2010

Substrates of social functioning in individuals with VCFS

Daniel Jacobson

Substrates of Social Functioning in Individuals with VCFS

by

Daniel Jacobson

Thesis

Submitted to the Department of Psychology

Eastern Michigan University

In partial fulfillment of the requirements

For the degree of

Masters of Science

in

Clinical Psychology

Thesis Committee:

Renee Lajiness-O'Neill, PhD

Alissa Huth-Bocks, PhD

Dean Lauterbach, PhD

May 16, 2010

Ypsilanti, Michigan

Abstract

Velocardiofacial Syndrome (VCFS) is a genetic disorder characterized by numerous physiological and psychological symptoms. Little is known regarding the neuropsychological substrates of social functioning in individuals with VCFS. This study was a secondary data analysis investigating the relationship between various brain structure volumes and social deficits in individuals with VCFS. Volumetric measures of brain regions based on magnetic resonance imaging (MRI) were compared between 6 VCFS individuals and 6 controls. Controls were identically matched according to age and gender. It was hypothesized that after covarying for total brain volume, VCFS patients would exhibit larger amygdala and insula volumes and smaller prefrontal cortex (PFC), orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC), insula, superior temorpal sulcus (STS), and anterior cingulate cortex (ACC) volumes relative to controls. In addition, scores on the Child Behavior Checklist (CBCL), a measure assessing problematic behaviors and social competency, would be correlated with volumes of amygdala, PFC, OFC, DLPFC, STS, and ACC in patients with VCFS. Specifically, it was hypothesized that regional volumes in patients with VCFS will be associated with increased problem scores and decreased social competency as measured by the CBCL. Amygdala volumes were found to be enlarged in individuals with VCFS relative to controls t (10) = 4.01, $p < .05$) and negatively correlated with the attention subscale of the CBCL $r(6) = -.98$, $p < .01$. Contrary to expectations, DLPFC volumes were larger in individuals with VCFS relative to controls $t(10) = 3.23$, $p < .05$).

Table of Contents

LIST OF TABLES

LIST OF FIGURES

Introduction

Velocardio-facial syndrome (VCFS) is a genetic disorder that has a number of physiological and psychological symptoms. VCFS is one of the most common genetic disorders and one of the most common causes of learning disability and mild mental retardation (Eliez, et al., 2001; Gothelf & Lombroso, 2001). Though the physiological symptoms associated with VCFS have been thoroughly studied, there is much to be understood with regard to the psychological features of the disorder. In particular, the neuroanatomical substrates underlying many of the social impairments expressed in these individuals have received little attention. Further examination of the neural substrates of social functioning in this population may provide insight into the brain-behavior relationships of social cognition. A review of the specific impairments associated with VCFS with an emphasis on social impairments and their neuoanatomical correlates will be presented. Specifically, this introduction will review the history of VCFS, the prevalence rate of the disorder, and the diagnostic tests used to identify the disorder. Furthermore, the physical, psychiatric, cognitive, and social deficits will be described along with the neurological anomalies associated with these symptoms.

History of VCFS Discovery

Velocardio Facial Syndrome was first described by Kirkpatrick and DiGeorge in 1968 as a constellation of immunologic deficiencies. It was renamed Shprintzen Syndrome following a re-categorization of the common presenting symptoms (Shprintzen, et al., 1978). Shprintzen (1978) described palate anomalies (Velo), congenital cardiovascular defects (Cardio), and mild facial dysmorphism (Facial) as characteristic of individuals with this particular disorder. Despite the consistent reemergence of the

aforementioned symptoms, there is a great deal of symptom heterogeneity expressed in these individuals, making it difficult to conclude that these individuals actually had the same disorder (Shprintzen, et al., 1978). In order to definitively categorize these seemingly independent symptoms as being part of a single disorder, it was necessary to link the immunologic deficiencies noted by Kirkpatrick and the symptoms noted by Shprintzen with a common etiology. It was discovered that all of the individuals expressing some combination of the symptoms described by Kirkpatrick and Shprintzen had a microdeletion in the long arm of chromosome 22 at band 22q11.2 (Kelly, et al., 1993). This finding allowed researchers to definitively conclude that the multitude of symptoms were part of the same syndrome. As research has progressed, the number of diagnostic symptoms has increased. At present, there are over 180 phenotypic characteristics of VCFS including congenital abnormalities, learning disabilities, and psychiatric disturbances (Gothelf, 2007). This has prompted researchers to begin using the title 22q11.2 deletion syndrome as opposed to VCFS, though the terms are still used interchangeably.

Prevalence and Diagnostic Tests

Despite consistent agreement among practitioners regarding the constellation of symptoms associated with VCFS, the exact prevalence of VCFS is difficult to ascertain. However, the best estimate to date is 1 in 5900 (Botto, et al., 2003). The actual prevalence is in all likelihood much higher than this figure (Gothelf, 2007). Gothelf identifies several reasons for the inability to get an accurate prevalence rate. First, only "at-risk" infants are screened for the disorder. Second, the phenotypic and cognitive symptoms can be quite

mild, resulting in a lack of diagnosis or delayed diagnosis. Third, the heterogeneous symptom presentation often leads clinicians to make an erroneous diagnosis.

Despite these barriers to gauging prevalence accurately, recent advances in genetic screening have enabled clinicians to determine with great accuracy whether a cluster of symptoms is due to VCFS. Using Florescence In Situ Hybridization (FISH), clinicians can determine whether a micro-deletion exists on chromosome 22 (Driscoll, et al., 1993). As a result, FISH has become the gold standard diagnostic test for VCFS. Though the diagnosis of VCFS can be made accurately and reliably, the cost of testing is a major barrier to expansive infant screening. Future variants of the FISH test are likely to be more cost-effective, making wide-spread infant screening for the disorder feasible. Researchers will then be able to determine with greater accuracy the prevalence rate of the disorder. Despite difficulties accurately assessing prevalence, the physical symptoms associated with VCFS have been extensively examined. The following section will describe the physical anomalies associated with VCFS.

Common Physical Symptoms Associated with VCFS

There are a wide range of physical symptoms associated with VCFS. These symptoms can be grouped into 5 categories. The first symptom category is congenital anomalies. These anomalies occur in nearly 75% of all individuals with VCFS and include tetralogy of fallot, ventricular septal defects, and truncus arteriosus (Digilio, et al., 2005). The second symptom category is abnormal facies (Gothelf, 2007). These facial anomalies are common in individuals with VCFS and include hypoplastic alae nasi, prominent nasal root, elongation of face with cheek flattening, narrow set eyes, small mouth, and retrudded chin. Many times these are the most prominent diagnostic features

of VCFS. The third symptom category is palatal abnormalities, which occur in approximately 75% of individuals with VCFS (Kirscher, 2005). Specifically, these anomalies include an insufficiency of the palate and hypernasal speech. The fourth symptom category includes T-cell immunodeficiency (Gothelf, 2007). According to Kirkpatrick and DiGeorge (1968), this deficiency results from a hypoplastic parathyroid and thymus. The fifth symptom category includes a heterogeneous set of other physical symptoms that covary with the disorder such as growth retardation, juvenile rheumatoid arthritis, and urinary abnormalities (Gothelf, 2005).

Etiological analysis of these symptoms has occurred on multiple levels. At the embryonic level, most of the symptoms observed appear to result from impaired migration of the neural crest cells (Prescott, et al., 2005). These cells represent the prelude to the formation of the mesenchyme of the third and fourth pharyangeal arches. From these arches emerge the face, cleft, thymus, parathyroid gland, and cardiovascular system. Thus, interference with the migration of the crest cells can result in a deleterious cascade in which numerous biological systems are impacted. Furthermore, this embryonic explanation accounts for the symptom heterogeneity observed in individuals with VCFS. That is, the level of impairment in the neural crest cell migration dictates the range of biological systems affected and the severity with which the pathology presents.

Another level of etiological analysis is genetic (Gothelf, 2007). One theory regarding the genetic etiology of VCFS is haploinsufficiency. Haploinsufficiency occurs when only a single functional copy of an essential gene is produced, resulting in insufficient gene product. Funke, Panditta, and Morrow (2001) noted that haploinsufficiency of one or more of a combination of genes may account for a multitude

of the physical and psychiatric symptoms associated with VCFS (Funke, Pandita, & Morrow, 2001). In support of this, McDermid and Morrow (2002) performed a knockout mutation for the TBX1 gene (McDermid & Morrow, 2002). TBX1 codes for a protein which is expressed in great quantity throughout numerous brain regions (Paylor, et al., 2006). Compared to control mice, knockout mice experienced numerous developmental abnormalities. Many of these abnormalities were correlates of the pathologies associated with VCFS. The deficits included cardiac abnormalities, abnormal facial structures, deformed vertebrae, and cleft palate. Thus, it is conceivable that VCFS might be related to genetic abnormalities of the TBX1 gene. Furthermore, the wide expression of the TBX1 protein explains the wide range of symptom heterogeneity in VCFS.

To conclude, there are two theories of etiological analysis. The first is the embryonic theory, which incorporates the concept of neural crest migration. The second theory is genetic, which suggests that limited protein expression from TBX1 mediates the symptomatology of VCFS. Both of these etiological theories account for the numerous symptoms associated with VCFS and the heterogeneity of symptom expression. However, more research is needed to determine how these two causal factors interact.

Psychiatric Symptoms of VCFS Throughout the Lifespan

In addition to many physical disorders that are observed in individuals with VCFS, there are numerous psychiatric disorders that co-occur with VCFS (Arnold, Siegel-Bartelt, Cytrynbaum, Teshima, & Schachar, 2001; Feinstein, Eliez, Blasey, & Reiss, 2002; Fine, et al., 2005; Gothelf, et al., 2003; Gothelf, et al., 2004; Lachman, et al., 1996; Shprintzen, 2000). These psychiatric disturbances emerge at different times throughout the lifespan. For example, during childhood, one psychiatric disturbance in individuals with VCFS is

ADHD (Arnold, et al., 2001; Feinstein, et al., 2002; Lajiness-O'Neill, et al., 2006). This is one of the most common psychiatric correlates of VCFS, with a prevalence rate of about 35% to 46%. In addition to ADHD, a significant proportion of children with VCFS present with non-verbal learning disorders (Lajiness-O'Neill, et al., 2006). Anxiety disorders are also commonly diagnosed in children with VCFS (Gothelf, et al., 2003; Prinzie, et al., 2002). Specifically, VCFS children present with generalized anxiety disorder, separation anxiety disorder, obsessive compulsive disorder, and specific phobias. Affective disorders are also comorbid with VCFS (Arnold, et al., 2001; Feinstein, et al., 2002). Arnold et al. (2001) noted high rates of depression among childhood populations of VCFS individuals. Furthermore, bipolar disorder was found in 66% of children with VCFS who demonstrated affective symptomatology (Papolos, Faedda, Veit, et al., 1996). Last, children with VCFS have a high prevalence rate for pervasive developmental disorders. For example, approximately 14%-45% of children who have VCFS also meet criteria for autism (Antshel, et al., 2007; Fine, et al., 2005; Niklasson, Rasmussen, Oskarsdottir, & Gillberg, 2001; Vorstman, et al., 2006).

During late adolescence and throughout adulthood, a different pattern of psychiatric symptomatology emerge (Gothelf, 2007). For example, VCFS adults have much more severe, persistent anxiety than what is observed in children with VCFS (Gothelf, Feinstein, et al., 2007). In addition, 32% of individuals with VCFS will develop schizophrenia or other psychotic disorders during late adolescence or early adulthood (Murphy, Jones, & Owen, 1999). Having 22q11 deletion syndrome is the highest genetic risk factor for the development of schizophrenia (Murphy, et al., 1999). These individuals are 25 times more likely to develop schizophrenia than the general population (Turner,

1989). Finally, Murphy (2002) noted that the prevalence rate for schizophrenia in individuals with VCFS is higher than in children with a schizophrenic parent (Murphy, 2002). This increased prevalence for schizophrenia and other psychiatric illness has led researchers to conceptualize VCFS as a significant genetic diathesis for the development of these disorders.

Cognitive Deficits and their Neurological Correlates in Patients with VCFS

In addition to the numerous psychiatric illnesses associated with VCFS, there are multiple cognitive impairments of note. For example, individuals with VCFS frequently have a borderline IQ (Swillen, et al., 1997). According to Swillen et al., approximately 25% to 40% have an IQ below 70 and meet criteria for mild mental retardation.

Furthermore, deficits in attention, cognitive flexibility, and working memory are common (Gothelf, Furfaro, Penniman, Glover, & Reiss, 2005). Many of these deficits have been associated with impaired executive network efficiency (Sobin, et al., 2004). The specific attention deficits can be ascribed to malformations of the head of the caudate nucleus (Sugama, et al., 2000). Sugama (2000) noted that patients with VCFS had a larger right head of the caudate relative to the left head, whereas controls demonstrated the reverse trend. Interestingly, this same trend has been consistently identified in individuals with ADHD (Castellanos, et al., 1994; Castellanos, et al., 1996; Hynd, et al., 1993). Taken together, these data suggest that this particular neuroanatomical anomaly mediates attention and other cognitive deficits in individuals with VCFS.

In conjunction with deficits in attention and working memory, individuals with VCFS also display impairments in response inhibition. This response inhibition has been associated with abnormal activation of the parietal cortex (Eliez, et al., 2001). Gothelf et

al. (2007) noted that individuals with VCFS performed comparably to controls on the Go/No Go response inhibition task (Gothelf, Hoeft, et al., 2007). However, VCFS individuals showed additional activation in superior and inferior parietal regions suggesting that more neurocognitive resources were necessary in order to inhibit particular responding. These results, taken together with the observed attentional impairments, may account for the high rate of ADHD in individuals with VCFS.

In addition to response inhibition difficulties, individuals with VCFS also show impairment in visuospatial and numerical abilities. These impairments have been associated with structural deficits of the parietal lobe (Eliez, et al., 2001; Kates, et al., 2004). Eliez et al. (2001) observed increased activation of the left supramarginal gyrus (LSMG) as a function of computational difficulty in individuals with VCFS. No such trend was observed in aged-matched controls. The authors concluded that the increased LSMG activation occurred as a result of parietal deficits and may contribute to limitations in numerical, mathematical, and spatial reasoning abilities in this population.

To summarize, individuals with VCFS have a number of cognitive deficits. These deficits include attention, working memory, memory, cognitive flexibility, response inhibition, visuospatial abilities, numerical processing, and language processing. Many of these deficits have neuroanatomical correlates which account for poor performance on related tasks. Indeed, it is possible that these cognitive deficits and their neurological etiology contribute to the many social deficits observed in individuals with VCFS. These social deficits will be the primary focus of the remainder of this discussion.

Social Impairments Observed in Individuals with VCFS

Though the physical symptomatology and genetic features of the disorder have been widely studied, there has been little advancement in the understanding of social phenotypes in VCFS and other genetic neurodevelopmental disorders (GNDD's) (Feinstein & Singh, 2007). One reason for this lack of research pertaining to the social deficits of these disorders is simply a failure to include assessments of social functioning when conducting research on these individuals. Frequently, the psychotic features, cognitive deficits, and genetic correlates take precedence when conducting research on GNDD's (Feinstein & Singh, 2007). Furthermore, diagnostic overshadowing has been problematic in elucidating the specific social deficits in VCFS. Specifically, the cognitive impairments are viewed as the etiology of social features and therefore little concern is placed on determination of independent etiologies for these social deficits (Hodapp & Dykens, 2005; Jopp & Keys, 2001). Indeed, these cognitive impairments contribute to the observed deficits in social functioning; however, there is neuroanatomical evidence suggesting that there is an independent etiology for the social deficits in VCFS.

Despite being overlooked throughout the history of VCFS research, recent research has identified a number of social deficits that commonly occur in individuals with VCFS. One social deficit observed in individuals with VCFS is communication. Interestingly, these individuals develop normal communication skills throughout the first two years of life but show significant delays acquiring the ability to use short phrases and sentences. Furthermore, their speech is typically unintelligible due to the emergence of compensatory articulation patterns (Golding-Kushner, Weller, & Shprintzen, 1985). The most common compensatory articulation in children with VCFS is the implementation of glottal stop

substitutions (Shprintzen, 1997). As a result of such communication difficulties, few utterances are understood and early speech attempts may not be reinforced or encouraged, leading to further disintegration of communication abilities.

Another social deficit that may emerge as a result of these communication issues is extreme shyness and withdrawal (Shprintzen, 2000). Swillen et al. (2001) administered the Child Behavior Checklist (CBCL) to both individuals with VCFS and individuals with speech pathology and learning impairments. He found the groups to differ substantially in the areas of withdrawal behavior, suggesting that the speech difficulties in VCFS interact with other features of the disorder to produce social withdrawal (Swillen, Devriendt, Ghesquiere, & Fryns, 2001).

One of the social deficits that may result from the shyness and social withdrawal is a failure to initiate interactions (Eliez, et al., 2000). In their case study describing the language, speech, and psychological features of five individuals with VCFS, Eliez et al. (2001), noted a significant deficit in the number of attempts made to interact. The authors attributed this social deficit to communication difficulties and the tendencies to engage in withdrawal behaviors.

In addition to their initiation deficits, VCFS individuals also show deficits in facial recognition (Stiers, et al., 2005). Stiers et al. noted that the substantial impairments in facial recognition correlated with decreased volume of the right inferior parietal and superior occipital lobe. In addition, there was a pronounced reduction of white matter behind the inferior frontal gyrus relative to controls. Thus, it is possible that the social deficits observed in these individuals relating to their inability to recognize faces may be mediated by abnormalities in these brain areas.

Further contributing to deficits in social functioning are impairments in processing facial expressions (van Amelsvoort, et al., 2006). VCFS individuals perform significantly worse on facial emotional processing tasks compared to age- and IQ-matched controls. This deficit was associated with decreased activation in the right insula and frontal lobe. Alternatively, there was increased activation in occipital regions relative to controls. The authors concluded that these genetically determined neuroanatomical anomalies may significantly contribute to social deficits due to their involvement in emotional processing.

In addition to their emotional processing difficulties, VCFS individuals have distinct personality characteristics which color many of their social interactions. VCFS individuals are less conscientious, less emotionally stable, more irritable, and more dependent than normal controls (Prinzie, et al., 2002). Furthermore, VCFS individuals have been shown to have severe attachment and anxiety issues, which may contribute to or exacerbate their personality deficits. For example, Shprintzen (2000) noted age-inappropriate separation anxiety in VCFS individuals when compared with normal controls. Also, children with VCFS are more phobic and present with obsessive compulsive personality disorder more frequently than controls (Papolos, et al., 1996). Indeed, the personality characteristics and anxious symptoms of people with VCFS greatly impede social development.

Last, these individuals show affective abnormalities that interfere with social relations. People with VCFS have been shown to have a flatter affect than normal controls during engagement in social interactions. Furthermore, their facial response tends to be expressionless or non-existent during social engagements that usually facilitate both affective and facial responses (Golding-Kushner, et al., 1985). Indeed, this would make it

difficult for individuals to sustain conversations with others and provide reinforcing feedback to those with whom they are communicating. As a result, these individuals may have shorter interactions with individuals they are meeting for the first time.

In summary, individuals with VCFS have numerous features contributing to their social deficits. It is likely that many of the genetically prescribed neuroanatomical deficits associated with VCFS contribute to these deficits. The following section will identify etiological theories for these social deficits with particular emphasis on the neuroanatomical structures that have been implicated in social and emotional processing.

Etiology of Social Impairments

One prominent theory regarding the etiology of social deficits in VCFS individuals suggests that the language deficits are the foundation for the other social impairments. Shprintzen (2000) argues that the language deficits observed in these individuals lead to ineffectual communication skills. These ineffectual communication skills then lead to social isolation due to lack of social reinforcement. Often times these children are ridiculed for their poor communication skills, leading to withdrawal and the formation of social anxieties. In this way, language impairment can account for a number of other social peculiarities associated with the disorder.

In addition to the language theory regarding the etiology of social deficits in individuals in VCFS, it has been proposed that abnormal blood supply to the brain may account for some of the deficits observed. Shprintzen (1997) noted that individuals with VCFS often have reduced blood flow to the brain that leads to the formation of central nervous system abnormalities. Many of these abnormalities have been linked to the learning and psychiatric disturbances observed in these individuals. These learning and

psychiatric disturbances then serve as the foundation for ineffectual and unrewarding communication, which ultimately results in social isolation, withdrawal, anxiety, and phobic behaviors (Shprintzen, 1997). Thus, in this hypothesis, the abnormal blood supply is the catalyst for the development of social impairment in individuals with VCFS.

Another physiological explanation for the etiology of social deficits is lesions. White matter hyperintensities and cysts have been consistently observed in individuals with VCFS (Mitnick, Bello, & Shprintzen, 1994). The individuals presenting with these abnormalities have the characteristic behavioral and social deficits commonly observed in this population. Though the lesions were not statistically related to the behavioral deficits, it is possible that they interact with other structural abnormalities to produce the social disturbances.

The remainder of this etiological analysis will focus on specific brain structures and sub-nuclei that have been associated with the social deficits observed. For example, one study found significant volumetric changes in amygdala, prefrontal cortex, and orbitofrontal cortex (Kates, et al., 2006). These volumetric differences were positively correlated with impaired performance on social competency scales such as the CBCL and other parent report measures.

With regard to the amygdala, Kates et al. (2006) noted that after controlling for total brain size, the amygdala to prefrontal cortex ratio in VCFS patients was found to be significantly larger than in sibling controls. As the amygdala as been implicated in emotional processing (Davidson & Irwin, 1999; LeDoux, 2000; Phillips, Drevets, Rauch, & Lane, 2003), learning and memory (Maren, 1999), and facial processing (Adolphs, Tranel, Damasio, & Damasio, 1994; Hamann, et al., 1996), this finding can account for

many of the social features observed in individuals with VCFS. Though it is tempting to conclude that the genetic anomalies associated with this disorder mediate this neuroanatomical deviation, it has been proposed that this increase in amygdala volume may be the result of high anxiety levels in this population (Feinstein, et al., 2002). Increased amygdala volumes have been observed in individuals with phobia and generalized anxiety disorders (Bellis, 2000). Dong and Greenough (2004) found that this increased anxiety leads to experience-dependent neuronal remodeling in the amygdala, which may contribute to its increased volume (Dong & Greenough, 2004). Thus, it is possible that the anxiety associated with these patients leads to the volumetric changes in the amygdala. These neuroanatomical changes then contribute to difficulties with emotional regulation, facial recognition, and affective style.

Though several studies have identified amygdala variations in VCFS patients, this finding has not been consistently reported (Antshel, et al., 2007; Kates, et al., 2006). Eliez et al. (2001) found no difference in amygdala volumes when VCFS individuals were compared with controls. Upon further longitudinal analysis, it was found that amygdala volumes were preserved throughout adulthood. Thus, there is some controversy with regard to the role the amygdala plays in the mediation of social deficits in VCFS patients.

In addition to amygdala volume discrepancies, individuals with VCFS also have a prefrontal cortex that is smaller than those of age-matched, non-clinical controls (Kates, et al., 2006). The prefrontal cortex has been implicated in the ability to modulate emotional stimuli and was found to be correlated with social impairments in individuals with VCFS (Kates, et al., 2006). In particular, smaller volumes were observed in the orbitofrontal cortex relative to controls. The orbitofrontal cortex has been implicated in the modulation

of anxiety (Breiter & Rauch, 1996; Rauch, Savage, Alpert, Fischman, & Jenike, 1997). Thus, it is possible that many of the attachment and anxiety issues in VCFS patients may be related to abnormalities in this particular structure.

Other subregions of the PFC have been implicated in social functioning. For example, the dorsolateral PFC (DLPFC) has been shown to be involved in the regulation of affect and has been implicated in the etiology of mood disorders such as depression (Gainotti, 1972; Robinson, Kubos, Starr, Rao, & Price, 1984; Sackeim, Decina, & Malitz, 1982). Thus, it is conceivable that volumetric changes in this subregion could mediate the mood symptoms that are frequently observed in individuals with VCFS. To date there has been limited research with regard to these particular subregions. These structures will be included in this analysis of the substrates of social functioning in individuals with VCFS.

In addition to the dorsolateral PFC, the ventromedial PFC (VMPFC) also has a role in social functioning. The VMPFC has been implicated in the anticipation of future consequences (Bechara, Damasio, Damasio, & Anderson, 1994). Specifically, individuals with damage to this region showed an inability to accurately anticipate both positive and negative consequences. Interestingly, individuals with damage to this region showed reduced electromodal responses when they were presented with a risky choice relative to controls, who demonstrated both conscious recognition of the risky choice and full electromodal responses (Bechara, Damasio, Tranel, & Damasio, 1997; Bechara, Tranel, Damasio, & Damasio, 1996). Indeed, it is possible that much of the impulsiveness and disinhibition observed in individuals with VCFS might be mediated by volumetric differences in this particular region. Despite this logical connection, there has been limited research with regard to this region of the frontal cortex in individuals with VCFS.

Taken together, these data suggest that volumetric anomalies in the prefrontal cortex mediate many of the social deficits observed in individuals with VCFS. Furthermore, specific sub-nuclei should be examined in individuals with VCFS in order to determine whether volumetric changes in these structures mediate the observed social deficits.

Additional neuroanatomical analysis in individuals with VCFS has found discrepancies in volume of the insular cortex (van Amelsvoort, et al., 2001). In addition to this volumetric difference, van Amelsvoort and Schmitz (2006) also noted decreased activation in right insula during tasks that involved facial processing (van Amelsvoort, et al., 2006). The insula has been shown to be involved in the processing of general emotions and has been implicated as one of the etiological factors of anxiety (Rauch, et al., 1995). Furthermore, it has been demonstrated that the insular cortex plays a critical role in regulating autonomic responses accompanying emotion. Also, the insula is a site that has been implicated in gustatory processing. It is especially active during exposure to disgusting foods and photos of disgusted faces suggesting one of its functions is the recognition of distasteful stimuli (Rozin, 1997; Young, 1997). Last, given the known input and output pathways of the insular cortex, Davidson and Irwin (1993) concluded that the insula is likely associated with the physiological changes that occur following autonomic activation (Davidson & Irwin, 1999). In sum, given what is known regarding the functions of the insular cortex, the anatomical and activation abnormalities in this structure may underlie such social deficits as withdrawal, inhibition, poor attachment and social anxiety. Though some speculation has been made regarding the insular cortex and social deficits in VCFS, no one to date has directly assessed the relationship between

insula volume and social deficits. This study will examine the relationship of insula volume and social functioning in individuals with VCFS.

In addition to the aforementioned structures, it is also possible that the STS mediates some of the social deficits observed in individuals with VCFS. The STS has been implicated in the development of theory of mind (ToM;(Moriguchi, Ohnishi, Mori, Matsuda, & Komaki, 2007). Theory of mind is defined as the ability to attribute mental states to the self and others. As such, it has been implicated in the development of social deficits in a number of disorders including autism and schizophrenia (Castelli, Frith, Happe, & Frith, 2002; Happe, et al., 1996; Ohnishi, et al., 2000). Given that individuals with VCFS experience a number of social deficits relating to theory of mind such as impairments in communication and social interaction, it is plausible that these individuals may show volumetric differences in the STS relative to controls. In addition to being a primary structure in the development of ToM, the STS has also been shown to be involved in controlling gaze (Garrett, Menon, MacKenzie, & Reiss, 2004). Individuals with activation deficits in this structure have difficulty controlling their gaze and maintaining appropriate social posturing, as is the case with individuals diagnosed with autism and schizophrenia. Furthermore, the STS has been implicated in the processing of vocal sounds (Gervais, et al., 2004). Autistic individuals showed decreased activation in this area during exposure to vocal sounds. Gervais et al. (2004) concluded that some of the social deficits observed in autism may be attributed to deficits in vocal processing. Indeed, given what is known with regard to the social functions of the STS, it is reasonable to hypothesize that volumetric differences in the STS are correlated with social

deficits in VCFS individuals. The relationship between STS volume and social impairment will be assessed in this study.

Yet another structure that has been implicated in social processing and may contribute to the social deficits observed is the anterior cingulate cortex (ACC). The ACC has been implicated in the ability to attend to emotional events (Posner, 1995). Additionally, Lang et al. (1997) showed increased activity in the ACC during tasks in which attention of emotional stimuli was required (Lane, et al., 1997). When subjects were asked to attend to non-emotional stimuli, no such activation in the ACC was recruited. It was therefore concluded that one of the roles of the ACC was to facilitate attention to emotional stimuli. The ACC has also been implicated in the mediation of other affective and cognitive functions (Fujiwara, et al., 2007). Specifically, the ACC helps modulate emotional responses and has been found to be an essential component in social cognition and mentalizing (Kopelman, Andreasen, & Nopoulos, 2005). Interestingly, volumetric differences in the ACC have been observed in schizophrenic patients relative to controls (Kopelman, et al., 2005). The smaller ACC volume has also been correlated with specific deficits in social cognition (Fujiwara, et al., 2007). Thus, decreased ACC volume seems to play a role in the development of social impairments. To date, this structure has not been researched in individuals with VCFS, and it is possible that decreased ACC volume in this population will be correlated with social deficits. This study will examine the relationship between ACC volume and social functioning in individuals with VCFS.

Hypotheses

Specific Aim 1 is to determine if there are differences between amygdala volume in individuals with VCFS relative to controls. Given the extensive role the amygdala plays in emotional processing and the controversy over amygdala volume in individuals with VCFS, further investigation of amygdala volume in this population is justified. Given that individuals with VCFS have difficulty with facial processing, increased anxiety and fear, and are less emotionally stable, it was hypothesized that VCFS individuals would have a significantly larger amygdala to prefrontal cortex ratio than sibling controls.

Specific Aim 2 is to assess the relationship between amygdala volume and obtained cognitive data. It was hypothesized that any greater amygdala volume would be correlated with greater anxiety and lower social competency as measured by the CBCL.

Specific Aim 3 is to determine if there are differences between orbitofrontal cortex volumes in individuals with VCFS relative to controls. As a result of the significant anxiety and attachment issues observed in individuals with VCFS, it was hypothesized that the orbital frontal cortex of individuals with VSFS would show volumetric differences when compared with matched controls. Specifically, it was hypothesized that this structure would be significantly smaller in volume in VCFS patients than in a matched control group.

Specific Aim 4 is to assess the relationship between orbitofrontal cortex volumes and cognitive measures in individuals with VCFS. It was hypothesized that the smaller volume of this structure would be correlated with greater attention problems and social problems as measured by the CBCL. Furthermore, it was hypothesized that the smaller

volume of the orbital frontal cortex in patients with VCFS will be correlated with lower social competency as measured by the CBCL.

Specific Aim 5 is to determine if any volumetric differences exist between individuals with VCFS and controls in other sub-nuclei regions of the PFC such as the DLPFC. As activity and functional impairments in the DLPFC have been implicated in the etiology and exacerbation of mood and affective symptoms, it was hypothesized that individuals with VCFS would have smaller DLPFC volumes relative to controls.

Specific Aim 6 is to assess the relationship between DLPFC volume and cognitive measures of social functioning. It was hypothesized that DLPFC volumes would be negatively correlated with anxious/depressed scores as measured by the CBCL. Furthermore, DLPFC volumes would be positively correlated with social competency as measured by the CBCL. Similarly, the VMPFC, has been implicated in the interpretation of consequences and the ability to inhibit certain behaviors. As such, it was also hypothesized to be smaller in individuals with VCFS and be negatively correlated with increased attention problems and delinquency as measured by the CBCL. Furthermore, VMPFC volume would be positively correlated with social competency as measured by the CBCL.

Specific Aim 7 is to determine if there are any volumetric differences in the insular cortex between VCFS patients and controls. Previous studies have demonstrated volumetric discrepancies in this population (van Amelsvoort, et al., 2001). However, these structural deviations have not been specifically correlated with social competency. In congruence with van Amelsvoort et al. (2001), it was predicted that insula volume will

be larger relative to controls. Furthermore, this volumetric anomaly would be positively correlated with withdraw and anxiety scales of the CBCL.

Specific Aim 8 is to assess the relationship between insula volume and measures of social functioning. It was hypothesized that insula volume would be negatively correlated with the social competency scale of the CBCL.

Specific Aim 9 is to compare STS volumes in individuals with VCFS and controls. As the STS has been implicated in the development of ToM, it was hypothesized that volumetric differences would be observed in individuals with VCFS. Specifically, it was hypothesized that individuals with VCFS would have smaller STS volumes relative to controls.

Specific Aim 10 is to assess the relationship between STS volume and social functioning. It was hypothesized that a decreased STS volume would be negatively correlated with the social problems scale of the CBCL and positively correlated with social competency.

Specific Aim 11 is to compare ACC volumes in individuals with VCFS and Controls. As numerous social impairments have been linked with volumetric discrepancies in the ACC and VCFS individuals share common social symptomatology with populations showing decreased volumes in this structure, it was hypothesized that individuals with VCFS would have decreased ACC volume relative to controls (Kopelman, et al., 2005).

Specific Aim 12 is to assess the relationship between ACC volume and measures of social functioning. It was hypothesized that any structural anomaly at this site would

be inversely correlated with the social problems scale of the CBCL and positively correlated with social competency measures of the CBCL.

Measures

Child Behavior Checklist (CBCL): The CBCL is a standardized, parent-report measure of children's (ages 4-18) behavior problems and competencies. The problem portion of the measure consists of 118 specific problem items that compose the 9 subscales (Withdrawn = 9 items, Somatic Complaints = 3 items, Anxious/Depressed = 14 items, Social Problems = 8 items, Thought Problems = 7 items, Attention Problems = 11 items, Delinquent Behavior = 13 items, Aggressive Behavior = 20 items, and Other Problems including Sex Problems = 33 items). The competency portion of the measure contains 20 items that compose the 3 subscales (Activities = 5 items, Social = 6, School = 4 items, and Other = 5 open items not scored in the profile).

CBCL Subscales and Compentency: For the problem scale, items are scored a 3-point Likert-type response scale with the following anchors: 0 = *Not True,* 1 = *Somewhat or Sometimes True,* 2 = *Very True or Often True*. Problem Scale scores can range from 0 to 236. Raw scores are converted into T scores for clinical analysis. A high total problem score (>T = 70) indicates that the child is experiencing a clinically significant level of disordered behavior. Furthermore, a child can have a low total problem score but have an elevated sub-scale (>T = 70), indicating significant behavior problems in the specific domain. For the competency scale, items are scored on a mix of three (0,1,2), and four (0,1,2,3,4) option Likert-type items as well as number of dichotomously scored items (0 = *no*, 1 = *yes*). Competency Scale scores can range from 0 to 23. The raw scores are then converted into T scores for clinical analysis. High total competency scores indicate a high

level of competence. Low total competency scores (<T = 30) indicate a low level of overall competence. Furthermore, a child can have relatively high competency scores but score low in one particular domain, indicating a lack of competency in the corresponding subscale.

Problem scales for the CBCL were derived from an item-level principal components analysis. Thus, the composition of items for each subscale is based on internal consistency of a group of items. The total problems scale has good overall internal consistency ($\alpha = .96$). The problem subscales also have acceptable internal consistencies (Withdrawn, $\alpha = .80$; Somatic, $\alpha = .72$; Anxious/Depressed, $\alpha = .86$; Social Problems, $\alpha = .76$; Thought Problems, $\alpha = .68$; Attention Problems, $\alpha = .83$; Delinquent Behavior, $\alpha = .83$; Aggressive Behavior, $\alpha = .92$). The competency scales were derived in a similar fashion using principal component analyses. The total competency scale has less overall internal consistency than the total problem score ($\alpha = .64$). Similarly, each competence subscale has lower internal consistency than the problem subscales (Activities, $\alpha = .42$; Social, $\alpha = .60$; School, $\alpha = .61$). This lower internal reliability is likely due to small number of items in each competency subscale relative to the problem subscales.

In addition to adequate internal consistency, the CBCL has high inter-interviewer reliability. Scores from three interviewers of 723 children were compared. The overall intra-class correlation coefficient (ICC) for problem items was .96 ($p < .001$). The overall ICC for the competence items was .93 ($p < .001$). Thus, inter-interviewer reliability is high.

The CBCL also has a high inter-parent reliability according to Cohen's (1988) criteria. The overall mean *r* for the total problems scale was .76 ($p < .01$). Each problem subscale also had a significant mean *r* indicating high inter-parent agreement (Withdrawn, $r = .66$; Somatic Complaints, $r = .52$; Anxious/Depressed, $r = .66$; Social Problems, $r = .77$; Thought Problems, $r = .48$; Attention Problems, $r = .79$; Delinquent Behavior, $r = .78$; Aggressive Behavior, $r = .77$; Sex Problems, $r = .52$). Similarly, the overall total competence scale has high inter-parent reliability indicated by a mean *r* of .79 ($p < .01$). Each competence subscale also had a significant mean *r* indicating high inter-parent agreement (Activities, $r = .59$; Social, $r = .73$; School, $r = .87$).

Furthermore, the CBCL has high test-retest reliability across a seven day interval. Scores from 80 subjects were used in the temporal stability analysis. The overall total competence scale had a mean *r* (averaged across all competency subscale scores) of .89 ($p < .001$). Each problem subscale also had a significant test-retest reliability (Withdrawn, $r = .82$; Somatic Complaints, $r = .95$; Anxious/Depressed, $r = .86$; Social Problems, $r = .87$; Thought Problems, $r = .82$; Attention Problems, $r = .90$; Delinquent Behavior, $r = .86$; Aggressive Behavior, $r = .91$; Sex Problems, $r = .83$). Similarly, the competence scale had high overall test-retest reliability in the analysis with a mean *r* of .87 ($p < .001$). Each competence subscale also had a significant mean *r* indicating high test-retest reliability (Activities, $r = .80$; Social, $r = .70$; School, $r = .92$).

In sum, the CBCL has high internal consistency, scores are stable over a brief time frame (one week), and there is acceptable inter-rater agreement for both interviewers and parents. Collectively, these data support the use of the CBCL in this experiment.

CBCL Validity: The problem scale of the CBCL has high convergent validity evidenced by high correlations with other behavioral measures including the Connor's Parent Questionnaire (1973) and the Quay-Peterson Revised Behavior Checklist (1983). The correlation between the total problem scale on the CBCL and the Connors Parent Questionnaire is .82 ($p < .0001$). The problem subscales were also highly correlated with related subscales on the Connors Parent Questionnaire (Somatic Complaints-Psychosomatic r=.70; Anxious/Depressed-Anxiety, r= .67; Attention Problems-Impulsivity/Hyperactivity, r=.59; Delinquent Behavior-Antisocial, r= .77; Aggressive Behavior-Conduct Problem, r= .86). The correlation between the total problem scale on the CBCL and Quay-Peterson Revised Behavior Checklist was r= .81 ($p < .0001$). The problem subscales were also highly correlated with related subscales on the Quay-Peterson Revised Behavior Checklist (Withdrawn-Anxiety, r= .66, Anxious/Depressed-Anxiety, r=.78; Thought Problems-Psychotic, r=.64; Attention Problems-Attention Problems, r= .77; Delinquent Behavior-Socialized Aggression, r= .59; Aggressive Behavior-Conduct Disorder, r= .88). Thus, the CBCL is highly correlated with measures and subscales purporting to measure similar constructs. Statistics for discriminate validity were unavailable for this particular measure.

The criterion-related validity of the CBCL is supported by the fact that the CBCL quantitative scale can discriminate between referred and non-referred children after removing the effects of demographics. The overall total problem score accounts for 32% of the variance in referral status. Most problem subscales also account for a significant percentage of the variance in referral status (Withdrawn= 16%; Anxious/Depressed= 21%; Social Problems= 24%; Though Problems= 16%; Attention Problems= 31%; Delinquent

Behavior= 21%; Aggressive Behavior= 24%). Similarly, the overall total competence score accounts for a significant amount of variance in referral status (26%). Additionally, two of the three subscales account for a significant amount of the variance in referral status (Social= 18%; School= 37%). Thus, because the CBCL can discriminate between clinical samples and non-clinical samples, it is said to have a high measure of criterion-related validity. In further support of criterion-related validity, clinical cut points on the scale scores were shown to discriminate between referred and non-referred children (Achenbach, 1991).

In sum, the CBCL has content validity, convergent validity, and criterion-related validity which support construct validity. Thus, its use in this particular experiment to assess the behavioral problems and social competency of individuals with VCFS is justified.

Methods

Participants

Subjects included 12 children (6 males and 6 females) ages 6-16 years who were previously tested for a pilot study conducted in May of 2003. Six of these children (3 male and 3 female) were diagnosed with VCFS (M = 6, SD= 1.81). The average intellectual quotient (IQ) of the VCFS children was 70.16 (SD=1.04). The other 6 children (3 male and 3 female) served as controls (M = 6, SD= 1.81). While formal intellectual testing was not conducted, the children were all of generally average intellectual ability based on academic performance as reported by parents. Previous experiments using volumetric analysis have demonstrated large effect sizes and minimal error variance justifying the use of 12 subjects (Kates et al., 2004). Children with VCFS

were recruited through the Department of Genetics at Henry Ford Hospital, The Neuropsychology Clinic at Henry Ford Health System, or through advertisement. Controls were recruited through the peer nomination and the neuropsychology clinic at Henry Ford. A small portion of the subjects were recruited through a letter describing the project that was mailed to prospective subjects by the Department of Genetics at Henry Ford.

Inclusion criteria for the current study included a VCFS diagnosis confirmed by FISH. Controls were identically matched with VCFS individuals on the variables of age and gender. Exclusion criteria for children with VCFS included the presence of pre- or perinatal pathology, head injury, or substance abuse. In controls, the exclusion criteria consisted of the presence of learning disabilities or other neurological insults. Those controls meeting criteria for a learning disorder were excluded from the study and referred for services. Informed consent was obtained from the parents of children with VCFS and controls upon the first consultation.

Subjects were paid a $50.00 incentive for their participation in the initial data collection.

Design

The design of this experiment was a secondary data analysis comparing the brain structure volumes in two groups: A VCFS group and a Control group. This design allowed for a volumetric comparison of the neuroanatomy between individuals with VCFS and controls. It was a between-groups design despite the fact that subjects were matched on certain characteristics. Individuals were assigned to groups based on the presence of VCFS.

Procedures

Neuropsychological Procedures/Protocol: Neuropsychological testing was completed by a trained psychometrician at the Neuropsychology Clinic at Henry Ford Health Systems in Detroit, MI, between the January 2003 and August 2005. Assent and consent was obtained from the child and his or her legal guardian, respectively, prior to the assessment. These assessments included a comprehensive evaluation of intellectual functioning, academic achievement, motor functioning, perceptual-motor abilities, visuospatial abilities, speech/language abilities, verbal and visual memory, attention, executive functioning, neurobehavioral functioning, and emotional functioning. Children underwent the neuropsychological assessment in the morning and this was followed immediately by the imaging acquisition.

MRI Protocol: MRI images were acquired with a GE Signa 3.0 Tesla scanner. Axial images were obtained using a double echo proton density T2-weighted sequence using these parameters: TE/TR=30,90/2800 ms, NEX=1, matrix size = 256X128, field of view=24 cm, slice thickness= 1.5 mm, 124 slices. Subjects were informed about the non-invasive nature of the MRI and were told to remain as still as possible during the MRI procedure. Specifically, subjects were told that the scanning period would last approximately 60 minutes. They were checked for any metal using standard screening materials and questionnaires. They were told to lie in a prone position while the imaging took place and that they would hear a loud banging noise throughout the imaging process. Subjects could ask to be removed from the magnet at anytime throughout the procedure.

Image Processing and Volume Measurement: The original MRI data are currently stored at Henry Ford Hospital in Detroit, MI. These data were transferred to an

image analysis laboratory at Eastern Michigan University. The coronal T1-weighted images were reformatted to the axial plane and registered to the axial proton-density T2-weighted images. The multi-parametric MRI was analyzed using the Eigentool image analysis software (Windham et al., 1988). The software was used to parcel each voxel into white matter, gray matter, CSF, and total brain volumes. Additionally, structural segmentation was conducted in order to estimate volumes of the normal tissues within specific brain structures (e.g. amygdala, dorsolateral prefrontal cortex, ventromedial prefrontal cortex, insula, superior temporal sulcus, and anterior cingulate cortex). This structural segmentation was accomplished using the T1 –weighted images in conjunction with a knowledge-based deformable model (Ghanei et al., 1998, 2001). Last, to identify regional differences, each MRI was registered and morphed to a standard brain atlas (Ghanei et al., 2000). The regions of interest were manually traced and identified using a brain atlas. Regional identifications were then confirmed by a doctoral level student and clinical neuropsychologist. Normal tissue volumes were then calculated.

Analysis

Analysis methods for both neuroimaging and neuropsychological test data included standard descriptive techniques for continuous variables. Assumptions of normality were checked using standard techniques including tests for normality, skew, and kurtosis (Tabachnick & Fidell, 1996).

Volumetric Differences between patients with VCFS and Controls: In order to control for possible differences in total brain volume between the two-groups, all structure volumes were converted to ratios of the subject's total brain volume. Specific analysis included multiple between-group *t*-tests in order to determine if there were significant

mean differences in specific structures of patients with VCFS and their matched controls. Specific regions of interest (ROI) to be analyzed were amygdala, dorsolateral prefrontal cortex, verntromedial prefrontal cortex, insula, superior temporal sulcus, and anterior cingulate cortex. It was anticipated that amygdala and insula volumes would be significantly larger in VCFS patients relative to controls. The dorsolateral prefrontal cortex, ventromedial prefrontal cortex, STS, and ACC were all hypothesized to be smaller in VCFS patients relative to controls. An alpha level was set at $p < .05$.

Correlations of Structural Volume and the Child Behavior Checklist (CBCL): In order to examine the behavioral ramifications of specific structural anomalies in individuals with VCFS, *Pearson r* correlations assessing the relationship between structural volume and specific subscales of the CBCL were conducted. Table 1 describes the specific analyses that were conducted in order to address the hypotheses in question. Of note is that all structures were correlated with the social competency scale in order to determine each structure's relationship to social competency.

Table 1

Summary of Analyses Between Neural Substrates and Subscales of the CBCL

Subscale	Amygdala	PFC	DLPFC	VMPFC	Insula	STS	ACC
Withdrawn					X		
Somatic Complaints							
Anxious/Depressed	X	X	X		X		
Social Problems		X				X	X
Thought Problems							
Attention Problems				X			
Delinquent Behavior				X			
Aggressive Behavior							
Social Competency	X	X	X	X	X	X	X

Note. CBCL = Child Behavior Checklist; PFC = Prefrontal Cortex; DLPF = Dorsolateral Prefrontal Cortex; VMPFC= Ventromedial Prefrontal Cortex; STS= Superior Temporal Sulcus; ACC= Anterior Cingulate Cortex.

Missing Data

As all subjects completed all aspects of the neuropsychological measures of interest, missing data are not a concern in this data analysis.

Results

This project examined volumetric anomalies of specific structures implicated in social functioning in individuals with VCFS. To do this, structural volumes were determined using the aforementioned analysis procedures. Additionally, the relationship between neuroanatomical structure and scores on the CBCL were examined. Table 2 provides the mean volumes for each structure analyzed for individuals with VCFS and

Controls. Table 3 provides means and standard deviations for each CBCL subscale analyzed for individuals with VCFS.

Table 2

Mean Volume (cc) and SD of Analyzed Structures in Individuals with VCFS and Controls

	VCFS		Controls			
Structure	*M*	*SD*	M	*SD*	*d*	Effect Size *r*
Amygdala	.001821	.004361	.000995	.000251	0.267	.133
PFC	.004057	.017322	.005798	.001732	-0.141	-.071
DLPFC	.184740	.050258	.100547	.039358	1.865	.682
VMPFC	.080646	.056501	.046992	.027015	0.760	.355
Insula	.008373	.002082	.011985	.004354	-1.058	-.468
STS	.027109	.005252	.029111	.008111	-.293	-.145
ACC	.006540	.001860	.006581	.001810	-.022	-.011

Note. PFC = Prefrontal Cortex; DLPF = Dorsolateral Prefrontal Cortex; VMPFC= Ventromedial Prefrontal Cortex; STS= Superior Temporal Sulcus; ACC= Anterior Cingulate Cortex; VCFS= Velocardio Facial Syndrome; SD= Standard Deviation.

Table 3

Mean scores for CBCL subscales for individuals with VCFS

Subscale	*M*	*SD*
WithdrawnSomatic Complaints	53.5	5.04975
Anxious/Depressed	57.2	8.20771
Social Problems	55.67	6.47045
Thought Problems	61.33	10.6332
Attention Problems	59.83	8.75024
Aggressive Behavior	69.5	6.15630
Delinquent Behavior	52.83	5.03653
Social Competency	40.33	9.71253

Note. VCFS= Velocardio Facial Syndrome; CBCL= Child Behavior Checklist; SD= Standard Deviation.

Specific Aim 1: It was predicted that the amygdala to total brain volume ratio would be larger in individuals with VCFS relative to matched controls. Figure 1 displays the mean amygdala volume in individuals with VCFS and matched controls. Results indicated that mean amygdala volume was significantly larger in individuals with VCFS relative to controls, $t\ (10) = 4.01$, $p < .05$.

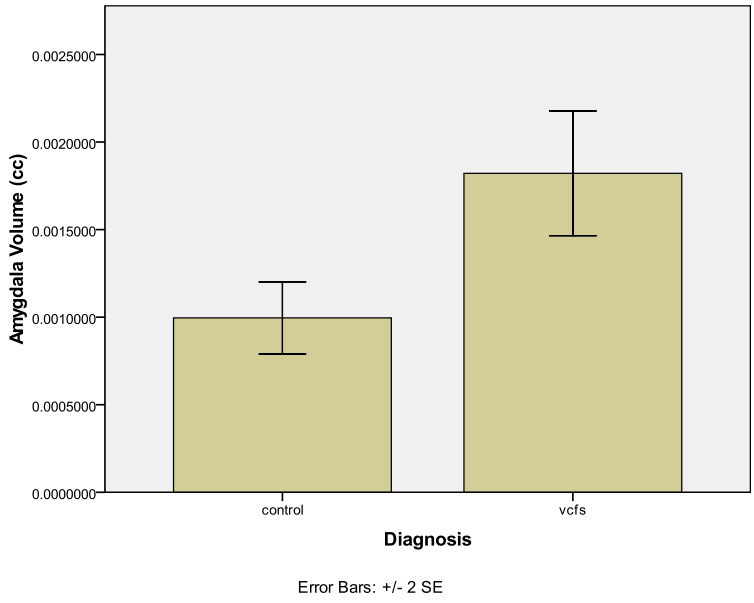

Figure 1. Mean bilateral amygdala volume (+*SE*) for controls (n = 6) and individuals with VCFS (n = 6).

Specific Aim 2: It was predicted that amygdala volume would be correlated with increased anxiety and decreased social competency as measured by the CBCL. There were no significant relationships observed between amygdala and the anxiety subscale $r(6)= .30$, $p = .56$) or the social competency subscale of the CBCL $r(6)= .45$, $p = .70$). A significant, inverse relationship was observed between amygdala volume and the attention subscale of the CBCL $r(6)= -.98$, $p < .01$. Figure 2 displays the correlation between amygdala volume and scores on the attention subscale of the CBCL.

Taken together these data suggest that the individuals with VCFS have a significantly larger amygdala volume relative to controls, and this anatomical discrepancy is related meaningfully to the modulation of attention in these individuals.

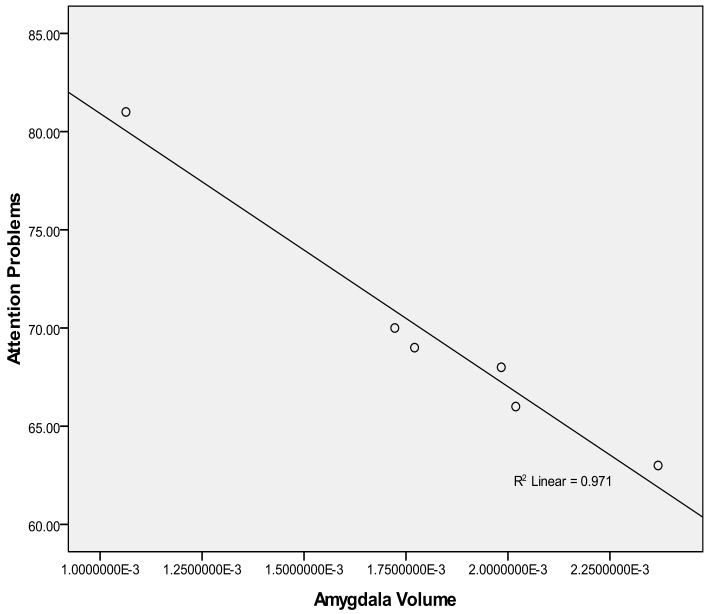

Figure 2. Relationship between the attention subscale of the CBCL and amygdala volume.

Specific Aim 3: It was predicted that prefrontal cortex volumes in individuals with VCFS would be smaller than those of matched controls. No statistical difference was observed in the frontal cortex of individuals with VCFS when compared with controls; t (10) = 1.42, p = .19.

Specific Aim 4: It was predicted that prefrontal cortex volumes would be associated with greater attentional difficulty and social problems as measured by the CBCL. In addition, the smaller frontal volume in individuals with VCFS would be associated with lower scores of social competency in individuals with VCFS. This hypothesis was not statistically supported, suggesting that the prefrontal cortex does not independently mediate social problems r(6)= -.30, p = .56), attentional deficits r(6)= -.64, p = .17), and social competency r(6) = -.14, p =.91) in individuals with VCFS.

Specific Aim 5: It was hypothesized that the dorsolateral and ventromedial sub regions of the frontal cortex would be significantly smaller in individuals with VCFS relative to

controls. Figure 3 displays the mean DLPFC volume in individuals with VCFS and matched controls. DLPFC volumes were significantly larger in individuals with VCFS relative to controls $t(10) = 3.23$, $p < .05$. VMPFC volumes were not significantly different from controls $t(10) = 1.32$, $p = .22$.

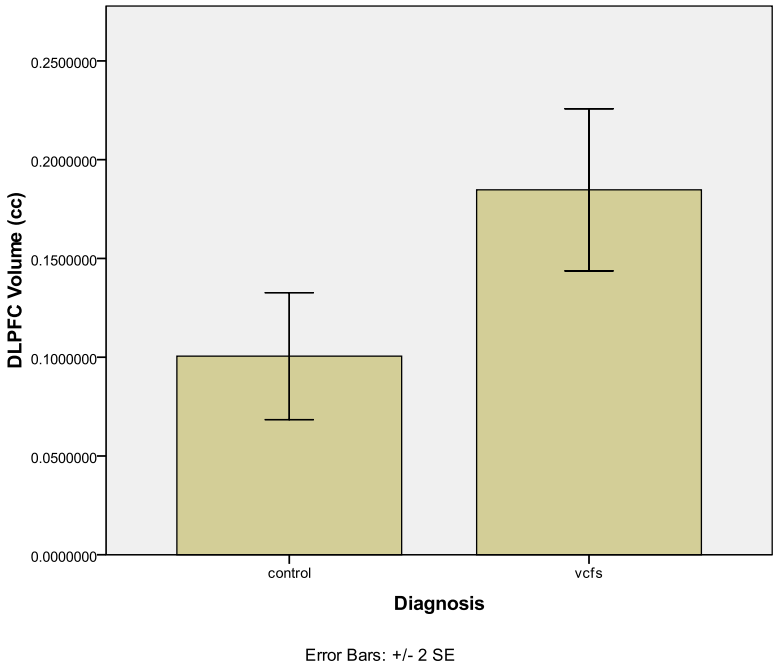

Figure 3. Mean bilateral DLPFC volume (+*SE*) for controls ($n = 6$) and individuals with VCFS ($n = 6$).

Specific Aim 6: It was hypothesized that smaller DLPFC volume would be correlated with greater anxious and depressed subscales of the CBCL. Additionally, it was hypothesized that smaller VMPFC volume would be correlated with greater attentional impairment and delinquency as measured by the CBCL. Furthermore, it was hypothesized that there would be reduction in both the DLPFC and VMPFC volumes that would be correlated with decreased social competency. Statistical analysis revealed no significant relationships between DLPFC volume and the anxious/depressed subscale of the CBCL $r(6) = .12$, $p = .82$ or social competency $r(6) = .83$, $p = .38$. Similarly, statistical analysis

revealed no significant relationships between VMPFC and the attention $r(6) = .70$, $p = .06$, delinquency, $r(6) = -.31$ $p = .550$ and social competency $r(6) = -.66$, $p = .54$ subscales of the CBCL.

Specific Aim 7: Previously literature has demonstrated volumetric anomalies in the insular cortex of individuals with VCFS and social impairment (van Amelsvoort, et al., 2001). In accordance with this literature, it was hypothesized that individuals with VCFS would have greater bilateral insula volumes. However, there were no significant differences between individuals with VCFS and controls with regard to insula volume $t(10) = 1.83$, $p = .10$.

Specific Aim 8: It was predicted that insula volumes would be correlated with high scores on the anxiety and withdraw subscales of the CBCL. In addition, it was predicted that insula volume would be associated with lower social competency scores. However, insula volumes were not significantly correlated with the anxiety $r(6) = .74$, $p = .09$ or withdraw $r(6) = -.09$, $p = .87$ subscales of the CBCL. In addition, insula volume was statistically unrelated to social competency scores; $r(6) = .95$, $p = .20$. Thus, despite the role that the insular cortex plays in various components of social cognition, particularly withdraw behaviors in response to anxiety-provoking stimuli, the insular cortex may not directly mediate specific deficits in this population.

Specific Aim 9: It was predicted that STS volumes would be smaller in individuals with VCFS relative to controls. However, there were no significant differences between individuals with VCFS and controls with regard to STS volume $t(10) = .51$, $p = .62$

Specific Aim 10: It was predicted that decreased STS volumes would be correlated with increased social problems and decreased social competency ratings as measured by the

CBCL. Statistical analysis found no significant relationship between STS volume and frequency of social problems $r(6)=.22$, $p = .67$ or overall social competency $r(6) = .75$, $p = .10$.

Specific Aim 11: It was hypothesized that the ACC in individuals with VCFS would be significantly smaller than controls. Statistical analysis indicated no significant difference in ACC volumes in individuals with VCFS relative to controls $t(10) = .04$, $p = .97$.

Specific Aim 12: It was predicted that decreased ACC volumes would be correlated with increased social problems ratings and decreased social competency. ACC volumes were not significantly associated with an elevated social problems scale $r(6) = .60$, $p = .20$ or reduced social competency ratings $r(6)=.99$, $p = .09$ as measured by the CBCL.

Discussion

This paper sought to identify the neurological substrates associated with social impairments in individuals with VCFS. In particular, one goal of this research was to elucidate brain-behavior relationships within the context of social cognition. As social cognition has been implicated in numerous psychiatric disorders including pervasive developmental disorders, psychosis, and mood disorders, understanding the neural substrates involved is essential in determining the etiology of social deficits in these disorders, informing treatment, and enhancing outcome. In this study, specific structures which have been identified as substrates of social cognition, such as amygdala, frontal cortex and subregions of the PFC, insula, and the STS, were analyzed for volumetric anomalies in a population with known social deficits. Volumes were then correlated with behavioral measures.

Volume of the Amygdala in Individuals with VCFS

The hypothesis that the amygdala would be larger in individuals with VCFS was supported. This is consistent with findings of Kates et al. (2006), who found a larger amgydala-to-prefrontal-cortex ratio in children with VCFS. Though it is tempting to conclude that the genetic anomalies associated with this disorder mediate this neuroanatomical deviation, it has been proposed that this increase in amygdala volume may be the result of high anxiety levels in this population (Feinstein et al., 2002). Increased amygdala volumes have been observed in individuals with phobic and generalized anxiety disorders (Bellis, 2000). Dong and Greenough (2004) demonstrated that this increased anxiety leads to experience-dependent neuronal remodeling in the amygdala, which may contribute to its increased volume (Dong & Greenough, 2004). Thus, it is possible that the anxiety associated with these patients leads to the volumetric changes in the amygdala.

Despite the theory suggesting that experience-dependent neuronal remodeling of the amygdala occurs as a result of increased anxiety, the Depression/Anxiety subscale of the CBCL was not correlated with amygdala volume. This may be due to the lack of sensitivity of the collapsed subscale, the combination of anxiety and depression items into a single subscale. Furthermore, in-depth assessments of anxiety and depression were not performed on these subjects in this study and thus, the generality of the CBCL may have been less sensitive in detecting symptoms of anxiety and depression in this population.

Though a significant relationship between amygdala volume and social competency was not observed, there was a significant relationship between amygdala volume and the Attention Problems subscale of the CBCL. Specifically, as amygdala

volume increased, attentional deficits diminished. This relationship between amygdala volume and attentional impairment has not been reported in this population. However, there is some evidence in the ADHD literature suggesting that the amygdala can support features of attention. For example, Shaefer et al. (2006) observed reduced response times and increased working memory performance in children with ADHD who have larger amygdala volumes. Thus, it seems that increased amygdala volume and activation may increase the level of vigilance, thereby facilitating attentional processing and response time. Furthermore, a specific examination of the relationship between amygdala and attention in this population is necessary in order to adequately understand how amygdala may be a structure that supports attentional systems.

In this study, amygdala volume was not significantly correlated with parent report measures of anxiety, depression, or social competence as was expected given previous research regarding the role of amygdala in affective responding (Davidson & Irwin, 1999; LeDoux, 2000; Phillips, Drevets, Rauch, & Lane, 2003). It is possible that affective features in this population are not mediated by amygdala alone but rather the amygdala to prefrontal cortex ratio as demonstrated by Kates et al. (2006).

Volume of the Frontal Cortex in Individuals with VCFS

The hypothesis of decreased frontal volumes in individuals with VCFS was not supported in this experiment. This is in contrast to Kates et al. (2006), who observed smaller prefrontal cortex volumes in individuals with VCFS. There are several explanations for this somewhat contradictory finding. First, it is possible that the sample size in this study was too small to detect small scale volumetric anomalies in patient populations. That is, perhaps volumetric anomalies of the prefrontal cortex are less robust

than alterations in amygdala volume in this population, thus requiring more subjects for statistical certainty. Second, it is possible that the frontal cortex has a limited impact on the social impairments presenting in VCFS. However, this is an unlikely conclusion given what is known about frontal cortex involvement in the mediation of attention and social competency (Adolphs, Tranel, & Damasio, 2003; Bechara, et al., 1996; Davidson & Irwin, 1999). Third, it is possible that there is some overall sparing of frontal cortex in individuals with VCFS, and differences may only be observed by further sub-parceling of the prefrontal cortex. Indeed, this research presents preliminary evidence supporting this conclusion which will be addressed below.

The frontal cortex was not associated with the Anxious/Depressed, Social Problems, or Social Competency subscales of the CBCL. This may provide evidence for a more "systems" approach to understanding the relationship between neurological morphology and behavior. That is, it is not a single structure that mediates broad constructs such as social cognition, but rather a system or network of structures such as the limbic system which facilitate social functioning. Though structural volumes may be examined in isolation in order to make determinations regarding adequate morphology, it may be more useful to analyze relationships with social constructs using a more network approach.

DLPFC Volume in Individuals with VCFS

The hypothesis that DLPFC volumes would be smaller than that of controls was not supported. Instead, DLPFC volumes in individuals with VCFS were significantly larger than control subjects. One possible explanation for this somewhat contradictory finding involves compensatory mechanisms that occur in response to amygdala

enlargement. That is, DLPFC enlargement may occur as a consequence of increased amygdala activation and emotional dysregulation. The DLPFC has a role in voluntary suppression of sadness and arousal (Lévesque et al., 2003). Increased amygdala activation may lead to increased experiences of negative affect requiring increased suppression via DLPFC. Thus, the increase in DLPFC activation may result in neural plasticity leading to overall frontal enlargement in this population. More research is needed in order to specifically assess the relationship between amygdala activity/enlargement and the consequential plasticity in DLPFC.

VMPFC Volume in Individuals with VCFS

The hypothesis that VMPFC volume would be smaller than that of controls was not supported. This may suggest that VMPFC integrity is spared in this disorder relative to other sub-regions of the frontal cortex. Preliminary analysis of VMPFC in schizophrenic populations, a clinical population strongly associated with VCFS, has yielded inconclusive results with regard to VMPFC volume (Ritter, Meador-Woodruff, & Dalack, 2003). More research is necessary in order to determine if volumetric anomalies of VMPFC occur in these patient populations. Furthermore, if consistent evidence for volumetric differences is observed upon further experimental examination, it would be important to determine the direction and magnitude of the volumetric discrepancy.

Relationships among Frontal Lobe Sub Regions and Social Behaviors

The DLPFC and VMPFC were not associated with elevated behavioral or social problems as measured by the CBCL. It is possible that the CBCL, being a broad measure of behavioral and social functioning, lacked the sensitivity to detect small-scale alterations in social functioning or behavioral pathologies. Future analysis may require tests which

assess specifically the integrity of the frontal cortex and sub-regions thereof. For example, in order to better assess the role of the VMPFC in social cognition, a test of consequence evaluation such as the Iowa Gambling Test (Nagy, et al., 2006) may be used. In addition, it is possible that involvement of frontal regions in social behavior is part of a network of systems. That is, there may not be a one-to-one relationship between structure and function. Instead, it may be that a certain pattern of activity or a certain morphometric profile involving multiple structures mediates constructs of social cognition. For example, it may be that it is the ratio of PFC volume to amygdala and hippocampal volume that is the most strongly associated with behavioral pathology and social impairment in children with VCFS. Further research is necessary in order to understand and identify the complex network of structures and relationships underlying the specific social behaviors associated with sub-regions of the frontal lobe.

Volume of the Insular Cortex in Individuals with VCFS

In contrast to the findings of van Amelsvoort et al. (2001), the hypothesis that the insular cortex would be smaller in individuals with VCFS relative to controls was not supported. In addition, insula volume was not associated with Withdrawal, Anxiety, or Social Competency as measured by the CBCL. That said, there was a clear trend suggestive of greater insular volume in the clinical population. Indeed, it is possible that the small sample size limited statistical power in this particular experiment, making it difficult to reject the null hypotheses. Furthermore, since this structure is involved in emotional processing and reasoning, a more logical analysis of these data may include an examination of the volume of the insular cortex in relation to other limbic or prefrontal structures instead of as a ratio to total brain volume as was done in this experiment. In this

way, an understanding of insula volume in relation to structures that mediate similar functions can be attained. Furthermore, van Amelsvoort et al. (2001) compared gray and white matter within this structure, noting significant differences. Thus, it may only be differences in the ratio of gray matter to white matter which mediate social impairments in children with VCFS. Another difference between this analysis and the one conducted by van Amelsvoort et al. (2001) was that insula volume was calculated as a ratio to total brain volume in the present study, whereas as the work of van Amelsvoort et al. (2001) used raw data for their volumetric analysis. This may also account for the contrasting results.

Volume of the ACC in Individuals with VCFS

The hypotheses that the ACC would be smaller in individuals with VCFS and be associated with the Social Problems and Social Competency subscale of the CBCL were not supported though there was a clear trend toward greater ACC volume in the clinical group. This is in contrast to what was anticipated given the volumetric differences in ACC observed in schizophrenic patients (Fujiwara, et al., 2007). One possible explanation for this somewhat contradictory finding is that ACC involvement in social pathology associated with VCFS is absent unless the patient presents with or develops schizophrenia. In the sample used in this study, it is unknown whether the children with VCFS went on to develop schizophrenia. Thus, it is plausible that ACC involvement is only observed in children with VCFS who go on to develop schizophrenia or other symptoms of psychosis. In sum, it may be the case that pre-morbid ACC volumes can be used along with other predictors of vulnerability to the development of schizophrenia or psychosis in individuals with VCFS. Longitudinal examination of VCFS children who

develop schizophrenia is necessary in order to more completely understand the complex relationships between ACC volume, VCFS, schizophrenia, and social impairment.

Limitations

One of the limitations of this study includes sample size. The data suggest that there are some differences in structural volumes between controls and individuals with VCFS that are approaching significance. With a larger sample, it is conceivable that significant differences in these structures would have been observed. In addition, it would be meaningful to have psychometric data on the control subjects in order to determine if there was a relationship between structural volume and behavioral measures of social functioning. Finally, it is tempting to conclude that the relatively low IQ of individuals in this study mediates social impairment in VCFS. However, using IQ as a covariate is not justified in this study because IQ is itself impacted by the presence of the neurodevelopmental disorder (Taylor, Fletcher, & Satz, 1984; Dennis et al., 2009). In other words, the presence of VCFS is driving the intellectual differences between the experimental group and the controls and thus should not be a covariate in this particular study.

Summary and Conclusions

Social competency is a complex process requiring the integration of a number of neurological networks and systems. In this study, a clinical sample, with well-established social impairments, was used to assess the neurological substrates of social behavior. As expected, clinically significant differences in amygdala and DLPFC volumes were observed in children with VCFS. Though it is likely that alterations in the structures observed mediate to some extent behavioral processes relating to social functioning, none

of the structures examined in this study were associated with social competency. This lends support for a systems theory of social competence. That is, it seems that there are limited structures which have a one-to-one correspondence with social competency. This is particularly true with regard to contemporary Theory of Mind (ToM) research, which suggests that the ToM is supported by a large array of networks and structures which include, but are not limited to, language-related regions, medial frontal lobes, and the temporal-parietal juncture (Adolphs, et al., 2003; Siegal & Varley, 2002). Furthermore, different features of social competency involve different structures. For example, empathy involves activation of paracingulate, anterior and posterior cingulate, and amygdala, whereas ToM involves activation of lateral orbitofrontal cortex, middle frontal gyrus, cuneus, and superior temporal gyrus (Vollm, et al., 2006). In other words, social cognition involves the activation of individual structures, the activation of networks mediating complex social processes, and the interaction between the networks involved in social cognition. Thus, it is likely that social processes and impairment in VCFS is mediated by multiple structures within each construct or domain of social functioning. For example, understanding and responding to the affect of others may be supported by the ToM network as suggested by Siegal and Varley (2002). Furthermore, shyness, withdrawal, and social anxiety maybe supported by limbic structures such amygdala and hippocampus. In summary, an even more complex network-level analysis of morphometry and function coupled with more sensitive psychometric measures of specific aspects of social cognition is likely necessary in order to further understand the substrates of social functioning in children with social impairment. Future work in this area may include an examination of the functional consequences of morphological anomalies, as

well as network-level analysis of each construct of interest. Finally, longitudinal and intervention-based research using this sample is necessary in order to gain a better understanding of symptom stability across time, response to intervention, and the overall impact of plasticity and neuronal remodeling mechanisms.

References

Adolphs, R., Tranel, D., & Damasio, A. R. (2003). Dissociable neural systems for recognizing emotions. *Brain Cogn, 52*(1), 61-69.

Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature, 372*(6507), 669-672.

Antshel, K. M., Aneja, A., Strunge, L., Peebles, J., Fremont, W. P., Stallone, K., et al. (2007). Autistic spectrum disorders in velo-cardio facial syndrome (22q11.2 deletion). *J Autism Dev Disord, 37*(9), 1776-1786.

Arnold, P. D., Siegel-Bartelt, J., Cytrynbaum, C., Teshima, I., & Schachar, R. (2001). Velo-cardio-facial syndrome: Implications of microdeletion 22q11 for schizophrenia and mood disorders. *Am J Med Genet, 105*(4), 354-362.

Bechara, A., Damasio, A. R., Damasio, H., & Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition, 50*(1-3), 7-15.

Bechara, A., Damasio, H., Tranel, D., & Damasio, A. R. (1997). Deciding advantageously before knowing the advantageous strategy. *Science, 275*(5304), 1293-1295.

Bechara, A., Tranel, D., Damasio, H., & Damasio, A. R. (1996). Failure to respond autonomically to anticipated future outcomes following damage to prefrontal cortex. *Cereb Cortex, 6*(2), 215-225.

Bellis, D. (2000). A pilot study of amygdala volumes in pediatric generalized anxiety disorder. *Biological Psychiatry, 48*(1), 51-57.

Botto, L. D., May, K., Fernhoff, P. M., Correa, A., Coleman, K., Rasmussen, S. A., et al. (2003). A population-based study of the 22q11.2 deletion: phenotype, incidence, and contribution to major birth defects in the population. *Pediatrics, 112*(1 Pt 1), 101-107.

Breiter, H. C., & Rauch, S. L. (1996). Functional MRI and the study of OCD: from symptom provocation to cognitive-behavioral probes of cortico-striatal systems and the amygdala. *Neuroimage, 4*(3 Pt 3), S127-138.

Castellanos, F. X., Giedd, J. N., Eckburg, P., Marsh, W. L., Vaituzis, A. C., Kaysen, D., et al. (1994). Quantitative morphology of the caudate nucleus in attention deficit hyperactivity disorder. *Am J Psychiatry, 151*(12), 1791-1796.

Castellanos, F. X., Giedd, J. N., Marsh, W. L., Hamburger, S. D., Vaituzis, A. C., Dickstein, D. P., et al. (1996). Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. *Arch Gen Psychiatry, 53*(7), 607-616.

Castelli, F., Frith, C., Happe, F., & Frith, U. (2002). Autism, Asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes. *Brain, 125*(Pt 8), 1839-1849.

Davidson, R. J., & Irwin, W. (1999). The functional neuroanatomy of emotion and affective style. *Trends Cogn Sci, 3*(1), 11-21.

Digilio, M. C., Marino, B., Capolino, R., Angioni, A., Sarkozy, A., Roberti, M. C., et al. (2005). Familial recurrence of nonsyndromic congenital heart defects in first degree relatives of patients with deletion 22q11.2. *Am J Med Genet A, 134*(2), 158-164.

Dong, W. K., & Greenough, W. T. (2004). Plasticity of non-neuronal brain tissue: roles in developmental disorders. *Ment Retard Dev Disabil Res Rev 10,* 85-90.

Driscoll, D. A., Salvin, J., Sellinger, B., Budarf, M. L., McDonald-McGinn, D. M., Zackai, E. H., et al. (1993). Prevalence of 22q11 microdeletions in DiGeorge and velocardiofacial syndromes: implications for genetic counselling and prenatal diagnosis. *J Med Genet, 30*(10), 813-817.

Eliez, S., Blasey, C. M., Menon, V., White, C. D., Schmitt, J. E., & Reiss, A. L. (2001). Functional brain imaging study of mathematical reasoning abilities in velocardiofacial syndrome (del22q11.2). *Genet Med, 3*(1), 49-55.

Eliez, S., Palacio-Espasa, F., Spira, A., Lacroix, M., Pont, C., Luthi, F., et al. (2000). Young children with Velo-Cardio-Facial syndrome (CATCH-22). Psychological and language phenotypes. *Eur Child Adolesc Psychiatry, 9*(2), 109-114.

Feinstein, C., Eliez, S., Blasey, C., & Reiss, A. L. (2002). Psychiatric disorders and behavioral problems in children with velocardiofacial syndrome: usefulness as phenotypic indicators of schizophrenia risk. *Biol Psychiatry, 51*(4), 312-318.

Feinstein, C., & Singh, S. (2007). Social phenotypes in neurogenetic syndromes. *Child Adolesc Psychiatr Clin N Am, 16*(3), 631-647.

Fine, S. E., Weissman, A., Gerdes, M., Pinto-Martin, J., Zackai, E. H., McDonald-McGinn, D. M., et al. (2005). Autism spectrum disorders and symptoms in children with molecularly confirmed 22q11.2 deletion syndrome. *J Autism Dev Disord, 35*(4), 461-470.

Fujiwara, H., Hirao, K., Namiki, C., Yamada, M., Shimizu, M., Fukuyama, H., et al. (2007). Anterior cingulate pathology and social cognition in schizophrenia: a study

of gray matter, white matter and sulcal morphometry. *Neuroimage, 36*(4), 1236-1245.

Funke, B., Pandita, R. K., & Morrow, B. E. (2001). Isolation and characterization of a novel gene containing WD40 repeats from the region deleted in velo-cardio-facial/DiGeorge syndrome on chromosome 22q11. *Genomics, 73*(3), 264-271.

Gainotti, G. (1972). Emotional behavior and hemispheric side of the lesion. *Cortex, 8*(1), 41-55.

Garrett, A. S., Menon, V., MacKenzie, K., & Reiss, A. L. (2004). Here's looking at you, kid: neural systems underlying face and gaze processing in fragile X syndrome. *Arch Gen Psychiatry, 61*(3), 281-288.

Gervais, H., Belin, P., Boddaert, N., Leboyer, M., Coez, A., Sfaello, I., et al. (2004). Abnormal cortical voice processing in autism. *Nat Neurosci, 7*(8), 801-802.

Golding-Kushner, K. J., Weller, G., & Shprintzen, R. J. (1985). Velo-cardio-facial syndrome: language and psychological profiles. *J Craniofac Genet Dev Biol, 5*(3), 259-266.

Gothelf, D. (2007). Velocardiofacial syndrome. *Child Adolesc Psychiatr Clin N Am, 16*(3), 677-693.

Gothelf, D., Feinstein, C., Thompson, T., Gu, E., Penniman, L., Van Stone, E., et al. (2007). Risk factors for the emergence of psychotic disorders in adolescents with 22q11.2 deletion syndrome. *Am J Psychiatry, 164*(4), 663-669.

Gothelf, D., Furfaro, J. A., Penniman, L. C., Glover, G. H., & Reiss, A. L. (2005). The contribution of novel brain imaging techniques to understanding the neurobiology

of mental retardation and developmental disabilities. *Ment Retard Dev Disabil Res Rev, 11*(4), 331-339.

Gothelf, D., Gruber, R., Presburger, G., Dotan, I., Brand-Gothelf, A., Burg, M., et al. (2003). Methylphenidate treatment for attention-deficit/hyperactivity disorder in children and adolescents with velocardiofacial syndrome: an open-label study. *J Clin Psychiatry, 64*(10), 1163-1169.

Gothelf, D., Hoeft, F., Hinard, C., Hallmayer, J. F., Stoecker, J. V., Antonarakis, S. E., et al. (2007). Abnormal cortical activation during response inhibition in 22q11.2 deletion syndrome. *Hum Brain Mapp, 28*(6), 533-542.

Gothelf, D., & Lombroso, P. J. (2001). Genetics of childhood disorders: XXV. Velocardiofacial syndrome. *J Am Acad Child Adolesc Psychiatry, 40*(4), 489-491.

Gothelf, D., Presburger, G., Zohar, A. H., Burg, M., Nahmani, A., Frydman, M., et al. (2004). Obsessive-compulsive disorder in patients with velocardiofacial (22q11 deletion) syndrome. *Am J Med Genet B Neuropsychiatr Genet, 126*(1), 99-105.

Hamann, S. B., Stefanacci, L., Squire, L. R., Adolphs, R., Tranel, D., Damasio, H., et al. (1996). Recognizing facial emotion. *Nature, 379*(6565), 497.

Happe, F., Ehlers, S., Fletcher, P., Frith, U., Johansson, M., Gillberg, C., et al. (1996). 'Theory of mind' in the brain. Evidence from a PET scan study of Asperger syndrome. *Neuroreport, 8*(1), 197-201.

Hodapp, R. M., & Dykens, E. M. (2005). Measuring behavior in genetic disorders of mental retardation. *Ment Retard Dev Disabil Res Rev, 11*(4), 340-346.

Hynd, G. W., Hern, K. L., Novey, E. S., Eliopulos, D., Marshall, R., Gonzalez, J. J., et al. (1993). Attention deficit-hyperactivity disorder and asymmetry of the caudate nucleus. *J Child Neurol, 8*(4), 339-347.

Jopp, D. A., & Keys, C. B. (2001). Diagnostic overshadowing reviewed and reconsidered. *Am J Ment Retard, 106*(5), 416-433.

Kates, W. R., Burnette, C. P., Bessette, B. A., Folley, B. S., Strunge, L., Jabs, E. W., et al. (2004). Frontal and caudate alterations in velocardiofacial syndrome (deletion at chromosome 22q11.2). *J Child Neurol, 19*(5), 337-342.

Kates, W. R., Miller, A. M., Abdulsabur, N., Antshel, K. M., Conchelos, J., Fremont, W., et al. (2006). Temporal lobe anatomy and psychiatric symptoms in velocardiofacial syndrome (22q11.2 deletion syndrome). *J Am Acad Child Adolesc Psychiatry, 45*(5), 587-595.

Kelly, D., Goldberg, R., Wilson, D., Lindsay, E., Carey, A., Goodship, J., et al. (1993). Confirmation that the velo-cardio-facial syndrome is associated with haplo-insufficiency of genes at chromosome 22q11. *Am J Med Genet, 45*(3), 308-312.

Kirscher, R. (2005). Palatal anomalies and velopharyngeal dysfunction associated with velocardio-facial syndrome. *Velo-cardio-facial syndrome: a model for understanding microdeletion disorders* (pp. 83-104). Cambridge, MA: Carmbridge University Press.

Kopelman, A., Andreasen, N. C., & Nopoulos, P. (2005). Morphology of the anterior cingulate gyrus in patients with schizophrenia: relationship to typical neuroleptic exposure. *Am J Psychiatry, 162*(10), 1872-1878.

Lachman, H. M., Morrow, B., Shprintzen, R., Veit, S., Parsia, S. S., Faedda, G., et al. (1996). Association of codon 108/158 catechol-O-methyltransferase gene polymorphism with the psychiatric manifestations of velo-cardio-facial syndrome. *Am J Med Genet, 67*(5), 468-472.

Lajiness-O'Neill, R., Beaulieu, I., Asamoah, A., Titus, J. B., Bawle, E., Ahmad, S., et al. (2006). The neuropsychological phenotype of velocardiofacial syndrome (VCFS): relationship to psychopathology. *Arch Clin Neuropsychol, 21*(2), 175-184.

Lane, R. D., Reiman, E. M., Bradley, M. M., Lang, P. J., Ahern, G. L., Davidson, R. J., et al. (1997). Neuroanatomical correlates of pleasant and unpleasant emotion. *Neuropsychologia, 35*(11), 1437-1444.

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annu Rev Neurosci, 23*, 155-184.

Maren, S. (1999). Long-term potentiation in the amygdala: a mechanism for emotional learning and memory. *Trends Neurosci, 22*(12), 561-567.

McDermid, H. E., & Morrow, B. E. (2002). Genomic disorders on 22q11. *Am J Hum Genet, 70*(5), 1077-1088.

Mitnick, R. J., Bello, J. A., & Shprintzen, R. J. (1994). Brain anomalies in velo-cardio-facial syndrome. *Am J Med Genet, 54*(2), 100-106.

Moriguchi, Y., Ohnishi, T., Mori, T., Matsuda, H., & Komaki, G. (2007). Changes of brain activity in the neural substrates for theory of mind during childhood and adolescence. *Psychiatry Clin Neurosci, 61*(4), 355-363.

Murphy, K. C. (2002). Schizophrenia and velo-cardio-facial syndrome. *Lancet, 359*(9304), 426-430.

Murphy, K. C., Jones, L. A., & Owen, M. J. (1999). High rates of schizophrenia in adults with velo-cardio-facial syndrome. *Arch Gen Psychiatry, 56*(10), 940-945.

Nagy, H., Bencsik, K., Rajda, C., Benedek, K., Beniczky, S., Keri, S., et al. (2006). The effects of reward and punishment contingencies on decision-making in multiple sclerosis. *J Int Neuropsychol Soc, 12*(4), 559-565.

Niklasson, L., Rasmussen, P., Oskarsdottir, S., & Gillberg, C. (2001). Neuropsychiatric disorders in the 22q11 deletion syndrome. *Genet Med, 3*(1), 79-84.

Ohnishi, T., Matsuda, H., Hashimoto, T., Kunihiro, T., Nishikawa, M., Uema, T., et al. (2000). Abnormal regional cerebral blood flow in childhood autism. *Brain, 123 (Pt 9)*, 1838-1844.

Papolos, D. F., Faedda, G. L., Veit, S., Goldberg, R., Morrow, B., Kucherlapati, R., et al. (1996). Bipolar spectrum disorders in patients diagnosed with velo-cardio-facial syndrome: does a hemizygous deletion of chromosome 22q11 result in bipolar affective disorder? *Am J Psychiatry, 153*(12), 1541-1547.

Paylor, R., Glaser, B., Mupo, A., Ataliotis, P., Spencer, C., Sobotka, A., et al. (2006). Tbx1 haploinsufficiency is linked to behavioral disorders in mice and humans: implications for 22q11 deletion syndrome. *Proc Natl Acad Sci U S A, 103*(20), 7729-7734.

Phillips, M. L., Drevets, W. C., Rauch, S. L., & Lane, R. (2003). Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biol Psychiatry, 54*(5), 504-514.

Posner, M. (1995). Neuropsychology. Modulation by instruction. *Nature, 373*(6511), 198-199.

Prescott, K., Ivins, S., Hubank, M., Lindsay, E., Baldini, A., & Scambler, P. (2005). Microarray analysis of the Df1 mouse model of the 22q11 deletion syndrome. *Hum Genet, 116*(6), 486-496.

Prinzie, P., Swillen, A., Vogels, A., Kockuyt, V., Curfs, L., Haselager, G., et al. (2002). Personality profiles of youngsters with velo-cardio-facial syndrome. *Genet Couns, 13*(3), 265-280.

Rauch, S. L., Savage, C. R., Alpert, N. M., Fischman, A. J., & Jenike, M. A. (1997). The functional neuroanatomy of anxiety: a study of three disorders using positron emission tomography and symptom provocation. *Biol Psychiatry, 42*(6), 446-452.

Rauch, S. L., Savage, C. R., Alpert, N. M., Miguel, E. C., Baer, L., Breiter, H. C., et al. (1995). A positron emission tomographic study of simple phobic symptom provocation. *Arch Gen Psychiatry, 52*(1), 20-28.

Ritter, L. M., Meador-Woodruff, J. H., & Dalack, G. W. (2003). Neurocognitive measures of prefrontal cortical dysfunction in schizophrenia. *Schizophrenia Research, 68*(1), 65-73.

Robinson, R. G., Kubos, K. L., Starr, L. B., Rao, K., & Price, T. R. (1984). Mood disorders in stroke patients. Importance of location of lesion. *Brain, 107 (Pt 1)*, 81-93.

Rozin, P. (1997). Disgust faces, basal ganglia, and obsessive-compulsive disorder: Some strange brain fellows. *Trends Cogn Sci, 1*, 321-322.

Sackeim, H. A., Decina, P., & Malitz, S. (1982). Functional brain asymmetry and affective disorders. *Adolesc Psychiatry, 10*, 320-335.

Shprintzen, R. J. (1997). Velo-cardio-facial syndrome: A distnctive behavioral phenotype. *Ment Retard Dev Disabil Res Rev, 6*(2), 142-147.

Shprintzen, R. J. (2000). Velo-cardio-facial syndrome: a distinctive behavioral phenotype. *Ment Retard Dev Disabil Res Rev, 6*(2), 142-147.

Shprintzen, R. J., Goldberg, R. B., Lewin, M. L., Sidoti, E. J., Berkman, M. D., Argamaso, R. V., et al. (1978). A new syndrome involving cleft palate, cardiac anomalies, typical facies, and learning disabilities: velo-cardio-facial syndrome. *Cleft Palate J, 15*(1), 56-62.

Siegal, M., & Varley, R. (2002). Neural systems involved in "theory of mind". *Nat Rev Neurosci, 3*(6), 463-471.

Sobin, C., Kiley-Brabeck, K., Daniels, S., Blundell, M., Anyane-Yeboa, K., & Karayiorgou, M. (2004). Networks of attention in children with the 22q11 deletion syndrome. *Dev Neuropsychol, 26*(2), 611-626.

Stiers, P., Swillen, A., De Smedt, B., Lagae, L., Devriendt, K., D'Agostino, E., et al. (2005). Atypical neuropsychological profile in a boy with 22q11.2 Deletion Syndrome. *Child Neuropsychol, 11*(1), 87-108.

Sugama, S., Bingham, P. M., Wang, P. P., Moss, E. M., Kobayashi, H., & Eto, Y. (2000). Morphometry of the head of the caudate nucleus in patients with velocardiofacial syndrome (del 22q11.2). *Acta Paediatr, 89*(5), 546-549.

Swillen, A., Devriendt, K., Ghesquiere, P., & Fryns, J. P. (2001). Children with a 22q11 deletion versus children with a speech-language impairment and learning disability: behavior during primary school age. *Genet Couns, 12*(4), 309-317.

Swillen, A., Devriendt, K., Legius, E., Eyskens, B., Dumoulin, M., Gewillig, M., et al. (1997). Intelligence and psychosocial adjustment in velocardiofacial syndrome: a study of 37 children and adolescents with VCFS. *J Med Genet, 34*(6), 453-458.

Turner, T. H. (1989). Schizophrenia and mental handicap: an historical review, with implications for further research. *Psychol Med, 19*(2), 301-314.

van Amelsvoort, T., Daly, E., Robertson, D., Suckling, J., Ng, V., Critchley, H., et al. (2001). Structural brain abnormalities associated with deletion at chromosome 22q11: quantitative neuroimaging study of adults with velo-cardio-facial syndrome. *Br J Psychiatry, 178*, 412-419.

van Amelsvoort, T., Schmitz, N., Daly, E., Deeley, Q., Critchley, H., Henry, J., et al. (2006). Processing facial emotions in adults with velo-cardio-facial syndrome: functional magnetic resonance imaging. *Br J Psychiatry, 189*, 560-561.

Vollm, B. A., Taylor, A. N., Richardson, P., Corcoran, R., Stirling, J., McKie, S., et al. (2006). Neuronal correlates of theory of mind and empathy: a functional magnetic resonance imaging study in a nonverbal task. *Neuroimage, 29*(1), 90-98.

Vorstman, J. A., Morcus, M. E., Duijff, S. N., Klaassen, P. W., Heineman-de Boer, J. A., Beemer, F. A., et al. (2006). The 22q11.2 deletion in children: high rate of autistic disorders and early onset of psychotic symptoms. *J Am Acad Child Adolesc Psychiatry, 45*(9), 1104-1113.

Young, A. W. (1997). Disgust faces, basal ganglia, and obsessive-compulsive disorder: Some strange brain fellows. *Trends Cogn Sci, 1*, 322-325.