A MULTIPLE CASE STUDY OF VERBAL SHORT-TERM MEMORY IN VELOCARDIOFACIAL SYNDROME.

Steve Majerus
University of Liege and Fonds National de la Recherche Scientifique, Belgium

Bronwyn Glaser, Martial Van der Linden and Stephan Eliez
University and University Hospital of Geneva, Switzerland

RUNNING TITLE: verbal STM in VCFS

Corresponding Author:
Steve Majerus
Department of Cognitive Sciences
University of Liege
Boulevard du Rectorat, B33
4000 Liege, Belgium
Tel: 0032 4 366 4656
Fax: 0032 4 366 2808
Email: smajerus@ulg.ac.be

Abstract

Background. Velo-cardio-facial syndrome (VCFS, 22q11.2 deletion) is characterized by severely delayed language development. The current study explored the integrity of verbal short-term memory, a cognitive function critically involved in language development, in 8 children with VCFS.

Method. Using a multiple case study design, we presented a series of short-term memory tasks exploring immediate serial recall for word and nonword lists to 8 children with VCFS (aged 8-12 years) and to chronological age-matched control groups. A first task assessed the integrity of phonological coding in verbal short-term memory by comparing recall for phonologically similar and dissimilar words. Subsequently, the interaction between verbal knowledge and short-term memory capacity was investigated by comparing recall for high and low imageability words, for high and low frequency words, and for words and nonwords. A final task assessed short-term serial order recognition for digit sequences.

Results. When computing the number of items recalled in the word recall tasks, independently of their serial position, only one patient presented consistent difficulties. Short-term recall of nonwords was normal in each patient. Phonological similarity and verbal knowledge influenced short-term memory performance to a similar extent in patients with VCFS and controls. On the other hand, when applying a strict serial recall criterion, difficulties with the word and nonword recall tasks were observed in most patients. Half of the patients were also impaired in the serial order recognition task.

Conclusions. Despite mild mental retardation, it is possible for short-term retention capacities for verbal *item* information to be at an age appropriate level in velo-cardio-facial syndrome. However, short-term memory for serial *order* information could be impaired more specifically.

Introduction

Velo-cardio-facial syndrome (VCFS) is a relatively frequent congenital, autosomal dominant condition defined for the first time by Shprintzen *et al.* (1978). Its prevalence is estimated at 1 per 6000 live births (Botto *et al.* 2003). In approximately 97% of the patients, a variably sized de novo deletion at chromosome 22q11.2 is responsible for the syndrome (Carlson *et al.* 1997; Driscoll *et al.* 1993; Lindsay *et al.* 1995; Scambler *et al.* 1992). The major features of velo-cardio-facial syndrome include cardiac malformations, cleft palate or velopharyngeal insufficiency, a characteristic facial appearance, and learning disabilities. More than 100 physical anomalies have been observed in association with the syndrome (Goldberg *et al.* 1993; Ryan *et al.* 1997). Further, VCFS is characterized by a high prevalence of psychiatric disorders, including schizophrenia in adolescence and adulthood (Murphy 2004; Murphy *et al.* 1999; Murphy & Owen 1996; Shprintzen *et al.* 1992). VCFS also has been associated with neuroanatomical abnormalities. A significant decrease of gray matter volume in the left parietal lobe, but increased gray matter volume in bilateral frontal areas has been found in affected children and adolescents (Eliez *et al.* 2000). Although gray matter volume in the temporal lobes is not significantly decreased in children, relative to whole brain volume (Eliez *et al.* 2000, 2001a), adults seem to present a more specific reduction of gray matter in the right temporal lobe and an increase in the left temporal lobe (Van Amelsvoort *et al.* 2001). Finally, widespread abnormalities in white matter tracts, including the frontal, parietal and temporal lobes, have been associated with children and adults with VCFS (Barnea-Goraly *et al.* 2003; Van Amelsvoort *et al.* 2001).

At the cognitive level, velo-cardio-facial syndrome (VCFS) is characterized by general intellectual functioning ranging from moderately retarded to low normal intelligence. Specifically, the associated cognitive profile appears uneven, with verbal abilities being often less impaired than visuo-spatial abilities. Individuals with VCFS generally present higher verbal than performance scores on standard intelligence tests. (Gerdes *et al.* 1999; Goldberg *et al.* 1993; Golding-Kushner *et al.* 1985; Moss *et al.* 1999; Swillen *et al.* 1997). Similarly, verbal long-term memory seems to be more preserved than visuo-spatial long-term memory or visuo-spatial perceptual abilities (Bearden *et al.* 2001; Henry *et al.* 2002). However, despite the relatively stronger verbal abilities, initial language development is severely delayed, verbal production usually appearing not before 30 months of age (Scherer *et al.* 1999, 2001; D'Antonio *et al.* 2001). Important improvements are then noticed between age 3-4 years of age (Shprintzen 2000; Solot *et al.* 2001). School-aged children perform close to or in the normal range on phonological tasks such as sentence repetition, reading and meta-phonological awareness (De Smedt *et al.* 2003; Glaser *et al.* 2002). However, semantic and conceptual aspects appear to be weaker, with impairments observed on semantic relationship judgment, semantic categorisation and reading comprehension tasks, though studies are not entirely consistent on this subject (Glaser *et al.* 2002; Moss *et al.* 1999; Swillen *et al.* 1997; Wang *et al.* 2000).

In sum, language in VCFS is characterized by a severe delay in both receptive and productive aspects of language development, but substantial developments are observed after 3-4 years for phonological processing, with persisting impairments in lexico-semantic and conceptual processing. The present study focuses on one of the factors that could contribute to this abnormal language development in VCFS: verbal short-term memory. In typically developing children, a substantial body of research has shown that verbal short-term memory capacity predicts many aspects of language development, such as productive and receptive vocabulary knowledge, speed of acquisition of new lexico-semantic information and sentence production (Adams & Gathercole 1995, 1996, 2000; Avons *et al.* 1998; Bowey 1996; Gathercole 1995; Gathercole & Adams 1993, 1994; Gathercole & Baddeley 1989, 1990, 1993; Gathercole *et al.* 1991,1992, 1999; Michas & Henry 1994; Service 1992). Moreover, children with developmental verbal short-term memory impairments display severe difficulties in acquiring a new vocabulary and foreign language vocabulary (*e.g.*, Hanten & Martin 2001). These empirical data have led to the development of a number of short-term memory models presenting strong interactions between verbal short-term memory and language processing (e.g., Baddeley *et al.* 1998; Gupta & MacWhinney 1997; Hartley & Houghton 1996). Certain models even consider verbal short-term memory to be a necessary gateway through which new verbal information entering long-term memory must pass (e.g., Baddeley *et al.* 1998).

Given these developments and given the relatively poor development of lexico-semantic language abilities in VCFS, we would expect verbal short-term memory capacity to be reduced. On the other hand, other aspects involving verbal short-term memory, such as sentence repetition, have been shown to be closer to the normal range than other language tasks (e.g., Glaser *et al.* 2002). However, it must be noted that in the study by Glaser *et al.* the standard score for sentence repetition (6.8) was nevertheless much lower than would be expected for normal children (10), and thus it is likely that a significant difference would have been obtained when comparing this group to a group of typically developing children. Only one study explored verbal short-term memory directly in VCFS : Wang *et al.* (2000) showed that mean digit span in a group of 36 children with VCFS was in the normal range, but once again, overall performance was nevertheless lower than would be expected for typically developing children and a number of children showed performance clearly outside control range. Furthermore, the Wang *et al.* study did not investigate short-term memory for other verbal material such as words or nonwords, nor did it specifically conduct a more qualitative exploration of the cognitive processes involved in verbal short-term memory functioning. Thus the status of verbal short-term memory functioning in VCFS remains largely undetermined and unexplored. In this study, we report a detailed investigation of both quantitative and qualitative aspects of verbal short-term memory processing in VCFS.

First, we determined memory span for phonologically similar and dissimilar words. In healthy children and adults, recall of lists of phonologically dissimilar words is superior to that of similar words (Baddeley 1966; Conrad & Hull 1964). The presence of a phonological similarity effect signals normal phonological coding of verbal information in short-term memory. Second, we investigated STM performance for immediate serial recall of nonwords. Nonword recall has been considered to be a relatively sensitive and pure measure of verbal short-term memory capacity, and is very closely related to vocabulary development in normal children (e.g., Gathercole *et al.* 1991, 1992). Third, we explored the interaction between language development and verbal short-term memory more directly, by comparing recall of high and low frequency word lists, high and low imageability word lists and word and nonword lists. Multiple studies in normally developing children and adults have shown higher recall for high frequency vs. low frequency words, for highly imageable vs. poorly imageable words, and for words vs. nonwords. (e.g., Gathercole *et al.* 1999; Hulme *et al.* 1991, 1997; Majerus & Van der Linden 2003; Walker & Hulme 1999). The presence of these effects of language knowledge indicates that short-term memory performance is also influenced by activation of lexico-semantic language knowledge (Majerus *et al.* 2004). Finally, we designed a short-term recognition task targeting specifically the retention of serial order information. In standard word and digit span tasks, item (i.e., recall of the words and their phonological and semantic caracteristics) and serial order information (i.e., the order in which the words are presented) are often confounded. However, many authors currently consider the processes underlying storage and recall of these two types of information as distinct (e.g. Burgess & Hitch 1999; Henson *et al.* 2003). This is also supported by a recent neuroimaging study showing that the retention of serial order information and not item information is specifically associated with the left parietal cortex (Marshuetz *et al.* 2000), a brain region where a specific reduction of gray matter has been found in children and adults with VCFS (Eliez *et al.* 2000, 2001a).

These tasks were administered to 8 children with VCFS with a mean age of 9 years 7 months and to age-matched control groups. We adopted a multiple case study design in order to take into account the heterogeneity that is typically observed in most neuro-genetic syndromes and which is likely to bias group analyses (e.g., Murphy 2004). With respect to the tasks used, several predictions are possible: (1) A reduction of general storage capacity in verbal short-term memory; in that case, we should observe poor recall on all short-term memory tasks but normal effects of phonological similarity and language knowledge; (2) Impaired phonological coding processes, in which case we should see reduced phonological similarity effects as well as poor recall on the different short-term memory tasks; (3) Impaired language knowledge; in that case, we should observe abnormal effects of language knowledge and especially poor recall performance on infrequent and low imageability word lists; (4) Difficulties with retaining serial order information, in which case performance should be poor for the serial order recognition task as well as for the other tasks when counting words correctly recalled and in correct serial position, but not when counting only words correctly recalled, independent of serial position.

Methods

Participants

Eight French-speaking children with VCFS participated in this study (mean age: 9 years 7 months; range: 8-12 years; 6 girls, 2 boys). The deletions were verified by two-color fluorescent *in situ* hybridization (FISH), with cosmid probes specific for the proximal and distal 22q regions respectively. Full-scale IQs ranged from 61 to 88 (mean: 75; WISC-III, 1991), with higher verbal (mean: 81; VIQ range: 65-92) than performance IQs (mean: 74; PIQ range: 60-87) (details are presented in Table 1). Onset age for speech production was significantly delayed, as suggested by parental report: 33 months for single word production (range: 9-60 months) and 42 months for short sentence production (range: 30-60).

Out of the eight patients, four had experienced heart problems associated with the syndrome and requiring an operation early in life. Five of the eight had a malformation of the palette, requiring a medical intervention. Although all eight patients were mainstreamed in normal classes, all of them had received at least two years of speech and language therapy and two of them had received at least two years of occupational therapy as well. Two of the patients showed signs of psychotic symptoms (either hallucinations or delusions), although neither was taking narcoleptic medications. Five of the eight patients were not currently taking any medications at all, two of the patients were taking medications for growth and one patient was taking medications to help with an ongoing tachycardia. None of the eight patients were being regularly followed by a psychologist or a psychiatrist.

Participants were recruited only through announcements at French and Swiss patient associations. All patients were Caucasian and native French-speaking. None of the patients had presented a history of recurrent or chronic hearing disorders. Written informed consent was received from all parents and/or subjects under protocols approved by the Institutional Review Board of the Geneva University School of Medicine.

Each patient’s performance was compared to age-matched normally developing children. For the tasks assessing phonological similarity and serial order recognition, the control sample consisted of 9 native French-speaking children with a mean age of 9 years 7 months (age range: 7 – 13 years; 5 boys, 4 girls). They all had chronological age appropriate IQ estimates (WISC-III, 1991): mean full scale IQ was 109 (range: 95-126), mean verbal IQ was 109 (range: 91-122) and mean performance IQ was 105 (range: 91-123). They had been recruited from public primary schools in the city of Geneva. All children showed age appropriate school records and grades. A diagnostic interviewed controlled for the absence of past or present neurodevelopmental disorders, recurrent hearing disorders, speech-language delay or other learning disabilities. Average household income of the participating families (VCFS and control) was equivalent to 70000 USD per year.

Due to the age range of the VCFS group, this first control group (mean age: 9;7 years) might have overestimated or underestimated deficits for the VCFS children at the extremes of the age range. For this reason, for the tasks assessing lexicality, word frequency and word imageability effects, which are characterized by a much larger variability in levels of performance, additional control data were derived from larger samples of twenty normally developing 8-year-olds and twenty 10-year olds which were more closely matched at the level of chronological age to the younger and older VCFS children, respectively. These control groups have already been described in Majerus and Van der Linden (2003). More precisely, for the tasks assessing the lexicality effect, mean chronological age was 8 years 5 months (age range: 8 years 0 months to 8 years 9 months; 9 girls, 11 boys) for the 8-year-olds, and 10 years 6 months (age range: 10 years 2 months to 10 years 11 months; 8 girls, 12 boys) for the 10-year-olds; for the tasks assessing the imageability and word frequency effects, mean chronological age was 8 years 5 months (age range: 8 years 1 month to 8 years 11 months; 9 girls, 11 boys) for the 8-year-olds and 10 years 5 months (age range: 10 years 3 months to 10 years 11 months; 13 girls, 7 boys) for the 10-year-olds. Although no IQ estimates were available for the latter control groups, the children were all normally developing children recruited from ordinary primary schools, with chronological age appropriate school records and no history of speech-language impairments or other learning difficulties or hearing disorders. Mean socio-economic status was comparable to that of the first control group and the VCFS group.

< INSERT TABLE 1>

Experimental tasks

Phonological Similarity effect

Two sets of 8 phonologically similar (“soie”, “doigt”, “poids”, “roi”, “loi”, “bois”, “noix”, “choix”) and 8 phonologically dissimilar words (“note”, “dinde”, “sol”, “fille”, “mode”, “chat”, “preuve”, “langue”) were selected. The words in both sets were all monosyllabic and matched for word frequency (mean frequency: 12091 and 12100 for the two word lists, respectively, according to Brulex ; Content *et al.* 1990) and word imageability (mean imageability rating: 3.6 and 3.8 for phonologically similar and dissimilar words, respectively, according to a rating scale ranging from 1 to 6; Hogenraad & Orianne 1981). The two word sets were randomly assigned to sequences ranging from 2 to 7 words, with 4 trials per sequence length. The sequences for the short and long word sets were presented in ascending order for immediate serial recall; testing was stopped when two or more trials of a given sequence length were incorrectly recalled. Short and long word span were determined by taking as a span measure the length of the last sequence where at least three trials were correctly recalled.

Nonword immediate serial recall

This task was a shortened version of a task previously developed by Majerus and Van der Linden (2003). The present list comprised 60 different CVC nonwords (e.g., /nal/, /dur/, /bam/, /riz/). The nonwords were all phonotactically legal. They were assigned to sequences ranging from 1 to 5 items in length, with 4 trials per sequence length. All sequences were presented for immediate serial recall; the total number of items correctly recalled, across all trials and sequence lengths, was determined, as a function of correct serial position or independently of correct serial position.

Lexicality, word frequency and word imageability effects

Lexicality effect. This was also a shortened version of a task previously developed by Majerus and Van der Linden (2003). The task comprised a list of 60 CVC words (e.g., “cave”, “four”, “bac”, “rire”). CV and VC diphone frequency of the words was matched to that of the nonwords in the preceding task. The words and nonwords were also constructed by sampling from the same pool of consonants and vowels. This was done in order to make the phonological structure of the words and nonwords as similar as possible, so that only lexical status differed between the two stimuli types (Majerus & Van der Linden, 2003). Diphone frequency was established by retrieving the frequency of occurrence of the various CV and VC segments in French spoken language from the *Corpus de transcription phonétique* developed by Tubach and Boë (1990). Phonotactic frequency of CV and VC diphones was 745 and 919, for words, and 713 and 837, for nonwords [$t(59) < 1$, n.s.]. The words were assigned to sequences ranging from 1 to 5 items, with 4 trials per sequence length. All sequences were presented for immediate serial recall. Number of items correctly recalled, as a function of correct serial position or independently of correct serial position, was determined. The lexicality effect was estimated by subtracting nonword from word recall.

Word frequency effect. The two lists of 108 high and low frequency words developed by Majerus and Van der Linden (2003) were used. Mean lexical frequency counts for high and low frequency lists was <200 and >10,000, respectively, according to Brulex (Content, *et al.* 1990). All items were bisyllabic. For each list, the items were assigned to sequences ranging from 2 to 7 items, with 4 trials per sequence. All sequences were presented for immediate serial recall. The measures were the same as those used in the previous task assessing lexicality effects. The frequency effect was determined by subtracting high frequency from low frequency word recall.

Word imageability effect. This task was also created by Majerus and Van der Linden (2003). It comprised two lists of 108 high and low imageability words. Imageability ratings were above 4 for high imageability words, and less than 3 for low imageability words, according to a rating scale ranging from 1 to 6 (Hogenraad & Orianne, 1981). Mean word length was 1.8 syllables in each list. Both lists were matched for word frequency. The procedure and measures were the same as in the preceding tasks. The imageability effect was determined by subtracting high imageability from low imageability word recall.

Serial order recognition task

Digit[1] sequences containing 3 to 9 digits were created. For each sequence length, there were 6 trials, comprising the presentation of one target sequence immediately followed by a probe sequence. In four of the 6 trials, the order of two adjacent digits in the probe sequence was reversed relative to the target sequence. To ensure that the children concentrated on order information, they were told in advance the set of digit items from which the sequences were sampled: for sequence length 3, these were the digits 1, 2 and 3, for sequence length 4, these were the digits 1, 2, 3 and 4, etc. All trials and sequence lengths were presented. Number of correct yes/no answers was determined.

General Procedure and Statistical Analysis

The stimuli for the different tasks were digitally recorded by a male native French-speaker and were presented at the rate of 1 item per second, via high quality loudspeakers

[1] In order to maximize requirements for processing serial order information while minimizing requirements for processing item information in this task, digits were chosen for stimulus material as they are highly familiar items. Furthermore, this allowed us to ensure that item information was known in advance: for sequences of length 3, the first three numerals were used; for sequences of length 4, the first four numerals were used, and so forth for the other sequence lengths. Thus only order information had to be retained and recognized. In another study, using a similar procedure but with highly familiar word lists, we obtained quite comparable results as those reported here (Majerus *et al.*, 2005).

connected to a CD-player. Responses were digitally recorded for verification and later scoring. In order to determine whether the scores for each patient were statistically different from those of the controls, a modified t-test was computed on the different measures obtained for each patient (Crawford & Garthwaite 2002). This test was developed specifically for doing inferential statistics on comparisons between data points of an individual patient (sample size: N=1) and those of a control group; it takes into account the mean and SD of the control group's performance, as well as its size. For sake of clarity, only results for comparisons with the larger and more closely matched control groups will be reported for the tasks assessing lexicality, word imageability and word frequency effects.

Results

Phonological Similarity

Short-term memory span for both phonologically similar and dissimilar word lists was in the normal range for all patients (Table 2). An advantage for phonologically dissimilar trials was observed in five patients. The remaining three patients showed no phonological similarity effect; this was however also true in two control subjects.

< INSERT TABLE 2>

Lexicality, word frequency and word imageability effects

Accuracy of recall. For item recall independent of correct serial position, the vast majority of patients scored within the normal range for recall of the five different word lists and the nonword list (Table 3). AN, AS and AE occasionally performed outside the control range, with a significant impairment on 1 out of 6 lists. Only patient NI showed more consistent difficulties as he was impaired on 3 out of 6 lists. Most notably, nonword recall was within the normal range for each patient. For items recalled in correct serial position, performance profiles differed notably (Table 4). Significant and consistent difficulties were observed in patients NI and AS (number of impaired lists: 6/6 and 3/6, respectively). More isolated impairments were observed in many other patients: AE was impaired on two lists, and JU, SA, JO and AN were impaired on one list. Only patient OL showed normal performance on all lists[2].

< INSERT TABLES 3 AND 4>

Lexicality effect. A significant advantage for word over nonword recall was observed in controls, for both item measures and item and order dependent measures (8-year old controls: item correct: F (1,19) = 367.12, p < .0001; item and order correct : F (1, 19) = 443,77, p < .0001; 10-year old controls: item correct: F (1,19) = 72.22, p < .0001; item and order correct: F (1,19) = 62.75, p < .0001). The magnitude of the lexicality effect was similar to controls in the patients, except for patient JU who presented a significantly reduced lexicality effect for item and order dependent measures (see Table 5).

<INSERT TABLE 5>

Word frequency effect. In controls, recall of high frequency words was significantly better than recall of low frequency words for both types of measures (8-year old controls: item correct: F (1,19) = 25.67, p < .0001; item and order correct : F (1, 19) = 45.94, p < .0001; 10-year old controls: item correct: F (1,19) = 27.33, p < .0001; item and order correct: F (1,19) = 30.43, p < .0001). As shown in Table 5, the patients showed word frequency effects of similar size to that of controls, although the word frequency effect was small in the case of three

[2] Results for comparisons with the first and smaller control group (mean age: 9;7 years) were virtually identical to those reported here, with the only exception that the youngest VCFS patient, JU (age: 8 years) showed significantly lower performance on a more important number (N=8) of word recall measures (item or item and order) than observed for the larger and more closely matched control group with respect to chronological age.

patients (JU, AN, AS) especially for order dependent measures. The effect was reversed in the case of one patient (SA). However, this was not significant given that similar results were observed in the controls.

Word imageability effect. Controls also recalled significantly more high imageability than low imageability words (8-year old controls: item correct: $F(1,19) = 6.67$, $p < .05$; item and order correct : $F(1, 19) = 38.31$, $p < .0001$; 10-year old controls: item correct: $F(1,19) = 31.72$, $p < .0001$; item and order correct: $F(1,19) = 25.72$, $p < .0001$). The imageability effect observed in the patients was of similar magnitude to that of the controls (Table 5). Only patient SA presented a reversed and significantly different imageability effect for item and order dependent measures. It must nevertheless be noted that some patients as well as some control children also demonstrated small or reversed imageability effects, most markedly for order dependent measures.

Serial order recognition

Four out of 8 patients presented significant difficulties in serial order recognition: JU, SA, AN and AS (see Table 6).

< INSERT TABLE 6>

General Discussion

The results of the present study suggest that most aspects of verbal short-term memory processing are preserved in VCFS. First, level of accuracy for immediate serial recall of word and nonword lists was in the normal range for item recall in most patients. Most strikingly, each patient presented normal recall performance for nonwords; these results suggest a general preservation of temporary storage capacity for verbal items, ruling out our first prediction. Second, the patients showed similar phonological similarity effects as controls, indicating normal phonological coding in short-term memory (Baddeley 1986) and thus ruling out our second prediction. Third, all patients presented normal lexicality, word frequency and word imageability effects. This shows that long-term lexical and semantic language knowledge support verbal short-term memory performance to a similar extent as in controls, ruling out our third prediction. With regard to these measures, the present results support the initial findings by Wang *et al.* (2000) by showing that verbal short-term memory performance can be in the normal range, relative to a control group matched on chronological age but not IQ.

However, when short-term memory performance was scored in terms of items recalled in correct serial position, difficulties became more apparent, with only one patient presenting no impairment at all. Similarly, in the serial order recognition task, half of the patients showed impaired performance. These results suggest that at least some patients with VCFS syndrome might have more important difficulties in storage of serial order information in verbal short-term memory, supporting our fourth prediction. However, due to the fact that we had no mental age-matched control group, we must remain cautious with respect to the interpretation of these difficulties and their relative specificity. Similarly, interpretation for the phonological similarity and serial order recognition measures should also be considered with care, as there was only one control group for these measures, with a relatively small sample size. At the same time, for the much more variable word and nonword list recall where we had control data from this first control group as well as from two larger control groups, we obtained quite similar results when using either the small or the larger control groups (except for JU, the youngest VCFS patient). Thus, despite not being IQ-matched, we can reasonably assume that the smaller control group provided nevertheless a valid comparison group for the VCFS children’s short-term memory performance.

Future studies will need to address the extent and implications of seemingly preserved short-term memory capacities for verbal item information with greater difficulties for processing serial order information. A first question that arises is whether this apparent deficit for retaining serial order information is still present when comparing the VCFS children's performance to a mental age-matched control group. In another study that focused specifically on short-term memory for serial order information, we observed that a different group of children and adults with VCFS showed consistent impairments for both serial order recognition and recall tasks when compared to mental age-matched control groups (Majerus *et al.* submitted), thus indicating that this impairment for processing serial order in short-term memory is most likely not simply a consequence of lower IQ. Second, given that verbal item information was preserved in the present data, it seems likely that the delayed and protracted language development observed in VCFS is not related to reduced capacities for retaining verbal item information in short-term memory. For example, in the patient sample of this study, mean onset age for single word production was 33 months, while typically developing children produce their first word at 12 months of age (*e.g.*, Kuhl 2004). Despite this language delay, verbal short-term memory performance was normal when serial order was not taken into account. It may, however, be the case that the serial order component of verbal short-term memory performance is specifically determinant for language development, as suggested by recent models of verbal short-term memory (e.g., Gupta & MacWhinney 1997; Gupta 2003). Indeed, when learning a new word, the crucial information that has to be retained is the order that binds the different constituent phonemes together. More studies will need to explore both lexical and short-term memory development in the same group of children with VCFS, to study these children as early as possible and to follow their language and short-term memory development in a longitudinal study design.

As mentioned in the introduction, children with VCFS appear to have a significant decrease of gray matter volume in the left parietal lobe (Eliez *et al.* 2000). A functional neuroimaging study in adult healthy controls precisely related short-term serial order recognition to activation in the parietal cortex (Marshuetz *et al.* 2000). Furthermore, the parietal cortex has also been implicated in other cognitive tasks that necessitate serial order processing, such as number processing, magnitude judgment and calculation (Chochon *et al.* 1999; Dehaene 2000) which are also deficient in VCFS (e.g., De Smedt *et al.* 2003; Simon *et al.* 2004). In agreement with these data, Eliez *et al.* (2001b) have shown abnormal activation in the supramarginal gyrus, part of the left parietal cortex, in 8 children with VCFS during an arithmetic computation task. The particular structural and functional neuroanatomical profiles in VCFS may explain why short-term memory for serial order information is less preserved than short-term memory for verbal item information. Future studies combining neuropsychological and neuroimaging measures will have to address this issue more directly in order to explore whether difficulties for serial order storage in VCFS are directly related to the amount of left parietal gray matter reduction. Likewise, the relationship between a serial order information processing deficit and the oft-noted impairment of mathematical abilities will need to be explored.

Acknowledgments

The research presented in this manuscript was supported from the National Swiss Research Fund to Dr. Stephan Eliez (3200-063135.00/1 and 3232-063134.00/1) and The National Belgium Research Fund (FNRS) to Dr. Steve Majerus. This work also was partially supported by a grant from the NARSAD Institute to Dr. Eliez. The authors thank Verane Braissand and Sarah Viollier for their help with data processing, as well as two anonymous reviewers for their comments on a previous version of this manuscript.

References

Adams A. M. & Gathercole S. E. (2000) Limitations in working memory: implications for language development. *International Journal of Language and Communication Disorders* **35**, 95-116.

Adams A. M. & Gathercole S. E. (1995) Phonological working memory and speech production in preschool children. *Journal of Speech and Hearing Research* **38**, 403-14.

Adams A. M. & Gathercole S. E. (1996) Phonological working memory and spoken language development in young children. *The Quarterly Journal of Experimental Psychology* **49A**, 216-33.

Avons S. E., Wragg C. A., Cupples L. & Lovegrove W. J. (1998) Measures of phonological short-term memory and their relationship to vocabulary development. *Applied Psycholinguistics* **19**, 583-601.

Baddeley A. D. (1966) Short-term memory for word sequences as a function of acoustic, semantic and formal similarity. *Quarterly Journal of Experimental Psychology* **18**, 362-5.

Baddeley A.D. (1986) *Working memory.* Clarendon Press/Oxford University Press, Oxford, UK.

Baddeley A.D., Gathercole, S. & Papagno C. (1998) The phonological loop as a language learning device. *Psychological Review* **105**, 158-73.

Barnea-Goraly N., Menon V., Krasnow B., Ko A., Reiss A. & Eliez S. (2003) Investigation of White Matter Structure in Velocardiofacial Syndrome: A Diffusion Tensor Imaging Study. *American Journal of Psychiatry* **160**, 1-7.

Bearden C. E., Woodin M. F., Wang P., Moss E., McDonald-McGinn D. M., Zackai E. H., Emanuel B. S. & Cannon T. D. (2001) The neurocognitive phentoype of 22q11.2 deletion syndrome: selective deficit in visuo-spatial memory. *Journal of Clinical and Experimental Neuropsychology* **23**, 447-64.

Botto L.D., May K., Fernhoff P.M., Correa A., Coleman K., Rasmussen S.A., Merritt R.K., O'Leary L.A., Wong L.Y., Elixson E.M., Mahle W.T., & Campbell R.M. (2003). A population-based study of the 22q11.2 deletion: phenotype, incidence, and contribution to major birth defects in the population. *Pediatrics* **112**, 101-7.

Bowey J. A. (1996) On the association between phonological memory and receptive vocabulary in five-year-olds. *Journal of Experimental Child Psychology* **63**, 44-78.

Burgess N. & Hitch G.J. (1999) Memory for serial order: A network model of the phonological loop and its timing. *Psychological Review* **106**, 551-81.

Carlson C., Sirotkin H., Pandita R., Goldberg R., McKie J., Wadey R., Patanjali S. R., Weissman S. M., Anyane-Yeboa K., Warburton D., Scambler P., Shprintzen R., Kucherlapati R. & Morrow B. E. (1997) Molecular definition of 22q11 deletions in 151 velo-cardio-facial syndrome patients. *American Journal of Human Genetics* **61**, 620-29.

Chochon F., Cohen L., van de Moortele P. F. & Dehaene S. (1999) Differential contributions of the left and right inferior parietal lobules to number processing. *Journal of Cognitive Neuroscience* **11**, 617-30.

Conrad R. & Hull A. J. (1964) Information, acoustic confusion and memory span. *British Journal of Psychology* **55**, 429-32.

Content A., Mousty P. & Radeau M. (1990) BRULEX. Une base de données lexicales informatisée pour le français écrit et parlé / BRULEX: A computerized lexical data base for the French language. *Année Psychologique* **90**, 551-66.

Crawford J. R. & Garthwaite P. H. (2002) Investigation of the single case in neuropsychology: confidence limits on the abnormality of test scores and test score differences. *Neuropsychologia* **40**, 1196-208.

D'Antonio L. L., Scherer N. J., Miller L. L., Kalbfleisch J. H. & Bartley J. A. (2001) Analysis of speech characteristics in children with velocardiofacial syndrome (VCFS) and children with phenotypic overlap without VCFS. *Cleft Palate and Craniofacial Journal* **38**, 455-67.

De Smedt B., Swillen A., Ghesquiere P., Devriendt K. & Fryns J. P. (2003) Pre-academic and early academic achievement in children with velocardiofacial syndrome (del22q11.2) of borderline or normal intelligence. *Genetic Counseling* **14** , 15-29.

Dehaene S. (2000). Cerebral basis of number processing and calculation. In: *The new cognitive neurosciences* (ed M.S. Gazzaniga), pp. 987-98. MIT Press: Cambridge, MA.

Driscoll D. A., Salvin J., Sellinger B., Budarf M. L., McDonald-McGinn D. M., Zackai E. H. & Emanuel B. S. (1993) Prevalence of 22q11 microdeletions in DiGeorge and velocardiofacial syndromes: implications for genetic counselling and prenatal diagnosis. *Journal of Medical Genetics* **30**, 813-17.

Eliez S., Blasey C. M., Schmitt J. E., White C. D., Hu D. & Reiss A. L. (2001a) Velocardiofacial Syndrome: Are Structural Changes in the Temporal and Mesial Temporal Regions Related to Schizophrenia? *American Journal of Psychiatry* **158**, 447-53.

Eliez S., Schmitt J. E., White C. D. & Reiss A. L. (2000) Children and Adolescents With Velocardiofacial Syndrome: A Volumetric MRI Study. *American Journal of Psychiatry* **157**, 409-15.

Eliez S., White C. D., Menon V., White C. D., Schmitt J. E. & Reiss A. L. (2001b). Functional brain imaging study of mathematical reasoning abilities in velocardiofacial syndrome (del22q11.2). *Genetics in Medicine* **3**, 49-55.

Gathercole S. E. & Baddeley A. D. (1990) Phonological memory deficits in language disordered children: Is there a causal connection? *Journal of Memory and Language* **29,** 336-60.

Gathercole S. E. & Adams A. M. (1993) Phonological working memory in very young children. *Developmental Psychology* **29**, 770-78.

Gathercole S. E. & Baddeley A. D. (1989) Evaluation of the role of phonological STM in the development of vocabulary in children: A longitudinal study. *Journal of Memory and Language* **28**, 200-13.

Gathercole S. E., Willis C. & Baddeley A. D. (1991) Nonword repetition, phonological memory, and vocabulary: A reply to Snowling, Chiat, and Hulme. *Applied Psycholinguistics* **12**, 375-9.

Gathercole S. E., Willis C. S., Emslie H., & Baddeley A. D. (1992) Phonological memory and vocabulary development during the early school years: A longitudinal study. *Developmental Psychology* **28**, 887-98.

Gathercole S. E. & Baddeley A. D. (1993) Phonological working memory: A critical building block for reading development and vocabulary acquisition? *European Journal of Psychology of Education* **8**, 259-72.

Gathercole S. E. & Adams A. M. (1994) Children's phonological working memory: Contributions of long-term knowledge and rehearsal. *Journal of Memory and Language* **33**, 672-88.

Gathercole S. E. (1995) Is nonword repetition a test of phonological memory or long-term knowledge? It all depends on the nonwords. *Memory and Cognition* **23**, 83-94.

Gathercole S. E., Service E., Hitch G. J., Adams A. M. & Martin A. J. (1999) Phonological short-term memory and vocabulary development: Further evidence on the nature of the relationship. *Applied Cognitive Psychology* **13**, 65-77.

Gerdes M., Solot C., Wang P. P., Moss E., LaRossa D., Randall P., Goldmuntz E., Clark B. J., Driscoll D. A., Jawad A., Emanuel B. S., McDonald-McGinn D. M., Batshaw M. L. & Zackai E. H. (1999) Cognitive and behavior profile of preschool children with chromosome 22q11.2 deletion. *American Journal of Medical Genetics* **85**, 127-33.

Glaser B., Mumme D. L., Blasey C., Morris M. A., Dahoun S. P., Antonarakis S. E., Reiss A. L. & Eliez S. (2002) Language skills in children with velocardiofacial syndrome (deletion 22q11.2). *Journal of Pediatrics* **140**, 753-8.

Goldberg R., Motzkin B., Marion R., Scambler P. J. & Shprintzen R. J. (1993) Velo-cardio-facial syndrome: a review of 120 patients. *American Journal of Medical Genetics* **45**, 313-9.

Golding-Kushner K. J., Weller G. & Shprintzen R. J. (1985) Velo-cardio-facial syndrome: language and psychological profiles. *Journal of Craniofacial Genetics and Developmental Biology* **5**, 259-266.

Gupta P. (2003) Examining the relationship between word learning, nonword repetition and immediate serial recall in adults. *Quarterly Journal of Experimental Psychology* **56A**, 1213-36.

Gupta P. & MacWhinney B. (1997) Vocabulary acquisition and verbal short-term memory: computational and neural bases. *Brain and Language* **59**, 267-333.

Hanten G. & Martin R. C. (2001) A developmental phonological short-term memory deficit: A case study. *Brain and Cognition* **45**, 164-88.

Hartley T. & Houghton G. (1996) A linguistically constrained model of short-term memory for nonwords. *Journal of Memory and Language* **35**, 1-31.

Henry J. C., van Amelsvoort T., Morris R. G., Owen M. J., Murphy D. G. M. & Murphy K. C. (2002) An investigation of the neuropsychological profile in adults with velocardiofacial syndrome (VCFS). *Neuropsychologia* **40**, 471-8.

Henson R., Hartley T., Burgess N., Hitch G. & Flude B. (2003) Selective interference with verbal short-term memory for serial order information: A new paradigm and tests of a timing-signal hypothesis. *Quarterly Journal of Experimental Psychology* **56A**, 1307-34.

Hogenraad R. & Orianne F. (1981) Valence d'imagerie de 1130 noms de la langue française parlée. *Psychologica Belgica* **21**, 21-30.

Hulme C., Maughan S. & Brown G. D. (1991) Memory for familiar and unfamiliar words: Evidence for a long-term memory contribution to short-term memory span. *Journal of Memory and Language* **30**, 685-701.

Hulme C., Roodenrys S., Schweickert R., Brown G. D., Martin S. & Stuart G. (1997) Word-frequency effects on short-term memory tasks: evidence for a redintegration process in immediate serial recall. *Journal of Experimental Psychology: Learning, Memory, and Cognition* **23**, 1217-32.

Kuhl P.K. (2004) Early language acquisition: cracking the speech code. *Nature Reviews Neuroscience* **8**, 831-43.

Lindsay E. A., Morris M. A., Gos A., Nestadt G., Wolyniec P. S., Lasseter V. K., Shprintzen R., Antonarakis S. E., Baldini A. & Pulver A. E. (1995) Schizophrenia and chromosomal deletions within 22q11.2. *American Journal of Medical Genetics* **56**, 1502-3.

Majerus S., Bressand V., Van der Linden M. & Eliez S. (2005) An investigation of verbal short-term memory children and adults with a chromosome 22q11.2 deletion. A specific deficit in serial order retention capacities? *Manuscript submitted for publication*

Majerus S. & Van der Linden M. (2003) The development of long-term memory effects on verbal short-term memory : A replication study. *British Journal of Developmental Psychology* **21**, 303-10.

Majerus S., Van der Linden M., Mulder L., Meulemans T. & Peters F. (2004) Verbal short-term memory reflects the sublexical organization of the phonological language network: Evidence from an incidental phonotactic learning paradigm. *Journal of Memory and Language* **51**, 297-306.

Marshuetz C., Smith E. E., Jonides J., DeGutis J. & Chenevert T. L. (2000) Order information in working memory: fMRI evidence for parietal and prefrontal mechanisms. *Journal of Cognitive Neuroscience* **12**, 130-44.

Michas I. C. & Henry L. A. (1994) The link between phonological memory and vocabulary acquisition. *British Journal of Developmental Psychology* **12**, 147-64.

Moss E. M., Batshaw M. L., Solot C. B., Gerdes M., McDonald-McGinn D. M., Driscoll D. A., Emanuel B. S., Zackai E. H. & Wang P. P. (1999) Psychoeducational profile of the 22q11.2 microdeletion: a complex pattern. *Journal of Pediatrics* **134**, 193-8.

Murphy K. C. & Owen M. J. (1996) Schizophrenia, CATCH 22 and FISH. *British Journal of Psychiatry* **168**, 397-8.

Murphy K. C., Jones L. A. & Owen M. .J. (1999) High rates of schizophrenia in adults with velo-cardio-facial syndrome. *Archives of General Psychiatry* **56**, 940-5.

Murphy K. C. (2004) The behavioural phenotype in velo-cardio-facial syndrome. *Journal of Intellectual Disability Research* **48**, 524-30.

Ryan A. K., Goodship J. A., Wilson D. I., Philip N., Levy A., Seidel H., Schuffenhauer S., Oechsler H., Belohradsky B., Prieur M., Aurias A., Raymond F. L., Clayton-Smith J., Hatchwell E., McKeaon C., Beemer F. A., Dallapiccola B., Novelli G., Hurst J. A., Ignatius J., Green A. J., Winter R., Brueton L., Brondum-Nielsen K., Scambler P. J. et al. (1997) Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: a European collaborative study. *Journal of Medical Genetics* **34**, 798-804.

Scambler P. J., Kelly D., Lindsay E., Williamson R., Goldberg R., Shprintzen R., Wilson D. I., Goodship J. A., Cross I. E. & Burn J. (1992) Velo-cardio-facial syndrome associated with chromosome 22 deletions encompassing the DiGeorge locus. *Lancet* **339**, 1138-9.

Scherer N. J., D'Antonio L. L. & Kalbfleisch J. H. (1999) Early speech and language development in children with velocardiofacial syndrome. *American Journal of Medical Genetics* **88**, 714-23.

Scherer N. J., D'Antonio L. L. & Rodgers J. R. (2001) Profiles of communication disorder in children with velocardiofacial syndrome: comparison to children with Down syndrome. *Genetics in Medicine* **3**, 72-8.

Service E. (1992) Phonology, working memory, and foreign-language learning. *Quarterly Journal of Experimental Psychology: Human Experimental Psychology* **45A**, 21-50.

Shprintzen R. J., Goldberg R. B., Lewin M. L., Sidoti E. J., Berkman M. D., Argamaso R. V. & Young D. (1978) A new syndrome involving cleft palate, cardiac anomalies, typical facies, and learning disabilities: velo-cardio-facial syndrome. *Cleft Palate Journal* **15**, 56-62.

Shprintzen R. J., Goldberg R., Golding-Kushner K. J. & Marion R. W. (1992) Late-onset psychosis in the velo-cardio-facial syndrome. *American Journal of Medical Genetics* **42**, 141-2.

Shprintzen R.J. (2000) Velo-cardio-facial syndrome: a distinctive behavioral phenotype. *Mental Retardation and Developmental Disabilities Research Reviews* **6**, 142-7.

Solot C. B., Gerdes M., Kirschner R. E., McDonald-McGinn D..M., Moss E., Woodin M., Aleman D., Zackai E. H. & Wang P. P. (2001) Communication issues in 22q11.2 deletion syndrome: children at risk. *Genetics in Medicine* **3**, 67-71.

Swillen A., Devriendt K., Legius E., Eyckens B., Dumoulin M., Gewillig M., & Fryns J. P. (1997) Intelligence and psychosocial adjustment in velocardiofacial syndrome: a study of 37 children and adolescents with VCFS. *Journal of Medical Genetics* **34**, 453-8.

Tezenas Du Montcel S., Mendizabai H., Ayme S., Levy A. & Philip N. (1996) Prevalence of 22q11 microdeletion. *Journal of Medical Genetics* **33**, 719.

Tubach J. L. & Boe L. J. (1990) *Un corpus de transcription phonétique.* Telecom: France.

van Amelsvoort T., Daly E., Robertson D., Suckling J., Ng V., Critchley H., Owen M. J., Henry J., Murphy K. C. & Murphy D. G. (2001) Structural brain abnormalities associated with deletion at chromosome 22q11. Quantitative neuroimaging study of adults with velo-cardio-facial syndrome. *British Journal of Psychiatry* **178**, 412-9.

Walker I. & Hulme C. (1999) Concrete words are easier to recall than abstract words: Evidence for a semantic contribution to short-term serial recall. *Journal of Experimental Psychology: Learning, Memory, and Cognition* **25**, 1256-71.

Wang P. P., Woodin M. F., Kreps-Falk R. & Moss E. M. (2000) Research on behavioral phenotypes: velocardiofacial syndrome (deletion 22q11.2). *Developmental Medicine and Child Neurology* **42**, 422-427.

Wechsler D. (1991) *WISC 3. Wechsler Intelligence Scale for Children 3.* The Psychological Corporation: London, UK.

Table 1.

Age, gender, first word production and IQ measures for the VCFS patients

	Age (years)	Gender	Reported onset age (month) of single word/short sentence production	WISC-III[1]			
				Full IQ	**PIQ**	**VIQ**	**PIQ-VIQ**
JU	8	F	9/54	61	60	71	-11
OL	9	F	24/30	78	69	92	-23
SA	9	F	48	76	78	79	-1
JO	9	M	36/48	68	77	65	12
AN	10	F	36/36	75	73	83	-10
AS	10	F	24/36	79	75	87	-12
AE	10	F	27/33	88	87	91	-4
NI	12	M	60/60	73	74	78	-4

[1] Wechsler Intelligence Scale for Children III (1991)

Table 2.

Word span for phonologically similar and dissimilar word lists.

	Word lists	
	Dissimilar	Similar
JU	2	2
OL	3	3
SA	3	3
JO	4	3
AN	3	2
AS	4	2
AE	4	2
NI	4	2
Controls 7-13	3.4 (2-4)	2.33 (2-3)

Note. The control group comprised 9 children aged 7-13 years (mean: 9 years, 7 months).

Control means and range of scores are displayed.

Table 3.

Number of items correctly repeated for immediate serial recall of the different word lists and the nonword list.

	Frequency		**Imageability**		**Lexicality**	
	High	Low	High	Low	Word	Nonword
JU	52	53	56	45	32	25
OL	73	65	81	71	56	33
SA	78	67	78	82	47	31
JO	73	65	79	63	42	28
AN	66	50	**62***	62	43	25
AS	66	61	**69***	61	45	31
AE	81	69	80	68	**36***	24
NI	64	**41***	**66***	**52***	40	23
Controls 8	64.85	55.50	66.20	58.55	43.00	28.15
	15-100	20-92	28-98	26-92	26-54	13-42
Controls 10	81.45	71.36	82.35	75.60	48.35	35.10
	66-96	46-96	74-91	58-86	37-58	23-48

Note. JU's performances were compared to a control group of twenty 8-year-old children; the remaining patients' performances were compared to a control group of twenty 10-year-old children. Control means and range of scores are displayed.

* $p < .05$ (modified t-test; Crawford & Garthwaite, 2002)

Table 4.

Number of items repeated in correct serial position for immediate serial recall of the different word lists and the nonword list.

	Frequency		**Imageability**		**Lexicality**	
	High	Low	High	Low	Word	Nonword
JU	40	29	32	31	**23***	21
OL	64	53	64	66	56	33
SA	**47***	49	55	69	45	28
JO	64	44	56	52	**27***	27
AN	**42***	40	52	57	37	23
AS	**35***	**33***	**42***	46	39	29
AE	76	52	72	53	**28***	**19***
NI	**40***	**27***	**44***	**37***	**31***	**19***
Controls 8	47.05	36.95	45.65	41.00	38.80	25.60
	14-88	14-67	15-88	18-63	25-52	13-39
Controls 10	66.30	55.40	67.90	60.05	45.30	33.30
	49-82	37-75	52-84	44-74	34-56	23-46

Note. JU's performances were compared to a control group of twenty 8-year-old children; the remaining patients' performances were compared to a control group of twenty 10-year-old children. Control means and range of scores are displayed.

* $p < .05$ (modified t-test; Crawford & Garthwaite, 2002)

Table 5.

Size of word frequency, imageability and lexicality effects on word immediate serial recall.

	Frequency		**Imageability**		**Lexicality**	
	Item	Item+Order	Item	Item+Order	Item	Item+Order
JU	1	11	11	1	7	**2***
OL	8	11	10	-2	23	23
SA	11	-2	-4	**-14***	16	17
JO	8	20	16	4	14	0
AN	16	2	0	-5	18	14
AS	5	2	8	-4	14	10
AE	12	14	12	19	12	9
NI	23	13	14	**7**	17	12
Controls 8	9.25	10.1	7.65	4.65	14.9	13.2
	-6-25	-5-23	0-20	-8-26	10-23	9-20
Controls 10	9.5	10.9	6.75	7.85	13.25	12.00
	-9-24	-9-22	-6-16	-2-27	2-26	0-24

Note. JU's performances were compared to a control group of twenty 8-year-old children; the remaining patients' performances were compared to a control group of twenty 10-year-old children. Control means and range of scores are displayed.

* $p < .05$ (modified t-test; Crawford & Garthwaite, 2002)

Table 6.

Number of correct responses for the serial order recognition task.

	Correct recognitions
JU	**24***
OL	30
SA	**21***
JO	27
AN	**21***
AS	**24***
AE	30
NI	29
Controls 7-13	30 (27-34)

Note. The control group comprised 9 children aged 7-13 years (mean: 9 years, 7 months).

Control means and range of scores are displayed.

* $p < .05$ (modified t-test; Crawford & Garthwaite, 2002)