performance in Autism, illustrates a multi-level approach in which dissociations are observed at the neural level that are not observed at the behavioural level. A similar approach was adopted by Sahyoun et al. (2009), using a pictorial reasoning task. They demonstrated that despite an association at the behavioural level, the Autism group exhibited reduced activation of frontal and temporal language regions, and reduced neural connections within this language network, relative to TD controls. Instead, the Autism group relied on posterior occipito-temporal and ventral temporal regions to complete the task. This suggests group differences in task completion strategy, with visual mediation, rather than verbal mediation, being employed in Autism.

The future of association and dissociations

Associations can often mask underlying dissociations. This is key to a fine-grained understanding of developmental differences across neurodevelopmental disorder groups. Analytic approaches which draw on error analyses, the practise of deriving sensitive measures, and the use of multi-level analysis, can often uncover that seemingly typical behaviour is being reached by alternative means. Multi-level analysis is becoming more accessible for use with neurodevelopmental disorders due to technological advances in genetic profiling as well as neural measurement techniques such as functional Near Infrared Spectroscopy (fNIRS), and wireless and portable EEG. With reference to behavioural measurement, standardised tasks can often lack sensitivity because they were not designed for the population that they are being tested on. The Benton Test of Facial Perception is one example; "normal" performance on this task can be achieved via a featural processing style (Duchaine & Weidenfeld, 2003). An understanding of whether a behaviour can be reached via alternative means enables us to understand the extent to which a phenotypic deficit is detrimental to performance vs.

whether it can be compensated for. This has implications for understanding both typical and atypical development.

Cross-syndrome comparison

"… it is critical to raise cross-syndrome questions at multiple levels of analysis, such as: is this brain/cognitive/behavioural deficit syndrome-specific or is it syndrome-general, that is, is it characteristic of all atypical development where learning difficulties obtain or unique to a particular syndrome?" (Karmiloff-Smith & Farran, 2012).

Cross-syndrome comparison has the advantage of enabling one to determine which patterns of performance are syndrome-specific and which are artefacts of having learning difficulties. With reference to early predictors of later atypical development, it can also help to determine areas of developmental vulnerability vs. disorder-specific risk factors.

Across a series of studies, some of which I discuss above, we used cross-syndrome comparison to investigate large-scale spatial navigation performance in individuals with WS and individuals with DS. These two groups present with contrasting cognitive profiles with respect to verbal and visuo-spatial ability. Furthermore, both groups also demonstrate atypicalities in the hippocampus (Pinter et al., 2001; Meyer-Lindenberg et al., 2004) which is strongly associated with navigation performance in the typical population (Doeller, King & Burgess, 2008). Coupled together, this suggested to us that navigation performance would be poor in both groups, but that performance would be associated with differing underlying mechanisms for each group.

Above, I describe one study in which the ability to learn a route from A to B was driven by different processes in DS, WS and TD groups (Purser et al., 2014), thus demonstrating that poor performance represented different limitations across these groups. In another study, participants were asked to learn two routes, A to B and A to C, within a grid environment (Farran et al., 2015; also see Courbois et al., 2013). Having learnt these routes, they were then asked to demonstrate a short-cut from B to C. Their ability to find the short-cut was our measure of configural knowledge (an understanding of the configural structure of the area; Siegel & White, 1975). We demonstrated that 59% of TD children could find the short-cut. This compared to only 10% of individuals with DS and 35% of individuals

with WS. In fact, the DS group often used the strategy of simply adding the two known routes together, which requires no configural understanding at all. Whilst configural knowledge was strongly related to non-verbal ability in the TD group, it was related to attention switching in the WS group (correlations were not useful in the DS group due to the low success rate). We suggest that the WS group are limited by their ability to switch perspectives from the egocentric first-person perspective that they experience in the environment itself (useful for gaining knowledge of a fixed route), to the allocentric viewer-independent perspective required to make decisions based on the configural structure of the environment. In contrast, the majority of individuals with DS are simply unable to develop configural knowledge; they do not have a cognitive map (also see Toffalini et al., 2018). Our current ongoing research will provide insight into any further group difference. We are working with individuals with WS and individuals with DS to determine the benefits of providing an aerial view satellite-navigation style map (i.e., configural information) to participants while they are navigating from a first person perspective. If enabling participants to map these two perspectives to one another is beneficial it might facilitate their ability to switch from an egocentric first-person perspective to an allocentric viewer-independent perspective. Based on the evidence above, this might facilitate performance for a WS group more than a DS group, and predicts a benefit to configural knowledge in the 'sat-nav' condition compared to the standard condition for the WS group, but not the DS group. This study has strong implications for navigation training. If our hypotheses are borne out, this would really have appealed to Annette with reference to its real-world application and the direct relevance to the families of individuals with neurodevelopmental disorders.

There are several neurodevelopmental disorders for whom deficits in functions associated with the dorsal visual stream have been reported. These include dyslexia, Autism, Developmental Coordination Disorder, Williams syndrome and Fragile X syndrome. Inspection of the data from individual disorder research suggests that the dorsal visual stream is developmentally vulnerable. However, the lack of cross-syndrome comparison means that it is currently not possible to differentiate between developmental vulnerability and phenotypically unique patterns of ability across the functions of the dorsal visual stream (see Grinter, Marberry & Badcock, 2010). The former are

relevant for understanding developmental characteristics of the brain, whilst the latter help us to understand the specifics of each disorder. This is a strong example of the potential benefit to the interpretation of research findings, that cross-syndrome comparisons would reap.

The future of cross-syndrome comparison

Cross-syndrome comparison enables one to determine whether a participant group characteristic reflects learning difficulties, developmental vulnerability or syndrome-specific phenotypic processing, i.e., it provides a more subtle comparison than with TD controls alone.

Whilst the detection of the early markers of a disorder using "at risk" populations is a relatively new area of research, it will be important to determine the specificity of these markers via cross-syndrome comparison. Similar to the dorsal stream vulnerability example above, Levit-Binnun, Davidovitch and Gollan (2013) suggest that motor and sensory deficits reported across a number of neurodevelopmental disorders are a reflection of vulnerability in brain networks. Equally, there is a high level of co-occurrence across disorders such as Autism, ADHD and DCD, and there might be common early markers or risk factors for the development of these disorders. Johnson, Gliga, Jones and Charman (2015) review the literature regarding early markers of Autism and ADHD to conclude that whilst each disorder demonstrates early deficits in sensory, attentional and motor domains, direct comparisons have not yet been made within a single study and comparisons across studies are difficult to make due to differences in the focus of studies across disorders. To my knowledge, whilst there are no published studies of cross-syndrome comparisons across these groups, labs often run parallel streams with common test protocols across, for example, Autism and ADHD streams, which allows for cross-syndrome comparison. This data will be vital if we are to further our understanding of developmental vulnerability, and I have little doubt that Annette will have sowed the seeds for cross-syndrome comparisons to be made with the data held at the CBCD.

Individual differences

"Consideration of individual variation at multiple levels opens a series of new questions… that remained hidden in studies at the… group level." (Karmiloff-Smith, 2016)

The literature on individual differences within neurodevelopmental disorders is currently scarce and, in published papers, can often only be inferred from looking at error bars. However, there is a growing impetus to acknowledge these differences and to use these to better understand the developmental processes which underpin disorder phenotypes.

Developmental trajectory analysis demonstrates individual differences. Data is plotted in the form of scatter plots and thus the score of each individual is visible. Because data is plotted cross-sectionally against mental age, differences in rates of development across neurodevelopmental disorder groups can also reveal individual differences in the impact of an underlying process on a task. In Purser et al. (2014), discussed above, we demonstrated that stronger non-verbal ability was associated with lower errors on the route learning task for all groups, but that the developmental trajectory for the DS group was steeper than for the TD group. That is, lower levels of non-verbal ability were more detrimental to route learning ability in DS than in the TD group, but at higher levels of non-verbal ability, the DS trajectory had "caught up", and levels of route learning ability were commensurate with their non-verbal mental age. These group differences in the slope function demonstrate a cascading impact of individual differences; the steeper function of the DS group demonstrates broader individual differences in route learning ability in DS than one might expect for the range of non-verbal mental age. At a cognitive level, the group differences at the lower end of the trajectory might reflect an inability for some individuals (those with lowest level of non-verbal ability), but not others (those with relatively stronger non-verbal ability), to compensate for low non-verbal ability.

Individual differences in DS was the topic of one of Annette's most recent papers (Karmiloff-Smith et al., 2016). She describes broad heterogeneity in DS at many levels, including genetic, neural and cognitive. For example, at the genetic level, there are individual differences in the mechanisms which give rise to an extra copy of chromosome 21 (the most common form of DS), as well as individual differences in gene expression. This, along with individual differences in neural development and environmental factors, all contribute to how the phenotypical outcome of DS in any one individual is expressed. Taking this into consideration, individual differences hold strong promise in uncovering the developmental pathways to phenotypic outcome at a more fine-grained level than has hitherto been considered.

Broad individual differences are not only observed in DS. In my research (Farran et al., 2015) we have shown that navigation competence in both DS and WS ranged from those who were not able to learn a simple route from A to B and back again, to those who could learn the configuration of a new environment in sufficient detail to be able to determine a novel short-cut within the environment. Thus, whilst navigation is considered a relative weakness in these groups, this is not the case for all individuals. These differences might stem from differences in input from underlying processes (e.g. attention, memory), or influences at different levels of description (genetic, neural, environmental), which act as constraints or facilitators on cognitive outcome (in this case, navigation).

Jones et al. (2014) describes individual differences in early development, and the impact that this has on later heterogeneity. They describe a study by Landa et al. (2012) in which infants who went on to develop Autism could be categorised into four different subgroups with respect to their early characteristics. These ranged from those with general developmental delay to those with accelerated early development. This demonstration of heterogeneity from the infant start-state has broad implications for the understanding of how phenotypes develop. Jones et al. (2014) point out that this is not only important theoretically, but also from a clinical standpoint with reference to the ability to predict the severity of a child's symptoms later in life, and parental treatment decisions.

The future of individual differences

Individual differences are inherent in any group of individuals. However, for neurodevelopmental disorders these individual differences are often broader than observed in the typical population. This can be detrimental to interpretation of results, as it is possible, particularly when small samples are involved, that sample characteristics are not representative of the broader population, leading to spurious findings. As researchers, we should be transparent in reporting individual differences. This can be as simple as representing group data as individual data points, for example by using scatter plots, violin plots or pirate plots, rather than presenting group means, to studies such as Landa et al. (2012) in which latent class analysis was used to categorise participants into subgroups. Furthermore, a multi-level approach of understanding input from genetic, neural and/or environmental factors will enable us to better understand the seemingly broad heterogeneity in neurodevelopmental disorder

groups. Annette liked to include many parental questionnaires in testing batteries. This can be a cost effective and time efficient way of gathering environmental data, such as SES and maternal depression scores, which might have a strong impact on the outcome of the participant. An understanding of individual differences has implications for intervention, but also asks questions more broadly regarding heterogeneity in phenotypic characteristics.

Realising neuroconstructivist principles and reproducible research

Throughout this chapter, I have illustrated neuroconstructivist principles that were strongly advocated by Annette. These principles are not mutually exclusive of course, and many of the examples illustrate more than one of the principles. Key considerations have surfaced, which can be used to both improve our understanding of typical and atypical development and improve the rigor of future research. Some of these considerations map onto recommendations that are easy to implement, whilst others require significant resources. First, we should strive to be transparent about heterogeneity within a group. Annette's most recent paper advocated a better understanding of individual differences; she would be thrilled that there is now a strong push to represent and understand individual differences in neurodevelopmental disorders. In its simplest form, we can plot individual data points rather than group means. This will enable the reader to better understand the range of performance of a group. And, beyond behaviour, Annette discussed individual differences at genetic and neural levels. Technological advances have and will make these kinds of individual differences more and more possible to investigate. Another example refers to the use of standardised tests. Standardised tests assume that the task is being completed using a typical strategy, and that the cognitive profile of the participant is uniform. We discussed above how performance in the normal range can be achieved on the Benton Test of Face Perception via an atypical strategy. Similarly, performance on the Test for Reception of Grammar (TROG; Bishop, 1983) is not fully representative of grammatical ability in WS on account of their poor performance on the spatial items in the task (Philips et al., 2004). I advocate taking an analytical approach to understanding task performance. While the use of standardised tasks has many advantages, detailed investigation of performance on such tasks (e.g.,

analysis of error types, looking performance, contributing mechanisms; e.g., Van Herwegen et al., 2011) is warranted in order to be certain that we understand what we are measuring.

The remaining considerations map onto recommendations that require broad resources in terms of time, money and geographical space. First, we need to study individuals longitudinally if we are to obtain a true picture of the dynamics of development (and Annette had begun to take this a step further, into the fetal brain, as part of her collaborations with Mary Rutherford - a legacy that continues via Michael Thomas and I). Cross-sectional data does not always map directly onto longitudinal developmental trajectories. To-date, with the exception of the cohorts of "at risk" groups, there are few longitudinal studies of neurodevelopmental disorders. This is particularly true of genetically defined disorders. Second, we should be cautious in labelling a deficit as disorder-specific until cross-disorder comparison has been carried out. Currently, most of the longitudinal studies of "at risk" groups are single disorder studies. This risks failing to answer questions that can be addressed via cross-disorder research, such as whether an identified antecedent of later diagnosis has specificity to that disorder. My final recommendation relates to sample size. This is a recognised issue when working with rare and vulnerable groups. Small sample sizes limit the kinds of analyses that we can employ (e.g., numerous studies, including many of my own, are designed to rely on determining differences in group means, simply because of the practical limitations in gaining the sufficient power required to employ designs such as associational designs or latent group / variable analyses). Furthermore, given that individual differences can be broader in an atypical group than observed in the typical populations, small samples also run an elevated risk of not being representative of the population. Acquiring adequately powered sample sizes is difficult. This, and the recommendations above require collaboration. In an era where reproducible science is at the forefront of our minds, it is important that labs work together to agree common protocols and to collect data collectively such that participant numbers are sufficient to produce reproducible findings (the WISDom group is an emerging example). This also ensures that the analyses chosen are driven by the research question, rather than being driven by limitations in the availability of participants.

There are two standout legacies of Annette that come from a more personal level. In terms of advocacy, we can all also aim to be like Annette when interacting with families and charities. I am very fond of my WS participants and their families, and have worked with many of them for nearly twenty years. As a legacy to Annette, we should continue to take time to chat to the parents and the individuals themselves, and to help when we are able to (a letter to a school about the capacity of children with WS can work wonders). Do not aim to just collect data; seek to chat to the families (I have learnt so much from this), give your time at the family events, interact with the charities… and go and dance at the WS disco! The second legacy relates to collaboration. Annette was also a collaborator extraordinaire. She had time for so many people, and inputted to so many of our lives. As a legacy to Annette, we should push to collaborate as a method for improving the science of neurodevelopmental disorders. This will enable us to ask bigger questions and to be confident in the reproducibility of our findings. One of Annette's strongest pieces of advice was to "Ask the big questions."

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