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Pituitary dysmaturation affects psychopathology and neurodevelopment in 22q11.2 Deletion Syndrome

Short Title: Pituitary development and psychopathology in 22q11DS

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Background

22q11.2 Deletion Syndrome (22q11DS) confers strongly increased genetic risk for multiple psychiatric disorders. Similarly to the general population, rates of psychiatric comorbidity suggest that common disease mechanisms are shared across dimensions of psychopathology. Such pleiotropic disease mechanisms remain however currently unknown. We hypothesized that pituitary dysmaturation, indicative of HPA-axis dysregulation, could correlate to reduced tolerance to daily life stressors and reflect pleiotropic risk factor for psychopathology. Moreover HPA-axis dysregulation could affect atypical cortical and hippocampal development previously described in 22q11DS.

Methods

Pituitary volume, hippocampal volume and cortical thickness measures were obtained from T1-weighted MRI images in a large longitudinal cohort of youth with 22q11DS (115 subjects, 260 scans, age-range=5.4-31.6) and healthy controls (151 subjects, 280 scans, age-range=5.1-32.3). We explored effects of pituitary dysmaturation on tolerance to stress, psychopathology and neurodevelopment employing mixed-models linear regression. Associations of pituitary and cortical development were correlated with the expression pattern of glucocorticoid receptor gene NR3C1 obtained from the Allen-Human-Brain-Atlas.

Results

We observed aberrant pituitary developmental trajectories in 22q11DS, with volumetric reductions emerging by young-adulthood ($P=0.0006$). Longitudinal pituitary decline was associated with to reduced tolerance to stress ($P=0.04$), higher overall psychopathology ($P=0.0003$) and increased risk of psychiatric comorbidity ($P=0.02$). Moreover, pituitary decline correlated with blunted growth of the right hippocampus ($P=0.03$) and to increased cortical thinning of mostly temporal and orbitofrontal regions mediated by NR3C1 gene expression.

Conclusion

Atypical pituitary development could reflect progressive extinction of HPAA due to chronic hyper-activation, in agreement with existing biochemical evidence in 22q11DS.

HPAA dysregulation could represent an endophenotype that confers pleiotropic vulnerability to psychopathology and atypical neurodevelopment in 22q11DS.

Keywords: Psychiatric Comorbidity, Hippocampus, Cortical Thickness, HPA-axis, Resilience

Word Count: Abstract: 248, Main Text: 5390, 1 Table, 4 Figures, 1 Supplementary Material

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1. Introduction

It is increasingly recognized that comorbidity among psychiatric disorders is more common than what would be expected by chance, with approximately 45% of patients meeting criteria for multiple diagnoses (Kessler et al., 2005). Such rates of comorbidity could reflect an incomplete understanding of the pathophysiology of psychiatric disorders, with common disease pathways that might be shared across clinically different forms of psychopathology (Caspi et al., 2014; Kapur et al., 2012). This hypothesis has been strongly supported by heritability studies, showing that effects of genetic vulnerability cut across traditional diagnostic boundaries (O'Donovan and Owen, 2016). Still, most mental health research has investigated patients meeting criteria for specific psychiatric diagnoses, such as Major Depressive Disorder (MDD) or Schizophrenia Spectrum Disorders (SSDs), separately from one another. As a consequence our understanding of the neurobiological pathways that make some individuals more vulnerable to any, and indeed multiple forms of psychopathology remains limited (Kapur et al., 2012).

22q11.2 Deletion Syndrome is a genetic disorder associated with strongly increased risk for psychopathology that is furthermore largely pleiotropic (Schneider et al., 2014). Indeed, in addition to a remarkable 30-40% risk of developing schizophrenia, affected individuals present a 30% risk of developing an anxiety disorder, a 30% risk of presenting an attention deficit hyperactivity disorder and a 20% risk developing a mood disorder at adulthood. Compared to other psychiatric cohorts, 22q11DS offers a unique opportunity to follow-up individuals prior to the development of full-blown psychopathology, given that the syndrome is often diagnosed due to somatic malformations (i.e. cardiac anomalies), manifesting at a young age. Longitudinal follow up individuals with 22q11DS can hence allow to investigate neurodevelopmental origins of psychopathology (Jonas et al., 2014). For instance,

22q11DS is characterized by increased cortical thinning during adolescence, that might be related to excessive cortical pruning, and that is accentuated in individuals with psychotic symptoms (Ramanathan et al., 2016; Schaer et al., 2009). Moreover high rates of anxiety may be related to an atypical profile of amygdala activation and connectivity (Zoller et al., 2019). Interestingly and similarly as in general population, different disorders are not mutually exclusive in 22q11DS, but instead co-occur more frequently than expected by chance, with rates of comorbidity that exceed 50% (Niarchou et al., 2017).

Converging lines of evidence in the general population suggest that environmental exposure to stress represents a pleiotropic risk factor for psychopathology that could contribute to the occurrence of psychiatric comorbidity (Caspi et al., 2014). Indeed, childhood trauma has been consistently associated higher levels of psychopathology across multiple dimensions, hence contributing to account for the statistical tendency for all forms of psychopathology to be positively correlated across subjects (Caspi et al., 2014). Accordingly, in a categorical perspective, traumatic life events are more strongly associated with the simultaneous occurrence of multiple conditions than with any individual disorders (van Nierop et al., 2015). Aside from exposure to stress, Zubin and Spring postulated that a core feature of the schizophrenia lies in the increased subjective vulnerability to stress, which might contribute to account for fluctuating clinical manifestations in response to the changing environment (Zubin and Spring, 1977). Recent findings, employing high-resolution experience sampling approaches, have confirmed and expanded on such intuition. Indeed, effects of traumatic life events on the development of psychopathology were mediated by the development of reduced tolerance to minor daily stressors (van Nierop et al., 2018). Moreover deleterious effects of reduced tolerance to stress were not specific to a single disorder and were instead observed across clinically different forms of psychopathology (Conway et al., 2016). These findings point to the importance of understanding mechanisms leading to reduced tolerance to stress, as a candidate multi-dimensional pathophysiological pathway contributing to psychiatric comorbidity.

Literature investigating neurodevelopmental origins of psychopathology in 22q11DS has largely focused on the genetic nature of the disorder, neglecting the potential role of the environment. However, according to the gene-environment interaction hypothesis, a key role of genetic predisposition to psychopathology is of increasing susceptibility to environmental factors (Moffitt et al., 2005). Of note, despite the popularity of this model, demonstrating the existence of such gene-environment interactions has proved exceedingly difficult, due to the complicated and multifactorial nature of psychiatric genetics and to significant potential confounds such as reverse causation (Moffitt et al., 2005). In this perspective the genetically homogenous and ex-novo nature of 22q11DS could make it an ideal model to understand mechanisms of gene-environment interaction. Indeed, in 2011 Beaton and Simon postulated that exposure to environmental stress, in relation to the syndrome complex somatic phenotype, in association with increased vulnerability to stress, may have a significant role in modulating risk for psychopathology in 22q11DS (Beaton and Simon, 2011). Recent findings are beginning to confirm this particularly this later hypothesis, by suggesting that individuals with 22q11DS present heightened susceptibility to environmental stressors. For instance we recently that even reduced exposure to reduced exposure to traumatic life events contributed to

psychopathology in 22q11DS, with effects being mediated by the use of negative emotional coping strategies (Armando et al., 2018). Moreover, individuals with 22q11DS present reduced tolerance to minor daily stressors even compared with non-deleted patients with similar levels of psychopathology (Tang et al., 2017). The neurobiological origins of such reduced tolerance to stress remain however unknown.

Despite some conflicting results, several lines of evidence and recent diathesis-stress models suggest that dysregulation of the Hypothalamus-Pituitary-Adrenal-Axis may participate in the disease pathways linking environmental stress to psychopathology (Pruessner et al., 2017). Indeed, in both humans and animal models alterations in HPAA functionality can be induced by traumatic events (Lupien et al., 2009). Acute exposure to stress can cause a hyper-activation of the axis and resulting hypercortisolemia, whereas chronic stress is thought to lead to a progressive de-sensitization of the HPAA due to negative feedback mechanisms, accounting for the hypocortisolism measured in children exposed to severe deprivation (Gunnar and Donzella, 2002; Lupien et al., 2009). HPAA is moreover crucial in orchestrating responses to stress and functional variability of the HPAA contributes to behavioral differences in response to stressful environments (Franklin et al., 2012; Lupien et al., 2009). Alterations in HPAA function have been reported throughout a breadth of psychiatric disorders and HPAA disturbances can have deleterious effects on brain structures that are thought to be implicated in several forms of psychopathology, such as the hippocampus (Sapolsky, 2000). To date 3 studies have investigated HPAA functionality in 22q11DS. Interestingly while 2 studies in children reported hyper-activation of the HPAA a study in adult patients reported hypo-activation (Jacobson et al., 2016; Sanders et al., 2017; van Duin et al., 2017). These results would suggest a developmental disturbance of HPAA functionality, but no longitudinal study has yet been conducted.

While biochemical characterization of circadian cortisol concentration and cortisol stress reactivity remains the gold-standard for assessing HPAA functionality, pituitary volume (PitVol), measured from structural MRI, is a valuable, albeit indirect approach (Pariante et al., 2004; Pruessner et al., 2017). Indeed, the pituitary gland is highly dynamic and can undergo volumetric changes in response to functional demands with for instance strong increases during pubertal hormonal peaks, due to hypertrophy of gonadotropic portion of the gland, whereas PitVol appears to be largely stable thereafter (Wong et al., 2014). Similarly increased activity of HPAA can lead to hypertrophy of ACTH secreting pituitary cells (Westlund et al., 1985). Such mechanism is thought to account for the correlation between pituitary volume and peripheral ACTH (Cooper et al., 2017) and cortisol concentrations (Axelson et al., 1992; Kaess et al., 2013; Kaess et al., 2018) reported in some studies. It is worth noting however that the association of peripheral markers of HPAA functionality and pituitary volume has not been unequivocally replicated across samples, with age, sex, antipsychotic medication and functionality of the gonadal hormonal axis (i.e puberty) representing the most significant additional confounders (Pruessner et al., 2017). Still, alterations of PitVol have been reported in multiple psychiatric disorders, with evidence being most abundant in the field of psychosis. Recent meta-analyses have concluded that PitVol is increased among subjects who are at risk for developing psychosis, such as first-degree relatives of affected patients and individuals with Clinical High Risk for psychosis (Nordholm et al., 2013; Saunders et al., 2018). Moreover, increases in PitVol are strongest

among individuals who later transition to psychosis (Nordholm et al., 2013; Saunders et al., 2018). For individuals suffering from a first psychotic episode results point to a milder trend-level increase in PitVol (Nordholm et al., 2013), whereas in later chronic stages of schizophrenia PitVol appears to be reduced (Pariante, 2008). This pattern suggests that longitudinal assessment of pituitary volume might provide a better picture of HPA dysfunction. In this perspective 22q11DS could serve as a unique model to investigate the relationship between pituitary dysmaturation and psychopathology.

The first objective of this study was to investigate whether previously reported alterations in PitVol in 22q11DS [17] emerge from atypical longitudinal development. We measured development of PitVol from childhood to adulthood in one of the largest longitudinal cohorts of individuals with 22q11DS worldwide that we compared to healthy controls.

The second objective was to investigate whether pituitary dysmaturation represents a pleiotropic vulnerability to psychopathology that predisposes to psychiatric comorbidity by influencing reduced tolerance to daily stressors. Despite the frequency of psychiatric comorbidity, to the best of our knowledge, no previous study has investigated neurobiological mechanisms that bridge across different forms of psychopathology in 22q11DS and contribute to their co-occurrence.

Finally, given the well-documented effects of HPA dysregulation on neurodevelopment (Lupien et al., 2009), we further investigated whether aberrant pituitary development was associated with atypical neurodevelopmental trajectories of hippocampal volume and cortical thickness previously described in 22q11DS. Of note, several peripheral hormones controlled by the pituitary gland are susceptible of influencing neurodevelopment and vulnerability to psychopathology. To address this concern we measured the cortical expression pattern of receptors for hormones governed by the pituitary gland as estimated in the Allen-Human-Brain-Atlas. We tested whether the association of pituitary and cortical development was specifically mediated by the expression patterns of the glucocorticoid receptor gene NR3C1 (French and Paus, 2015; Hawrylycz et al., 2012).

We hypothesized that HPA-axis dysregulation, captured by atypical pituitary development may represent a core disease mechanism that is associated with atypical brain maturation that bridges across dimensions of psychopathology in 22q11DS.

2. Materials and Methods

2.1. Cohort

This study was conducted in the context of one of the largest prospective longitudinal study on 22q11DS worldwide, described in previous literature (Schaer et al., 2009). Recruitment, which began in 2000 was performed through patient associations and word of mouth and is currently ongoing. 22q11DS was confirmed using quantitative fluorescent polymerase chain reaction. Healthy controls (HCs) were recruited among unaffected siblings of patients (N=51) and from the Geneva State School System (N=100). Inclusion criteria for the present study were the presence of high-quality structural T1-weighted MRI scan leading to the yielding 115 subjects with 22q11DS and 151 HCs. Given the reduced prevalence of 22q11DS, currently estimated at 1/3000-1/6000 live births (McDonald-McGinn et al., 2015), age at recruitment varied across subjects. Once recruited, both patients and HCs were followed up longitudinally every 3.68 ± 1.49 years in HCs and 3.65 ± 1 in 22q11DS. Extent of longitudinal follow-up also varied from 1 to 5 visits leading to a total of 282 visits in healthy controls

and 259 visits in 22q11DS. Detailed description of structure of the longitudinal dataset is included in Table 1. The 22q11DS cohort presented a significantly lower proportion individuals with 2 visits ($p=0.007$) but a higher proportion of individuals with 3 and 4 visits leading to an overall higher mean number of visits per subject (2.27 vs 1.86 , $p=0.004$). As detailed in the statistical analysis section mixed models linear regression was employed to deal with the complex structure of the dataset.

Groups were matched for Sex (Males/Females= $76/75$ in HCs and $57/58$ in 22q11DS, $p=0.98$) and Age (16.94 ± 6.5 in HCs and 16.13 ± 5.42 in 22q11DS, $p=0.11$) and time between visits (3.68 ± 1.49 in HCs and 3.65 ± 1 in 22q11DS, $p=0.81$). See Table 1.

2.2. MRI Acquisition and Analysis

T1-weighted images were acquired with a three-dimensional volumetric pulse sequence with a Philips 1.5T Intera scanner (sequence parameters: TR=35ms, TE=6ms, flip angle=45°, NEX=1, matrix size=256×192, field of view=24cm², slice thickness=1.5mm, 124 slices) and Siemens Trio or Prisma 3T scanners (sequence parameters for 3T scanners: TR=2,500ms, TE=3ms, flip angle=8°, acquisition matrix=256×256, field of view=22cm, slice thickness=1.1mm, and 192 slices). The 3 scanner types were matched across populations ($p=0.22$) and residual effects were accounted for with linear regression. Images were imported in FreeSurfer software package <http://surfer.nmr.mgh.harvard.edu/fswiki>, for a precise and semi-automatic reconstruction of the internal and external cortical surface, employing the standard adult pipeline. Mean cortical thickness (CT) was computed in 68 brain regions using the Desikan-Killiany atlas (Desikan et al., 2006). Measures of supra-tentorial brain volume (STBV) and hippocampal volume (HipVol) were also extracted using FreeSurfer.

The pituitary gland was manually traced with Mango Software (<http://ric.uthscsa.edu/mango>), by a single rater (MC) blind to diagnosis. MC had been previously trained for pituitary tracing with high inter-rater reliability with CS (inter-class correlation coefficient = 0.93 computed on a random subset of 20 cases). The tracing protocol was adopted from previous literature and included the posterior pituitary while excluding the pituitary stalk (Sassi et al., 2001). The anterior and posterior boundaries of the gland were identified on a mid-sagittal view (See figure 1) and the pituitary was then traced on sequential coronal slices. Intra-rater reliability computed on 4 random subsets of 10 cases was high (mean intraclass correlation coefficient = 0.912). We corrected for effects of sex, STBV and scanner type with linear regression.

2.3. Clinical Measures

Tolerance to daily life stressors was measured using the general symptoms item (G4) of Structured Interview for Prodromal Syndromes (SIPS)(Miller et al., 2002) and was available for 93/115 patients and 201/260 visits.

Levels of psychopathology across multiple dimensions and subscales were assessed with the Child Behavioral Checklist (CBCL) in children and with the Adult Behavioral Checklist (ABCL) in adults older than 18 years of age, considering age-normalized T-Scores (L.A., 2003).

We considered several confounding factors that are susceptible of mediating the association between pituitary development and psychopathology including pubertal sexual maturation which was assessed using a self-questionnaire (Tanner maturational scale) in 98/115 patients (Marshall and Tanner, 1969; Morris and Udry, 1980), height and use of antipsychotic medication.

The presence of DSM-IV psychiatric disorders was assessed by means of the Diagnostic Interview for Children and Adolescents-Revised and the psychosis supplement from the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version for individuals below 18 years of age (Kaufman et al., 1997; Reich, 2000). For adult participants we used the Structured Clinical Interview for DSM-IV Axis I Disorders (First MB, 1996). All psychiatric assessments including SIPS interviews were performed by a single experienced rater (SE). The prevalence of psychiatric disorders is reported in Table 1. We reported a disorder if it was diagnosed in at least one of multiple visits. Psychiatric comorbidity was quantified as the number of lifetime psychiatric diagnoses.

2.4 Allen Human Brain Atlas Data on Cortical Expression of Hormonal Receptor Genes

The pituitary gland plays a key role in controlling the concentration of several peripheral hormones, besides cortisol, that are susceptible of influencing neurodevelopment and explain the association between pituitary and cortical development. In order to address this concern we took advantage of gene expression data quantified postmortem in the Allen Human Brain Atlas (AHBA) (Hawrylycz et al., 2012) and mapped to the 68 cortical regions of the Desikan-Killiany atlas, employing the pipeline development by French and Paus (French and Paus, 2015). We hypothesized that the pattern of association between pituitary and cortical maturation would be associated with the cortical expression pattern of the N3RC1 gene, coding for the glucocorticoid receptor as opposed to receptors for hormones controlled by the pituitary gland but unrelated to the HPAA, such as with the androgen, estrogen, progesterone, prolactin and thyroid hormones.

3. Statistical Analysis and Results

3.1. Objective 1: Characterizing longitudinal trajectories of pituitary development in 22q11DS

3.1.1. Statistical Analysis

We employed mixed-models linear regression (MMLR), to characterize and test differences in developmental trajectories of pituitary between HCs and 22q11DS. Indeed, MMLR is ideally suited for longitudinal samples with variable number of visits across subjects and variable age at the first (Mutlu et al., 2013). Our approach, which has been detailed in previous publications from our group (Mutlu et al., 2013), consisted in fitting models of increasing order, from constant to cubic, to each variable being

tested using the *nlmfit* function implemented in MATLAB_R2018a (Mathworks). Subsequently, the Bayesian information criterion (BIC) was employed to select the optimal model order, while avoiding over-fitting. Finally we applied a likelihood ratio test to evaluate differences in trajectories between groups both in terms of shape differences (curves that do not follow a parallel path for both groups) and intercept differences (curves that follow parallel paths in both groups, but at different intercepts).

3.1.2. Results

PitVol underwent a quadratic developmental trajectory in both HCs and 22q11DS peaking in early adulthood. Overall individuals with 22q11DS displayed a significant reduction of PitVol compared to HCs (p-val group effect= 0.0006). Moreover, pituitary developmental was aberrant in 22q11DS (p-val interaction=0.0079) with peak maturation occurring earlier in 22q11DS compared to HCs and PitVol showing sharper volumetric decline in 22q11DS starting from late-adolescence. As a consequence of such late-adolescent volumetric decline, reductions of PitVol became more evident from early adulthood in 22q11DS, when confidence intervals of developmental trajectories of the two populations no longer overlapped. See Figure 1A. As supplementary analysis we examined whether atypical pubertal development contributed to such atypical pituitary trajectory. We observed that Tanner scale was on average significantly reduced in 22q11DS (P-Group=0.015) but had similar longitudinal maturation (P-interaction=0.124) compared to HCs (See Supplementary Figure 10). Even after accounting for different pubertal development trajectories of PitVol remained significantly different in 22q11DS (P-group=0.04, P-interaction=0.04), with corrected PitVol being higher in 22q11DS compared to HCs during childhood and lower beginning from early adulthood. Collectively these results suggest that pubertal development may contribute to lower PitVol in 22q11DS but does not account for atypical age-related longitudinal decline. Moreover supplementary analysis confirmed that such atypical pituitary trajectories were not driven by the use of antipsychotic medication (See Supplementary Figure 9 and Table 1).

3.2. Objective 2: Investigate the association between pituitary dysmaturation, tolerance to daily stressors and psychopathology

3.2.1. Statistical Analysis

We firstly tested the association between pituitary development and psychopathology by clinically dichotomizing patients in subgroups according who at one point did or did not meet a cutoff of 60 in the total psychopathology, internalizing, externalizing and thought disorder scales. We then separately tested for differences in trajectories of pituitary development between such 4 sub-groups. Moreover we were interested in modeling separately effects of average PitVol from those of purely longitudinal pituitary increase or decrease and to test for the existence of potential pleiotropic effects. Hence, we fit a mean curve only to patients with 22q11DS using the MMLR approach detailed above. Patients with 22q11DS were then separated according to if either mean PitVol over multiple time-

points or rate of PitVol change observed between first and last visit was higher or lower than what expected for the normative curve at equivalent ages. (see figure 1 Analysis 2A and 2B respectively). This yielded 2 subgroups of patients with either High/Low PitVol or Growing/Declining PitVol respectively, described demographically in Table 1. Such groups were firstly compared in terms of non-HPAA related confounds such as height, pubertal development and use of psychotropic medication. Subsequently groups were compared in terms of trajectories of tolerance to daily stressors and of all psychopathology subscales using MMLR. Finally, groups were compared in terms rates of psychiatric comorbidity.

3.2.2. Results

Dividing patients according to either total psychopathology, externalizing psychopathology or thought disorder scales did not reveal differences in pituitary development (P-val interaction= 0.10, 0.31 and 0.43 respectively P-val group effect=0.16, 0.49 and 0.55 respectively). See Supplementary Figure 1. However, patients with clinically significant (>60) internalizing psychopathology presented aberrant pituitary development (P-val interaction= 0.042, P-val group=0.08) with higher PitVol up to 15 years of age followed by increased volumetric reductions over time leading to lower PitVol by early adulthood. See Figure 1 Analysis 1B.

To disentangle the effects of PitVol from those of longitudinal pituitary decline, we compared trajectories of psychopathology between patients divided according to either mean PitVol or to purely longitudinal pituitary rate of change.

As expected, separating patients according to mean pituitary volume yielded two subgroups characterized by similar development of pituitary volume (P-val interaction=0.09) but massively different mean pituitary volume (P-val group<0.00001), defined as High/Low PitVol subgroups. See Figure 1 Analysis 2A. Compared to the Low PitVol group the High PitVol group was significantly older (19.93 ± 5.44 vs 15.1 ± 5.15 , $p=0.006$) and had more advanced pubertal development even when accounting for age (P-val group=0.0069, P-val interaction=0.38, See Figure 1 Analysis 2D), whereas height and other demographic features were comparable (see table 1). The high/low PitVol subgroups did not differ significantly in terms of tolerance to daily life stressors, any measured psychopathology scale or in number of lifetime psychiatric diagnoses ($P > 0.12$). See Figure 1 Analysis 2C.

Separating patients according purely to longitudinal pituitary development identified a subgroup of individuals that presented slightly higher pituitary volume during childhood, when confidence intervals of developmental trajectories were still overlapping, but then underwent strong longitudinal decline in pituitary volume leading to reductions of PitVol by late-adolescence (P-group<0.0001, P-interaction<0.0001). See Figure 1 Analysis 2B. Such growing/declining PitVol subgroups did not differ in terms of height, tanner scale development or use of psychotropic medication. However the subgroup of patients presenting with longitudinally declining PitVol presented higher reactivity to daily stressors (P-group=0.043, P-interaction=0.111, see Figure 1 Analysis 2F) and more severe psychopathology across multiple dimensions compared to patients with increasing PitVol (see Figure 1 Analysis 2H), including higher total psychopathology (P-group =0.0003), internalizing symptoms (P-group=0.0004),

externalizing symptoms (P-group=0.019), anxious/depressed scores (P-group=0.0009), withdrawn/depressed scores (P-group=0.016) and attention problems (P-group=0.001) and more severe social problems particularly during adolescence (P-group=0.0003, P-interaction=0.0009). The between-group difference was not statistically significant for aggressive behavior (P-group=0.17), somatic complaints (P-group=0.064), thought problems (P-group=0.092) or pubertal development (P-group=0.89, P-interaction=0.67). Finally, patients with a declining PitVol presented a higher risk of psychiatric comorbidity, indicated by a higher number of lifetime psychiatric diagnoses (1.73+/-1.3 vs 1.09 +/-1, p=0.04), and an increased likelihood of presenting more than 2 lifetime psychiatric diagnoses (13/45 vs 1/22; chi-square=5.29 p=0.021). See Figure 1 Analysis 2G. Results are resumed in Supplementary Table 1. All reported associations between atypical pituitary development and psychopathology subscales remained significant after accounting for the use of antipsychotic medication (See supplementary figure 9) and survived correction for multiple comparisons with False Discovery Rate (See supplementary table 1).

3.3. Objective 3: Investigate the association between pituitary dysmaturation, and atypical neurodevelopment.

3.3.1. Statistical Analysis

We characterized patterns of atypical neurodevelopment in 22q11DS compared to healthy controls by comparing trajectories of Cortical Thickness (CT) and hippocampal volume with the same MMLR approach employed for pituitary volume, accounting for the effects of scanner, sex and STBV. We corrected for multiple comparisons using False-Discovery-Rate at $P < 0.05$.

To explore the association between Pituitary maturation and neurodevelopment we firstly employed MMLR to correlate PitVol with HipVol and CT, additionally accounting for the effect of age and age². For subjects with multiple time-points (83 out of 151 HCs and 67 out of 115 22q11DS) we also correlated longitudinal pituitary change with the change of CT and HipVol, additionally correcting for changes in all covariates. Results were corrected for multiple comparisons using False-Discovery-Rate at $P < 0.05$. Moreover to have a better grasp of the association between atypical pituitary maturation and neurodevelopment we compared developmental trajectories of cortical and hippocampal development between growing/declining PitVol subgroups that were compared to each other and to healthy controls.

3.3.2. Results

HipVol was bilaterally strongly reduced and underwent an atypical blunted growth (P-group Left<0.0001. P-group Right<0.0001, P-interaction Left= 0.0013, P-interaction Right = 0.0003). Left HipVol was not significantly associated with PitVol (B=0.06, p=0.16) or pituitary development (B=0.08, p=0.21). However right HipVol was positively correlated with PitVol (B=0.168 , p=0.0008), and stronger effects observed for correlations between pituitary and hippocampal rate of change

($B=0.21$, $p=0.0004$) indicating that pituitary decline was associated with reduced right hippocampal growth. See Figure 2. In a subsequent post-hoc analysis we compared trajectories of hippocampal maturation between growing/declining PitVol subgroups and HCs. This analysis revealed that atypical right hippocampal development observed in 22q11DS was driven by patients with pituitary decline, who presented blunted hippocampal growth both compared to HCs (P-group Right <0.0001 , P-interaction Right <0.0001) and to the growing pituitary volume sub-group (P-group Right $=0.06$, P-interaction Right $=0.03$). See Figure 2D2 As supplementary analysis we compared developmental trajectories of amygdala volume across growing/declining pituitary volume subgroups. Trajectories were similar to those described for hippocampal volume but differences between groups were non statistically significant (P-group Left $=0.139$, P-interaction Left $=0.064$, P-group Right $=0.65$, P-interaction Right $=0.45$) (See Supplementary Figure 12).

CT was significantly increased in 54/68 cortical regions in individuals with 22q11DS compared to HCs, whereas significant reductions were observed in the right superior temporal and left parahippocampal gyrus. See supplementary figure 3. Such widespread pattern of altered cortical morphology is consistent with results of a recent large multi-center Enigma consortium study conducted on 22q11DS (Sun et al., 2018). Moreover, patients with 22q11DS presented a widespread bilateral pattern of increased age-related cortical thinning involving the middle, inferior and medial temporal cortices, fusiform gyrus, orbitofrontal cortex and precentral gyrus. See Figure 3A.

After controlling for the effect of age, PitVol was negatively correlated with CT of the bilateral, middle frontal gyrus and left superior frontal gyrus, whereas positive correlations were observed in the right entorhinal cortex and inferior temporal gyrus. See Supplementary Figure 5. Correlations were more widespread for CT and PitVol development, with positive correlations observed in the bilateral inferior temporal gyrus, fusiform gyrus, entorhinal cortex and the right parahippocampal cortex, temporal pole and orbitofrontal cortex. See Figure 3B.

There was a significant spatial correlation between atypical cortical maturation pattern observed in 22q11DS, and the regression coefficient quantifying of CT/PitVol development correlations ($R=-380$, $p=0.001$). Indeed regions undergoing increased cortical thinning in 22q11DS had more positive correlations with pituitary development than expected by chance ($P<0.0001$), indicating that pituitary decline was associated with increased cortical thinning in the same regions undergoing atypical neurodevelopment in 22q11DS.

To better grasp such interactions, in a subsequent post-hoc analysis we compared trajectories of cortical maturation between growing/declining PitVol subgroups and HCs. This analysis revealed that atypical cortical development observed in 22q11DS was driven by the subgroup of patients with declining pituitary volume, who presented increased cortical thinning in temporal and orbitofrontal regions compared to healthy control (See Figure 3A3 and Supplementary Figure 8). Patients with growing pituitary volume showed intermediate trajectories of cortical maturation that were not significantly different, in terms of age-interaction effect, to either HCs or the Declining PitVol subgroup (See Supplementary Figure 8).

3.4. Objective 4: Test mediating role of hormonal receptors in pituitary/CT correlation pattern.

3.4.1. Statistical Analysis

We tested 3-way associations between: 1) the pattern of atypical development observed in 22q11DS quantified as the statistical significance of the age-interaction effect 2) the pattern of pituitary/cortical thickness association estimated from the B values of the MMLR and 3) hormonal receptor gene expression derived from the Allen-Human Brain Atlas. Significance of spatial correlations was firstly determined through Pearson correlations across 68 regions. Moreover 3-way associations of brain patterns were tested non-parametrically with permutation testing. We computed the mean gene-expression across regions with either a significant interaction effect or with significant positive or negative PV/CT development correlations. Under the null hypothesis mean expression values would be close to zero on average, with as many selected regions having high expression as those having low expression. To test statistical significant we hence computed a null-distribution of such mean expression value by averaging gene-expression across an equal number of randomly selected regions for 1000 permutations. The P-Value of association between spatial maps was computed as the probability of observing a mean expression value higher than the empirical one by chance.

3.4.2. Results

Cortical expression pattern of the glucocorticoid receptor gene NR3C1 was significantly associated with both patterns of atypical neurodevelopment in 22q11DS ($R=0.267$, $p=0.02$) and Pituitary/CT development correlation ($R=-0.259$, $p=0.03$). Indeed both regions with increased cortical thinning and positive Pituitary/CT correlations had lower NR3C1 expression than expected by change ($P=0.004$ and $P<0.0001$ respectively). Regions with negative CT/PitVol correlations were not significantly enriched in NR3C1 expression ($P=0.47$). Moreover, in accordance with cortisol's affinity with the mineralcorticoid receptor, we also observed significant associations with the mineralcorticoid receptor gene NR3C2, for both accelerated cortical thinning ($P=0.005$) and positive CT/PitVol correlations ($P=0.0029$) (See Supplementary Figure 11).

Interestingly such spatial association was specific for to receptor genes with affinity to cortisol as no significant associations were found for progesteron, estrogen, androgen, prolactin and thyroid hormone receptor expression patterns for either the pattern of atypical neurodevelopment observed in 22q11DS or with pituitary/CT development correlation pattern (see supplementary figures 7). These results could implicate cortisol and the HPAA axis in the observed association between pituitary and cortical development in regions that undergo atypical increased cortical thinning in 22q11DS.

4. Discussion

We observed aberrant development of pituitary volume (PitVol) in 22q11DS that was associated with reduced tolerance to daily stressors, pleiotropic vulnerability to psychopathology and hence increased risk of psychiatric comorbidity. Pituitary development was also associated with atypical hippocampal and cortical maturation in 22q11DS. These results suggest that dysregulation of the Hypothalamus-Pituitary-Adrenal-Axis (HPAA) could represent a disease mechanism that bridges across dimensions of psychopathology and contributes to psychiatric comorbidity and atypical neurodevelopment in 22q11DS.

4.1. Aberrant Development of Pituitary Volume in 22q11DS

We previously reported reductions of PitVol after the age of 18 in 22q11DS in a cross-sectional sample (Armando et al., 2018). The present longitudinal results indicate that PitVol reductions in 22q11DS emerge from aberrant pituitary development characterized by a premature peak of maturation followed by an increased volumetric decline. Previous studies have associated pituitary development with puberty (Wong et al., 2014). Tanner pubertal stage, available in a sub-sample of patients, was related to higher PitVol in 22q11DS. However, no association was observed for longitudinal pituitary change, suggesting that pubertal development did not contribute to altered pituitary trajectories.

Aberrant pituitary development observed in 22q11DS could be related to a negative feedback mechanism associated with prolonged HPAA hyper-activation. In animal models, acute stress can lead to hypertrophy of ACTH-secreting pituitary cells (Westlund et al., 1985). This mechanism is thought to account for increased PitVol observed in early stages of psychosis (Pariante, 2008). However, chronic stress in animals can lead to reduced pituitary ACTH secretion and hypocortisolism in response to a novel stressor (Andrew G. Goliszek, 1996; Houshyar et al., 2001). Such hypocortisolism has been attributed to an enhanced negative feedback on pituitary ACTH secretion exerted by chronic elevated cortisol (Houshyar et al., 2001). HPAA exhaustion in response to chronic stress has been measured in chronically deprived infants presenting hypocortisolism (Gunnar and Donzella, 2002) and could account for reductions of PitVol observed in chronic stages of psychosis (Pariante, 2008).

While knowledge about the dynamics of cortisol secretion in 22q11DS remains preliminary, existing data is in agreement with the hypothesis of progressive HPAA exhaustion due to chronic hyper-activation. Specifically, two studies conducted in children with 22q11DS reported elevated blood cortisol (Jacobson et al., 2016; Sanders et al., 2017) while a study in adults reported strongly reduced cortisol (van Duin et al., 2017). Our results are the first to suggest atypical HPAA maturation in single longitudinal sample of individuals with 22q11DS. The observation that PitVol reductions emerge during late adolescence might be related to the ongoing maturation of the negative feedback exerted by cortisol on the ACTH secretion, reported during adolescence in animal models (Andrew G. Goliszek, 1996).

4.2. Association between Pituitary Development and Psychopathology

Our results suggest that aberrant pituitary development with increased in PitVol during childhood followed by subsequent reductions of PitVol is associated with higher internalizing symptoms in 22q11DS. As previously discussed, this trajectory is compatible with evidence in 22q11DS indicating early hypercortisolism during childhood followed by later HPAA exhaustion in adulthood (Jacobson et al., 2016; Sanders et al., 2017; van Duin et al., 2017). Given these findings, we hypothesized that the dynamic process of HPAA exhaustion might be central to psychopathology. Indeed, when dividing patients according to PitVol, we did not observe differences in psychopathology but only in pubertal stage. However, when dividing patients according to purely longitudinal pituitary change, patients displaying relative decline of PitVol, suggestive of HPAA exhaustion, presented higher reactivity to daily life stressors and higher psychopathology across multiple dimensions. These findings suggest that longitudinal follow up is crucial to capture the impact of HPAA dysfunction on psychopathology. The bi-directional importance of considering longitudinal associations between PitVol and psychopathology has been also highlighted in previous work, showing that during early adolescence higher PitVol is not associated with psychopathology at baseline but rather with an increase in psychopathology over a 3-year longitudinal follow-up period (Zipursky et al., 2011).

The effects of pituitary decline were observed across multiple dimensions pointing to a pleiotropic effect on psychopathology. It was proposed that common disease pathways, shared across clinically different forms of psychopathology, could account for the occurrence of psychiatric comorbidity (Caspi et al., 2014). Our results confirm this hypothesis given that pituitary decline was associated with an increased risk of presenting multiple lifetime psychiatric diagnoses.

While observable across different forms of psychopathology, effects of pituitary decline were strongest for internalizing symptoms such as anxiety/depression and social problems particularly during adolescence. These associations are similar to the effects of stress exposure described in the general population, with strongest effects on the general psychopathology factor and internalizing symptoms (Caspi et al., 2014). Moreover, recent evidence suggests that effects of environmental exposure to trauma on psychopathology may be mediated by the subsequent development of reduced tolerance to daily stressors (Conway et al., 2016). Still a major open question is why this deleterious cascade of events occurs only in a proportion of individuals exposed to stress. According to the gene-environment interaction model the genetic background of an individual participates in moderating vulnerability to environmental factors. Still, both specific genetic factors and underlying downstream mechanism have remained unclear.

The HPAA is crucial in mediating behavioral differences in response to stressful environments (Franklin et al., 2012). Interestingly, both classical heritability studies and modern GWAS approaches have demonstrated that variability in HPAA functionality is partially genetically determined with the strongest effects reported for the Cortisol Awakening Response and Hair Cortisol Measurements (Bolton et al., 2014; Rietschel et al., 2017; Van Hulle et al., 2012). Such genetically mediated variability may moreover have functional consequences. For instance, difference in HPAA functionality being reported across mouse genetic strains with different stress reactivity (Zaharia et al., 1996). In humans HPAA dysfunction was measured among unaffected first degree relatives of depressed patients (Holsboer et al., 1995). Moreover a GWAS linked common genetic variation to both

depressive symptoms and HPAA dysregulation (Velders et al., 2011). These findings suggest that HPAA dysregulation could represent an endophenotype that mediates the effect of genetic predisposition on psychopathology, through reduced tolerance to stress. Our results support this gene-environment interaction model, suggesting that 22q11DS is genetically associated with dysfunctional HPAA activity that contributes reduced tolerance to daily life stressors and vulnerability to psychiatric comorbidity. In accordance with this hypothesis we recently observed reduced exposure but heightened susceptibility to stressful life events in 22q11DS (Armando et al., 2018). Interestingly, our results suggest that, atypical HPAA maturation may not affect all individuals with 22q11DS uniformly, with patients with Growing-PitVol being more resilient to daily stress and relatively protected from risk of psychopathology. Future research should investigate the sources of such variability, which might for instance originate from genetic variability outside the 22q11 deletion site. In this perspective, considering HPAA dysregulation as an endophenotype could in help dissect such Gene-Gene interaction mechanisms. Moreover, future research should investigate whether environmental factors, such early life stress contribute to such variability. This is especially important considering that 22q11DS is associated with high rates of early-life hospitalization due to a complex somatic phenotype.

4.3. Association between Aberrant Brain Development and Aberrant Pituitary Development

We observed atypical neurodevelopmental trajectories in 22q11DS, with increased trajectories of cortical thinning particularly in temporal and orbitofrontal cortices and bilaterally blunted hippocampal growth. Both atypical cortical and hippocampal development have been consistently described in previous literature on 22q11DS (Ramanathan et al., 2016; Schaer et al., 2009; Scott et al., 2016) and could arise from several non-mutually exclusive factors. Here we observed significant associations between atypical brain maturation and pituitary development. Indeed both blunted right hippocampal growth and increased cortical thinning were driven by patients presenting longitudinal pituitary decline, pointing to a potentially common underlying process.

A possible interpretation for these associations is that chronic hyper-activation of the HPAA during childhood contributes to both pituitary decline and atypical neurodevelopment in 22q11DS. In support of this hypothesis, hyper-activation of the HPAA has been measured in two samples of children with 22q11DS (Jacobson et al., 2016; Sanders et al., 2017). Moreover, converging evidence both in humans and animals have demonstrated that prolonged hypercortisolism induced by chronic stress can affect brain, and particularly hippocampal, development (Lupien et al., 2009). Indeed, chronic stress can affect dendritic arborization of CA3 (Sousa et al., 2000) and CA1 (Donohue et al., 2006) hippocampal pyramidal neurons. Such mechanism likely contributes to hippocampal volumetric loss observed in patients exposed to chronic elevated cortisol (Lupien et al., 1998) or presenting with stress-related psychopathology (Sapolsky, 2000). Moreover, in animal models chronic stress during puberty was shown to affect hippocampal development leading to blunted hippocampal growth and altered microstructure (Isgor et al., 2004). In this sense our results suggest that hypercortisolism, previously reported during childhood in 22q11DS, could contribute to both pituitary volume decline and to

blunted trajectories of right hippocampal growth. Aside from the hippocampus, the cerebral cortex is also susceptible to the effects of chronic stress (Lupien et al., 2009). For instance, chronic stress can induce dendritic shortening and spine loss in pyramidal neurons of layer II/III the medial prefrontal cortex in rats (Radley et al., 2004). Moreover, a recent study in maltreated children observed a direct correlation between hypercortisolism and reduced cortical thickness of inferior-temporal and orbitofrontal cortices (Liu et al., 2015).

To support the role of HPAA dysregulation in contributing to atypical neurodevelopment in 22q11DS, we quantified the overlap with the cortical expression patterns of receptors for pituitary-regulated hormones. The only expression pattern to be significantly associated by both atypical cortical development and with Pituitary/CT development correlation was that of the glucocorticoid receptor gene NR3C1. Interestingly, and somewhat counter-intuitively, this overlap was driven by a significant under-expression of NR3C1 in regions that were both positively correlated with pituitary development and showed increased thinning in 22q11DS. A possible interpretation for this result is related to the dynamic and adaptive epigenetic control of NR3C1 expression in the brain. Indeed regions that are particularly sensitive to the effects of cortisol in mice, such as the hippocampus, respond to both chronic stress and exogenous corticosterone by down-regulating NR3C1 expression (Weaver et al., 2004). In humans similar hippocampal down-regulation of NR3C1 was reported in two studies of suicide victims (Labonte et al., 2012; McGowan et al., 2009). The lack of epigenetic data in our sample renders our interpretations necessarily speculative. However, our results could suggest that temporal and orbitofrontal cortices present increased sensitivity to hypercortisolism, and undergo both increased cortical thinning in 22q11DS and adaptive down-regulation of NR3C1 gene expression. It should nonetheless be noted exposure to stress was not measured Allen-Human-Brain Atlas donors, with no evidence to support hypercortisolism in this sample.

5. Conclusions and Limitations

Our results are the first to demonstrate atypical longitudinal pituitary development in individuals at high genetic risk for psychopathology. They suggest that HPAA axis dysregulation could represent an endophenotype that mediates the multidimensional effects of genetic predisposition to psychopathology, conferring liability to psychiatric comorbidity and atypical neurodevelopment.

The main limitation of the present study is the lack of data on cortisol levels in our sample. While our findings are in accordance with existing cortisol measurements in 22q11DS (Jacobson et al., 2016; Sanders et al., 2017; van Duin et al., 2017), they also suggest that longitudinal follow-up may be essential to capture the effects of HPAA dysregulation on psychopathology and neurodevelopment. Gold-standard longitudinal characterization of HPA-axis functionality in 22q11DS should be a focus of future research, which might help identify pleiotropic biomarkers of vulnerability to psychopathology. A second limitation relates to the complexity of our sample with age at recruitment and number of longitudinal assessments varying from 1 to 5 across subjects. While dedicated statistical tools were employed to deal with such complexities our results should be replicated in a more homogenous and ideally larger sample. A final limitation is that epigenetic characterization was unavailable in our

sample, rendering our interpretations of the associations with NR3C1 necessarily speculative. Future research should characterize epigenetic status of NR3C1 in peripheral tissue, testing for associations with neurodevelopmental trajectories in 22q11DS.

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Disclosures

The authors report no conflict of interest.

Figure Legends

Figure 1

Analysis 1: A: Developmental trajectories of pituitary volume compared between healthy controls and 22q11DS. **B:** Trajectories of pituitary volume compared between individuals with 22q11DS divided according to a cut-off of 60 in the Internalizing Symptoms Subscale **Analysis 2: A:** Developmental trajectories of pituitary volume compared between patients divided according to mean pituitary volume (High/Low Pituitary Volume Subgroups). **B:** Developmental trajectories of pituitary volume compared between patients divided according to longitudinal pituitary development. (Growing/Declining Pituitary Volume Subgroups). **C1-2:** Number of lifetime psychiatric diagnoses and levels of total psychopathology compared across High/Low Pituitary Volume Subgroups. **D1-2:** Pubertal development and height compared across High/Low Pituitary Volume Subgroups. **E1-2:** Pubertal development and height compared across Growing Declining Pituitary Volume Subgroups. **F:** Reactivity to daily stressors compared across growing/declining pituitary volume subgroups. **G1-2:** Prevalence of psychiatric comorbidity compared across growing/declining pituitary volume subgroups. **H:** Developmental trajectories of different psychopathology subscales compared across growing/declining pituitary volume subgroups. **H1:** Total Psychopathology Subscale, **H2:** Externalizing Symptoms Subscale, **H3:** Thought Disorder Subscale, **H4:** Internalizing Symptoms Subscale, **H5:** Aggressiveness Subscale, **H6:** Attention Problems Subscale, **H7:** Anxiety/Depression Subscale, **H8:** Social Problems Subscale.

Figure 2

A: Developmental trajectories of left hippocampal volume: **A1** and right hippocampal volume: **A2** in 22q11DS compared to healthy controls.
B: Association of pituitary volume with left hippocampal volume: **B1** and right hippocampal volume: **B2**
C: Association of pituitary volume development with left hippocampal volume development: **C1** and right hippocampal volume development: **C2**
D: Effects of pituitary decline of hippocampal development for left hippocampal volume: **D1**, and right hippocampal volume: **D2**

Figure 3

A1: Regions undergoing aberrant developmental trajectories in 22q11DS as indicated by a significant interaction effect at $p < 0.05$ after FDR correction for multiple comparisons.
A2: Developmental trajectories of cortical thickness averaged across regions with significant interaction effect at $p < 0.05$ after FDR correction for multiple comparisons. Trajectories for individual regions are displayed in Supplementary Figure 2.

A3: Developmental trajectories of cortical thickness averaged across regions with significant interaction effect in 22q11DS. Subjects with 22q11DS are subdivided according to pituitary development, in a growing pituitary volume and declining pituitary volume subgroup. Trajectories for individual regions compared between Declining PitVol and HCs are displayed in Supplementary Figure 6. No regions showed significant interaction effect between Growing PitVol and HCs.

B1: Pattern of cortical regions with significant correlations of cortical thickness with pituitary development at $p < 0.05$ after FDR correction for multiple comparisons. Shades of red indicate significant negative correlations and shades of blue indicate significant positive correlations. **B2-3:** Correlation of pituitary development and cortical thickness development averaged across regions with significant positive (**B1**) and negative (**B2**) correlations at $P < 0.05$ after FDR correction for multiple comparisons. Correlations for individual regions are displayed in Supplementary Figure 4.

Figure 4

A1: Association of P-value of age by diagnosis interaction effect, quantifying aberrant neurodevelopment in 22q11DS, and pituitary volume/cortical thickness development regression coefficient across 68 brain regions.

A2: Association of aberrant neurodevelopment in 22q11DS and pituitary volume/cortical thickness development regression coefficient evaluated through permutation testing. Dashed line indicates mean regression coefficient across regions undergoing aberrant neurodevelopment in 22q11DS (p of interaction effect < 0.05 after FDR correction). Blue circles indicate mean regression coefficients computed across an equal number of randomly selected regions for each of 10000 permutations.

B1: Association of P-value of age by diagnosis interaction effect, quantifying aberrant neurodevelopment in 22q11DS, and cortical expression pattern of NR3C1 gene across 68 brain regions.

B2: Association of aberrant neurodevelopment in 22q11DS and cortical expression pattern of NR3C1 gene evaluated through permutation testing. Dashed line indicates mean NR3C1 expression values across regions undergoing aberrant neurodevelopment in 22q11DS (p of interaction effect < 0.05 after FDR correction). Blue circles indicate mean expression values computed across an equal number of randomly selected regions for each of 10000 permutations.

C1: Association of pituitary volume/cortical thickness development regression coefficient and cortical expression pattern of NR3C1 gene across 68 brain regions.

C2: Association of pituitary volume/cortical thickness development correlation pattern and cortical expression pattern of NR3C1 gene evaluated through permutation testing. Dashed line indicates mean NR3C1 expression values across regions with significant positive pituitary volume cortical thickness development correlations at $p < 0.05$ FDR corrected. Blue circles indicate mean expression values computed across an equal number of randomly selected regions for each of 10000 permutations.

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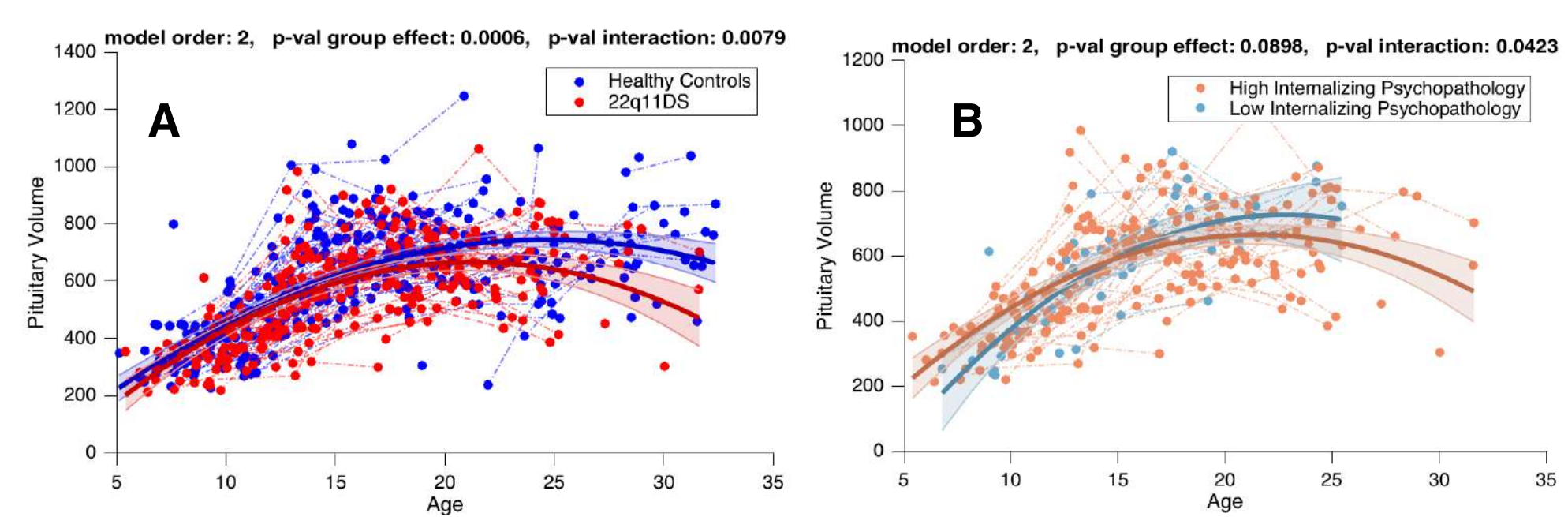
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Tracing Protocol

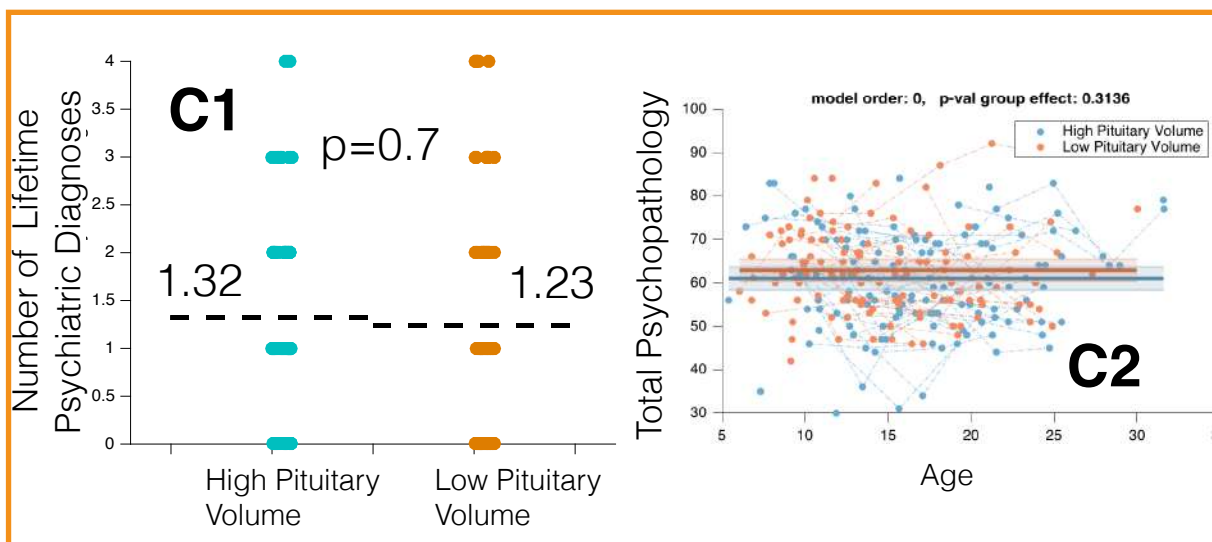


Pituitary Stalk Posterior Portion of Pituitary Gland

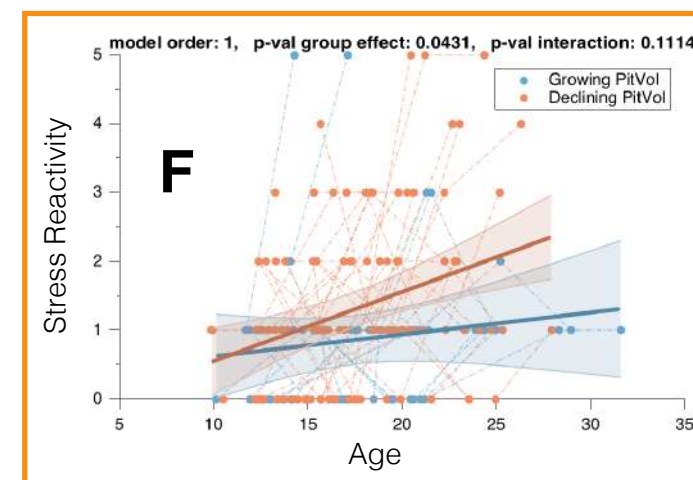
Analysis 1



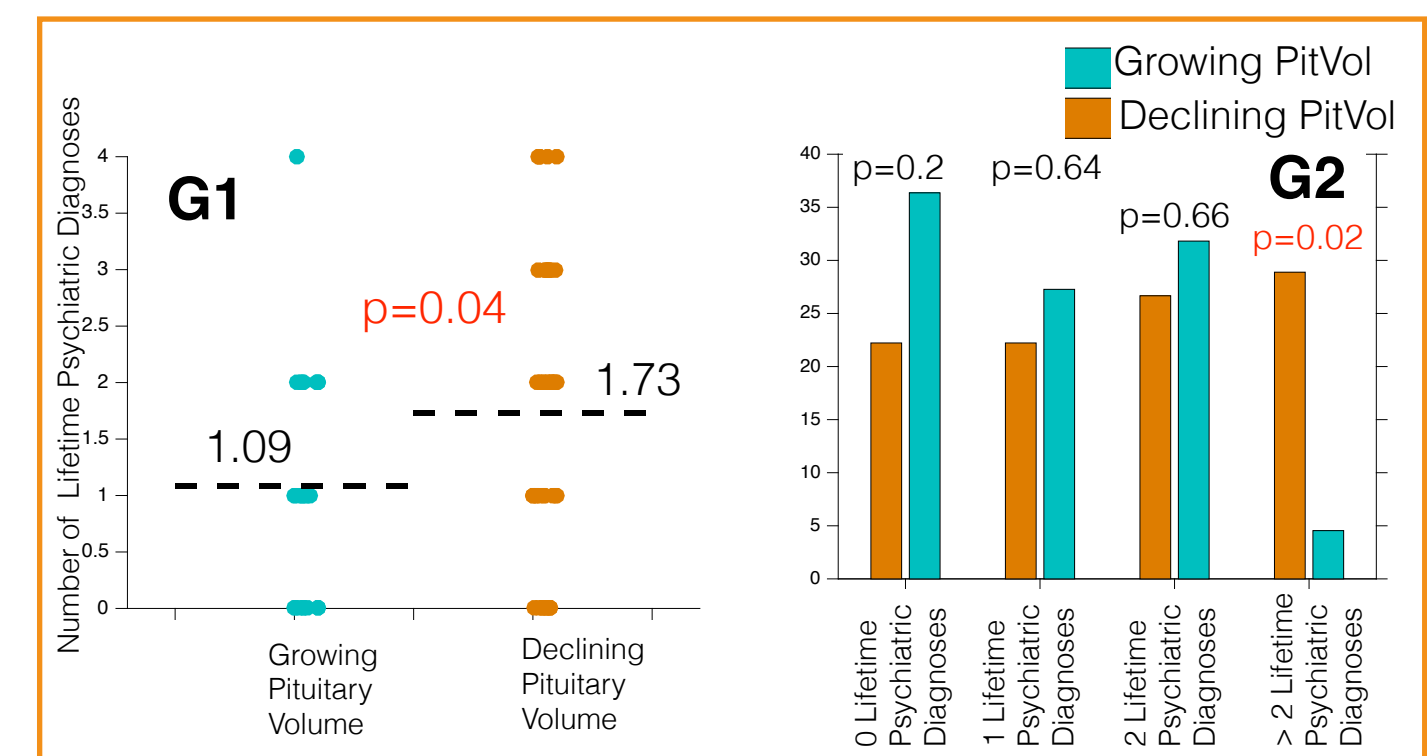
Analysis 2



Effects on Psychopathology

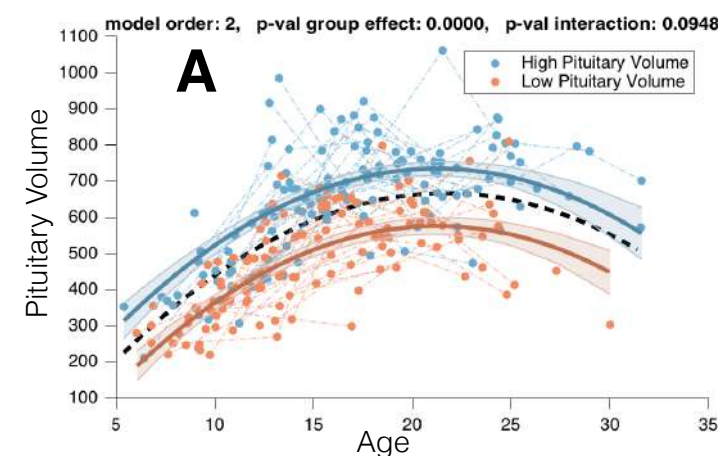


Effects on Reactivity to Stress

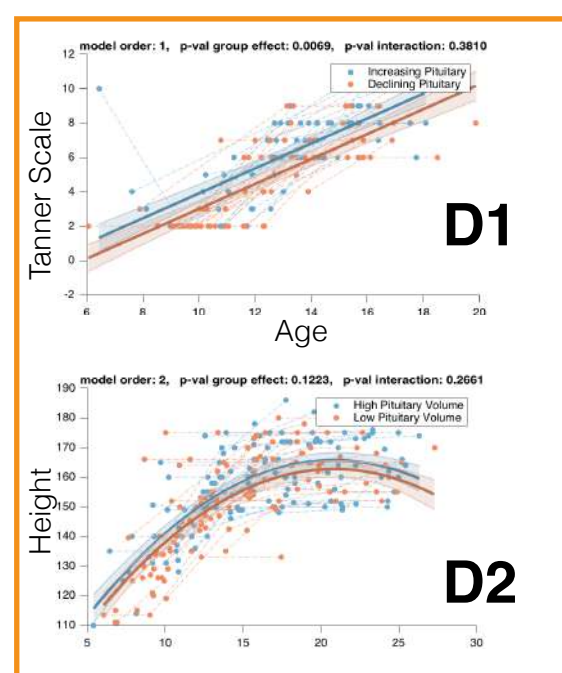


Effects on Liability to Psychiatric Comorbidity

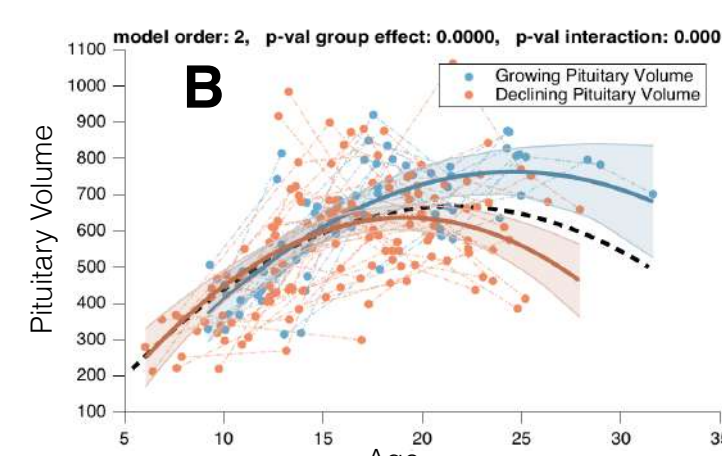
Effects of Mean Pituitary Volume



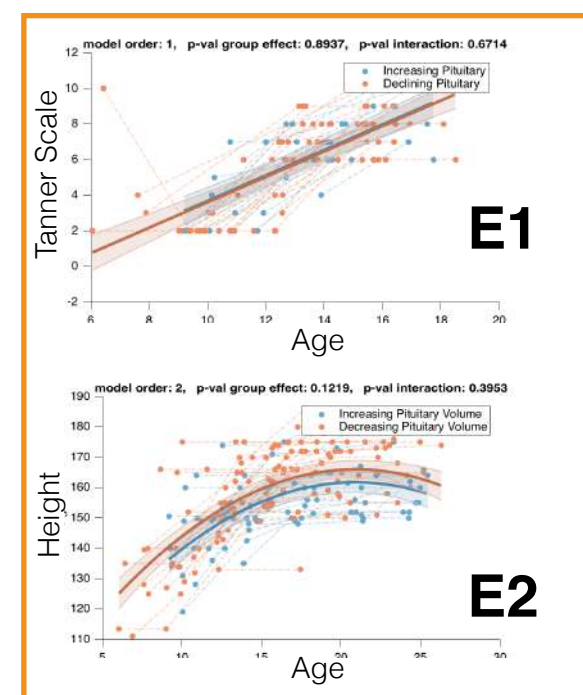
Effects on non-HPAA confounds



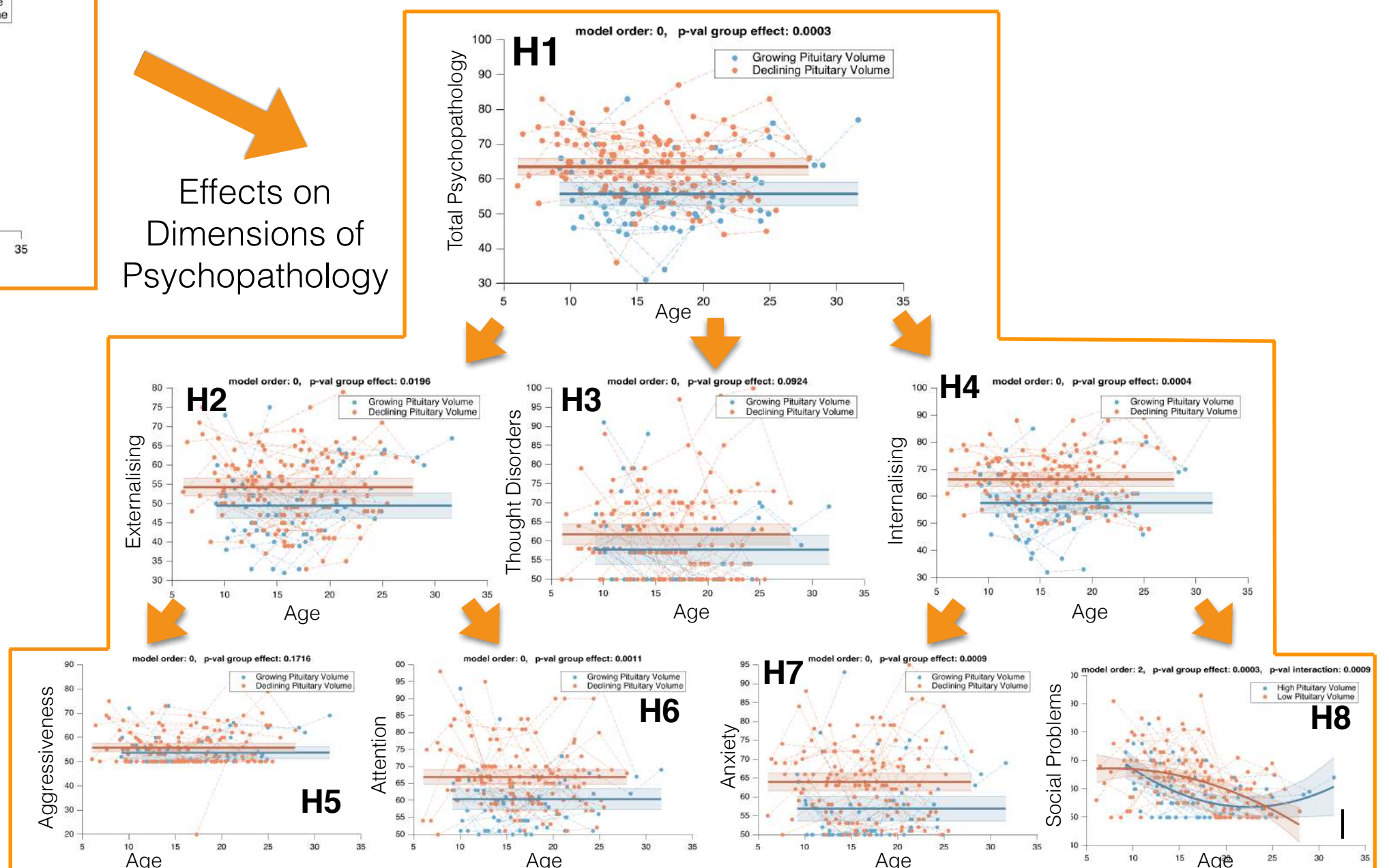
Effects of Longitudinal Pituitary Decline



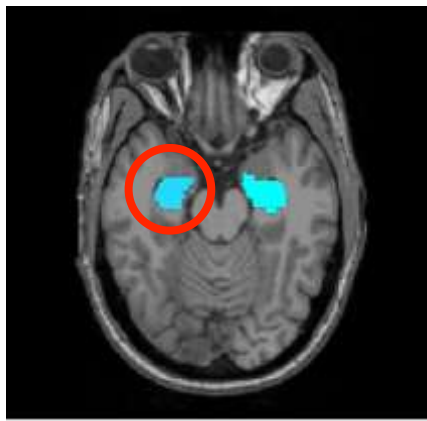
Effects on non-HPAA confounds



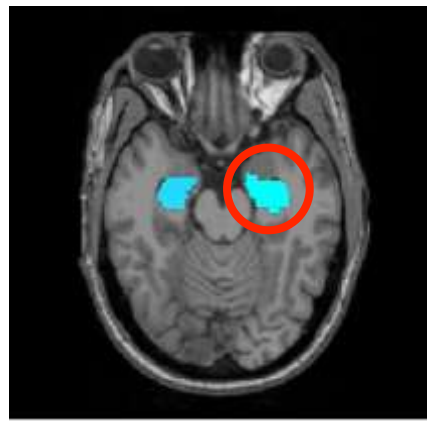
Effects on Dimensions of Psychopathology



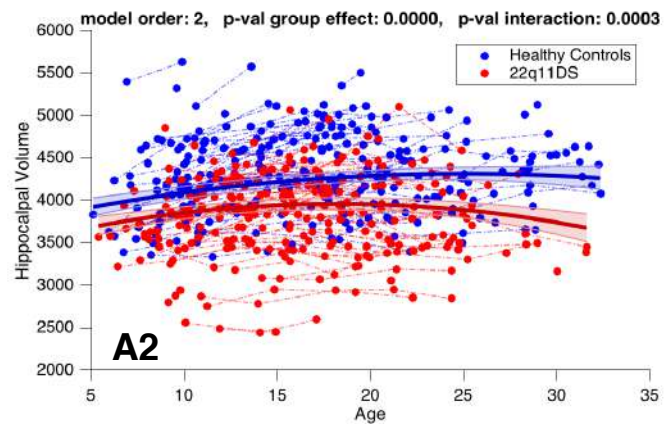
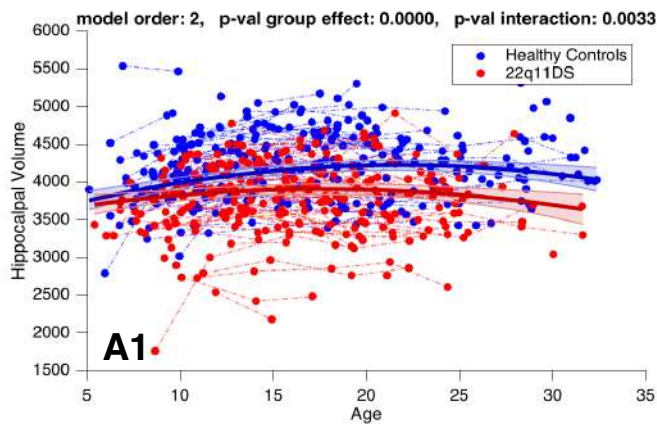
Left Hippocampus



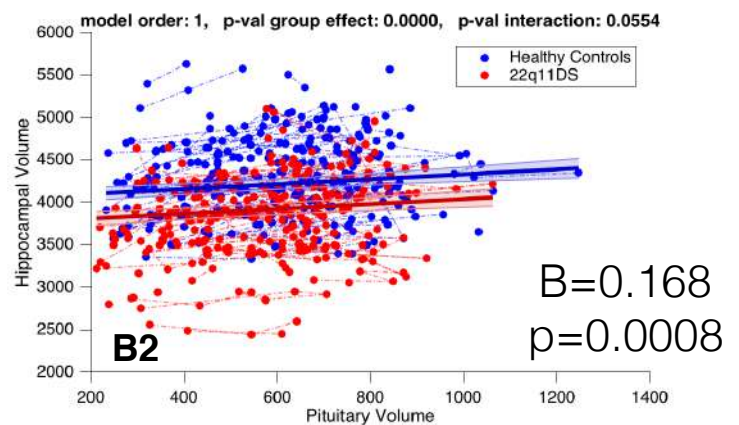
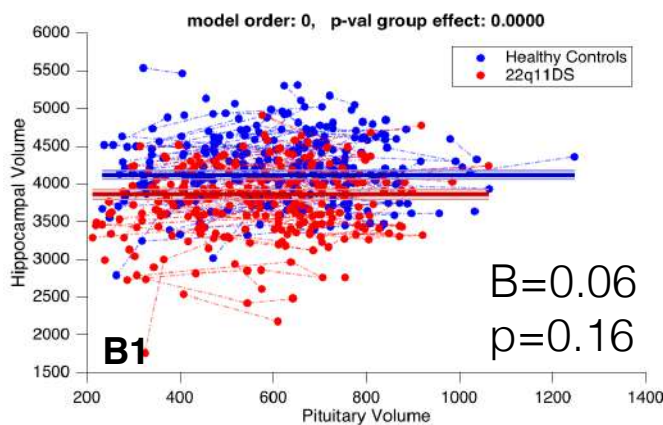
Right Hippocampus



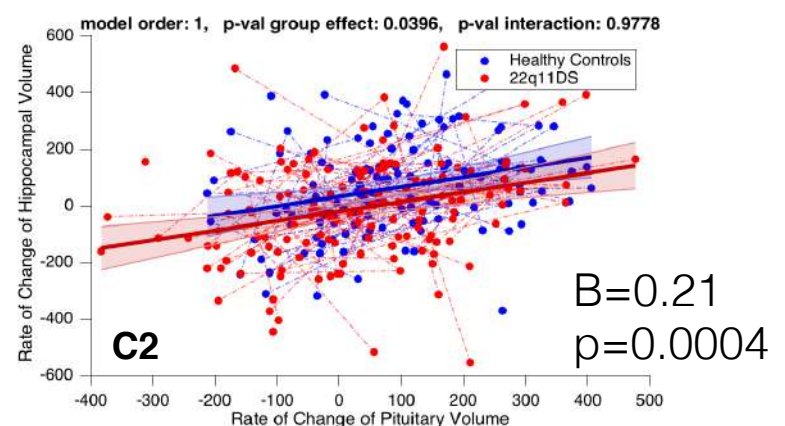
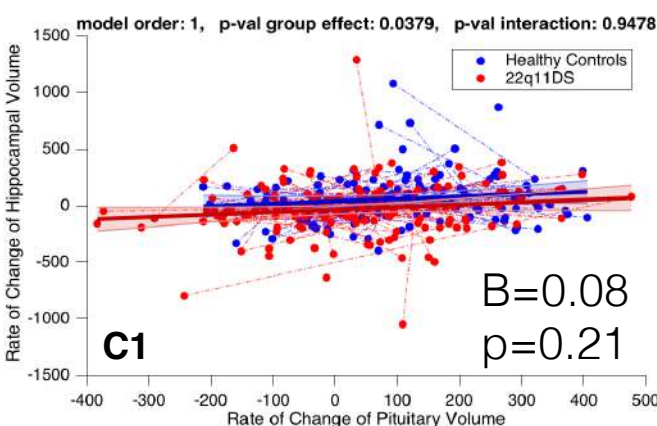
A: Developmental Trajectory of Hippocampal Volume



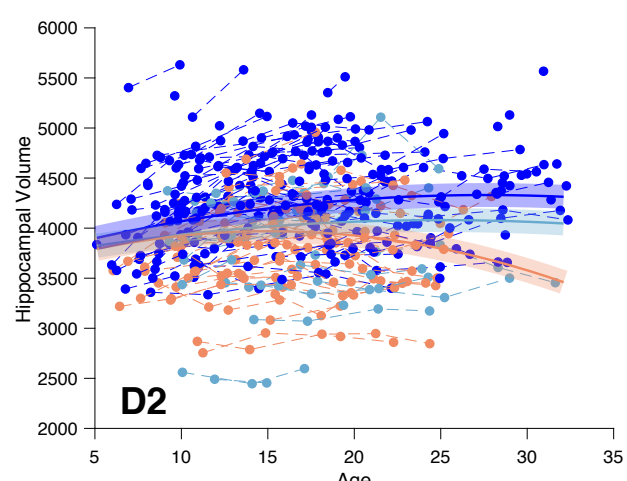
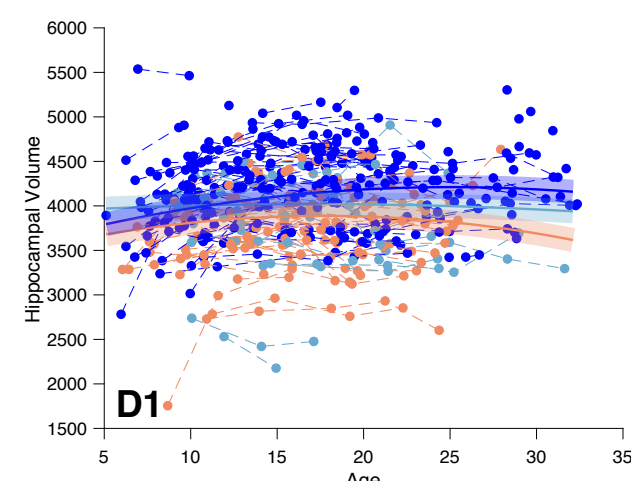
B: Association of Hippocampal and Pituitary Volume



C: Association of Hippocampal and Pituitary Development



D: Effects of Pituitary Decline on Hippocampal Development



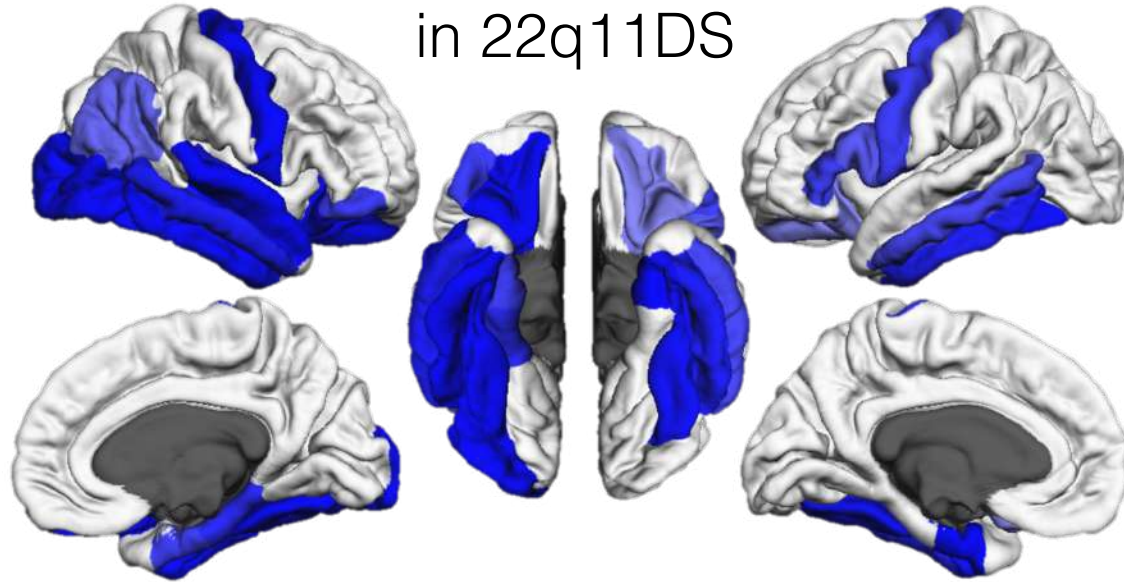
A1

Accelerated
Cortical Thinning
in 22q11DS

Accelerated
Cortical Thinning
in 22q11DS
 $P < 0.001$

$P = 0.05$
 $P = 0.05$

$P < 0.001$
Decreased
Cortical Thinning
in 22q11DS



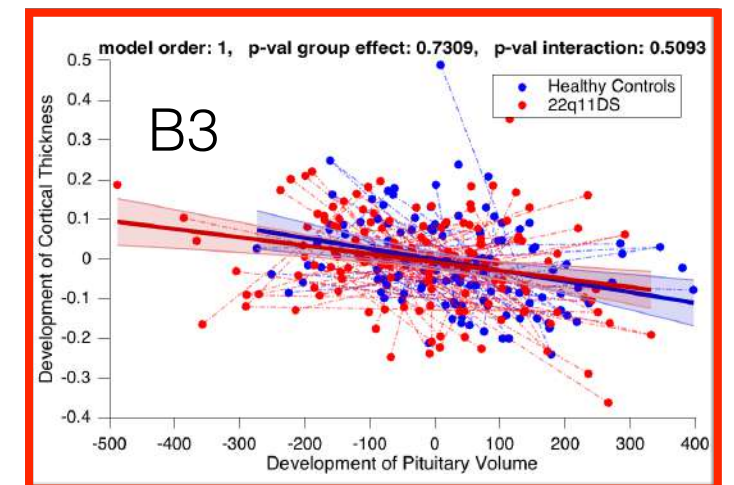
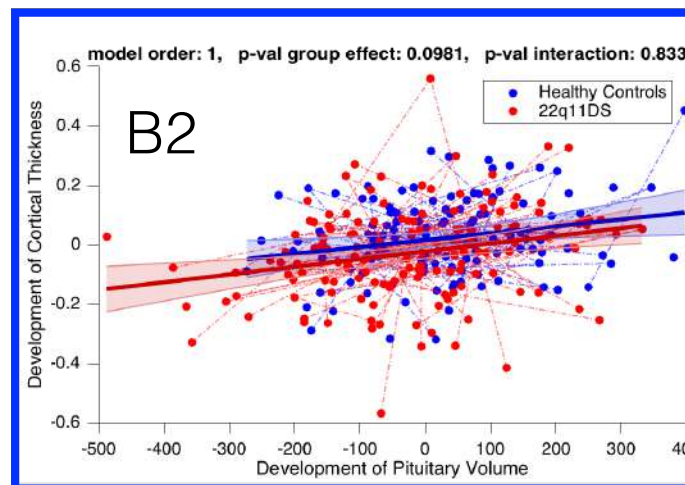
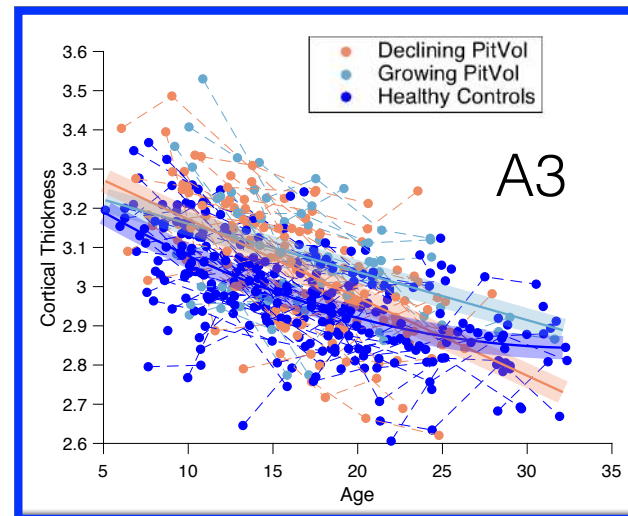
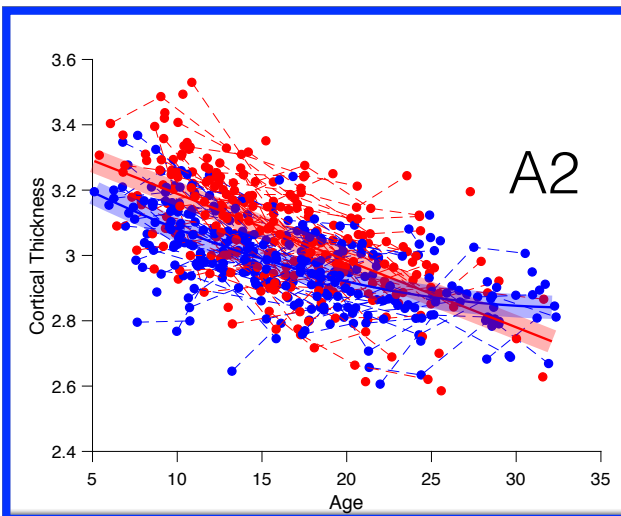
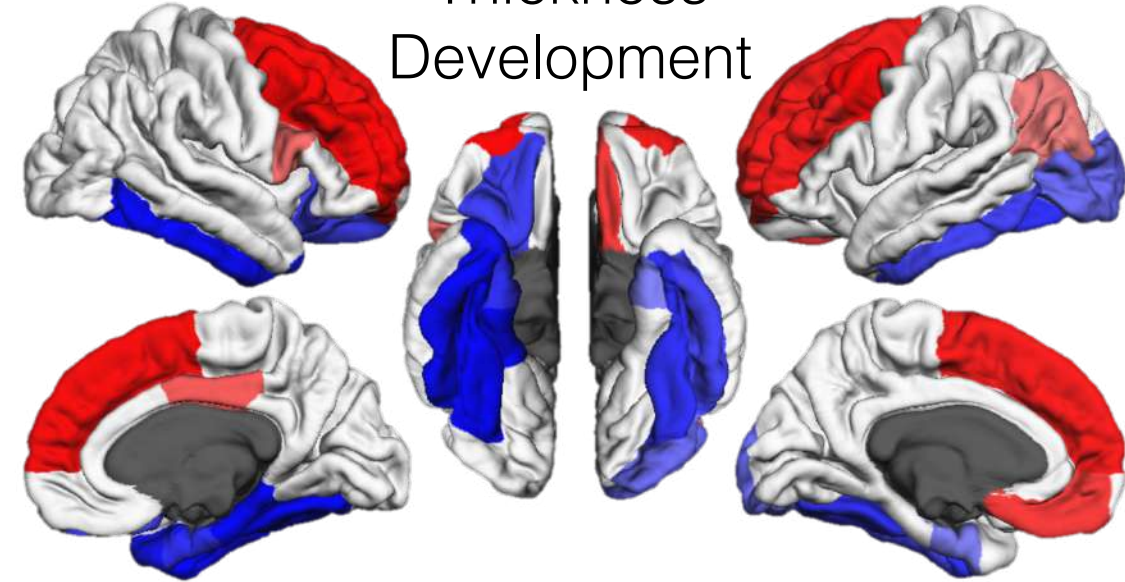
B1

Correlation of Pituitary
Volume and Cortical
Thickness
Development

Positive Correlation of
Pituitary and Cortical
Development
 $P < 0.001$

$P = 0.05$
 $P = 0.05$

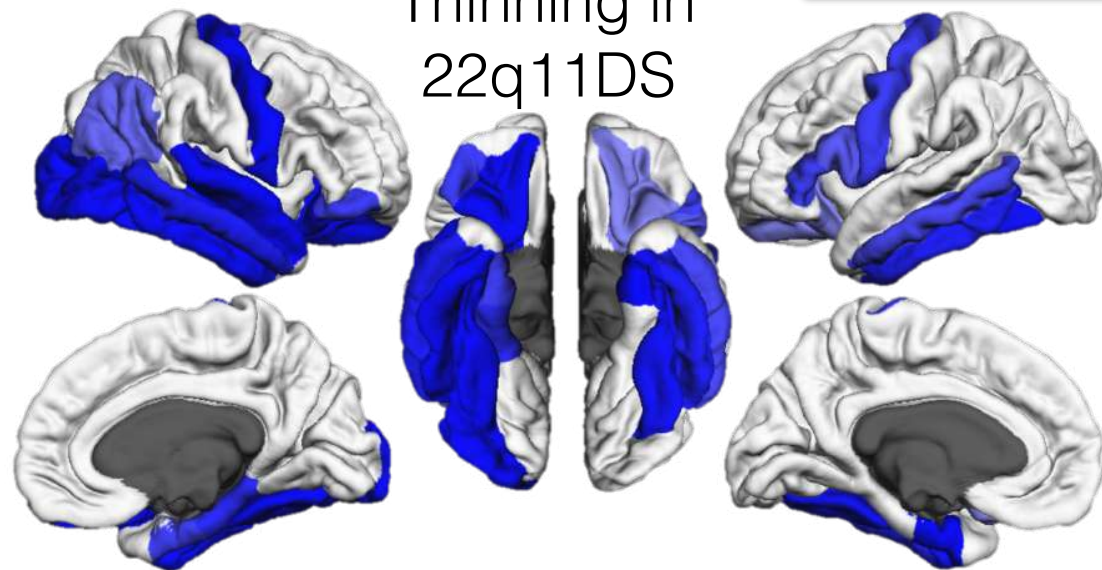
$P < 0.001$
Negative Correlation
of Pituitary and
Cortical Development



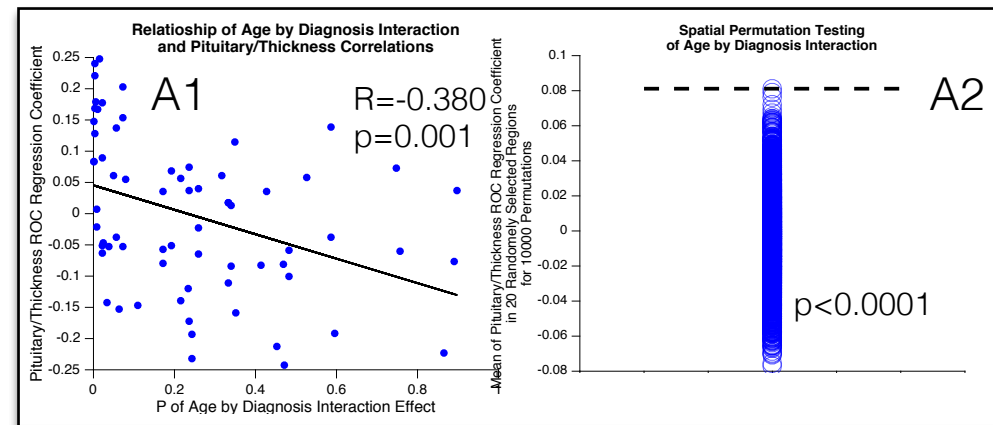
Accelerated
Cortical Thinning
in 22q11DS
 $P < 0.001$

$P = 0.05$
 $P = 0.05$

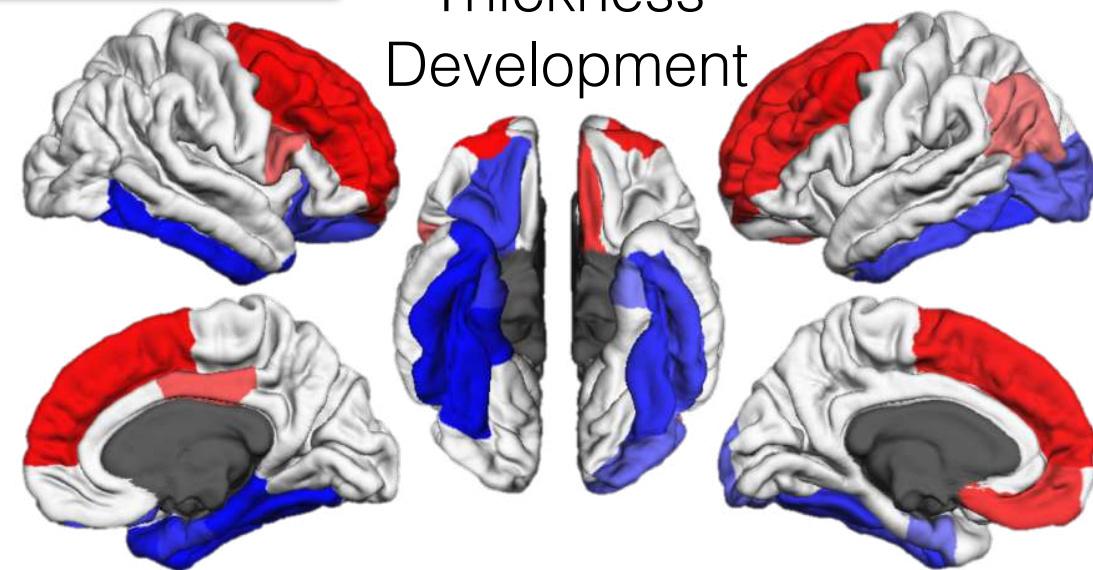
$P < 0.001$
Decreased
Cortical Thinning
in 22a11DS



Accelerated
Cortical
Thinning in
22q11DS



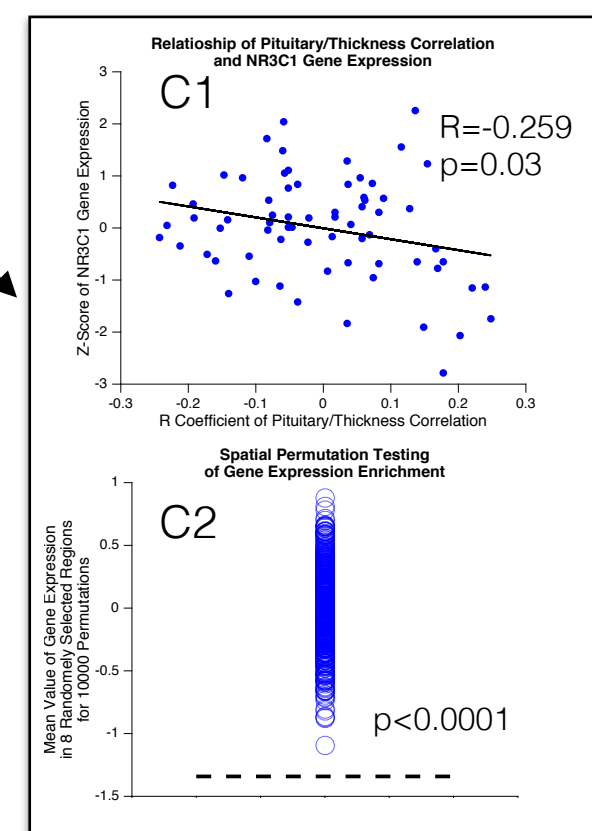
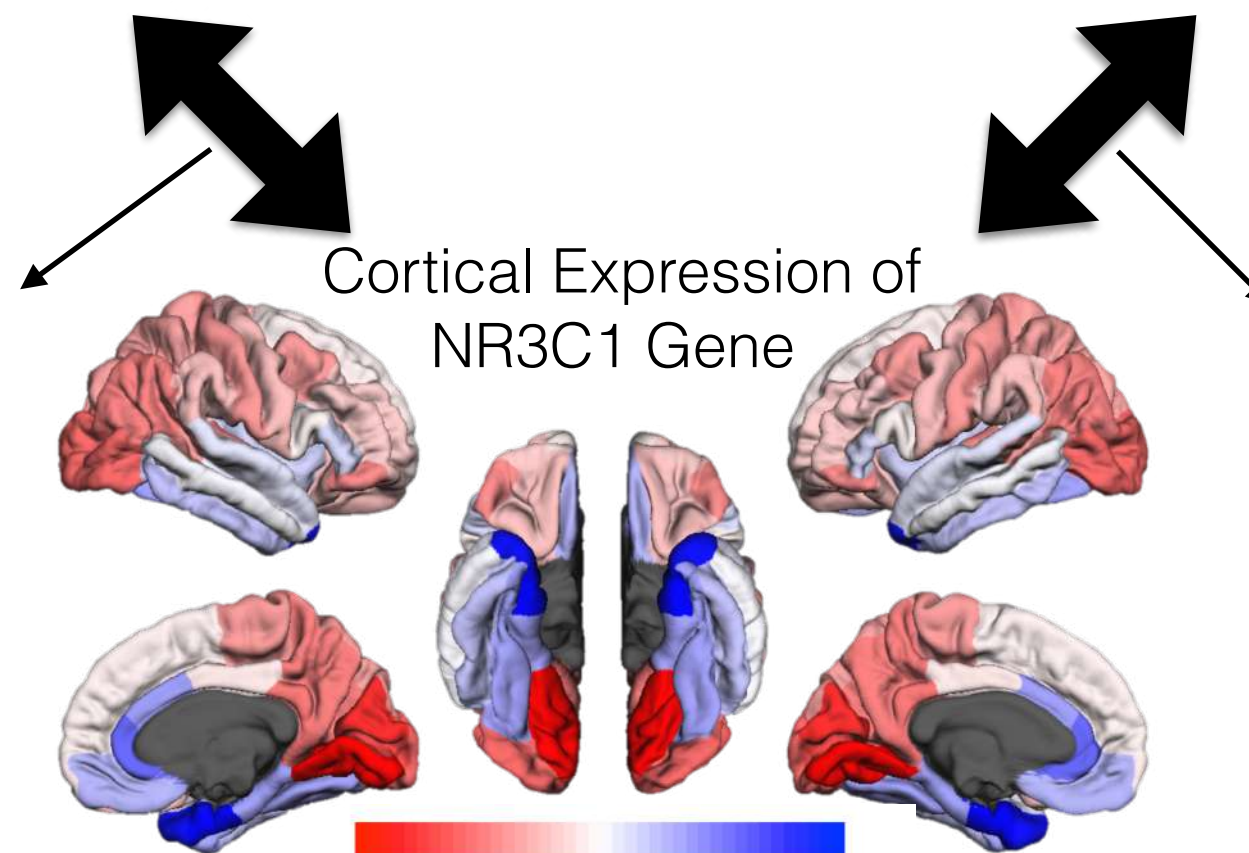
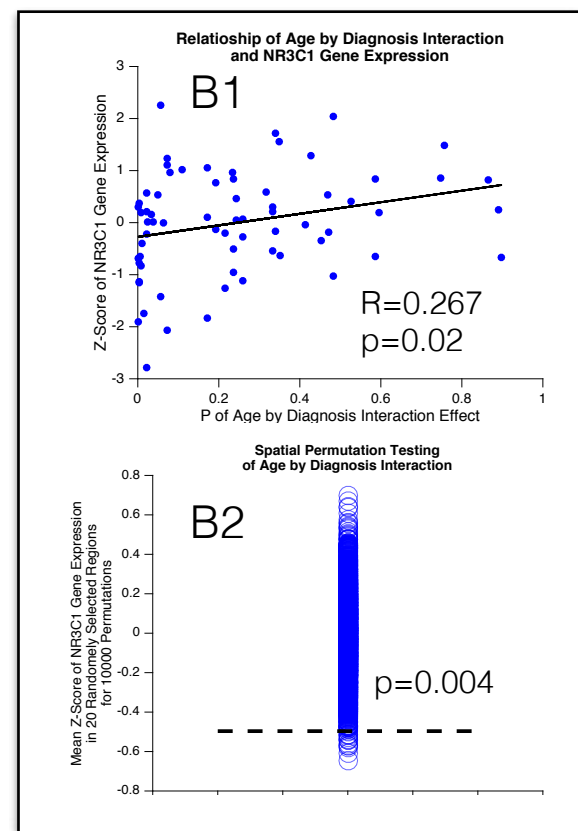
Correlation of
Pituitary Volume
and Cortical
Thickness
Development



Positive Correlation of
Pituitary and Cortical
Development
 $P < 0.001$

$P = 0.05$
 $P = 0.05$

$P < 0.001$
Negative Correlation
of Pituitary and
Cortical Development



	Healthy Controls N=151 Visits=282	22q11DS N=114 Visits=259	P-Value of Difference HC/22q11DS	High Pituitary Volume N=56 Visits=134	Low Pituitary Volume N=58 Visits=123	P-Value of Difference High/Low PitVol	Growing Pituitary Volume N=22 Visits=69	Declining Pituitary Volume N=45 Visits=141	P-Value of Difference Growing/ Declining PitVol
Gender (M/F)	76/75	57/57	0.98	25/31	32/26	0.24	12/10	24/21	0.93
Age	16.94 +/- 6.5	16.13 +/- 5.42	0.11	16.93 +/- 5.44	15.1 +/- 5.15	0.006	16.3+/- 5.16	16.9 +/- 4.8	0.35
Number of Visits (V)	1V=68 2V=50 3V=20 4V=11 5V=2 Mean=1.86	1V=47 2V=21 3V=21 4V=18 5V=7 Mean=2.27	0.51 0.007 0.24 0.02 0.03 0.004	1V=21 2V=10 3V=10 4V=12 5V=3 Mean=2.39	1V=26 2V=12 3V=11 4V=5 5V=4 Mean=2.12	0.43 0.71 0.87 0.056 0.73 0.26	1V=0 2V=7 3V=8 4V=6 5V=1 Mean=3.0	1V=0 2V=15 3V=13 4V=11 5V=6 Mean=3.1	N/A 0.87 0.53 0.79 0.27 0.61
Time Between Visits	3.68 +/- 1.49	3.65+/- 1	0.81	3.58 +/- 0.73	3.7 +/- 1.26	0.44	3.58 +/- 0.86	3.67 +/- 1.07	0.59
Full Scale IQ	110.6 +/- 13.13	70.2 +/- 11.79	<0.001	70.09 +/- 11.92	72.04 +/- 11.69	0.19	70.92 +/- 11.9	72.05 +/- 11.28	0.51
Scanner Type (1.5T/3T_Trio/3T_Prisma)	69/149/64	50/138/72	0.22	29/71/34	21/66/37	0.55	17/39/13	30/74/37	0.43
Lifetime Psychiatric Disorders									
ADHD				23/41.2%	22/37.2%	0.66	6/27.2%	24/53.3%	0.04
Any Anxiety Disorder				22/39.2%	18/30.5%	0.32	9/40.9%	21/46.6%	0.64
Any Mood Disorder				8/14.2%	6/10.1%	0.50	4/18.1%	9/20%	0.46
Enuresis/Encopressis				8/14.2%	13/22%	0.28	2/0.9%	10/22%	0.02
Oppositional Defiant Disorder				5/8.9%	8/14.2%	0.37	3/13.6%	7/15.5%	0.83
Any Psychotic Disorder				8/14.2%	6/10.1%	0.14	0	7/15.5%	0.05
Lifetime Psychotropic Medication									
Methylphenidate				12/21.4%	14/23.7%	0.76	5/22%	14/31%	0.44
Anxiolytics				3/5.3%	6/1%	0.18	1/4%	4/8%	0.54
Antidepressants				15/26.7%	9/15.2%	0.13	4/18.1%	16/35.5%	0.15
Neuroleptics				9/16.5%	9/15.2%	0.84	3/13.6%	7/15.5%	0.83
Antiepileptics				3/5.5%	3/5%	0.90	0/0%	5/11%	0.1