Executive Function across Syndromes Associated with Intellectual Disabilities:

A Developmental Perspective

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In J. A. Burack. & R. M. Hodapp, G. Iarocci, & E. Zigler (Eds). Handbook on Intellectual Disabilities and Development. New York: Oxford University Press

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Executive function is a general construct used to represent brain functions related to the conscious control of thought and action (e.g., Zelazo & Muller, 2001). It is needed, for example, to evaluate alternatives and decide on a course of action; or to flexibly change plans or actions. Improvement in EF is considered to be related to development in a wide range of intellectual and social behaviors as children grow older (Case, 1985; Flavell, 1971; Siegler, 1983). For example, EF is related to school performance, reading, mathematical and problem solving skills (Bayliss, Jarrold, Gunn, & Baddeley, 2003; Cowan, Saults, & Elliott, 2002; Swanson, 2006), as well as to social-emotional development (Blair, 2003; Eslinger, Flaherty-Craig, & Benton, 2004; Hill & Frith, 2003).

The historical roots of research on EF can be traced back to clinical neuropsychological investigations of lesion patients (e.g., the case of Phineas Gage; Tranel, 2002), in which, despite intact performance on IQ tests, adults with damage to the prefrontal cortex (PFC) show performance deficits on classic EF tasks such as the Wisconsin Card Sorting Task (WCST; Heaton et al., 1983) and the Tower of Hanoi (Simon, 1975). On the WCST, patients with PFC lesions commit more errors of perseveration as compared to typically developing (TD) individuals (e.g., Anderson, Damasio, Jones, & Tranel, 1991; Stuss et al., 2000), while on the Tower of Hanoi, they fall short at recognizing the ultimate goal and resolving short-term goal conflicts (e.g., Goel & Grafman, 1995).

The performance of children on measures of EF reflects the slow maturation of the PFC (Dempster, 1992; Stuss, 1992). As children grow older, they become better able to control EF functions, giving rise to improvements in performance on laboratory measures such as the WCST, and the Tower of Hanoi. At first glance, the performance of school aged children appears to resemble that of adult patients with PFC lesions in some ways. For example, similarly to patients with PFC lesions, school aged children perseverate and have difficulty with set-maintenance on the WCST (e.g., Chelune & Baer, 1986;

Huizinga & Van der Molen, 2007; Welsh, Pennington, & Groisser, 1991), as well as with planning towards the goal on the Tower of Hanoi task (e.g., Bull, Espy, & Senn, 2004; Welsh et al., 1991). Of course, children are not PFC lesion patients and EF difficulties in childhood are related to maturational processes within the prefrontal cortex and those that enhance neuronal transmission within the prefrontal cortex, such as synaptic pruning and myelination (Giedd et al., 1999; Gogtay et al., 2004; Huttenlocher, 1979; Sowell, Delis, & Stiles, 2001; Yakovlev & Lecours, 1967), suggesting that brain maturation yields changes in EF abilities.

The organization of executive function. The attempt to understand the organization of EF is complicated by inconsistent neuropsychological studies. In some studies, PFC patients show impairments on the WCST or the Tower of Hanoi but not on both. In others, persons with different brain lesions show impaired performance on both tasks (for a review, see Stuss, 2006). These inconsistencies led to two general schools of thought, with some authors considering EF to be a group of multi-faceted processes that include distinct sub-functions, with focal neural correlates (Stuss, Shallice, Alexander, & Picton, 1995; see Garon, Bryson, & Smith, 2008 for a review) and others that consider it a unitary construct (Baddeley, 1986; Cohen & Servan-Schreiber, 1992; Kimberg, D'Esposito, & Farah, 1997; Norman & Shallice, 1986).

There is evidence for both the unitary and componential views of EF. For example, behavioral (Brocki & Bohlin, 2004; Lehto, 1996; Lehto, Juujaervi, Kooistra, & Pulkkinen, 2003; Welsh et al., 1991) and neuroimaging (e. g., Aron, Robbins, & Poldrack, 2004; Narayanan et al., 2005; Rushworth, Walton, Kennerley, & Bannerman, 2004) studies with a variety of executive function tasks, have indicated low or non-significant correlations between tasks, supporting the componential view, while factor-analytic studies have tended to yield multiple EF factors that have some common variance, supporting the unitary view. In one factor-analytic study, Miyake et al. (2000) used confirmatory factor analysis to assess common variance across experimental tasks thought to assess both similar (e.g. multiple inhibition tasks) and different (set shifting and inhibition tasks) EF components. They identified three unique factors

which they identified as inhibition of pre-potent responses, working memory, and set shifting but these were all moderately correlated with each other. The underlying relationship between variables reflected in the correlations between factors may be related to an important function of the prefrontal cortex, the regulation of perception, thoughts and behaviors carried out through the inhibition or excitation of other brain areas (e.g. Shallice, 2002).

The practical distinctions between unitary versus multi-faceted approaches to EF are especially relevant to the study of genetic syndromes. If EF is a unitary construct, such that its components are interdependent and have concordant developmental trajectories, then any organic insult or injury that impacts one EF process should affect all EF processes. In contrast, if EF is a dissociable process, then each EF subcomponent would have its own unique developmental trajectory and an insult or injury to one area of functioning could selectively impact one process in different ways than the other processes. In addition to providing information regarding profiles of performance among persons with IDs, the study of EF in these populations is useful for understanding how, when, and what factors are necessary and sufficient to develop a mature, typical EF processing system.

The development of EF among typically developing children

Overall, the general development of EF is characterized as an inverted U-shaped curve, with important periods of development occurring in childhood and adolescence, hitting a plateau in young adulthood, and beginning a steady decline in later adulthood (Zelazo & Muller, 2001). Its development is characterized by an increased ability to control one's thoughts, behaviors, and actions, and to override reflexive actions. The notion of EF as a developing process (in both unitary and componential perspectives) is evident in infancy when behavior is a simple reaction to internal or external cues. The adage 'it's easy to take candy from a baby' exemplifies this, as all one must do is to provide another salient stimulus (e.g., a toy) and the infant's attention is automatically captured by this new stimulus, forgetting the old (the candy). This stage does not last long, and very soon, toddlers acquire "will" and the ability to formulate (simple) goals such as wanting a specific cup or toy and showing impressive tenacity

until their goal is attained (much to the dismay of their parents at times). This ability to represent a problem, formulate a plan, and act on this plan continues to develop into the childhood years, with great transformations in the preschool period (e.g., Carlson, 2005; Espy, 1997; Kirkham, Cruess, & Diamond, 2003; Munakata & Yerys, 2001; Zelazo, Müller, Frye, & Marcovitch, 2003).

Adult-level performance on the various components of EF appears to be attained at different ages during childhood and adolescence (e.g. Huizinga et al., 2006; Luciana & Nelson, 1999). More specifically, it is generally in place around age 12 for set shifting and inhibition, and matures a little later in adolescence for working memory (see e.g. Cepeda, Kramer, & Gonzalez de Sather, 2001 and Kray, Eber, & Linderberger, 2004 for studies on the development of task/set shifting; Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2003 and Van den Wildenberg & Van der Molen, 2004 for studies on the development of inhibition; and Gathercole, Pickering, Ambridge, & Wearing, 2004; and Luna, Garver, Urban, Lazar, & Sweeney, 2004 for studies of the development of working memory). The observed improvement of EF during development has been attributed to PFC activation that becomes less diffuse and more focal as children grow older (e.g., Amso & Casey, 2006; Casey, Tottenham, Liston, & Durston, 2005). Of course, this description of different developmental trajectories for different facets of EF seems, on the surface, to support the componential view of EF but is really a question of definition. If one adheres to the notion that EF is one construct, then it cannot really be broken down into subcomponents. However, one of the most common ways of studying a construct (such as EF) is to deconstruct it into its parts and study each of these separately. Therefore, the notion of a protracted development of different EF components can only emerge from a componential view of the construct. For those who think that EF is one thing, then these distinctions between subcomponents are in attempts by researchers to break things down into manageable, rather than meaningful parts.

A ‘different’ kind of EF, characterized as ‘hot’ EF, is mediated by ventromedial areas of the prefrontal cortex, and is related to the notion that people are not always able to act accordingly even when they are able to cognitively determine the correct answer to a problem. Thus, ‘hot’ EF is concerned more

with emotionally related decision making, and is thought to have a different, more protracted developmental trajectory than 'cold' EF. The construct of 'hot' EF is mentioned here for the sake of completeness, although no studies of 'hot' EF of persons with intellectual disabilities have yet been published and this distinction will thus not be discussed further.

Experimental tracking of the development of EF. The developmental sequence of EF is often tracked with experimental paradigms that are sensitive to changes with regard to speed and accuracy of performance over time or as a function of age, but are generally only appropriate for finite age ranges (e.g., Diamond, 1995; Zelazo, Muller, Frye & Marcovitch, 2003). Based on adult paradigms in which multiple EF processes need to be recruited for successful performance, tasks used in the study of the development of EF are designed to isolate a specific component of EF. This allows for a more precise developmental profile across the individual components of EF, but is based on the artificial scenario in which the components act independently rather than in some integrated, systematic way that is more typical of general developmental processes. In many cases, the utility of the experimental tasks are limited for the study of development as they are usually only appropriate for limited age ranges, although developmental progression can be assessed in some cases with incremental decreases or increases in the difficulty of the experimental task that help minimize floor and ceiling effects in performance.

An example of a successful downward extension of an EF task from the adult literature to the preschool and infant literature concerns the process of set shifting, the ability to flexibly shift from one sorting rule to another (Miyake et al., 2000). In the WCST, which is commonly used to assess set shifting among adults, especially those with brain damage or injuries, participants are presented with cards that match targets on several dimensions (e.g., color, number of elements on a card, and shape) and are asked to sort the cards according to an undetermined rule (e.g. color). They are only told whether their sort was correct or incorrect, and after 10 correct trials, the rule is changed (e.g. shape) and the participant must then switch their mindset and figure out the new sorting rule. This complex task relies mostly on set shifting, but also to a certain extent on other EF components such as working memory- the ability to keep

track of the sorting rules (Huizinga et al., 2006)- and inhibition, the ability to inhibit the desire to sort the cards according to a now incorrect but learned dimension. However, as this task is too difficult for very young children and entails multiple EF processes that are potentially confounded (Huizinga et al., 2006, 2007; Miyake et al., 2004), the establishment of norms has only occurred for children over the age of 6.5 years. Downward extensions of this task have been developed to allow for a more specific focus on the set shifting component and can be used with infants as young as 6 months.

The Dimensional Change Card Sort Task (DCCS; Frye, Zelazo, & Palfai, 1995) was designed as a simplified, child friendly version of the WCST to assess set shifting in children between the ages of 3 and 6 years. It is a three level task that requires sorting first by one rule (e.g., color, pre-switch phase) and then switch and sort by a second rule (e.g., shape, post-switch phase). In a third level, children are presented with cards that either do or do not have a black border around them and are asked to sort by the color (or shape) rule if they see a card with a black border and sort by shape (or color) if the card has no black border (complex version). In using this task, Frye et al. (2005) and others (e.g. Zelazo, Mueller, Frye, & Marcovitch, 2003) were able to show that 3 year old children were able to sort by the first dimension presented (e.g. color) but could not shift to the second rule, despite being reminded of the appropriate sorting rule on every trial. The perseveration, or lack of set shifting, noted in the three year olds is particularly striking since the children are specifically told that they will no longer be playing the color game and that they must now sort by shape. Despite stating that they understood the rule and frequently telling the experimenter to stop repeating the instructions, the children continued to sort by the previously established color rule. However, children between the ages of 4 and 5 years were able to switch flexibly to the second rule, but were unable to complete a more complex version of the task with an extra layer of rules (see also Smidts, Jacobs, & Anderson (2004) for similar findings using a different task) .

In a further downward extension of the WCST, set shifting among children even younger than 3 years of age is generally measured with typical A-not-B tasks (for infants 6 months and up) (Piaget, 1954)

and its variants (e.g, Kaufman, Leckman, & Ort, 1989). In an example of an A-not-B task, infants are shown two wells, and a toy is placed in one of the wells in front of the infant, and the infant is prompted to retrieve it. After the toy has been correctly chosen by the infant for several consecutive trials, the toy is placed in the second well, again in full view of the infant and the infant is prompted to search for the toy again. Variations on the A-not-B require infants to flexibly shift their search between wells or locations and are appropriate for toddlers over 23 months of age. For example, the multilocation search task, utilizes 3 rather than 2 wells, and in the spatial reversal task, the toddler does not see where the treat is placed initially, nor that a change in the location of the treat has occurred (e.g Espy, Kaufman & Glisky, 1999). Although here we have provided an example of a downward extension of set shifting tasks, similar simplified versions of adult tasks have been developed in the areas of planning, inhibition and working memory.

EF in ID

In the remainder of this chapter, we examine EF among persons with specific etiologies associated with an ID that include Down Syndrome (DS), Fragile X syndrome (FXS) and Prader-Willi Syndrome (PWS) and Phenylketanouria (PKU). In so doing, we structure our interpretations of findings to fit within the context of a developmental framework and consider the methodological issues inherently related to the study of EF in persons with ID's. Briefly, the methodological challenges, which are not specific to the study of EF but which apply more broadly to studying any cognitive process among persons with ID's, stem from the basic notion that by definition, a diagnosis of an intellectual disability implies an inherent difference between chronological age (CA) and developmental level (Mental age: MA). This raises the questions of whom, and on what basis, one should compare the performance of persons with ID to determine whether skills are intact, delayed or deficient in some way, and how one accounts for this CA/MA discrepancy when making comparisons and interpreting research findings.

This review is not exhaustive as we have chosen to include only those studies in which meaningful comparisons are made between persons with IDs and another group of comparison

participants. More specifically, studies were included in this review if the group of children with ID's were the primary group of interest (rather than if they served as the comparison group for another population), and if the authors made a general effort to compare their groups on the basis of developmental level, be it to a group of other persons with intellectual impairments matched on chronological age or a group of TD individuals matched on the basis of mental age. All studies that were included in this review were published before 2008, and were found either via Pubmed, Eric or MeSH searches by entering the term 'executive function' and each of the 4 specific IDs that are being reviewed. Studies in which working memory was the primary EF studied were also excluded as these are being reviewed in another chapter (see chapter by Jarrold & Brock, this volume). These inclusion and exclusion criteria yielded 3 studies of EF among persons with DS, 4 studies of persons with FXS, 1 among persons with PWS and 2 among persons with PKU.

EF among persons with Down Syndrome (DS)

As a result of the increased rates of Alzheimer's disease among adults with DS, working memory has been the primary EF studied among this population (see Jarrold, this volume). The literature on EF, in areas other than WM, in which persons with DS are the primary participants, includes only 3 behavioral studies. In all three studies, the participants were adults with DS, and the studies varied with respect to both the component of EF and methodology. Differences in matching methodology along with and the emphasis of different facets of EF in DS, limit the conclusions that can be drawn from these studies, although they provide some convergent evidence that the development of set shifting but not all other facets of EF, may be delayed in their development among persons with DS.

Planning, inhibition and fluency in DS. Pennington, Moon, Edgin, Stedron and Nadel (2003) administered multiple measures of prefrontal executive functioning and hippocampal functioning in a study of 28 children and adolescents with DS and IQ matched TD children. The goals were to see if evidence of reduced cerebral volume in prefrontal and hippocampal regions which are noted in post mortem studies of persons with DS could be seen in functional developmental delays on tasks assessing

these areas. The participants with DS were between the ages of 11 and 19 years (mean chronological age 14.7 years) and had mean mental ages of 4.5 years, while the TD children were on average 4.92 years old. Pennington et al. included tasks that converged on EF processes requiring the 'holding [of] information in active or working memory to guide action selection' (p. 80). Their experiments were thus biased toward assessing WM, but also included other EF processes such as planning, fluency and inhibition.

The hippocampal measures included verbal and spatial long term memory, a test of pattern recognition and a test of associated pair learning taken from either the NEPSY (Korman, Kirk, & Kemp, 2001) or the CANTAB (e.g. Luciana & Nelson,2002) which are both well-normed and validated neuropsychological test batteries assessing multiple functional domains such as memory, language and learning. Specifically, Pennington et al. (2003) assessed verbal memory with a list learning task, in which participants are presented with a list of 15 words and asked to recall as many as possible on 5 successive trials, after which an interfering list is presented (which must also be recalled) before the memory of the target list is assessed again both immediately and after 30 minutes, assessing long term memory for words. The spatial memory task was a water maze presented on a computer in which participants had to use spatial cues learned with visual prompts to navigate to a target location in the absence of those visual prompts. In their measure of pattern recognition, the participants were required to view a series of 12 abstract patterns (two different trials were presented) for 3 seconds each and then to make a forced-choice response on which of two patterns had already been presented. They also completed a paired associates test that required that they associate an abstract pattern with its spatial location. Finally, Pennington et al. included their own ecological long term memory task using a questionnaire in which the participants were asked to recall events (18 in all) such as what they had eaten for lunch, what time they had gotten up that morning, the date of their birthday and the name of the examiner.

The prefrontal measures of planning, fluency, inhibition and working memory, were similarly to the hippocampal measures, also taken from the NEPSY and the CANTAB. Planning was measured via the two-, three- , four- and five-move problems from the Stockings of Cambridge, on which participants

are required to move target balls one at a time in order to match a model in the shortest number of moves possible. The fluency tasks consisted of verbal and design fluency tasks from the NEPSY. On the verbal fluency task, participants were asked to generate as many words of animals and foods as they could in one minute, and in the design fluency task, the participants were asked to make as many designs as possible by joining two or more of five dots using straight lines. On one trial, the participants were presented with dots configured to resemble the way a 5 is presented on a dice, and in a second trial they were presented with a random configuration. The inhibition task entailed pressing one button when participants saw an 'X' and another button when they saw an 'O', but to refrain from pressing any button when a tone was presented with the letter. The span tasks, which assess working memory, included a spatial working memory task in which participants searched for a target in an increasingly complex spatial array. To succeed on this task, the participants needed to remember the spatial locations they chose on earlier trials because they were told that the target would never be presented in the same spatial location twice. A similar measure was used to test working memory for numbers.

Pennington et al (2003) found that the performance of the participants with DS was worse than that of the TD children on the hippocampal, but not the prefrontal measures, suggesting that some aspects of EF, including planning and inhibition, are not impaired in younger populations of persons with DS. Rather, they found that the persons with DS were better (though non-significantly) on the prefrontal tasks than the TD children, which might be related to their older chronological ages. Although neuroanatomical findings of prefrontal microcephaly may lead one to conclude that inhibition and planning would be impaired in this population, the results from this study suggest typical developmental trajectories for planning and inhibition abilities. Perhaps difficulties appear later on or would appear on more complex tasks, but it would seem that inhibition and planning abilities develop in relation to general MA among persons with DS, at least up until a MA level of around 4 and a half years.

Set-shifting in DS. Zelazo, Burack, Benedetto, and Frye (1996) examined the relationship between set shifting and Theory of Mind (ToM) among adults with DS whose mental ages ranged from 3

to 6 years as measured by the Peabody Picture Vocabulary Test (PPVT; mean MA was 5.1) and whose chronological ages were around 22 years, and compared their performance to TD preschoolers of the same mental age (MA = 5.2 years). They found that individuals with DS performed less well than their TD peers on both the measures of executive function and ToM. Zelazo et al. used two deception-based ToM tasks, the crayon box task and the red cellophane task, and asked similarly structured questions for both. As an example, on the crayon box task, the participants were initially shown a crayon box containing straws. They were then presented with a crayon and a straw and were asked to point or respond verbally to the question: 'what is in the box?' (reality question). After the experimenter put the box away, a puppet was introduced to the participants who was asked three questions: 'what does the puppet think is in the box, straws or crayons?' (false-belief question); 'what is truly and really in the box, straws or crayons?' (reality question); and 'what does this look like it has in it right now, straws or crayons?' (appearance question). To assess set shifting, the pre, post and complex phases of the DCCS were administered after a set of practice trials in each of the two sorting conditions (color and shape) were introduced. Zelazo et al. (1999) found that the individuals with DS performed worse than the mental age matched TD children on all of the tasks. Persons with DS had difficulty abstracting what another person might think and perseverated on the first sorting dimension (e.g., color) of the DCCS suggesting a difficulty in switching mental sets. Zelazo et al. concluded that individuals with DS showed delays in the development of both set shifting and ToM, which was reflected in a floor effect in performance for the participants with DS.

Zelazo et al. (1996) went a step further with their data analysis by characterizing participants' individual performance on a 5 point scale intended to reflect a participant's ability to use increasingly complex rules and rule structures. A score of 0 meant individuals were unable to learn the rules in the practice phase of the task, a score of 1 meant they learned the rules in the practice phase but could not use them during the test phase. Scores of 2, 3 and 4 meant participants passed the pre- post and complex phases respectively. The TD children displayed performance that was concordant with their

developmental level as most passed the post-switch phase of the task. In contrast, the participants with DS frequently displayed difficulty simply learning the rules. Four of the 12 participants with DS scored 0, while 5 participants scored 1. Only 2 of the participants with DS were able to pass the post-switch phase and only 1 was able to pass the complex version of the task. The inability to correctly complete even the pre-switch phase was particularly surprising as the MAs of the participants with DS (MA = 5.2 years) suggested that these tasks were developmentally appropriate. The findings that individuals with DS were unable to learn the sorting rules on the DCCS and were thus below developmental expectations, suggest a fundamental delay in the development of rule learning, a precursor to flexible rule use. The finding that three of the participants with DS were able to show some flexibility in their use of rules suggests that there may be individual differences in the level of achievement reached in the area of cognitive flexibility, and may also support the notion that among persons with DS, there is a significant delay, rather than a complete deficit, in set shifting in this group.

In another study of set shifting, Rowe, Lavender and Turk (2006) compared the performance of adults with DS with adults with an unspecified ID matched on the basis of age (mean chronological age = 33 years) and verbal abilities as measured by the British version of the Peaboby Picture Vocabulary Test (no descriptive information regarding the mean mental ages of their participants were provided). The authors administered a series of EF and attention measures that included tests of set shifting and planning, to a group of persons with DS, and a heterogeneous group of individuals with ID. The set shifting task was the Weigl Color-Form Sort (Weigl, 1941), which is similar to the DCCS used by Zelazo et al. (1996) except that three rather than two test cards (circles, squares and triangles of three different colors) need to be sorted first according to one dimension (e.g. color) and then to another (e.g. shape). The number of cards does not impact the difficulty level in TD children (see Zelazo et al., 2003), but the Weigl is more complex than the DCCS because the sorting rules are not explicitly stated on each trial. Scoring on the Weigl is based on a point system similar to the one used by Zelazo et al. (1996), although participants are given more points for sorting by form than by color without prompting. The planning measure the authors

used was the Tower of London which is similar to the Stockings of Cambridge task that was used by Pennington et al. (2003). After correcting for multiple comparisons, the only difference that remained between the groups was on the measure of set shifting.

Since the set shifting task and the scoring system used by Zelazo et al (1996) and the Rowe et al (2003) were similar, the findings of the two studies can be compared. In both studies, the participants with DS were able to sort by both shape and form, but had difficulty applying these rules to the experimental tasks, suggesting a general difficulty with both flexible rule use and set shifting. There were however three major drawbacks to the Rowe study which lead us to interpret their findings with caution. The first issue relates to the use of a mixed group of persons with unidentified IDs, which is problematic because the composition of the mixed group is impossible to replicate and thus findings of strengths or weaknesses in relation to this group is not replicable (see e.g. Burack, 1990; Burack, Evans, Klaiman & Iarocci, 2001b; Burack, Iarocci, Bowler & Mottron, 2002 for a more in depth discussion of these issues). The second issue related to the authors' choice of matching procedure, as they matched their groups on the basis of receptive language abilities, as measured by the British Peabody Picture Vocabulary Test, but neither administered nor scored according to the standardized guidelines outlined in the manual as they had all participants start at the first item. Three, they did not provide any indication of the mental ages of their participants such that their results are impossible to frame within the context of development.

Conclusions about EF in DS. The findings reviewed provide preliminary evidence that rule use and set shifting may be particularly delayed among persons with DS, whereas other components of EF such as inhibition and planning might follow a more typical developmental trajectory in this group, at least until an MA of 4 ½ years. Pennington et al (2003) found that the performance of persons with DS was slightly better than that of matched TD children on some components of EF, including working memory, planning and inhibition, while both Zelazo et al. (1996) and Rowe et al. (2006) found impairments in set shifting. One main difference between the Pennington studies and those of Zelazo and Rowe relates to the nature of the tasks used, as the authors chose to examine completely different facets

of EF. Second, both the DCCS (used by Zelazo) and the Weigl (used by Rowe) are both heavily reliant on language abilities, the presentation of rules requires participants to understand what is being asked of them and to potentially use verbal rehearsal strategies to guide their placements of the target cards, even if no verbal response is required. In contrast, Pennington et al. (2003) specifically chose tasks that were non nonverbal in nature. As individuals with DS show specific strengths in non-verbal areas relative to weaknesses in verbal areas, differences in findings might in part be attributable to their language content. One way to better tease apart the relationship between language and EF would be to design verbal and nonverbal versions of the same task that assesses the same facet of EF, to determine whether unevenness in cognitive profile among persons with DS might be related to findings of impaired or intact EFs. The preliminary evidence however suggests that persons with DS show impairments on measures of set shifting that have a strong verbal component while their inhibition, planning, and fluency abilities are consistent with their developmental level.

EF among persons with FXS

Increased numbers of Cytosine Guanine Guanine (CGG) repeats are associated with the presence, classification (i.e., full vs. premutation), and severity of deficits among persons with fragile X. Increased CGG repeats lead to diminished levels of fragile X mental retardation protein, a protein influential in embryonic development and regulation of synaptic activity (FMRP; e.g., Pierreti et al., 1991; Tassone et al., 2000), and are directly related to the degree of impairment observed in cognitive and executive functioning (e.g., Thompson et al., 1994) among persons with FXS. For example, females with a full mutation show greater deficits in inhibitory functioning and set shifting ability as compared to females with a permutation (e.g., Bennetto, Taylor, Pennington, Porter, & Hagerman, 2001; Cornish et al., 2001; Mazzocco, Pennington, & Hagerman, 1993; Sobesky, Pennington, Porter, Hull, & Hagerman, 1994; Sobesky, Taylor, Pennington, Riddle, and Hagerman, 1996). In addition, females with the full mutation show less severe impairments in relation to males with the full mutation and females with the premutation are likely to show similar developmental trajectories to TD females (e.g., Baily, Hutton, & Skinner, 1998;

Rousseau, et al., 1994). Thus, analyses of EF among persons with FXS must include, in addition to all of the other developmental factors outlined in this chapter, the number of CGG repeats in their interpretation of findings.

Inhibition in FXS. Inhibition is notably impaired throughout childhood and adulthood among persons with FXS, and may represent a significant and persistent area of weakness. For example, in a study of children with FXS, Munir, Cornish, and Wilding (2000b) investigated the inhibitory functioning of boys with FXS with a mean CA of 10.88 years and Verbal Mental Ages (VMA) of 6.77 years and contrasted their performance with that of, groups of boys with DS (mean CA 11.17 years; VMA 6.09 years), TD boys with poor attention skills (mean CA 7.58 years; VMA 6.96 years), and TD boys with good attention skills (mean CA 7.97 years; VMA 7.77 years) matched on verbal mental ability as measured by the short form of the British Picture Vocabulary Scale (BPVS). Inhibition ability was measured using the walk task and the same-opposite task from the Test of Everyday Attention for children (Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994). In the walk task, children are asked to mark dots along a column of printed feet. Two tones, each representing a rule the children must follow, are presented at intervals. One tone indicates that the child should place a mark on the next step and the other tone indicates that the child should refrain from responding, thus measuring the ability to both follow rules and inhibit a prepotent response. In the same-opposite task, the children are timed as they follow a path and name the digits 1 and 2 presented along the path. During the second part of the task, the children are asked to say "one" when they see a 2 and say "two" when they see a 1, again measuring inhibitory processing. Munir et al. found that the children with FXS were less able to inhibit or delay their responses on the walk task in relation to all of the comparison groups and were significantly slower when performing the same-opposite task in relation to the two groups of TD children. These findings are consistent with the behavioral phenotype of persons with FXS who show impulsivity and hyperactivity and suggest a deficit in inhibitory functioning among children with FXS that is more pronounced than MA matched TD children with poor attentional abilities.

Among adults with FXS, inhibitory function has mainly been studied with the contingency naming task (CNT), which requires the naming of designs based on a given rule (Bennetto et al., 2001; Sobesky et al.,1996). On the CNT, the participants are presented with red and blue triangles and squares and asked to name either the color or the shape of the stimulus. Difficulties in inhibitory processing appear to persist into adulthood in females with full mutation but not in females with the permutation form of FXS who perform similarly to their TD counterparts from childhood into adulthood (Bennetto et al., 2001; Sobesky et al., 1996).

Set-shifting in FXS. Individuals with FXS also show difficulties in the ability to switch between mental sets (Cornish et al., 2001) in relation to individuals with DS and TD, with the severity of impairment seemingly related to the severity of the disorder. For example, a positive relationship between the number of perseverative responses on the Wisconsin Card Sorting Task (with higher perseveration related to worse performance) and the number of repeats of the CGG sequence was found in a series of studies of women with the full mutation and those with the premutation (Mazzocco et al., 1993; Sobesky et al., 1994; Thomspon et al., 1994), However, these findings need to be interpreted with caution as the IQs of the women with the premutation were higher than those with the full mutation and the higher cognitive abilities if the permutation group may have accounted for the group differences.

Conclusions about persons with FXS and EF

The initial evidence of EF in persons with FXS provides an example of the link between genotypic and phenotypic expression and the relationship between genetics and outcome. Among individuals with FXS, the number of CGG repeats and the number of FMRP levels are intrinsically linked with the severity of the disorder as well as with the specific severity of deficits across at least one area of EF, inhibition. These findings highlight the need to further assess the extent to which genetic abnormalities lead to delays and deficits in EF within syndromes and between subgroups within each syndrome.

Phenylketanuria (PKU)

PKU is one of the most treatable causes of intellectual disabilities, and since the development of early screening measures, most individuals with PKU have been spared from the major effects of the disorder. However, a large proportion of females with PKU are now entering childbearing age which presents new risks, as elevated levels of phenylaline in the mother are harmful to the developing fetus. Maternal PKU (MPKU) arises when mothers with PKU are not treated adequately during pregnancy, and leads to ID in 97% of offspring, with microcephaly (73%), low birth weight (40%), and congenital heart disease (12%) being the most common comorbid problems (Lenke & Levy, 1980; Levy & Ghavami, 1996). Although the toxic elements of PKU and maternal PKU (MKU) are the same, differences in the timing of children's exposure to this toxicity in turn lead to differences in the expression of cognitive strengths and weaknesses (Antshel & Waisbren, 2003). In metabolic disorders, neurochemical aberration and the timing of exposure can be measured which may help shed light on how metabolic factors can disrupt the pathogenesis of EF at specific pointes in development (Antshel & Waisbren, 2003). For this reason, most studies of persons with PKU measure phenylaline levels and correlate these with the level of impairment.

EF in PKU

Even in the absence of the global cognitive impairment among persons with early treated PKU, difficulties across several EF components that include visuo spatial memory and planning are still present. For example, Leuzzi et al. (2004) studied EF among 14 early and continuously treated children with PKU whose average age was 10 years, relative to a comparison group of TD children matched on overall IQ as measured by the WISC-R, gender, chronological age and socioeconomic status. Both groups were administered several measures of EF, including those of set shifting, maze learning, sorting, searching, planning and visuo-spatial memory. Despite being matched on the basis of IQ, the individuals with PKU performed worse than the TD children on the Tower of London, Elithorn's Perceptual Maze Test and the copy section of the Rey-Osterreich Complex Figures Test, which all suggest specific deficits in planning

abilities. This deficit was related to dietary control with the participants with PKU with worse dietary control performing worse than those whose PKU was better controlled.

Inhibition in PKU. To compare differences in the EF abilities of persons with different subtypes of PKU, Antshel and Waisbren (2003) compared the performance of children and adolescents with inherited PKU, those with MPKU and a group of TD participants on measures of inhibition of return, auditory/verbal learning, visuo-spatial visuoconstruction, visual memory and organization skills, word retrieval, and visuo-motor integration. EF and attention were also assessed by parent report using the BRIEF, a questionnaire designed to assess EF difficulties as they would appear in everyday activities, and which yields indices of Behavioral Regulation, Metacognition and a Global Executive Composite; and the ADHD rating scale, which is an 18 item questionnaire that differentiates between attention difficulties that would be classified as inattentive at one end and impulsive at the other. Groups of 46 children with PKU, 15 with MPKU and 18 TD participants, all between the ages of 7 and 16 years, were matched on the basis of IQ as measured by two subtests (Block Design and Vocabulary) of the Weschler Intelligence Scale for Children-III. Levels of phenylaline were measured subsequent to the completion of the testing battery to assess the relationship between test performance and level of phenylaline for all groups.

The participants with PKU and those with MPKU shared similar score profiles in some areas but not others. Both groups had similar word reading speeds, as measured by the Stroop Word Reading Score. However, the individuals with MPKU displayed greater difficulties with EF aspects reflecting behavioral regulation when compared to both TD participants and those with PKU. The results from this study indicated that individuals with MKU were more severely affected as they displayed symptoms of inattention, hyperactivity and behavioral regulation difficulties whereas the children with inherited PKU only showed symptoms of inattention. These findings suggest that the type of EF difficulty that is evident among persons with PKU is related to how the disorder was acquired and as a function of the level of toxicity.

Conclusions about persons with PKU.

The findings from studies of PKU provide an example of the link between genetics, environment and outcome. Individuals with early and continuously treated PKU tend to have generally positive outcomes with only minor attentional issues. In contrast, untreated or poorly controlled PKU can have important consequences that significantly interfere with both the day to day functioning and the general outcome of these children.

EF in PWS

Preliminary support for differences in EF skills between persons with PWS and TD individuals is based on behavioral descriptions of persons with PWS that include rigidity and difficulty dealing with change (Clarke et al., 1996; Dykens & Kasari, 1997). Only one study was found in which the EF performance of persons with PWS was compared to another group on the basis of developmental, rather than chronological age. Although their comparison group consisted of a group of persons with ID of mixed etiology, which as we know is problematic, in nonetheless reported here. Walley and Donaldson (2005) did not find any significant EF differences on measures of initiating, planning, set shifting, inhibition, and working memory ability between 12 persons with deletion PWS and 6 with UPD PWS (caused by maternal uniparental disomy of chromosome 15 which results in the inheritance of two copies of maternal chromosome 15 and an absence of a paternal copy of chromosome 15; Nicholls, 1993) and a matched group of persons with ID's of various etiologies. Participants were all between the ages of 16 and 49 with VIQs (verbal IQs; as measured by the vocabulary and similarities subtests of the Wechsler Adult Intelligence Scale – Revised) between 51 and 93. These findings provide some initial support for developmentally appropriate maturation of EF processes among persons with PWS.

Conclusions about persons with PWS.

The preliminary data presented here indicate that among persons with PWS, EF appears intact in relation to mental aged matched participants. However, more research will need to be conducted to substantiate this claim and investigate the pattern of strengths and weaknesses in EF ability of persons with PWS. These include making comparisons between persons with PWS and a homogeneous group of

persons with ID's as well as making comparisons to TD individuals matched on the basis of MA. A second consideration in the study of EF among persons with PWS is that under the general umbrella of PWS are several different subtypes that seem to differentiate individuals' performance on EF tasks. For example, persons with different subtypes of PWS such as those with the deletion and UPD subtypes demonstrate different patterns of strengths and weaknesses in EF performance. As such, comparisons between different subtypes and TD persons are warranted and necessary for understanding how subtle changes in a disorder are acquired and can impact brain development and functional outcomes. Profiles of EF development will need to be developed for both groups separately and in relation to both TD persons and persons with other genetic syndromes.

Summary

The literature reviewed here supports the notion of a componential view of EF, as some disorders were associated with intact performance on some areas of EF, but not others. For example, individuals with DS were as able as developmentally matched peers in areas related to working memory and inhibition (Pennington et al., 2003) but were clearly impaired in their abilities to switch flexibly between mental sets (Zelazo et al., 1996). This sparing of certain areas (in relation to developmental level) is inconsistent with the notion of a unitary view, which would imply that difficulty in one area of EF would mean difficulty in all areas of EF. Although the findings reviewed here still leave open the question of whether some combination of unitary and componential views, we provide evidence to suggest that a purely unitary view is not likely.

As the origin of more genetic disorders is uncovered, the number of cognitive and executive function profiles of different groups that can be gathered will multiply. The development of dynamic, etiologically specific profiles of cognitive and executive functioning will allow for a developmental perspective on genetic disorders related to intellectual impairments and will also serve to inform the TD literature by providing initial links between genetic markers and neurocognitive functioning. The confluence of findings from studies of persons with genetic syndromes is also relevant to a more specific,

precise understanding of the relationship between cognitive abilities and executive function among TD individuals, for whom the development of these processes are inextricably intertwined. The study of executive function profiles among persons with ID allow us to understand not only the limits of development that are related to a specific etiology, but also inform us about the malleability and boundaries of typical trajectories of development. The evidence presented in this chapter suggests that general intellectual disability is not unilaterally related to overall EF deficit, but rather can be expressed in intact, delayed, or impaired performance.

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