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Cognitive Characteristics of Children with Genetic Syndromes

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Abstract

The cognitive profile of several different populations of children, each with a distinct neurogenetic disorder that has been described as fitting the pattern of a “nonverbal learning disorder”, is examined. In particular, this paper presents the view that a cognitive endophenotype, specified in terms of specific cognitive processes involving the spatial, temporal and attentional domains, can be used to generate an explanation of the neurocognitive foundation of the common impairments found in these disorders. Methods for evaluating cognitive impairments are first compared and contrasted and the concept of “nonverbal learning disorders” is described. The paper then examines data from experimental tests of spatiotemporal and executive cognitive function acquired from children with one of several disorders to determine whether such a cognitive endophenotype holds promise for moving from descriptions of to explanations for the impairments observed and whether prescriptions for therapeutic interventions might flow from such an account.

Synopsis—This paper presents the cognitive profile observed in children with one of several common genetic syndromes associated with “nonverbal learning disorders”. It introduces the concept of a cognitive endophenotype in order to help explain the similar pattern of impairments across the syndromes. It explores the explanation of diverse impairments in higher-order visual, spatial, temporal, numerical and executive cognitive competencies deriving from origins in more basic attentional and spatial cognitive dysfunctions. The importance of a developmental approach to understanding dysfunction is stressed.

Keywords

Cognition; Genetics; Syndrome; Child; Spatial; Numerical

The symptoms that are associated with genetic syndromes generally form a large and diverse array of physical and behavioral characteristics. Knowledge about the relationship of these features to each disorder’s genotype varies greatly. The cognitive and behavioral phenotypes of most genetic disorders are typically less well characterized than the physical/medical ones and are less clearly linked to genetic causes. Behavioral scientists have tended to focus on global impairments measured in terms of intelligence quotients (or IQ) while clinical geneticists concentrated on describing physical features, medical complications, salient traits and degree of retardation associated with specific genetic etiologies¹. Recently, much progress has been made in the development of highly characterized behavioral, cognitive and neurocognitive phenotypes for a range of disorders with known genetic causes and in the establishment of genotype/phenotype relationships. This paper will concentrate on a particular cognitive phenotype observable in children from several populations that have clearly defined genetic disorders.

Such studies are carried out using two complementary sets of tools.. Neuropsychological testing studies use a battery of standardized tests to generate a broad profile of the subject’s

abilities in the intellectual, academic and behavioral domains. Normative scores are used to compute the participant's "mental age" for each domain. A percentile score is also generated so that the participant's abilities can be compared both between individuals, i.e. to the normed population, and within the individual to determine domains of particular strength or weaknesses. Standardized testing has strong descriptive power and enables testing over many domains at once. However, it has weak explanatory power because the behavior measured by such tests is quite complex and hard to link directly to the cognitive and neurobiological substrates that generate it. In other words, it reveals little about the mental representations being used, the manner in which they are processed, the brain circuits upon which those computations depend and the neurotransmitters involved.

Alternatively, researchers using cognitive experimentation studies develop small sets of experiments, usually in the form of computer-based tasks. They are designed to test hypotheses about how specific cognitive functions work and the nature of the representations that they process. Such experiments are increasingly used in the context of functional neuroimaging studies to explore relationships between brain structure and cognitive function. Hypotheses are evaluated by determining whether or not the predicted performance patterns were observed. Typically new, more detailed, hypotheses emerge from such analyses, further experiments are designed, and the process progresses towards an ever more highly specified explanatory account. Such cognitive neuroscience studies can investigate how information is processed, which brain circuits and even neurotransmitters are involved, and how these interact. Of course, there are limitations to this method also. The range of behaviors tested is, by design, very limited, the samples tend to be small and typically no normed population data are present. Therefore, any individual experiment has weak reliability and needs to be replicated. Also, the training required for this method means that results are not easily interpretable by other professionals. However, the tradeoff is that the explanatory power of this method is high.

Essentially, what experimental cognitive studies of genetic disorders attempt to develop is similar to the idea of an endophenotype, although no hereditary component is necessarily implied. This concept is being used to simplify investigations of the biological basis of psychiatric disorders by decomposing the entirety of their behavioral manifestations into discrete components more amenable to analysis. Gottesman and Gould² defined endophenotypes as "measurable components unseen by the unaided eye along the pathway between disease and distal genotype [that] may be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological in nature", p. 636. This paper will briefly review the phenotypic profiles generated for a small set of genetic disorders with the use of standardized neuropsychological instruments. It will then concentrate on the "cognitive endophenotypes", insofar as they have been described, that attempt to specify the possible causes of impairment in terms of specific cognitive functions and the representations they process. The goal of such studies is to develop explanatory accounts of why particular sets of observed impairments consistently co-occur. From that it is hoped that predictions and inferences about areas of function not directly studied will be possible, along with the generation of hypotheses about the nature and potential efficacy of cognitive and behavioral interventions.

Such cognitive endophenotypes enable the identification of underlying dysfunctions that produce "cascaded effects" in higher-level impairments. This means that the demands of specific mental activities, such as counting, call upon a range of foundational or component processes that vary as a function of the demands of the task. In counting a set of physical objects these would include: searching for and identifying a countable item, incrementing a counting list, "marking" the item as counted, disengaging from the counted item, searching for the next countable object and repeating the necessary steps for that item. Some of these same components would be required in other tasks, such as using landmarks to find a specific room

in a building. When a component process is dysfunctional it creates different patterns of impairment in the contexts of the tasks in which it is deployed. However in all cases it should be possible to partly explain the difficulty in terms of the dysfunction in the component processes themselves. Since these are likely to develop earlier in life than the actual task in which the difficulty is assessed, it is important to take a developmental approach and to focus on candidate processes that contribute to the cognitive endophenotype. Therefore, accounts developed in terms of basic cognitive processes can generate explanations for impaired functions that are distal both in the sense of being much higher-level in nature or in what might appear to be a very different domain of “behavior”. An example of the former is the case of visuospatial attentional dysfunction and impairments in the development of numerical competence. An example of the latter is the relationship between executive attentional impairments and psychiatric disorders from Attention Deficit Disorders to Obsessive Compulsive Disorders to Schizophrenia.

One important caveat to keep in mind when considering both typical and atypical development is the understanding that structure/function mappings (of brain and mind) will change as a function of the interaction between experience, maturation and the nature of the “start state” of the individual^{3, 4}. Thus, explanations of impairment will not be found in the form of “broken” versions of fully developed cognitive systems or modules, as is the case for adult neuropsychological single case studies. For example, inferior parietal damage in typical adults, particularly involving the left angular gyrus, classically induces the Gerstmann syndrome, a component of which is the loss of most or all previously acquired mathematical ability^{5, 6}. However, it would be wrong to assume that all mathematical disability can be explained by left angular gyrus dysfunction alone. Instead it will be necessary to study the cognitive processing profiles of children with developmental disorders, along with structural and functional assessments of brain development, preferably with the use of longitudinal designs.

This paper focuses primarily on several syndromes that tend to get grouped together into the category of “Nonverbal Learning Disorders” (NLDs) because the consistencies in their cognitive impairments suggest the presence of a shared explanatory intermediate phenotype at some neurobiological level.

Overview of “NLD” Genetic Disorders

Rourke defines NLD as having characteristic primary impairments in tactile and visual perception and complex psychomotor skills, secondary impairments in tactile and visual attention and tertiary impairments in tactile and visual memory, concept formation, problem-solving and hypothesis-testing. Associated psychosocial problems, externalizing in early development and internalizing later, are characteristic.g.⁷.

In Fragile X syndrome X (hereafter FXS) “Approximately 50% of females with the full mutation have mental retardation [while the] remaining 50% may manifest borderline to normal intellectual functioning, learning disability, and/or psychosocial difficulties. [...] The majority of males with Fragile X syndrome have mental retardation”⁸. Nevertheless, even “among affected females *without* mental retardation, deficits are seen in measures of visual-spatial skills, attention and ‘executive function’, and math achievement scores are lower than reading achievement scores. [...]. In contrast to math skills performance, verbal skills are relatively spared in females with Fragile X, although girls with Fragile X do have lower verbal skills relative to their unaffected sisters”⁸. Characteristic among the greater impairments seen in males with Fragile X are “deficits in visual-spatial abilities, visual short-term memory, arithmetic, and processing of sequential information”⁹.

Females with Turner syndrome (hereafter TS) manifest a specific neurocognitive profile where verbal ability (including Verbal IQ) is generally normal¹⁰⁻¹³, while nonverbal ability (visual-

spatial/perceptual, visual-motor), attention, working memory, motor function, and executive function (planning, organizing) are relatively impaired^{14, 15}. The risk for learning disabilities, particularly in mathematics, in girls with TS is high¹⁶. It has been argued that their poor math performance is due to increased operation and alignment errors and decreased fact retrieval, perhaps secondary to slower response time, impaired working memory, executive, and visual-spatial abilities^{17, 18}.

An extensive set of investigations into cognitive functioning has been concerned with Williams syndrome (hereafter WS) e.g.¹⁹⁻²¹. Most individuals with this disorder rank in the mild to moderately retarded range, with Full Scale IQ scores ranging from 40 to 90 with a mean of around 55 and no clinically significant difference between Verbal (VIQ) and Performance (PIQ) intelligence scores²¹. Individuals with Williams syndrome demonstrate deficits in cognitive domains such as basic conceptual knowledge, visual-spatial and attentional abilities and they “have difficulty in mathematics and its application to everyday life”²¹. In contrast, the cognitive abilities of individuals with Williams syndrome are relatively spared in the domains of expressive, but not spatial, language, auditory processing and face processing.

In the chromosome 22q11.2 deletion or Velocardiofacial²² syndrome (hereafter VCFSⁱ) a subset of impairments is particularly evident in the areas of visuospatial and arithmetical performance²³⁻²⁷. Despite their early language delays, children with VCFS still score higher on standardized tests of verbal abilities than those that test visuospatial abilities. To be more specific, “analysis of the IQ test subtest scores suggest relative strengths in the area of rote verbal knowledge and great weaknesses in the areas of visual-perceptual-spatial abilities and nonverbal reasoning”²⁸.

The visuospatial, visuomotor and numerical impairments in Williams, Turner, full mutation Fragile X (i.e. FXS) and chromosome 22q11.2 deletion syndromes are both striking in their degree of overlap, e.g.²⁹ and puzzling in that other commonalities are limited. Because of the intimate connection between space and time, one prediction that flows from the above findings is that impairments should also be found in temporal processing. In fact, the two interdependent domains of function are often described with a single label, that of spatiotemporal cognition. This paper will examine the small but growing set of cognitive experimental studies that attempt to identify the neurocognitive basis for these impairments. Since an important focus will be on various functions of the human attention system, a review of several of its key concepts follows.

In their seminal work, Posner and Petersen³⁰ proposed a subdivision of the concept of attention into three components, each subserved by a distinct neural network, whose functions and computations can be defined in cognitive terms. The three attentional networks were considered to be those necessary for: “(a) orienting to sensory events; (b) detecting signals for focal (conscious) processing, and (c) maintaining a vigilant or alert state”. Subsequently, Posner and colleagues developed the attentional networks test (or ANT) to evaluate what have become known as the (a) orienting, (b) executive and (c) alerting networks³¹. The orienting system plays a primary role in responding to cued information in the environment or in the volitional search for and selection of salient information. It is associated with a frontoparietal network that appears to be strongly associated with cholinergic neurotransmitters^{31, 32}. This network primarily comprises the superior parietal lobule, intraparietal sulcus, pre- and post-central sulci and frontal eye fields³³. The executive system supports the task of detecting and prioritizing signals for conscious processing by engaging in error detection, conflict monitoring

ⁱThe abbreviation VCFS is used in this article for consistency with others in the current edition. However, because not all children with deletions of chromosome 22q11.2 exhibit velopharyngeal, cardiac and facial anomalies, the author prefers to refer to the disorder with the more inclusive term of “chromosome 22q11.2 deletion syndrome”.

and inhibiting distracting or irrelevant information. It is most directly associated with medial frontal lobe structures such as anterior cingulate cortex and dorsolateral prefrontal cortex and depends heavily on the neurotransmitter dopamine. The alerting system supports the complementary functions of maintaining vigilance for novel information and the need to concentrate during continuous performance. It is associated with right frontal and parietal regions and depends heavily on the neurotransmitter norepinephrine.

Experimental Studies of Attentional and Spatial Processing

The most relevant attention system to the “NLD” cognitive phenotype is the orienting attention system. This is because it plays a role in selecting objects and locations in space for more detailed processing and is likely to support the development of some key early numerical cognitive processes.

Simon and colleagues³⁴ had children with VCFS and age-matched typical controls complete a visual search task, which is designed to test the orienting attention system. As predicted, children with VCFS had much greater difficulty than typical controls when attention was initially cued to a location other than where a target subsequently appeared. These results indicate that children with VCFS are impaired at navigating the visuospatial environment in the absence of specific indications of where to direct their attention. They are particularly handicapped when previously allocated attentional resources need to be disengaged and reallocated to other locations in a self-directed fashion.

Bish and colleagues³⁵ compared similar groups of children with VCFS to age-matched typical controls using the ANT, primarily to investigate the executive attention system, which will be discussed later. For the more reactive orienting test than the more volitional one used in Simon et al’s study there was not a significant difference between groups for what is referred to as the “invalid cue” condition, even though children with VCFS responded more slowly and did show a larger difference between the two conditions. Together, the results suggest that children with VCFS suffer from a localized impairment in the ability to volitionally search visual space in a goal directed fashion.

Scerif and colleagues³⁶ compared the performance of eight 3- to 4-year-old boys with FXS and eight similarly aged boys and girls with WS to one another and to groups of chronological and mental age-matched typical controls on a visual search task. Their task required using the orienting system to find target “monsters” hidden behind a subset of disks shown on a touchscreen. Toddlers with either disorder made more errors than did controls. While the number of errors did not differ between the two genetic disorder groups, the error types did. Toddlers with WS searched in inappropriate locations more often than those with FXS and controls. Toddlers with FXS revisited disks that had not concealed “monsters” more often than toddlers in the other two groups. In each case it is clear that processing goal directed visual attentional search is less effective in children with either FXS or WS and that these impairments, though slightly different in nature, can be detected quite early in development. Munir and colleagues³⁷ found similar results when they tested 8-15 year old boys with FXS on a similar visuospatial search task. They produced significantly fewer correct target identifications, slower responses and more incorrect identifications of distractors as targets than age matched typical controls, even those selected on the basis of having poor attentional capabilities.

Patterns of impairment in visuospatial processing and their implications for the development of higher-level abilities are not just limited to visual search. Several experiments show that mental manipulation of the spatial characteristics of objects is also impaired in children with genetic disorders. Within the context of a functional MRI experiment, Kesler and

colleagues³⁸ & this issue tested girls with monosomy Turner syndrome aged 7-18 years and typical age matched controls on the standardized Judgment of Line Orientation (JLO) task and found that they performed more poorly than controls on difficult problems. A similar group of participants was also tested during fMRI scanning³⁹ by Haberecht and colleagues on a visuospatial memory task. Girls with Turner syndrome were both less accurate and slower than controls when attempting to retain in memory and match spatial information about objects over time. Similar results to both above studies were reported by Hart and colleagues⁴⁰ using similar experimental tests before and during fMRI scans. In all of the above cases, reduced activation in parietal lobe areas that are typically associated with spatial processing was observed in the individuals with Turner syndrome.

Because of the strong contrasts in cognitive strengths and weaknesses and interesting developmental progression, Williams syndrome has attracted many experimental studies. Landau and colleagues revealed some important strengths and weaknesses regarding visuomotor and visuoconstructive processing in children with WS. They asked children with WS and typical controls matched either for mental or chronological age were asked to name everyday objects displayed on a computer screen⁴¹. The task tested object recognition processes, typically associated with temporal lobe or ventral visual processing functions, and mental rotation processes, which typically depend on parietal or dorsal stream functions. Children with WS performed as accurately as did mental age matched controls and almost as well as chronological age matched controls and adults on object recognition but they performed dramatically more poorly than their chronologically age matched peers and adults when mental rotation was required. The results indicate that children with WS may require less clarity to recognize objects (i.e. they have a relative strength in analyzing an object's features) than other children. However, they are impaired in mentally executing spatial transformations on objects to bring them into a typical "viewpoint" that facilitates recognition. In other words their impairment seems to be highly selective to the spatial domain.

A related study⁴² used the standardized Block Assembly task that requires participants to recreate a geometric pattern using a set of colored blocks. Landau et al. compared actions based on "executive mechanisms" (checking for errors, attempting repairs) or "spatial representations" (creating and maintaining a representation of the identity and location of the components of the overall shape). Results indicated that children with WS showed no executive processing impairments compared to mental age matched typical controls and adults. Instead, their impairments were attributable to poorer quality mental representations of the characteristics of the component blocks and the spatial relationships among them in the model that they were attempting to reproduce. Consistently, a study with adults who have WS⁴³ also showed a particular spatial impairment in their ability to determine whether pairs of geometric shapes could or could not be combined to complete a square. By contrast, the ability to detect matches between similar items was not impaired. This study even located the problem within the dorsal stream parietal region by showing lower activation in WS adults in a functional imaging task and reduced gray matter in the adjoining region in a structural imaging study.

Finally, Landau's group⁴⁴ showed that visuospatial impairments in children with WS also extend to their use of the orienting attention system to track moving objects. Children with WS performed much more poorly than mental age matched typical controls when tracking moving objects but not on a similar task with static objects. The results suggest that children (and adults) with "NLD"-like disorders suffer from impairments in the mental manipulation of spatial relationships within and between objects.

Simon has contended that such an ability, and thus impairments in it, will be strongly related to competence in the higher-level cognitive domain of numerical processing^{34, 45}. This is because a range of basic functions in visuospatial attention has been implicated in several

numerical subdomains. This is especially true of counting visually presented objects and reasoning about the relationships between different quantities. Quantities acquire ordinal relations that are mentally represented in linear spatial terms (e.g. two comes before three, 300 is far beyond 30). Therefore, spatial attention has been shown to be a critical component in simple numerical abilities like counting and magnitude comparison. This small but growing literature suggests that the attentional and spatiotemporal impairments described above are specific in nature and limited to particular patterns of processing. Higher-order processes, particularly in the domain of numerical cognition discussed in the next section, that depend on these basic functions also show significant impairments and it is likely that this is due to the difficulty of constructing typical higher-level competencies on the foundation of impaired basic ones.

Experimental Studies of Numerical Cognition

Simon and colleagues³⁴ showed that impaired visuospatial attentional search in children with VCFS likely contributed to poorer performance when counting items randomly arranged in visual displays that did not afford the use of eye movements or other visuomotor actions (like touching) to facilitate the process. This essentially left children only with the tool of visuospatial attention to search for and enumerate items in the display. Since enumeration of around 1-3 items, a process known as subitizing, has been shown either to operate independently of or to depend minimally on the spatial attention system⁴⁶⁻⁴⁸, the impairment was not seen until children with VCFS began to use the search-based counting process. They also made that transition for smaller set sizes (i.e. counting from 3 rather than 4 items) than was the case for controls. Similar results have apparently been found in a similar task with children with Williams syndrome⁴⁴.

In the same study, Simon et al. examined a magnitude comparison task where children were asked to determine whether a stimulus representing a specific magnitude (1, 4, 6, or 9) was larger or smaller than a memorized standard (in this case 5). Magnitudes were depicted either as patterns of dots or as Arabic numerals. Such tasks are typically carried out by comparison of one magnitude to another in terms of their position on a mentally represented “number line” with reduced “distance” between the items leading to more uncertainty due to proximity or overlap^{49, 50}. There is even evidence that brain regions commonly associated with spatial attention activate when adults and children carry out such a task^{51, 52}. Results showed that children with VCFS performed more poorly with the spatial dot notation compared to the Arabic notation. Analyses showed that control children demonstrated the typical distance effect for both notations (dots and Arabic numbers) and for both small and large numbers. In contrast, children with VCFS demonstrated a significant distance effect for small Arabic numerals only, and trended toward a typical distance effect for large numbers of dots. This suggests that the relationships between numerical magnitudes depicted in spatial terms on a putative “mental number line” were likely disturbed in the children with VCFS.

A similar experiment was used by Paterson and colleagues⁵³ with children and adults with WS whose mental age averaged 6.9 years. Results showed that the individuals with WS did not produce the standard distance effect, even though the trend was in that direction. In contrast, mental age and chronological age matched controls did show the effect. This suggests that, like children with VCFS, individuals with WS also suffer from some disturbance of space/number relationships in their mental representations.

Poor visuospatial search and disturbed representations of spatial relationships can not only have a detrimental effect on simple visual counting and approximate numerical reasoning. It can also “cascade” further into negative effects on exact arithmetical computation and several other number processing tasks. In an extension of her magnitude comparison work, Paterson

and colleagues tested the same individuals with WS and controls on 9 numerical and arithmetical tasks⁵³. Individuals with WS had considerable difficulty with almost all of the tasks and this impairment was generally much greater than that of another clinical group (individuals with Down's syndrome). Counting in a non-automatic fashion (i.e. from 25-35 or backwards) was very hard for the participants with WS, as was a task asking "what comes before?" and "what comes after?" a given number. Reading multidigit Arabic numbers aloud produced significant impairment as did serializing dots patterns with respect to numerical value and matching dot patterns to Arabic numerals. Few individuals with WS could complete the full set of addition, multiplication and addition tasks.

In related studies, Ansari and colleagues⁵⁴ examined the relative contributions of visuospatial and verbal competence to the development of counting in children with WS and mental age matched controls. Children with WS understood the cardinality principle of counting (stating the final number word as the magnitude of the counted set) as well as much younger mental age matched controls. Also they performed just as well, on the small number, and just as poorly, on the large number components, as controls on a "give a number" task where they were asked to give the experimenter a specific number of marbles from a bowl. The authors report that performance on this latter task was accounted for by the visuospatial development (measured as spatial mental age on the British Abilities Scales) of the control children. However, by contrast, performance of children with WS was accounted for by the language development (measured as verbal mental age on the British Abilities Scales). They state that "individuals with WS may rely on their relative strength in language to bootstrap or scaffold their understanding of the cardinality principle [whereas] visuo-spatial ability rather than language predicted success in the control group" p. 59. This provides further illustrations of impaired visuospatial ability in WS and the relation of that competence to numerical cognition. It is also a clear example of an atypical developmental trajectory to apparently typical performance on a given task.

Little work in this domain seems to have been done using experimental methods with children who have Turner syndrome, although one study with adults does show some consistency with the above findings. Bruandet and colleagues⁵⁵ tested 12 adults with monosomy TS and 13 age matched typical controls on 9 numerical and arithmetical tasks and did not detect many major differences in basic number processing. Adults with TS erred more on estimation questions (e.g. how long is a bus?) particularly on questions regarding length, and always in the direction of underestimating. No differences were found on a magnitude comparison task requiring the choice of the larger of two digits that varied in numerical value differences from 1 to 7. This finding may have been due either to the age of the participants or the particular individuals involved because a study by Simon et al⁵⁶, that included essentially the same task for a similar sized group of children with TS, found very large group differences. In an enumeration task similar to that of Simon et al., described above, Bruandet et al. only found differences in the subitizing range. The authors suggest that adults with TS may have been counting in this range instead of subitizing but this interpretation may be a result of how the analysis was done. Simon et al'.s study⁷⁶ with children found the major difference between children with TS and controls, but not between children with TS and those with VCFS, was in the counting range, as would be expected. The main results that Bruandet et al. report from their arithmetic tasks were slower response times but not more errors in the adults with TS. Despite the difficulty in interpretation of the results in this paper it does suggest that adults with TS have some problems with basic numerical and arithmetical processing that are somewhat consistent with the above findings. Our own studies of younger girls with TS find that the overlap with children who have VCFS and difference from age-matched controls is significant in tasks where visuospatial abilities strongly underlie numerical performance.

One other study⁵⁷ used non-experimental standardized tests to measure spatial processing in 12- to 22-year-old girls and women with TS and controls closely matched on age and other characteristics. Seven of the thirteen had monosomy TS and 6 had a mosaic form of TS. Females with TS scored significantly lower than controls on all the tests on many spatial ability tests, which is consistent with the above pattern. Several studies have reported impairments in arithmetical processing in individuals with Turner syndrome^{16, 18, 58} and some have related these to brain structure and function differences^{59, 60}.

Studies of Temporal Cognition

Surprisingly, very few experimental investigations of temporal cognition have been carried out thus far with “NLD” populations. In one such study, Debanné and colleagues⁶¹ presented 6- to 39-year-old individuals with VCFS and typical age matched controls with two temporal judgment tasks. In general, individuals with VCFS were impaired in their representation and processing of temporal information. They were less able to maintain the correct cadence in the finger-tapping task and tended to speed up, which closely parallels the general tendency to underestimate length in Bruandet’s study of individuals with Turner syndrome⁵⁵. In the temporal judgment task, they required larger intervals between two durations than the controls before they could as accurately tell them apart. This finding resembles the “distance effect” results reported for magnitude comparison, where values less close together tend to be confused more easily by affected individuals than is the case for typical controls who are able to distinguish values with smaller numerical distance between them.

Consistent with these results are the findings from several temporal processing tasks in Silbert Turner syndrome study⁵⁷. While they did not show significantly poorer performance on similar tapping tasks to the one above, girls with Turner syndrome were significantly less able to distinguish between pairs of different rhythmic patterns presented at 92 beats per minute each. This indicates that, like individuals with VCFS, these participants with Turner syndrome also had an impairment in retaining analyzing and comparing temporal information.

Summary

The results reviewed above provide strong support for the view that impairment in the cognitive endophenotype that comprises a wide range of attentional, spatial and numerical tasks is not the result of a broken space or number “module” within the neurocognitive system of children from several genetic disorders. Instead it appears to be the result of a constructive process whereby an impaired outcome emerges as the result of development along an atypical trajectory. Or, as reported by Ansari et al., typical performance is produced by the deployment of atypical processes for the task in question. The start state might be constituted such that it can produce quite typical responses to the simplest tasks. Beyond that, atypical representations and processes soon develop until the resulting competence diverges significantly from that of the typical population. Much evidence presented here suggests that this occurs in the case of early-developing attentional and spatiotemporal cognitive dysfunctions and their interaction with the demands of numerically relevant task processing. The weak foundation cannot support the construction of typical, higher-level, representations and the processes required to generate typical outputs from them. As a result, low-level dysfunctions in one or several domains subsequently “cascade” their effects to impairments in a potentially broad range of developmentally distal, higher-level tasks on which their construction depends.

A clear example comes from the work of Paterson and colleagues⁶², who showed that two- to three-year-olds with WS performed as well as mental and chronological age matched controls on a simple task requiring numerical change detection between pairs of displays containing one, two, or three objects. Variants of this task have often been interpreted as evidence for the earliest numerical competence in infants, e.g.^{63, 64} but see also^{45, 65, 66}. At very least this

shows that, in a domain where the “end state” is recognized as a hallmark of impairment for a particular genetic disorder (i.e. numerical competence in Williams syndrome) one measure of the “start state” indicates no difference at all from the typical population.

Experimental Studies of Executive Function

Since the case has been made above that much of the phenotype observed in individuals with “NLD” profiles represents the cascaded effect of attentional and spatiotemporal cognitive impairments, it is important to note that some aspects of what is called “executive function” should also be considered as essential. This is because some executive functions work in tight integration with other components of the attention system. This is especially true of the exercise of cognitive control over the process of goal directed visuospatial attentional search. The term “executive function” is used broadly to encompass many functions from planning to problem solving and working memory to inhibitory control that are associated with functions thought to depend on the frontal lobes of the brain. We shall limit discussions here to functions thought to be controlled by the “executive attention system” described earlier, namely error detection, conflict monitoring and inhibition.

In an experiment testing a close link between visuospatial search and executive control, Scerif and colleagues⁶⁷ found that male toddlers with FXS were impaired relative to typical age matched controls at suppressing eye movements to locations signaled by a cue but not subsequently rewarded with a pleasing visual stimulus. This indicates that the affected toddlers were less able to inhibit irrelevant spatial cue information and effectively manage their eye movements in order to optimally navigate a visual scene for optimal selection of relevant information. Wilding and colleagues⁶⁸ added a response-switching component to an attentional search task so that inhibition of responses to one type of stimulus was required in order to focus on the other type. The result of this requirement was that boys with FXS (aged 8 to 15 years) performed poorly. They found fewer targets and misidentified more distractors as targets than did mental age matched controls, even ones selected as having attentional problems. Experiments by Bish and colleagues³⁵ and Sobin and colleagues⁶⁹ showed that children with VCFS are significantly impaired at inhibiting the processing of irrelevant “flankers”. Flankers are stimuli on either side of a target stimulus that convey either consistent or conflicting information to that carried by the target. Children with VCFS were especially impaired when conflicting flankers were present. This showed that they too have problems processing conflicting information and inhibiting inappropriate responses to it.

By contrast, Landau et al. found that individuals with WS demonstrated relatively intact “executive mechanisms” compared to “spatial representations” when attempting to solve block design puzzles. This suggests that they do not suffer from significant impairments in this aspect of cognitive processing. Several results reported by Atkinson and colleagues⁷⁰ on “frontal” conflict-based tasks support this conclusion. Finally, while there seems to be a consensus based on standardized testing that some executive dysfunction exists in Turner syndrome, no experimental studies of specific inhibitory functions appear to have been published to date.

Comparison with Cognitive Processing in Down’s Syndrome

Few other genetic syndromes have been the subject of serious cognitive experimental investigations with the exception Down’s syndrome (DS), which has been extensively studied. Down’s is probably the most common neurodevelopmental disorder, with a prevalence estimated to be about 1:800 live births. In 95% of cases it results from a full trisomy, or three copies, of chromosome 21. Mental retardation is very common and “individuals with Down’s syndrome probably comprise the majority of infants and children with mental retardation” p. 198⁷¹. The pattern of strengths and weaknesses in this disorder is less clear and thus less

amenable to a generative explanatory framework regarding the neurocognitive basis of impairments than is the case with “NLD” populations. In general, the “caricature” of individuals with DS has been the inverse of “NLD”, i.e. extreme deficits in language abilities that exceed impairments in visuospatial and related abilities.

Because of the similarity in global intellectual impairment to individuals with Williams and males with Fragile X syndromes in particular, and because of their apparent difference in cognitive profile, individuals with DS have often been studied in cognitive experiments as a comparison group. This is the case in some of the studies described earlier. For example, in Paterson's⁵³ study of individuals with WS, nine individuals with DS were matched to those with WS on the distance effect task. In contrast to the lack of distance effect shown by the individuals with WS, those with DS “did by contrast display a robust distance effect” p.195, thus reinforcing their relative strength in visuospatial and related numerical domains. In the same study, the difficulty experienced by individuals with DS on the battery of number processing and calculation tasks was less severe than for individuals with WS although, as expected, their performance was still significantly poorer than that produced by typical controls. Yet, when Paterson and her colleagues⁶² used a simple numerical change detection task, toddlers with DS showed no evidence of detecting novel numerical set sizes while, surprisingly, those with WS did.

This finding underscores the importance of the developmental approach since very simple tests produced results in two genetic disorder populations that were exactly the opposite of what would be expected based on their “end states”. However, these findings indicate that the characteristic learning and memory impairments in DS, in particular as relates to the language domain, can be found quite early in childhood. Wilding's⁶⁸ experiment showing executive dysfunction in 8- to 15-year-old boys with FXS also included similarly aged boys with DS. Performance on the single target spatial search task produced similar impairments in boys with DS as those with FXS, although the latter group's false alarm errors were much more likely to be repetitions of the same object than was the case for boys with DS. In the alternating target search task, which involved an inhibitory component, the results were similar. So in this case, boys with DS showed similar visuospatial and executive impairments to boys with FXS though they did tend to be less perseverative.

Overall Summary

This paper presents a cognitive profile associated with the childhood presentation of several common genetic syndromes, all of which have labeled “nonverbal learning disorders”. Characteristic NLD impairments include visual perception and complex psychomotor skills, tactile and visual attention and tactile and visual memorye.g. ⁷. In order to understand and begin to explain the basis for the similar pattern of impairments the concept of a cognitive endophenotype was introduced as a way to integrate the specific components that contribute to higher-level functions in which the impairments are observed. The concept also advances the effort to more specifically link genes to complex behavioral and cognitive phenotypes. It has been argued that children with genetic disorders likely begin life with an altered neurocognitive substrate that contributes to an atypical developmental trajectory through the process of acquiring many different domains of cognitive competence. Using the example of several genetic disorders that are associated with “non-verbal learning disabilities”, the paper has explored the explanation of diverse impairments in higher-order visual, spatial, temporal, numerical and executive cognitive competencies deriving from origins in more basic attentional and spatial cognitive dysfunctions. These dysfunctions imply, and a small amount of evidence now demonstrates, that congenital or early developing changes in the neural substrate also exist and contribute to atypical development.

Understanding the cognitive impairments of children with genetic disorders in this way has several implications. Primarily, it provides a more unifying account for understanding the variety of cognitive and behavioral disturbances that are observed in children with genetic disorders. Further, from the perspective of basic science, this approach can help to reduce the complexity in identification of the genetic basis of specific impairments and of structure and function relationships between brain and cognition. From the perspective of translational science, it is hoped that this approach will lead to evidence-based, targeted interventions ranging from pharmacotherapy to early cognitive and behavioral “brain training”.

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