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Review article

Cognitive phenotype of velocardiofacial syndrome: A review

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ABSTRACT

The behavioural phenotype of velocardiofacial syndrome (VCFS), one of the most common human multiple anomaly syndromes, includes developmental disabilities, frequently including intellectual disability (ID) and high risk of diagnosis of psychotic disorders including schizophrenia. VCFS may offer a model of the relationship between ID and risk of major mental health difficulties. This paper reviews literature on the cognitive phenotype and its relationship with a polymorphism of the gene coding for catechol O-methyltransferase (COMT), a gene haploinsufficient in VCFS which modulates prefrontal dopamine levels. Principal features of the variable cognitive phenotype of VCFS in young people are ID, superiority of verbal over performance I.Q. and verbal over visuospatial memory, and difficulties with number and object magnitude comparisons, time perception and memory for serial order, and orienting of attention. Despite some improvements with age, problems with higher order attentional tasks involving planning persist, possibly modulated by COMT activity levels. Candidate cognitive endophenotypes include problems with retrieval of contextual information from memory and in executive control and focussing of attention. Longitudinal research using common core batteries of psychometric assessments, and experimental measures of cognitive function capable of direct translation for use with animal models, will further advance understanding of the developmental dynamics of VCFS.

Contents

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1. Introduction

Velocardiofacial syndrome (VCFS) is one of the most common multiple anomaly syndromes in humans, with an estimated prevalence of 1:4000 (Gothelf & Lombroso, 2001; Shprintzen, 2005, 2008). The syndrome results from an autosomal dominant microdeletion on the long (q) arm of chromosome 22. The microdeletion, which occurs *de novo* at the 22q11.2 region in approximately 90% of cases and is inherited in approximately 5–10% (Prescott & Scambler, 2005), gives the syndrome its most common alternative label of 22q11.2 deletion syndrome (22q11.2DS). Most persons with VCFS have a 3 Mb interstitial deletion, but a minority have smaller deletions of 1.5–2 million base pairs, and in rare cases terminal deletions and balanced translocations also cause the syndrome (Prescott & Scambler, 2005). The phenotypic presentation of VCFS is extensive and shows substantial variability across individuals (Ryan et al., 1997). The characteristic behavioural phenotype involves high rates of behavioural, psychiatric, neuropsychological and communication disorders (Stevens & Murphy, 2005). A salient feature in the cognitive phenotype of VCFS is intellectual disability (ID) (De Smedt et al., 2007a; Jones, Morley-Canellas, Owen, & Murphy, 2001; Murphy, Jones, Griffiths, Thompson, & Owen, 1998). The 22q11.2 microdeletion represents one of the highest risk factors for diagnosis of schizophrenia and other psychotic disorders (Murphy & Owen, 2001; Stevens & Murphy, 2005). VCFS thus presents a specific model for understanding relationships between cognitive disabilities and the development of severe mental health problems. In this paper we review research on the cognitive phenotype of VCFS.

2. Overall cognitive phenotype in VCFS

Interest in a possible cognitive phenotype of VCFS emerged early in the study of the disorder. Kok and Solman (1995), reporting on the use of computer-assisted instruction with 6 children with VCFS, noted problems with attention and impulsiveness in their students. Swillen et al. (1997) completed formal developmental or intelligence tests with 37 children and young people (age 3 months–20 years). For the 20 children tested with Wechsler (WPPSI or WISC-R) scales, the mean verbal I.Q. (VIQ) of 78 was significantly higher than the mean performance I.Q. (PIQ) of 70. Subtest profiles for children tested using the WISC-R suggested specific difficulties with perceptual–spatial and planning abilities. Addition of another 66 children to this initial sample (De Smedt, Devriendt et al., 2007) found a range of full-scale I.Q. (FSIQ) from 50 to 109, normally distributed around a mean of 73, and confirmed that for the whole group VIQ was significantly higher than PIQ. Thirty-seven (36%) of the young people had FSIQs between 55 and 70, while 4 (3.9%) had FSIQs below 55. De Smedt et al. (2007a) noted that whereas an elevation of verbal over performance I.Q. of over 15 points was found in 18 children, 5 showed a similar discrepancy in favour of PIQ.

Other studies have confirmed an overall cognitive phenotype comprising developmental delay, problems in motor development, attentional difficulties (especially with attention-shifting rather than simple sustained attention), extensive difficulties with both receptive and expressive language, frequent but not universal superiority of VIQ over PIQ, and better performance in reading than mathematics and in verbal memory compared with visuospatial memory. Measures of development and language do not differ between subgroups of children with and without the cardiac disease which is a common feature of the physical phenotype, but children with a familial deletion have significantly lower mean developmental scores than those with *de novo* deletions (Eliez et al., 2000; Gerdes et al., 1999; Glaser et al., 2002; Scherer, D'Antonio, & Kalbfleisch, 1999; Scherer, D'Antonio, & Rodgers, 2001; Shprintzen, 2000; Swillen et al., 1999; Woodin et al., 2001). Sobin et al. (2005) however, contrary to the findings of most previous studies, found that the performance of 40 children with VCFS (ages from 5 to 12) on a measure of verbal ability (Stanford-Binet Vocabulary subtest) was not superior to their performance on a test of mathematical abilities (Stanford-Binet Quantitative subtest) although performance on a test of verbal memory (Stanford-Binet Sentence Recall) was superior to that on a test of visuospatial memory (Stanford-Binet Bead Memory). Sobin et al. suggested that the previously found superiority of verbal abilities might become evident only with older children for whom assessments of mathematical skills presented more conceptually challenging tasks.

In the first systematic study of the cognitive phenotype of adults with VCFS, Henry et al. (2002) compared the performance of 19 adults with VCFS on a range of neuropsychological assessments with that of a control group of people with mild intellectual disability or borderline intellectual functioning. No significant differences were found between the groups on FSIQ, VIQ, PIQ, or VIQ-PIQ discrepancy; six participants with VCFS had a significant (11 or more points) advantage for VIQ, but three showed a significant advantage for PIQ, and 10 showed no significant discrepancy. No differences were found between the groups on tests of verbal and visual memory, simple sustained attention, cognitive flexibility, spatial working memory, and verbal fluency. The VCFS group did however perform less well than control participants on two subtests of the Visual Object and Space Perception Battery (Warrington & James, 1991), Silhouettes and Object Decision, both assessing object perception rather than space perception, suggesting problems in right parietal functioning. Results from a test of planning ability (Tower of London Test: Morris et al., 1988) showed that participants with VCFS performed worse while using less planning time than control participants, reflecting possible difficulties with impulsivity and/or planning ability related to frontal or prefrontal lobe functioning.

3. Analysis of the cognitive phenotype in VCFS

3.1. Discrepancy between verbal and visuospatial memory performance

Early studies thus demonstrated that although the scale of the discrepancy may reduce with age, children with VCFS frequently showed higher VIQ than PIQ. Bearden, Woodin, Wang, and Moss (2001), in a study of 29 children aged 5–17,

sought to further define the nature of the difficulties encountered by children with VCFS. The children's mean WISC-3 VIQ was significantly higher than their PIQ, their mean WISC-3 Verbal Comprehension factor score was significantly higher than their Perceptual Organization factor score, and mean Wechsler Individual achievement test reading composite score was significantly higher than mathematics composite score. Comparisons of standardized scores showed that the children's verbal memory performance (WRAML Verbal Learning test: Sheslow & Adams, 1990) was significantly better than their visuospatial memory performance (CMS Dot Locations test: Cohen, 1997). Further, mean score on a measure of nonverbal (object) memory not involving memory for spatial location (WRAML Design Memory: Sheslow & Adams, 1990) significantly exceeded that for Dot Locations but did not differ significantly from that for Verbal Learning. The magnitude of the difference between scores on visuospatial and verbal memory tests was not related to FSIQ. Bearden et al. (2001) suggested that the difficulties of children with VCFS might be linked to disruption of right posterior parietal processing of information on the spatial location of objects. Majerus, Glaser, Van der Linden, and Eliez (2006) showed further in a study of 8 children with VCFS that although they performed comparably to typically developing control participants on tasks involving immediate recall of words and nonwords independent of correct serial position, several experienced difficulties in recalling or recognising the correct serial position of items.

Simon et al. (2002), following Wang, Woodin, Kreps-Falk, and Moss's (2000) observation that arithmetical ability might be associated with visuospatial memory, suggested that the performance of children with VCFS on simple arithmetical operations, such as judging relative magnitude of two values, might be impaired because such operations are typically performed on the basis of spatial representations of the quantities involved. Simon et al. also observed that dissociation of performance on tests of memory for object appearance from that on tests for memory of object location was consistent with research suggesting that these properties of visually perceived objects are processed by distinct neural processing pathways (Ungerleider & Haxby, 1994). Lajiness-O'Neill et al. (2005) evaluated this hypothesis that aspects of the cognitive phenotype of VCFS might result from disruption of the dorsal occipitoparietal pathway responsible for processing information about object location. Nine children with VCFS (mean FSIQ 70), eight of their siblings (mean FSIQ 102), 11 children with autistic disorder (mean FSIQ 90) and 14 children functioning within the low average range of intellectual ability (mean FSIQ 89) completed a comprehensive test of memory functioning, the Test of Memory and Learning (Reynolds & Bigler, 1994). Unlike the children with autism or the control group of children with I.Q. in the low average range, both children with VCFS and their siblings performed better on two subtests of verbal memory than on two subtests of nonverbal memory. The four groups did not however differ in their performance on the "Visual Selective Reminding" subtest despite the fact that the task involved requires processing of spatial locations and is not obviously amenable to use of verbal strategies. Lajiness-O'Neill et al. (2005) argued that their finding of a verbal/nonverbal memory discrepancy in both children with VCFS and their siblings implied that the discrepancy might not be directly related to the 22q11.2 deletion, perhaps resulting instead from some factor which both contributes to the verbal–nonverbal discrepancy and increases risk for the deletion.

3.2. Difficulties with arithmetic

Simon, Bearden, McDonald-McGinn, and Zackai (2005) examined performance on a task requiring the child to say as fast as possible how many objects were presented on a computer screen. In the subitizing ranges in which the number of objects is immediately perceived without counting (1–2 objects for children with VCFS and 1–3 for comparison children) the slope of the increase in reaction time with number of objects did not differ between children with VCFS and comparison children. However, when counting processes were engaged, the slope for children with VCFS was significantly steeper than that for the comparison group. Simon et al. (2008) reported similar results on a task requiring participants to indicate which of two bars varying in height, or which of two numbers, was greater.

De Smedt, Devriendt et al., 2007 provided a finer-grained analysis of the difficulties which children with VCFS experience with mathematics. Eleven children (aged 10–12) with VCFS performed as well as 11 control children on number reading, counting backwards, dot counting, single-digit multiplication, and single-digit addition and subtraction with no carrying over. Children with VCFS were significantly slower than control participants on comparison of numbers differing by one only, counting forwards, and single-digit addition and subtraction with carrying. Analysis of strategies used in single-digit arithmetic showed that children with VCFS were as fast as control participants in solving problems using a retrieval strategy (i.e., no calculation process was reported) but slower in applying calculation strategies. De Smedt et al. suggested that this pattern of results suggested that children with VCFS had no impairment of the verbal subsystem involved in number processing, based in the angular gyrus, but were impaired in the quantity subsystem based in the intraparietal sulcus (Dehaene, Piazza, Pinel, & Cohen, 2003). De Smedt et al. (2009) provided further evidence for a specific quantity subsystem impairment in children with VCFS, who were shown to be significantly slower than typically developing comparison children on number comparison but not number reading. Consistent with the hypothesis that this quantity subsystem deficit underlies their arithmetical difficulties, number comparison performance of children with VCFS was associated with their performance on single-digit subtraction and harder problems in single-digit addition and multiplication. Further support for the possibility of a specific difficulty in comparison of quantities has been provided by the finding that people with VCFS also experience difficulties with perception of time (Debbané, Glaser, Gex-Fabry, & Eliez, 2005).

3.3. Attention

As noted earlier, people with VCFS also experience problems with attention (Lewandowski, Shashi, Berry, & Kwapil, 2007), frequently meeting diagnostic criteria for the "inattentive" subtype of ADHD (Antshel et al., 2007; Niklasson, Rasmussen, Óskarsdóttir, & Gillberg, 2009). In a series of elegant experiments Simon and his colleagues (Bish, Chiodo, Mattei, & Simon, 2007; Simon et al., 2005) have demonstrated that children with VCFS have particular difficulties with orientation of attention in space. Studies of measures of "executive function" have produced less clear results, frequently finding deficits on some measures but not others when I.Q. is taken into account (Lewandowski et al., 2007).

4. Possible cognitive endophenotype in VCFS

Three streams of work have considered whether some or all of the apparently diverse features of the cognitive phenotype associated with VCFS can be explained as resulting from an underlying impairment or set of impairments comprising a cognitive endophenotype. Debbané, Glaser, and Eliez (2008) examined integrity of encoding and retrieval processes in the memory performance of 33 adults and children with VCFS and 33 age and gender matched typically developing participants. Results from a task in which each word in a visually presented list was followed by a cue indicating that the word was to be remembered or forgotten showed that participants with VCFS showed a normal "directed forgetting" effect (i.e. more "to be remembered" than "to be forgotten" words were subsequently correctly recognised) suggesting appropriate selective encoding in persons with VCFS. Participants with VCFS however mistakenly "recognised" more distractor items as words previously studied. In a second experiment, participants viewed a series of sets of pictures with some items repeated both within and across lists; the task was to indicate whether each item was novel or repeated within the current list, i.e. a picture previously seen in a preceding list was to be classified as "novel" within the current list. Participants with VCFS and typically developing controls did not differ in correct recognition of within-list repetitions, but participants with VCFS classified more previous-list distractors as current-list repetitions than the control group, suggesting a deficit in retrieval of temporal contextual information associated with test items reflecting possible difficulty in selectively retrieving relevant information.

Sobin et al. (2004), hypothesizing that difficulties with visual attention and executive function might underpin the difficulties of children with VCFS in arithmetic and visuospatial memory, examined the performance of 32 children with VCFS and 20 of their siblings on an "attention network test" (ANT) in which participants were asked to identify the orientation of a stimulus either presented alone or accompanied by four flanker stimuli, two on either side of the primary stimulus, which might be congruent (pointing in the same direction as the primary stimulus) or incongruent (pointing in the opposite direction). Executive network scores (reaction time with incongruent flankers minus reaction time with congruent flankers) were significantly larger for children with VCFS than for control siblings, consistent with difficulties with executive control of visual attention in the children with VCFS. Sobin, Kiley-Brabeck, and Karayiorgou (2005a) subsequently demonstrated that children with VCFS also showed reduced prepulse inhibition (PPI) (the reduction in startle response to an intense stimulus observed when that stimulus is preceded by a related stimulus of an intensity not producing a startle response) by comparison with sibling controls. Modulation of PPI is believed to depend on pathways linking prefrontal cortex and basal ganglia structures, and Sobin, Kiley-Brabeck, and Karayiorgou (2005b) showed that PPI and executive network scores were inversely related, consistent with these nonredundant measures of attentional processing depending on a common deficit in prefrontal control.

In addition to deficits in memory retrieval processes and executive function, a third potential cognitive endophenotype in VCFS has been proposed by Simon (2008), who hypothesised that the difficulties which persons with VCFS experience in processing spatial, temporal and numerical information result from developmental changes in the structure and function of neural networks processing timing information and controlling spatial attention, resulting in a reduction in resolution of the mental representations associated with these processes which Simon refers to as "spatiotemporal hypergranularity". The difficulties which children with VCFS experience in enumerating objects, comparing quantities, comparing intervals, and focussing attention are hypothesised to result from this hypergranularity and to underpin their difficulties with arithmetic and visuospatial memory.

5. Effects of COMT genotype on cognitive functioning

One of the genes mapping to the region of chromosome 22 deleted in VCFS codes for catechol O-methyltransferase (COMT), an enzyme particularly important in metabolism of dopamine in the prefrontal cortex (PFC) (Boot et al., 2008). A functional polymorphism involving a valine/methionine substitution is associated with higher or lower activity of COMT. A variety of evidence implicates COMT genotype as a possible risk factor for a range of psychiatric symptomatology (Bearden et al., 2005) but despite the proposal that deficits in prefrontal functioning may underlie a range of cognitive difficulties in VCFS, few studies have examined the potential effect of COMT genotype on cognitive function. Bearden et al. (2004) reported that after controlling for I.Q., their 16 Met-hemizygous participants performed significantly better than 28 Val-hemizygous participants on two measures related to executive function, namely Trails B and WISC-3 digit span. However, Baker, Baldeweg, Sivagnanasundaram, Scambler, and Skuse (2005) comparing the performance of 25 adolescents with VCFS and 25 comparison participants matched for age and I.Q. on a variety of measures including tests of verbal and visuospatial working

memory, found that for both cognitive measures the control group outperformed VCFS Met-hemizygous but not VCFS Val-hemizygous participants, with the two VCFS groups not differing significantly.

Subsequent studies have found higher FSIQ and VIQ, Wechsler Individual Achievement Test Broad Mathematics scores, and performance on a measure of sustained attention, for Met-hemizygous children but no difference between Met-hemizygous and Val-hemizygous children on measures relevant to executive function (Shashi et al., 2006), no differences between the performance of Met-hemizygous and Val-hemizygous children and adults on a battery of measures of I.Q., immediate and delayed visual and verbal memory, and executive function (Glaser et al., 2006) and nonsignificant trends for Met-hemizygous girls but not boys to score better than Val-hemizygous participants on the total trials to first category measure on the Wisconsin card sorting test and for Met-hemizygous participants to score better than Val-hemizygous participants on the perseverative errors measure (Kates et al., 2006). Takarae, Schmidt, Tassone, and Simon (2009) examined the effect of the COMT Val/Met polymorphism on "conflict adaptation" in a version of the ANT described above. Conflict adaptation occurs when performance improves on trials preceded by trials with the same flanker condition (congruent vs. incongruent). Previous research (Bish, Ferrante, McDonald-McGinn, Zackai, & Simon, 2005) had demonstrated that children with VCFS showed conflict adaptation on successive trials with congruent flankers, but deterioration in performance over successive trials with incongruent flankers. Takarae et al. found that the response times of 16 Met-hemizygous and 11 Val-hemizygous children with VCFS, and 21 typically developing children, showed no difference between groups on conflict adaptation over sequences of congruent trials, but evidence for impaired conflict adaptation over sequences of incongruent trials for (some) Met-hemizygous, but not Val-hemizygous, participants. Gothelf et al. (2005) reported results from a prospective longitudinal study in which 24 participants with VCFS and 23 participants with idiopathic developmental disabilities matched for age, gender, ethnicity and I.Q. were evaluated in childhood and followed up in late adolescence or early adulthood. The VCFS group showed a significant decline in verbal I.Q. and on a measure of expressive language between initial assessment and follow-up, with Met-hemizygous participants showing greater declines in verbal I.Q., expressive language score, and prefrontal cortex grey matter volume, than did Val-hemizygous participants. Participants with idiopathic developmental disabilities showed no marked changes over time in verbal I.Q. or expressive language score.

Overall, therefore, although two studies have found higher intellectual or academic or attentional or executive functioning in Met-hemizygous than in Val-hemizygous children with VCFS, others find no effect of COMT genotype, nonsignificant trends, or contrary results. Findings on effects of COMT genotype on various measures regarded as relevant to executive function are particularly variable. Vorstman et al. (2009) have recently demonstrated that smooth pursuit eye movement (SPEM) performance, which is believed to depend on dopaminergic signalling in the PFC, is impaired in Met-hemizygous children and adolescents with VCFS who have high plasma proline levels, possibly via increases in PFC dopamine levels stimulated by increased hippocampal glutamatergic signalling modulated by proline. Proline dehydrogenase (PRODH), the enzyme catalyzing the first stage in proline metabolism, is also encoded by a gene located at 22q11.2; however, plasma proline levels are elevated in only approximately 50% of persons with VCFS (Vorstman et al., 2009). Variability in proline levels may therefore account for the impact of the COMT polymorphism on PFC-dependent cognitive functions such as executive function. Gothelf et al.'s (2005) finding of greater longitudinal decline in measures of intellectual functioning associated with Met-hemizygosity is consistent with the hypothesis of an inverted *U*-shape relation between PFC functioning and PFC dopamine level. Possibly therefore aspects of the intellectual performance of Met-hemizygous children benefit from higher levels of prefrontal dopamine, but further increases in dopaminergic signalling during adolescence raise PFC dopamine levels in Met-hemizygotes to levels which impair cognitive performance.

6. Methodological issues, conclusions, and future directions

VCFS is known to be extremely variable in its phenotypic expression (Ryan et al., 1997) and its cardiovascular, craniofacial and thymic manifestations are partially understood as a consequence of disturbance of developmental pathways resulting from deletion of the TBX1 gene located within the deleted region, modified by other genetic, environmental, and stochastic processes (Aggarwal & Morrow, 2008). Aspects of the cognitive phenotype of VCFS, such as the degree and direction of discrepancy between PIQ and VIQ, appear equally variable across individuals and probably vary in the course of development. Results from recent longitudinal studies including volumetric brain measurements suggest disordered or delayed patterns of brain maturation in young people with VCFS (Schaer et al., 2009).

Although some discrepancies in results between studies remain to be resolved, the principal features of the cognitive phenotype of VCFS in young people are now relatively well established and comprise intellectual disability, superiority of VIQ over PIQ, and better performance in reading than mathematics. The VIQ/PIQ discrepancy however appears to be less robust than a superiority of verbal compared with visuospatial memory. The difficulties of children with VCFS in mathematics are underpinned by difficulties in counting, comparison of numbers of objects outside of subitizing ranges, and comparisons of object and numeral magnitude. These difficulties impair the performance of children with VCFS on arithmetical tasks involving counting and/or use of calculation strategies, while leaving unimpaired performance on (sometimes superficially more difficult) problems by direct verbal retrieval of solutions. Difficulties with visuospatial memory and judgement of quantity are accompanied by difficulties in perception of time and memory for serial order. Attentional difficulties in children with VCFS have been less analysed than memory difficulties, but appear to involve primarily difficulty in orienting and refocusing attention, particularly across space rather than within objects, rather than sustaining attention once focussed. Candidate cognitive endophenotypes involving impairment of retrieval of contextual

information from memory, compromised executive control of visual attention, or difficulties in focussing of attention leading to reduced resolution of mental representations of spatial, temporal and numerical information, have been proposed. The extent to which other specific difficulties experienced by children with VCFS, such as in processing of facial information, can also be explained in terms of more fundamental difficulties with attention and memory remain to be investigated.

The limited research on adults with VCFS suggests that many of the specific difficulties experienced in childhood may improve over the course of development, but that difficulties with higher-order attentional tasks involving planning may continue. Imaging studies using volumetric MRI, fMRI and DTI suggest that children with VCFS have reduced parietal volumes and possibly reduced connectivity between white matter tracts and adjacent parietal cortex, with increases in activity possibly compensating for structural impairments when these children engage in cognitive tasks typically recruiting parietal areas (Karayiorgou, Simon, & Gogos, 2010). The improvement seen with age may reflect some degree of improvement in structural abnormalities as delayed maturational processes proceed (Schaer et al., 2009).

Understanding of the cognitive difficulties of persons with VCFS has advanced substantially in what is still a limited period of research. Nevertheless, many questions remain unresolved and existing research displays several methodological limitations. Although several research groups have now begun to make progress on longitudinal studies of substantial cohorts, many studies to date have used relatively small samples and have relied primarily on cases identified through clinical referral. Given the variability of expression of the syndrome, the possibility of gender, age and I.Q. effects on aspects of cognitive functioning in people with VCFS (Antshel, AbdulSabur, Roizen, Fremont, & Kates, 2005; Jacobson et al., 2010) the possible effects of COMT genotype, and the possibility that varying proportions of participants may experience mental health difficulties impacting on performance, it is therefore often possible that findings from individual studies may prove of limited generalizability, and instances of contradictory findings between studies may result from sample differences. Moves towards larger multi-centre studies are therefore to be welcomed. However, a recent study which controlled the above sources of variability by including only children and adolescents with I.Q. $\leq$ 80 and no psychiatric diagnoses, and compared individuals' performances on Wechsler scales generating directly comparable I.Q. and index scores, replicated earlier results on the superiority of VIQ to PIQ; further, although no significant difference was found between verbal and visuospatial memory indices, supplementary analyses suggested a relative weakness of visuospatial memory (Jacobson et al., 2010).

With the exception of the use of the Wechsler intelligence and memory scales, and possibly the use of versions of the continuous performance test of attention, there has been limited consensus on use of specific neuropsychological tests to measure specific functions in VCFS. Use of a consistent core battery of assessments of intelligence, memory, and different aspects of attentional function across studies would enable a clearer distinction between fundamental agreements and conflicts of findings and those which may relate to differences in psychometric measures employed. Difficulties in selecting appropriate control groups have often been discussed in the studies reviewed above, and although most agree that ideally controls would include typically developing children matched for age, a group of siblings of children with VCFS, and either a group of participants with comparable intellectual difficulties of varied aetiology, or several groups with intellectual difficulties of defined aetiology, only a small number of studies have approached or achieved these ideals. The need for longitudinal studies has been equally frequently identified by researchers in the field. Finally, although potentially invaluable animal models of VCFS exist (Paylor & Lindsay, 2006) there have been few attempts in clinical research to examine cognitive functions using techniques which can also be used directly in animal studies. For example, prepulse inhibition, an index of basic attentional "gating" often used in animal studies, could also be used in clinical studies, while analogues of the attentional tasks used, for example, by Gothelf et al. (2007) and Simon et al., 2005 could possibly be developed for use with animals.

People with VCFS present a distinctive but dynamic and developing cognitive phenotype together with a high risk of experiencing severe mental health problems. The syndrome offers a potentially valuable model for understanding relationships between brain development, cognitive development, and the experience of mental ill-health. In a companion paper to this we describe the behavioural and psychiatric phenotype and discuss the extent to which cognitive difficulties may contribute to the development of these problems. Further longitudinal studies, preferably employing a consistent core battery of cognitive measures including some which can be directly compared with data from studies of animal models of the disorder, will advance our understanding of this intriguing condition.

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