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## Cortical Gyrfication in Velo-Cardio-Facial (22q11.2 Deletion) Syndrome: A Longitudinal Study

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### Abstract

**Introduction**—Velocardiofacial syndrome (VCFS) has been identified as an important risk factor for psychoses, with upto 32% of individuals with VCFS developing a psychotic illness. Individuals with VCFS thus form a unique group to identify and explore early symptoms and biological correlates of psychosis. In this study, we examined if cortical gyrfication pattern, i.e. gyrfication index (GI) can be a potential neurobiological marker for psychosis.

**Method**—GIs of 91 individuals with VCFS were compared with 29 siblings and 54 controls. Further, 58 participants with VCFS, 21 siblings and 18 normal controls were followed up after 3 years and longitudinal changes in GI were compared. Additionally, we also correlated longitudinal changes in GI in individuals with VCFS with prodromal symptoms of psychosis on the Scale of Prodromal Symptoms (SOPS).

**Result**—Individuals with VCFS had significantly lower GIs as compared to their siblings and normal controls. Longitudinal examination of GI did not reveal any significant group-time interactions between the three groups. Further, longitudinal change in GI scores in the VCFS

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Drs. Shprintzen and Antshel, and Anne Marie Higgins received research support from Aton Pharma during the past three years. The rest of the authors declare that no financial support or compensation has been received from any individual or corporate entity over the past 3 years for research.

Contributors:

Arun Kunwar analyzed the imaging datasets and wrote a portion of the manuscript.

Seethalakshmi Ramanathan completed the statistical analyses and wrote a portion of the manuscript.

Joshua Nelson analyzed the imaging datasets and managed the references.

Kevin M. Antshel conducted the cognitive assessments on all participants, and a portion of the psychiatric assessments.

Wanda Fremont conducted a portion of the psychiatric assessments on the participants.

Anne Marie Higgins recruited all participants and managed the logistics of their participation at both time points of the study.

Robert J. Shprintzen contributed to the overall design of the protocol.

Wendy R. Kates designed the study protocol, oversaw subject recruitment and assessment, and wrote a portion of the manuscript.

group was negatively correlated with positive prodromal symptoms, with the left occipital region reaching statistical significance.

**Conclusion**—The study confirms previous reports that individuals with VCFS have reduced cortical folding as compared to normal controls. However over a period of three years, there is no difference in the rate of change of GI among both individuals with VCFS and normal controls. Finally, our results suggest that neuroanatomical alterations in areas underlying visual processing may be an early marker for psychosis.

## Keywords

VCFS; Gyrfication index; prodromal symptoms; occipital cortex

## 1. Introduction

Velocardiofacial syndrome (VCFS) results from a microdeletion spanning over 40 genes (Carlson et al, 1997) at 22q11.2, with an estimated prevalence of 1 in 2000–4000 births (Shprintzen, 2005). Physical features include a characteristic facial appearance, and cardiac and pharyngeal abnormalities. Additionally, VCFS is associated with behavioral abnormalities including disinhibition, impulsivity, schizoid features, social withdrawal, and flat affect (Feinstein et al, 2002; Swillen et al, 1999). Significantly, it has been reported that up to 32% individuals with VCFS develop a psychotic illness in adulthood (Arnold et al, 2001; Bassett and Chow, 1999; Green et al, 2009; Murphy et al, 1999; Shprintzen et al, 1992). The high rate of psychosis in VCFS suggests that, with the exception of being the offspring of a dual mating or the monozygotic co-twin of an affected individual, the specific microdeletion of chromosome 22q11 associated with VCFS represents the highest known risk factor for the development of schizophrenia. This strong association between schizophrenia and VCFS implies that a gene or genes mapping to chromosome 22q11 may play a role in the etiology of schizophrenia.

It is therefore not surprising that several investigators have explored this unique relationship between VCFS and schizophrenia. Qualitative (Chow et al, 1999; Lynch et al, 1995; Mitnick et al, 1994; van Amelswoort et al, 2001; Vataja and Elomaa, 1998) and quantitative (Eliez et al, 2000; 2001; Kates et al, 2001; 2006; Simon et al, 2005; Tan et al, 2009) neuroimaging studies have identified neuroanatomic overlap between individuals with VCFS and schizophrenia, including enlarged ventricles, midline brain abnormalities (e.g. cavum septum pellucidum), and volumetric reductions in prefrontal, parietal, temporal and occipital GM and WM, and hippocampal volumes. Similarly, studies of individuals with schizophrenia (Cahn et al, 2002; Corsona et al, 1999; Davatzikos et al, 2005; Hazlett et al, 1999; Pearlson and Marsh, 1999; Pol et al, 2002; Shenton et al, 2001; Wright et al, 2000) have reported reductions in the volumes of total and prefrontal GM, temporal and parietal lobes, caudate nucleus, thalamus, hippocampus and amygdala.

Overlapping anomalies in cortical complexity have also been reported in studies of individuals with schizophrenia and those with VCFS. The complexity of cortical folding has been represented in most studies with the gyrfication index (GI). Gyrfication abnormalities in schizophrenia have been reported in the left hemisphere (Sallet et al, 2003), left frontal and right temporal regions (Harris et al, 2004a). Pre-existing differences in gyral folding have also been identified as a potential trait marker for individuals who subsequently develop schizophrenia. Harris et al (2004b) reported that right prefrontal lobe GI was significantly increased in individuals who subsequently developed schizophrenia.

In individuals with VCFS, findings are variable. Whereas Bearden and colleagues (2009) observed GI increases in the occipital lobe, Srivastava et al (2012) noted GI reductions in

frontal and parietal lobes relative to controls. In their cross-sectional sample, Srivastava and colleagues further noted that GI in VCFS-affected youth ages 6–15 years (but not in controls) decreased with age, particularly in the parietal lobes. Similarly, Schaer et al showed a significant decrease in the GI in frontal (2006) and parietal lobes (2006, 2008, 2009) of adolescents and adults with VCFS relative to controls. Interestingly, the study by Schaer and colleagues (2009) observed that relative to typical controls, individuals with VCFS had differential rates of cortical maturation that were more magnified in patients who later developed schizophrenia. However, neither study of cortical gyrification in VCFS followed the same cohort over time to investigate longitudinal changes in GI.

In an effort to complement and extend previous studies, we examined longitudinal changes in gyrification patterns in a cohort of youth with VCFS, and explored the extent to which alterations in GI were associated with early symptoms of psychosis. We have previously reported, in the same cohort, that among individuals with VCFS, contractions in the surface morphology of the temporal cortex were associated with overall prodromal symptoms of psychosis (Kates et al, 2011), and longitudinal decrements in volumes of temporal lobe GM were associated specifically with positive prodromal symptoms of psychosis (Kates et al, 2011). The current report expands on these findings as well.

Based on previous GI studies in both VCFS and schizophrenia, we hypothesized that:

*Hypothesis 1a:* Individuals with VCFS will have reduced GI relative to controls and siblings.

*Hypothesis 1b:* On longitudinal assessment, individuals with VCFS will have a slower rate of change in GI as compared to typically developing controls.

*Hypothesis 2:* GI patterns, particularly in the frontal and temporal regions, will be associated with prodromal symptoms. We propose this hypothesis as our findings on cortical surface morphology suggest that psychotic symptoms are related to change in frontal and temporal cortices.

## 2. Materials and Methods (Details in Appendix I)

### 2.1. Participants

The current sample, described in Table 1, comprises data acquired for two studies:

1. A cross-sectional study (Study 1) of children with VCFS between the ages of 6 and 9 years, and age-matched community controls. This group of participants was not invited for longitudinal assessments.
2. A longitudinal study (Study 2) of 9–15 year old children with VCFS, their unaffected siblings within the same age range, and age-matched community controls. For Study 2, all participants were invited to return for a second time point, three years after their initial visit.

The data from Study 1, and the baseline data from Study 2, are combined in this report to form the “Baseline” sample (age range from 6–15 years). Data from the participants (9 to 15 years of age at baseline) who were followed longitudinally comprise the “Follow-up” sample. At the first time point (Baseline visit, henceforth referred to as Time 1 or T1), all participants underwent an MRI scan. At Follow-up visit (henceforth referred to as Time 2 or T2), three (range: 1.5–5.3) years later, participants underwent a repeat MRI scan using the same protocol as Time 1. In Study 2, attrition between T1 and T2 was 16% for individuals with VCFS, 21% for siblings, and 37% for controls.

## 2.2. MRI acquisition

Magnetic resonance imaging scans were acquired in the axial plane on a 1.5 T Philips Gyroscan scanner (Philips Medical Systems, Best, The Netherlands). Images were imported into BrainImage (Reiss, 2004) for removal of non-brain tissue, and were subsequently spatially normalized using a 3D Talairach grid (Kates et al, 1999; Talarach and Tournoux, 1998), which was used to determine GI in the four major lobar regions (frontal, parietal, temporal and occipital).

## 2.3. Calculation of Gyrfication Index

GI was measured following a semi-automated protocol described by Schmitt and colleagues (2002). GI is calculated as the ratio of the length of the inner perimeter of the cortex (including the depths of the sulci) to the length of the outer perimeter (Zilles et al, 1988):

$$GI = \text{Length of inner contour} / \text{Length of outer contour}$$

**Behavioral Assessments**—The Scale of Prodromal Symptoms (SOPS) (Miller et al, 2003) was used to assess prodromal symptoms of psychosis. The SOPS is a clinician-based instrument (based on self-report and observation) that categorizes prodromal symptoms into four categories: Positive (P), Negative (N), Disorganized (DOS) and General (G) symptoms. Total (T) score was calculated as the sum of P, N, DOS and G scores. For most assessments, Total and Positive subscale scores were used.

**Statistical Analyses**—Data were analyzed using STATA SE 11.0. All major lobar regions were examined – frontal, parietal, temporal and occipital. Further, as the two hemispheres differ in their GI patterns due to functional specialization, left and right GI for each lobe were analyzed separately (Armstrong et al, 1995). Cross-sectional analyses were carried out using MANCOVA, with age and gender as covariates. For longitudinal analyses, we used repeated measures MANOVA, controlling for gender. GI change score was calculated as the difference between GI at T2 and T1. This change score was used in ZIP regressions with P and Total scores. Throughout, we corrected for multiple comparisons using Bonferroni correction;  $p < 0.006$  (0.05/8) was considered as statistically significant for the cortical regions.

## 3. Results

### 3.1. Demographic Profile (Table 1)

At Time 1, as was expected due to the combination of the two samples, a significant difference was noted in the ages between the three groups ( $p = 0.01$ ). Neither gender distribution ( $p = 0.22$ ) nor handedness ( $p = 0.69$ ) differed between groups. At time 2, the three groups did not differ significantly in age ( $p = 0.87$ ), gender ( $p = 0.78$ ) or handedness ( $p = 0.49$ ).

### 3.2. Cross-sectional Analyses

#### 3.2.1. Comparison of GI among the three groups (MANCOVA) (Table 2 & 3)—

Table 2 (df=3, 170) presents the GIs (average and SD) for lobar regions in the three groups at the two time points. Table 3 reports the MANCOVA results comparing the GIs in the

<sup>1</sup>In study 2, participants who did not follow up for the second part of the study (11.9 years) were noted to be similar in age as compared to the participants who followed up (12.5 years). This held true between the three groups as well. Further, no differences were noted in the GIs of any lobar regions between these two groups. When the three groups were treated separately, only the siblings who dropped out were noted to have significantly lower GIs in the frontal regions and left parietal region. These differences, however, did not survive Bonferroni correction.

frontal, parietal, temporal and occipital regions of the three groups at each time point controlling for age and gender.

Significant differences were noted among the three groups at both time points. At T1, significant differences were noted in the frontal (Right:  $F=7.57$ ,  $p=0.00$ , Left:  $F=10.83$ ,  $p=0.00$ ) and parietal regions (Right:  $F=14.64$ ,  $p=0.00$ , Left:  $F=13.52$ ,  $p=0.00$ ) bilaterally. At T2, the three groups continued to differ significantly in the same regions (right frontal:  $F=6.34$ ,  $p=0.00$ , Left frontal:  $F=9.11$ ,  $p=0.00$ , right parietal:  $F=16.67$ ,  $p=0.00$ , left parietal:  $F=12.66$ ,  $p=0.00$ ) bilaterally. Post-hoc analyses revealed that these differences were driven by participants in the VCFS group who had significantly lower GI's in all regions than the other two groups (reported in Table 2). GI scores were the highest for the sibling group, with the exception of the right frontal and parietal regions, which were highest in community controls.

### 3.3. Longitudinal Analyses

**3.3.1. Comparison of GI among the three groups over the two time periods (Repeated Measures MANOVA with gender as covariate) (Table 3)**—Repeated measures MANOVA ( $df=2, 94$ ) examining changes in GI over time showed no significant group-X-time interactions. However, post-hoc analyses revealed a similar time effect in all groups. GI's among all three groups changed significantly over time ( $p<0.01$ ), i.e., GI at baseline in frontal, parietal and temporal regions was significantly higher than GI at follow-up among all three groups. These differences held when corrected for multiple analyses in all regions except right parietal ( $p=0.008$ ). In both occipital lobes, the GI at follow-up was not significantly different from the GI at baseline (right occipital lobe ( $F=1.06$ ,  $p=0.31$ ); left occipital lobe ( $F=0.74$ ,  $p=0.39$ )).

**3.3.2. Correlations of GI with SOPS score (ZIP regression) (Table 4)**—ZIP analyses revealed negative correlations between GI change scores in all areas and the positive SOPS score, suggesting that lower GI change scores were associated with positive SOPS. SOPS Positive Symptom score correlated significantly with GI scores in right temporal ( $p=0.040$ ), left frontal ( $p=0.041$ ), and left occipital ( $p=0.002$ ) lobes, while SOPS total scores correlated with right frontal ( $p=0.008$ ), right parietal ( $p=0.007$ ) and both occipital GI scores (right occipital region:  $p=0.006$ , left occipital region:  $p=0.018$ ). When Bonferroni - corrected for multiple comparisons, the negative association between SOPS Positive symptoms and left occipital GI persisted. Similarly, a negative correlation between right occipital GI and the SOPS Total score remained statistically significant, although the parietal and frontal regions were close to surviving the correction.

## 4. Discussion

In this longitudinal study, individuals with VCFS were followed over a three year period, along with their siblings and community controls. Our first hypothesis was partially supported. Individuals with VCFS had lower gyrification indices relative to age and sex-matched siblings and community controls in frontal and parietal (but not temporal) lobes. This pattern of lower baseline GI among individuals with VCFS was also noted in the same regions during the follow-up visit 3 years later. Qualitative observations of anomalous cortical gyrification, including pachygyria and polymicrogyria in the frontal and parietal regions were among the earliest structural abnormalities reported in individuals with VCFS (Bingham et al, 1998; Bird and Scrambler, 2000; Cramer et al, 1996; Ehara et al, 2000; Ghariani et al, 2002; Kawame et al, 2000; Koolen et al, 2004; Sztriha et al, 2004; Worthington et al, 2000). Schaer et al reported that compared to typically developing individuals, those with VCFS had lower GIs in the frontal (2006) and parietal regions (2006,

2008, 2009). Similar to our finding, Schaer et al (2006) did not observe differences in the temporal GIs among individuals with VCFS and typically developing controls. These GI reductions in individuals with VCFS may reflect aberrant/ weaker intercortical connections in frontal and parietal cortices. Barnea-Goraly et al (2003) reported reduced fractional anisotropy in the frontal and parietal regions.

Longitudinal analyses identified that GIs among all three groups decreased over the three years. However, no significant differences were noted between the three groups. This time effect was not noted in the occipital lobe, i.e., the rate of decrease in GI in the occipital lobe is slower than other regions. Srivastava et al (2012) noted that, relative to typically developing children, children with VCFS had both higher and lower rates of age-related change in GI in various parts of the parietal lobe; however none of these changes were significantly different. These authors do not report significant differences in the developmental rates of the occipital lobe, although their cross-sectional results are not directly comparable to our longitudinal findings. A longitudinal exploration of cortical changes by our group (Kates, 2011) noted that changes in cortical morphology were similar among individuals with VCFS, their siblings and typically developing controls. These morphological changes represented changes in protrusions and contractions of the cortical surface, putatively associated with changes in the local volumes of cortical brain regions (Petersen, 2010). In contrast, our measure of gyrification represents changes in the degree of cortical complexity or convolutions of the brain. As such, cortical gyrification can be used to infer changes in the shape, as opposed to local volumes, of the cortical surface.

Our second hypothesis examined the association between longitudinal changes in GI and development of psychosis. Several authors (Harris et al, 2004b; Jou et al, 2005) have proposed that aberrant gyrification patterns influence the development of psychiatric symptoms including psychosis. Harris et al (2004b) noted that abnormal GIs could be a trait marker for schizophrenia. When we explored the correlation of rate of change of GI with the incidence of prodromal symptoms, after correcting for multiple analyses, we found that longitudinal decreases in GI in the left occipital lobe were associated with greater positive scores whereas in the right occipital lobe they were associated with total SOPS scores. As noted earlier, the rates of change of GI were the slowest in the occipital lobes as compared to the other regions. However, in individuals with VCFS, greater longitudinal reduction in GI in the occipital lobe was associated with positive symptoms. It is however still possible that further longitudinal follow-up may reveal a catch-up in the change of GI in the occipital regions. The differential rate of change in the occipital lobe and association with prodromal symptoms suggests that occipital lobar connections may become dysfunctional or fail to develop normally, thereby influencing onset or development of prodromal symptoms.

Several studies (Schaer et al 2009, Bearden et al, 2007) have suggested that individuals with VCFS have cortical abnormalities in the regions responsible for visuospatial functioning. In a cross-sectional study of a similar age group, Bearden et al (2009) noted increased gyral complexity in the occipital lobe. There are contradictory findings about the involvement of the occipital lobe in schizophrenia, with some studies (Davatzikos et al, 2005; Onitsuka et al, 2007; Zipursky et al, 1992) reporting reductions and others (Giuliani et al, 2005; Goldstein et al, 1999; Shenton 2001) noting no significant changes. Onitsuka et al (2007) have reported reductions in the gray matter areas of the visual association area. They further suggest that these changes may contribute to early visual processing abnormalities noted in schizophrenia.

We also noted that the right frontal and left parietal change scores attained near significance with total SOPS scores. This was in the opposite direction of the occipital lobe, suggesting that in individuals with prodromal symptoms, GIs in the frontal and parietal regions increase

on follow-up. This is also discrepant from the longitudinal trajectory noted in these regions in all three groups; GIs in these regions decrease as a general rule. Accordingly, it appears that when the direction of change in frontal and parietal cortical complexity deviates from that of both neurotypical individuals and most subjects with VCFS, prodromal symptoms appear. Further, the correlation with total scores and not positive scores suggest that these areas may be involved in other symptoms including disorganization, negative and general or may influence the intensity of the prodromal symptoms. Parietal and frontal cortical changes have been reported in individuals with increased risk for developing schizophrenia (Prasad et al, 2010). Further, our group (Kates et al, 2011) noted differential longitudinal trajectories in parietal and frontal cortical surface morphology in individuals with VCFS at high risk for developing schizophrenia. Most studies of schizophrenia associate positive symptoms with the temporal lobe. Although we have recently noted associations between changes in temporal gray matter volume and surface morphology and prodromal symptoms of psychosis in individuals with VCFS (Kates, 2011), we were unable to demonstrate here an association with changes in temporal lobe GI. It is possible that temporal GI changes may become evident on further follow-up.

GI reflects cortical folding and is established by the age of 6–9 months following which GI decreases until it stabilizes in adulthood (Armstrong et al, 1995). The morphogenetic model (Toro & Burnod, 2005) suggests that the cortical plate develops at a different rate than the inner plate, which results in cortical folding. Van Essen (1997) discussed a mechanical model which explains that the pattern of cortical folding is determined by the mechanical tension exerted by the longer subcortico-cortical (in a radial fashion) and shorter local intercortical axons (in a tangential manner) during development. More compact longer axons and weaker local (cortical interconnections) axonal development leads to smaller gyri with smaller sulci, thereby decreased GI. On the other hand, looser long radial axons and stronger local interconnections lead to increased GI. Additionally, authors (Guerrini et al, 2000) have suggested that gyrification abnormalities can coexist due to vascular anomalies. Schaer et al noted that individuals with congenital heart disease have reduced gyrification than individuals with normal heart functioning. They proposed that these could be secondary to a common genetic mechanism through *TBX1* or the consequence of reduced blood flow resulting from cardiac dysfunction. A final hypothesis that has been proposed is that synaptic pruning may be involved in the formation of sulci and gyri. White et al (2003) propose a model based on pruning of the connections in the sulci that can contribute to further remodeling of the gyral system. Thus, measurement of GI provides some indication of both neurodevelopmental (such as neuronal migration and proliferation leading to alteration in neuronal tension and altered pruning) and neurodegenerative (including vascular changes) processes. Our cross-sectional and longitudinal findings of differences in GI among the three groups suggest that prodromal symptoms in VCFS may be a developmental rather than degenerative process, although the influence of the latter process cannot be ruled out completely.

Our results should be examined in the context of their limitations. Although we used a previously validated (Kates et al., 1999) 3D Talaraich grid to identify lobar regions, our method for measuring GI specifically was limited in its 2D anatomical definition. Additionally, all statistical analyses were done using the most restrictive method (repeated measures MANOVA and Bonferroni correction) available. While it demonstrates the robustness of our findings (Keselman et al, 1991), it also increases the chances of Type II errors. We also noted that siblings of VCFS had higher GI values as compared to typically developing controls. A similar finding was noted in the rate of change of orbitolateral cortical volumes examined in the same group (siblings had a greater increase in volumes than typically developing controls). We believe that these changes may reflect a familial influence rather than any particular genetic pattern. Further, we did not exclude controls who

had ADHD or learning disabilities to ensure a control sample that would appropriately match for our higher functioning VCFS subjects. So their lower GI values may have reflected their developmental challenges to some extent.

To summarize, the study affirms earlier findings that individuals with VCFS have reduced cortical folding than typically developing individuals. The study also noted that GI in individuals with VCFS changes at a rate similar to typical controls. However, this longitudinal trajectory appears to be deviant in “high-risk” individuals with VCFS. Finally, we identified significant associations between longitudinal alteration in the GI of the occipital lobe and prodromal symptoms, raising the question of whether deficits in visual processing in VCFS may represent a vulnerability marker for the development of psychosis.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**TABLE 1**

Description of demographic profile of the three groups

Baseline Sample	VCFS (n-91)	Siblings (n-29)	Controls (n-54)	p-value
Age (Years)	11.33(SD- 2.5)	12.27(SD- 2.11)	10.61(SD- 2.59)	0.01 *
Gender				
Male	47 (51.6%)	12 (41.4%)	33 (61.1%)	0.22
Female	44 (48.3%)	17 (58.6%)	21 (38.9%)	
Handedness				
Right	80 (87.9%)	27(93.1%)	49 (90.7%)	0.69
Left	11 (12.1%)	2(6.9%)	5 (9.3%)	
Follow-up Sample	VCFS (n-58)	Siblings (n-21)	Control (n-18)	p-value
Age (Years)	14.99 (SD- 2.05)	15.19 (SD- 2.15)	15.23 (SD- 2.01)	0.87
Gender				
Male	30 (51.7%)	11 (52.4%)	11 (61.1%)	0.78
Female	28 (48.3%)	10 (47.6%)	7 (38.9%)	
Handedness				
Right	49 (84.5%)	19 (90.5%)	17 (94.4%)	0.49
Left	9 (15.5%)	2 (9.5%)	1 (5.6%)	

\*  
p<0.05

**TABLE 2**  
Description of GIs (mean (SD)) of the three study groups over the two time periods.

	VCFS		Siblings		Controls	
	T1 (n=91)	T2 (n=58)	T1(n=29)	T2(n=21)	T1 (n=54)	T2 (n=18)
R Frontal	3.09 (0.36)	2.81 (0.35)	3.26 (0.34)	3.04 (0.31)	3.28 (0.39)	3.09 (0.34)
L Frontal	3.07 (0.41)	2.82 (0.38)	3.21 (0.41)	3.08 (0.35)	3.30 (0.35)	3.04 (0.31)
R Parietal	3.17 (0.46)	2.91 (0.36)	3.47 (0.49)	3.21 (0.32)	3.57 (0.43)	3.37 (0.43)
L Parietal	3.01 (0.40)	2.71 (0.33)	3.23 (0.35)	3.03 (0.34)	3.36 (0.44)	3.04 (0.43)
R Temporal	2.76 (0.45)	2.49 (0.37)	2.97 (0.48)	2.68 (0.51)	2.83 (0.51)	2.60 (0.40)
L Temporal	2.67 (0.41)	2.45 (0.36)	2.78 (0.45)	2.61 (0.41)	2.60 (0.53)	2.49 (0.38)
R Occipital	2.05 (0.36)	1.99 (0.36)	2.82 (0.46)	2.17 (0.44)	2.05 (0.53)	2.05 (0.49)
L Occipital	2.01 (0.29)	2.05 (0.35)	2.17 (0.39)	2.19 (0.51)	2.04 (0.47)	2.05 (0.43)

**TABLE 3**

MANCOVA controlled for age and gender among the three diagnoses at T1 (df-2, 1, 170) & T2 (df-2, 1, 93) and repeated measures MANOVA, controlled for gender (df- 2, 1, 93) between T1 and T2.

	T1 (n=174)		T2 (n=97)		T2-T1 (n=97) Group-Time Interaction	
	F	P	F	P	F	P
Right						
Frontal	7.57	<b>0.0001</b> *	6.34	<b>0.0006</b> *	0.36	0.6992
Parietal	14.64	<b>0.000</b> *	16.67	<b>0.0000</b> *	0.30	0.7427
Temporal	1.48	0.2215	1.60	0.1946	0.71	0.4923
Occipital	2.25	0.0839	1.11	0.3499	0.32	0.7273
Left						
Frontal	10.83	<b>0.0000</b> *	9.11	<b>0.0000</b> *	0.11	0.8934
Parietal	13.52	<b>0.000</b> *	12.66	<b>0.0000</b> *	0.20	0.8212
Temporal	1.02	0.3843	1.03	0.3826	0.05	0.9549
Occipital	2.92	0.0354	0.83	0.4796	1.16	0.0141

Applying Bonferroni correction for cortical regions: \* p (0.05/8) = 0.006

TABLE 4

Zero-inflated Poisson regression (n=57)

	Positive		Total (N+P+G+DOS)	
Right	Z	P	Z	P
Frontal	0.15	0.878	2.65	<b>0.008</b>
Parietal	-0.15	0.879	0.74	0.459
Temporal	-2.05	<b>0.040</b>	-0.69	0.491
Occipital	-0.77	0.440	-2.74	<b>0.006*</b>
Left				
Frontal	-2.05	<b>0.041</b>	-0.86	0.392
Parietal	-1.17	0.242	2.68	<b>0.007</b>
Temporal	-0.59	0.556	-0.31	0.758
Occipital	-3.09	<b>0.002*</b>	-2.37	<b>0.018</b>

Applying the Bonferroni correction: \* p (0.05/ 8) = 0.006

Vuong Test: p<0.05 for all regressions.