

Substrates of Social Functioning in Individuals with Velocardiofacial Sydrome

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Velocardiofacial Syndrome (VCFS) is a genetic disorder characterized by numerous physiological and psychological symptoms. This study investigated the relationship between neurological morphometry and social deficits in individuals with VCFS. Volumetric measures of brain regions based on magnetic resonance imaging (MRI) were compared between 6 individuals with VCFS and 6 controls. Controls were matched according to age and gender. 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. Dorsolateral Prefrontal Cortex (DLPFC) volumes were larger in individuals with VCFS relative to controls t(10)= 3.23, p < .05). Amygdala enlargement in individuals with VCFS may be involved in the regulation of attentional processes in this population. DLPFC enlargement in this population may be related to the voluntary suppression of anxiety.

Keywords: velocardio facial syndrome, social competency, DiGeorge syndrome, 22q.11 deletion syndrome, neuroimaging, attention

Velocardio-facial syndrome (VCFS) is a genetic disorder that has a number of physiological and psychological symptoms and a common cause of learning disabilities 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.

Social Impairments Observed in Individuals with VCFS

Despite little advancement in the understanding of social phenotypes in VCFS, research has identified a number of social deficits including communication. 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). As a result, few utterances are understood and early speech attempts may not be reinforced leading to disintegration of communication abilities.

Another social deficit that may emerge is extreme shyness and withdraw (Shprintzen, 2000). Swillen et al. (2001) administered the Child Behavior Checklist (CBCL) to both individuals with VCFS and individuals with speech and learning impairments. They found the groups to differ substantially in the areas of withdrawal behavior suggesting that speech difficulties in VCFS interact with other features of the disorder to produce social withdrawal (Swillen, Devriendt, Ghesquiere, & Fryns, 2001) resulting in a failure to initiate interactions (Eliez et al., 2000). In their case study describing the language, speech, and psychological features in individuals with VCFS, Eliez et al. (2001), noted a significant deficit in the number of attempts made to initiate interactions with others.

Individuals with VCFS also show deficits in facial recognition (Stiers et al., 2005). Stiers et al. noted substantial impairments in facial recognition that were correlated with decreased volume of the right inferior parietal and superior occipital lobes along with a pronounced reduction of white matter

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behind the inferior frontal gyrus relative to controls. It is possible that social deficits observed in these individuals relating to their inability to recognize faces may be mediated by abnormalities in neural networks within these brain regions.

Further deficits in social functioning include impairments in processing facial expressions (van Amelsvoort et al., 2006). Individuals with VCFS 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. Moreover, there was increased activation in occipital regions relative to controls. The authors concluded that these neuroanatomical anomalies may significantly contribute to social deficits.

In addition, individuals with VCFS have distinct personality characteristics impacting social interactions such as decreased conscientiousness and emotional stability, and increased irritability and dependency than normal controls (Prinzie et al., 2002). Furthermore, severe attachment and anxiety issues have been shown. For example, Shprintzen (2000) noted age-inappropriate separation anxiety in individuals with VCFS 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).

Lastly, these individuals show affective abnormalities that interfere with social relations. Individuals with VCFS present with a flatter affect than normal controls during engagement in social interactions. Furthermore, their facial responses tend to be expressionless or non-existent (Golding-Kushner et al., 1985) making sustained conversations with others difficult due to their inability to provide reinforcing feedback to those with whom they are communicating.

Neuroanatomical Etiology of Social Impairments

There is evidence to suggest that neuranatomical anomalies are related to many of the social deficits observed in individuals with VCFS. One study found significant volumetric differences in amygdala, prefrontal cortex, and orbitofrontal cortex relative to controls (Kates et al., 2006). These volumetric differences were positively correlated with impaired performance on social competency scales.

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 significantly larger than in sibling

controls. As the amygdala has 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 may account for many of the social features observed in individuals with VCFS.

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 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.

Individuals with VCFS have also been shown to have a smaller prefrontal cortex (PFC) when compared to age-matched, non-clinical controls (Kates et al., 2006). In particular, smaller volumes were observed in the orbitofrontal cortex relative to controls. Since the orbitofrontal cortex has been implicated in the modulation of anxiety (Breiter & Rauch, 1996; Rauch, Savage, Alpert, Fischman, & Jenike, 1997), it is possible that many of the attachment and anxiety issues in VCFS patients may be related to abnormalities in this region.

Other sub regions 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 (Gainotti, 1972; Robinson, Kubos, Starr, Rao, & Price, 1984; Sackeim, Decina, & Malitz, 1982). Volumetric changes in this sub region could mediate the mood symptoms frequently observed in individuals with VCFS. The ventromedial PFC (VMPFC) also has a role in social functioning and has been implicated in the anticipation of future consequences (Bechara, Damasio, Damasio, & Anderson, 1994). Much of the impulsiveness and disinhibition observed might be mediated volumetric differences in this particular region.

Additional neuroanatomical analysis has found discrepancies in volume of the insular cortex (van Amelsvoort et al., 2001). Van Amelsvoort and Schmitz (2006) noted decreased activation in right insula during tasks involving facial processing (van Amelsvoort et al., 2006). Furthermore, the insular cortex plays a critical role in regulating autonomic responses accompanying emotion. Also, the insula is especially active during exposure to disgusting foods

and photos of disgust faces suggesting one of its functions is the recognition of distasteful stimuli (Rozin, 1997; Young, 1997). Davidson and Irwin (1993) concluded that the insula is likely associated with the physiological changes that occur following autonomic activation (Davidson & Irwin, 1999).

In addition to the aforementioned structures, it is possible that the superior temporal sulcus (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). Given that individuals with VCFS experience social deficits relating to ToM such as impairments in communication and social interaction, it is plausible that these individuals may show volumetric differences in the STS relative to controls. The STS has also been implicated in gaze control (Garrett, Menon, MacKenzie, & Reiss, 2004) resulting in individuals with activation deficits in this structure having difficulty controlling their gaze and maintaining appropriate social posturing.

Another region implicated in processing is the anterior cingulate cortex (ACC). The ACC has been implicated in the ability to attend to emotional events (Posner, 1995). Increased activity in the ACC during tasks requiring attention of emotional stimuli have been observed (Lane et al., 1997) while no activity was observed when subjects were asked to attend to non-emotional stimuli. The ACC has also been implicated in the mediation of other affective and cognitive functions (Fujiwara et al., 2007) including modulation of emotional responses which has been found to be an essential component in social cognition and mentalizing (Kopelman, Andreasen, & Nopoulos, 2005). Smaller ACC volumes have also been correlated with specific deficits in social cognition (Fujiwara et al., 2007).

Hypotheses

Given the extensive role the amygdala plays in emotional processing and the equivocal finding 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 decreased emotional stability, it was hypothesized that individuals with VCFS would have a significantly larger amygdala to prefrontal cortex ratio than sibling controls and that amygdala volume would be correlated with greater anxiety and lower social competency as measured by the CBCL.

As a result of the significant anxiety and attachment issues observed, it was hypothesized that the orbitofrontal cortex of individuals with VCFS would be significantly smaller in volume in VCFS patients than in a control group and that the volume of this region would be correlated with greater attention and social problems. Furthermore, volume of the orbitofrontal cortex in individuals with VCFS will be correlated with lower social competency.

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 and that volume would be negatively correlated with measures of anxiety and depression. Also, DLPFC volumes would be positively correlated with social competency. Similarly, the VMPFC, has been implicated in the interpretation of consequences and the ability to inhibit certain behaviors. As such, this region was hypothesized to be smaller and be negatively correlated with attention problems and delinquency. Furthermore, VMPFC volume would be positively correlated with social competency.

In congruence with van Amelsvoort et al. (2001), it was predicted that insula volume would be larger relative to controls. Furthermore, this volumetric anomaly would be positively correlated with measures of withdraw and anxiety and negatively correlated with social competency.

As the STS has been implicated in the development of ToM (Moriguchi, Ohnishi, Mori, Matsuda, & Komaki, 2007), it was hypothesized that volumetric differences would be observed. Specifically, it was hypothesized that individuals with VCFS would have smaller STS volumes relative to controls and STS volume would be negatively correlated with the social problems subscale and positively correlated with social competency.

As numerous social impairments have been linked with volumetric discrepancies in the ACC and individuals with VCFS share common social symptomatology with populations showing decreased volumes in this structure (Lane et al., 1997), it was hypothesized that individuals with VCFS would have decreased ACC volume relative to controls and that ACC volumes would be inversely correlated with social problems and positively correlated with social competency.

Measures

Child Behavior Checklist (CBCL): The CBCL is a standardized, parent-report measure of children's (ages 4-18 version) behavior problems and

competencies. The problem portion of the measure consist 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).

Methods

Participants

Subjects included 12 children (6 males and 6 females) ages 6-16 years. Six of these children (3 male and 3 female) were diagnosed with VCFS. The average intellectual quotient (IQ) of the VCFS children was 70.16 (SD=1.04). Mean age of children with VCFS was 10.5 (SD=3.39). The other 6 children (3 male and 3 female) served as controls. Mean age of controls was 10.3 (SD=3.72). While formal intellectual testing was not conducted, the children were all of generally average intellectual ability based on academic performance as reported by parents and were all in mainstreamed educational settings. Children with VCFS were recruited through the Department of Genetics at Henry Ford Hospital and Childrens Hospital of Michigan and diagnoses was confirmed by FISH (fluorescent in situ hybridization). Controls were recruited through peer nomination and advertisement. Inclusion criteria for the current study included a VCFS diagnosis confirmed by FISH. Controls were matched with individuals with VCFS on the variables of age and gender. Exclusion criteria for children with VCFS and controls included the presence of pre- or perinatal pathology, head injury, or substance abuse in the mother. Subjects were paid a \$50.00 incentive for their participation in the initial data collection.

Procedure

Neuropsychological testing was completed by pre-doctoral level interns or post-doctoral fellows at the Neuropsychology Clinic at Henry Ford Health Systems in Detroit, MI between January 2003 and August 2005. All procedures for obtaining informed consent and working with human subjects as outlined by IRB and APA ethical guidelines were followed.

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 followed immediately by the imaging acquisition.

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 procedure. They were checked for any metal using standard screening materials and questionnaires.

The coronal T1-weighted images were reformatted to the axial plane and registered to the axial proton-density T2-weighted images. The multiparametric 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 or regions of interest (ROI's)(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). Lastly, to identify regional differences, each MRI was registered and morphed to a standard brain atlas (Ghanei et al., 2000). The ROI's were manually traced and identified using a brain atlas and confirmed by a clinical neuropsychologist.

Analysis

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 ROI to be analyzed were amygdala, dorsolateral prefrontal cortex, verntromedial prefrontal cortex, insula, superior temporal sulcus, and anterior cingulate cortex. Alpha was set at p < .05.

Table 1 - Mean Volume (cc), SD and Effect Size of Analyzed Structures in Individuals with VCFS and Controls

	VCFS		Controls		
Structures	M	SD	M	SD	Effect size (d)
Amygdala*	.001821	.004361	.000995	.000251	.267
PFC	.004057	.017322	.005798	.001732	141
DLPFC*	.184740	.050258	.100547	.039358	1.865
VMPFC	.080646	.056501	.046992	.027015	.760
Insula	.008373	.002082	.011985	.004354	-1.058
STS	.027109	.005252	.029111	.008111	293
ACC	.006540	.001860	.006581	.001810	022

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. * statistical significance

Table 2 – Mean Scores (T-scores) for CBCL Subscales for Individuals with VCFS

Subscale	M	SD
Withdrawn Somatic Complaints	53.50	5.04975
Anxious/Depressed	57.20	8.20771
Social Problems	55.67	6.47045
Thought Problems	61.33	10.6332
Attention Problems	59.83	8.75024
Aggressive Behavior	69.50	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.

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. All structures were correlated with the social competency scale.

Results

This paper examined volumetric differences of specific structures implicated in social functioning in individuals with VCFS. dditionally, the relationship between neuroanatomical structure or regions and scores on the CBCL were examined. Table 1 provides the mean volumes for each structure analyzed for individuals with VCFS and Controls. Table 2 provides means and standard deviations for each CBCL subscale analyzed for individuals with VCFS.

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 controls. Average amygdala volume was significantly larger in individuals with VCFS relative to controls, t(10)=4.01, p<.05.

There were no significant relationships observed between amygdala and the anxiety subscale or the social competency subscale of the CBCL. 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.

It was hypothesized that the dorsolateral 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.

No significant volumetric changes or correlations were observed in any of the other structures examined. 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.

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,

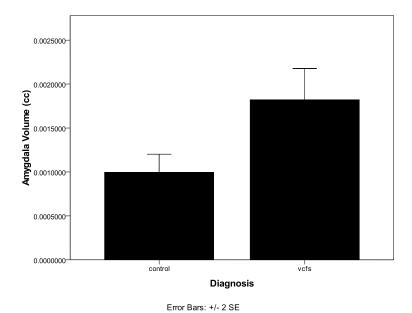


Figure 1. Mean bilateral amygdala volume (+SE) for controls (n = 6) and individuals with VCFS (n = 6).

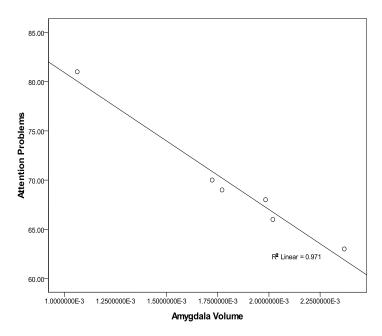
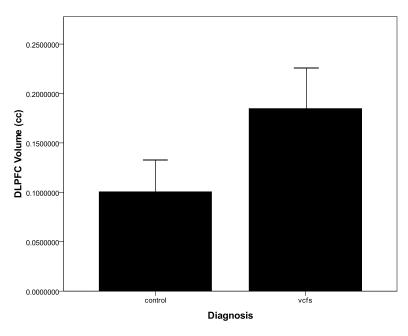


Figure 2. Relationship between the attention subscale of the CBCL and amygdala volume in individuals with VCFS (n = 6).



Error Bars: +/- 2 SE

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

p=.56), attentional deficits r(6)=-.64, p=.17), and social competency r(6)=-.14, p=.91) in individuals with VCFS.

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. 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=.87subscales 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.

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. 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.

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. 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. Specifically, one goal of this research was to elucidate brainbehavior 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 implicated in social processing were analyzed for volumetric anomalies in a population with known social deficits. Normalized volumes were then correlated with behavioral measures.

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. It is possible that this increase in amygdala volume may be the result of high anxiety levels in this population. Increased amygdala volumes have been observed in individuals with autism, phobic and generalized anxiety disorders (Bellis, 2000). Additionally, it has been concluded that this increased anxiety leads to experiencedependent neuronal remodeling in the amygdala which may contribute to increased volume (Dong & Greenough, 2004). It is possible that the anxiety associated with this population 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. 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, reported symptoms of attentional deficit diminished. This relationship amygdala volume and attentional impairment has not been reported in this population. However, there is some evidence in ADHD literature suggesting that the amygdala can support features of attention. For example, Schaefer, 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. A specific examination of the relationship between amygdala and attention in this population is necessary in order to adequately understand how the 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).

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. It is possible that the frontal cortex has a limited impact on the social impairments presented in VCFS. However, this is unlikely given what is known about the frontal cortex involvement in the mediation of attention and social competency. Also, it is possible that there is some overall sparing of frontal cortex in individuals with VCFS and differences may only be observed by further subparceling of the prefrontal cortex.

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 social cognition, but rather a network of structures. 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.

The hypothesis that DLPFC volumes would be smaller relative to controls was not supported. Instead, DLPFC volumes in individuals with VCFS were significantly larger than control subjects. One possible explanation involves compensatory mechanisms that occur in response to amygdala enlargement. 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. 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 plasticity in DLPFC.

The DLPFC was 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. 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. Further research is necessary in order to understand and identify the complex network of structures and relationships underlying specific social behaviors associated with sub-regions of the frontal lobe

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. However, there was a clear trend suggestive of greater insular volume in the clinical population. The small sample size limited statistical power in this particular experiment making it difficult to reject the null hypotheses. Since this structure is involved in emotional processing and reasoning, future analyses of this 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.

Conclusion

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 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. 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, 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. It is likely that social processes and impairment in VCFS is mediated by multiple structures within each construct or domain of social functioning. 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.

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