Neuropsychologia 47 (2009) 1034–1044

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

A comparative study of cognition and brain anatomy between two neurodevelopmental disorders: 22q11.2 deletion syndrome and Williams syndrome☆

Linda E. Campbell[a,b,*], Angela Stevens[a], Eileen Daly[a], Fiona Toal[a,d], Rayna Azuma[a], Annette Karmiloff-Smith[c], Declan G.M. Murphy[a], Kieran C. Murphy[d]

[a] Section of Brain Maturation, Institute of Psychiatry, King's College London, United Kingdom
[b] Priority Research Centre for Brain & Mental Health, University of Newcastle, Australia
[c] Centre for Brain & Cognitive Development, Birkbeck, University of London, United Kingdom
[d] Department of Psychiatry, Royal College of Surgeons in Ireland, Dublin, Ireland

ARTICLE INFO

Article history:
Received 18 March 2008
Received in revised form 14 October 2008
Accepted 31 October 2008
Available online 13 November 2008

Keywords:
22q11.2 deletion syndrome
Velo-cardio-facial syndrome
Williams syndrome
Magnetic resonance imaging
Cognition

ABSTRACT

Background: 22q11.2 deletion syndrome (22q11DS) is associated with intellectual disability, poor social interaction and a high prevalence of psychosis. However, to date there have been no studies comparing cognition and neuroanatomical characteristics of 22q11DS with other syndromes to investigate if the cognitive strengths and difficulties and neuroanatomical differences associated with 22q11DS are specific to the syndrome. Hence, it is difficult to know if the observed features of 22q11DS are simply due to a non-specific effect of having a genetic disorder or are specific to 22q11DS.
Methods: In this study, cognition and brain anatomy of 12 children with 22q11DS were compared to 12 age, gender and full scale IQ (FSIQ) matched children with William syndrome (WS) in order to investigate which cognitive and neuroanatomical features are specific to 22q11DS. We chose WS since the literature suggests that both groups have areas of physical/cognitive/behavioural overlap but as yet there has been no direct comparison of the two groups.
Results: Despite being matched on FSIQ the WS group had significantly greater impairment than those with 22q11DS on tests of Performance IQ, while performing significantly better on tasks measuring verbal, social and facial processing skills. Moreover there were significant differences in brain anatomy. Despite similar overall brain volumes, midline anomalies were more common among the 22q11DS group, and regional differences such as increased striatal volumes and reduced cerebellar volumes in the 22q11DS group were detected.
Conclusions: These findings suggest that although the behavioural phenotype is similar in some aspects there are key differences in cognition and neuroanatomy between the two groups. Different neuropsychological profiles need to be considered when designing educational frameworks for working with these children.

1. Introduction

Velo-cardio-facial syndrome, or 22q11.2 Deletion Syndrome (22q11DS), one of the most common genetic syndromes, occurs with a prevalence of 1:4000–5000 (Botto et al., 2003). People with 22q11DS often have lowered intellectual functioning and problems with cognitive functions such as attention, executive functions and memory (Bearden et al., 2001; Bish, Ferrante, McDonald-McGinn, Zackai, & Simon, 2005; Henry et al., 2002). Also, behavioural problems such as Attention-Deficit/Hyperactivity disorder, autism spectrum disorders and psychosis are prevalent (Gothelf et al., 2004; Murphy, Jones, & Owen, 1999; Vorstman et al., 2006).

However, the majority of studies have used non-full scale IQ (FSIQ) matched control groups. A few studies of cognition in people with 22q11DS have used learning disabled control groups (Debbané, Van der Linden, Glaser, & Eliez, 2008; Glaser et al., 2002;

Abbreviations: 22q11DS, 22q11.2 deletion syndrome; WS, Williams syndrome; MRI, magnetic resonance imaging.

☆ Presented at the Society for the Study of Behavioural Phenotypes 11th Annual Scientific Meeting, Royal College of Surgeons, Dublin, Ireland, 2006.

* Corresponding author at: Priority Research Centre for Brain & Mental Health, Officers Quarters Complex, James Fletcher Hospital, Newcomen Street, Newcastle, NSW 2300, Australia. Tel.: +61 2 4924 6648; fax: +61 2 4924 6608.
E-mail address: Linda.e.campbell@newcastle.edu.au (L.E. Campbell).

0028-3932/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuropsychologia.2008.10.029

Henry et al., 2002). In one such study, Glaser et al. (2002) investigated language skills in children with 22q1DS compared with children with idiopathic developmental delay. They report that the pattern of expressive and receptive impairments were different in the two groups, with the 22q11DS children performing better on expressive compared with receptive language. However, both clinical groups were equally impaired on word associations compared with a group of typically developing controls. This approach is important in providing information about the general pattern of impairment in the syndrome and whether some domains are 'spared' (although this does not necessary mean that the processes are intact). However, it is also important to compare 22q11DS with other developmentally delayed groups with a known genetic aetiology to investigate if there are specific aetiology-related strengths and difficulties associated with 22q11DS and/or if characteristics are shared by some other aetiological groups or perhaps are shared with most people with a learning disability. One such study has recently been published, Simon et al. (2008) conducted a study of numeracy in children with 22q11DS compared with females with Turner Syndrome and found that both clinical groups performed similarly on the tasks despite differences in intellectual ability indicating that the impairments were not due to global differences in intelligence but rather due to deficits of specific cognitive functions. Such understanding is vital in selecting appropriate educational remediation strategies for children with genetic syndromes. Especially since it has been found that genetic disorders, with particular behavioural phenotypes, can elicit specific behaviours from others, modulating interaction and reinforcement (Ly & Hodapp, 2005) and also influence type of education offered, potentially resulting in underachievement (Whittington et al., 2004). There have been a few studies investigating the behavioural phenotype in 22q11DS compared with e.g., people with Prader-Willi syndrome, Fragile X and Williams syndrome. One such study indicated that while the children with 22q11Ds were equally extravert and agreeable, they were less conscientious and emotional stable and more irritable and dependent compared with other groups (Prinzie et al., 2002). Although cross-syndrome comparisons have been made at the behavioural level, there exist no studies that have compared the neuroanatomical phenotype of 22q11DS with other syndromes. Such imaging data can provide additional insights into the neural and genetic basis of the behavioural phenotype.

The current study is the first to compare cognitive function and neuroanatomical characteristics in 22q11DS children with an FSIQ matched group of children with another microdeletion disorder, facilitating the identification of specific characteristics in both groups. We chose to use Williams syndrome since it has been reported that children with Williams syndrome (WS) share many characteristics with those of 22q11DS children. People with 22q11DS and WS share a high prevalence of physical problems such as heart abnormalities, feeding difficulties, sensitive hearing and facial dysmorphology. The two groups also share many personality characteristics and experience problems with peer relations, anxiety, concentration and over-activity (Prinzie et al., 2002). The commonalities between the two syndromes, especially the shared environmental influences from early corrective surgeries, problems with social interaction and learning problems, makes WS an interesting comparison group to 22q11DS.

In addition, both syndromes are characterised by lower intellectual functioning, including problems with non-verbal abilities (Mervis & Klein-Tasman, 2000; Swillen et al., 1997). Indeed, it has been reported that 63% of people with 22q11DS meet all the criteria for the characteristic 'Williams Syndrome Cognitive Profile' (WSCP, Bearden, Wang, & Simon, 2002). While people with both syndromes have a relatively preserved (volume) of the frontal lobes there are volumetric reductions of the posterior parts of the brain, such as reductions of grey matter in the parieto-occipital regions. It has also been reported that both syndromes have larger reductions of white matter compared with grey matter (Boddaert et al., 2006; Campbell et al., 2006; Eliez, Schmitt, White, & Reiss, 2000; Kates et al., 2001; Reiss et al., 2004, 2000). While there has only been one study of brain anatomy in school-aged children with WS (Boddaert et al., 2006) reporting reductions in the parieto-occipital regions, several such studies in 22q11DS have reported anatomical differences compared with 'typically' developing controls. When comparing these findings to those reported in studies of children and adults with WS some regions appear differentially affected by the deletions. For example, there have been reports of reduced amygdala volume reductions in 22q11DS (Deboer, Wu, Lee, & Simon, 2007) whilst this region is increased in Williams syndrome (Reiss et al., 2004). Conversely the basal ganglia has been found to be larger in people with 22q11DS compared to 'typically' developing brains while the region is volumetrically smaller in people with WS (Campbell et al., 2006; Chiang et al., 2007). Furthermore, structural alterations of the cerebellum and fusiform gyrus have been reported in people with 22q11DS (Campbell et al., 2006; Glaser et al., 2007) while these regions appear well preserved in people with WS (Chiang et al., 2007).

The current study is one of the first studies to use a comprehensive battery to compare children 22q11DS and children with other disorders at a cognitive and neuroanatomical level. On the basis of previous literature, we hypothesised that: (1) children with 22q11DS would have similar intellectual profiles to WS children, with increased verbal relative to non-verbal abilities since this has been reported in both groups but in separate studies. However, it is not known whether this effect is stronger in either group; (2) the WS group would perform better on sociability and social cognitive functioning than the 22q11DS group. Although both groups experience social interactive problems, the pattern is reversed with the WS children often described as hypersocial and the 22q11DS children as hyposocial: (3) there would be syndrome specific changes in the amygdala, fusiform gyrus, lateral ventricles, cerebellum, and striatum. These regions have been found to be structurally different in 22q11DS and/or WS compared with 'typically' developing children.

2. Methods

2.1. Participants

The study included 12 children with 22q11DS (9 had a de novo deletion, 5 girls, 7 boys, mean age = 11 (SD = 3), mean FSIQ = 59 (SD = 6)) with a demonstrated chromosome 22q11.2 deletion using fluorescence in situ hybridisation (FISH) (Oncor Inc., Gaithersburg, MD 20877, USA). The comparison group consisted of 12 children with Williams syndrome (WS) (5 girls, 7 boys, mean age = 12 (SD = 4), mean FSIQ = 58 (SD = 6)) with a confirmed microdeletion at chromosome 7q11.23 using a FISH test. The cohorts were matched for gender, age and FSIQ. The mean FSIQ in the 22q11DS group was lower than typically reported for the syndrome. In a recent study, De Smedt and colleagues reported a mean FSIQ of 73 (range 50–109) in a study of 103 children with 22q11DS (De Smedt et al., 2007). Hence the current sample was compared with a larger group of 22q11DS people (n = 38, mean FSIQ = 68, partly reported in Campbell et al. (2006, in preparation) on the tasks used in the current study. The two groups differed on the WISC-III FSIQ score, but did not differ on the cognitive tasks administered in the present study. The participants were recruited from the 22q11DS (UK) support group and the Williams Syndrome Foundation to minimise ascertainment bias. Each family was provided with a complete description of the study before consent was obtained under protocols agreed by local ethical committees. Some individuals did not complete the MRI scan. Anatomical results are based on a subgroup of nine pairs matched on chronological age, gender and FSIQ.

2.2. Procedure

The cognitive battery was designed to assess general cognitive function and psychoeducational abilities. To measure intellectual functioning the children completed the full '*Wechsler Intelligence Scales for Children—third edition (UK)*' (WISC-III UK; Wechsler, 1991). This provides four index scores, representing the