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An integrative approach to linking genes, brain, and behavior in 22q11.2 copy number variations

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy in

Neuroscience

by

Amy Lin

2021

ABSTRACT OF THE DISSERTATION

An integrative approach to linking genes, brain, and behavior in 22q11.2 copy number variations

by

Amy Lin

Doctor of Philosophy in Neuroscience

University of California, Los Angeles, 2021

Professor Carrie E. Bearden, Chair

Efforts to bridge the gap between genes, brain, and behavior are facilitated by the study of highly-penetrant, disease-associated copy number variations (CNV). CNVs at the 22q11.2 locus present as deletions and duplications, each associated with clinical phenotypes that implicate perturbed neurodevelopmental processes. In fact, 22q11.2 CNVs confer some of the greatest known genetic risks for psychiatric disorders, and thus represent a compelling model to yield biological insights into how gene dosage may influence downstream brain and behavior. In this body of work, I present three studies that offer a comprehensive approach tethering cortical morphometric changes, cognitive and behavioral impairments, and transcriptomic dysregulation to reveal novel insights about the molecular effects of 22q11.2 CNVs. The first two studies are published in *The Journal of Neuroscience* and *Biological Psychiatry*, respectively, while the third study will soon be submitted to *Brain, Behavior, and Immunity*.

In Chapter 1, I briefly introduce the challenge of studying neurodevelopmental psychiatric disorders, and how the use of highly penetrant, disease-associated CNVs can help

to mitigate some of these biological complexities. Then, I explain how reciprocal 22q11.2 CNVs have great potential to offer key insights into the underlying biology of neuropsychiatric disorders. In Chapter 2, I show for the first time that 22q11.2 deletions (22qDel) and duplications (22qDup) confer global opposing effects on brain morphometry by comparing 66 molecularly-confirmed 22qDel carriers, 21 22qDup carriers, and 56 demographically-matched controls. 22qDel was associated with widespread reductions in cortical surface area, with corresponding enlargement in 22qDup. Cortical thickness showed the opposite pattern, but with more localized effects. Regional patterns of thickness difference between 22qDel and 22qDup carriers were also observed in subcortical regions which, in concert with the diffuse surface area changes, imply global and early impacts of 22q11.2 CNVs on brain development. Lastly, these findings were not accounted for by a subset of the sample, but rather the entire distribution was shifted, which suggests a highly penetrant effect of gene dosage.

In Chapter 3, I systematically examine neurodevelopmental phenotypes relevant to intellectual functioning, Autism Spectrum Disorder (ASD), and psychosis in 106 22qDel carriers, 38 22qDup carriers, and 82 demographically-matched controls. This study aimed to leverage dimensional phenotyping, based on the hypothesis that variation in specific quantitative traits may better reflect underlying biological variation than categorical diagnoses. I found that reciprocal 22q11.2 deletions and duplications were associated with distinct impacts on intellectual functioning and psychosis-related symptomatology, but shared global deficits in the domain of ASD-related symptomatology. However, when more fine-grained subdomain measures of ASD-related traits were assayed, subtle differences in ASD profiles were found to distinguish deletion and duplication carriers. Lastly, while controls showed an inverse relationship with cortical thickness and processing speed, this association was absent in both CNV groups. This altered relationship between normative cortical thinning and cognitive processing speed implies disrupted development of the cortical mantle may underlie impaired processing efficiency in 22q11.2 CNV carriers.

In Chapter 4, I leverage high-throughput transcriptomic data as an additional lens by which to gain mechanistic insights. This study represents the first genome-wide gene expression study to characterize transcriptomic dysregulation in peripheral blood in reciprocal 22q11.2 CNV carriers. Specifically, analyzing samples from 82 22qDel carriers, 29 22qDup carriers, and 68 demographically-matched controls, I showed that the 22q11.2 deletion significantly alters gene expression across the genome, and that these differences are substantially attenuated after adjustment for cell type heterogeneity. Moreover, expression of two cytoskeletal- and ASD-relevant genes differed between 22q11.2 CNV carriers with and without a diagnosis of ASD. I also extend findings regarding cell type differences between 22q11.2 deletion carriers and controls beyond known T cell differences to include mast cell and macrophage subtypes, two cell types that have multifunctional, immune-related roles throughout the body. These findings demonstrate the challenges inherent in using peripheral blood, a common tissue of analysis in psychiatric genetics, to study brain-related diseases. Nevertheless, this work shows how blood tissue, which contains a wealth of information regarding the immune system, can still offer valuable insights regarding immune mechanisms in psychiatric disorders, provided confounds such as cell type heterogeneity are properly accounted for.

In sum, the work described herein seeks to reveal fundamental biology, generate hypotheses for future targeted experiments to validate and test in animal or *in vitro* models, and ultimately inform novel therapeutic targets.

The dissertation of Amy Lin is approved.

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Paul Thompson

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Carrie E. Bearden, Committee Chair

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2021

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Members of the Bearden lab have been integral in cultivating the supportive and open environment that allowed me to prosper the last several years. Leila Kushan-Wells opened her home to me during various lab gatherings, and it's been a joy to see her family grow as well. Jen Forsyth was yet another fantastic role model and friend who also opened her home to me for various birthday and holiday celebrations. I felt my time with Eva Mennigen and Gil Hoftman were cut too short but in the few years that we overlapped, but I have greatly appreciated their perspectives on medicine and its intersection with social justice. I'd also like to thank the rest of the Bearden Lab, including research assistants, undergraduate volunteers, and those from the Center for the Assessment and Prevention of Prodromal States (CAPPS) who have created a vibrant, reassuring, and exciting place to work. I am so privileged to have learned from all the brilliant and kind-hearted people of the Bearden Lab, past and present, who have made the best colleagues, mentors, and friends.

I would be remiss if I did not also mention the instrumental role that Jenny Lee, our program's Graduate Advisor, played in making my graduate school experience such a joy since I first interviewed at UCLA. Like a true "mama bear", she kept me on track, lent an ear and shoulder when I was feeling overwhelmed, and looked out for me when I didn't know I needed looking out. Not every program has someone who cares so genuinely and deeply about their students, but Jenny showed up in ways that felt beyond the call of duty. I'm so glad she was a part of my journey.

Of course, it all started with my parents. I am endlessly grateful to them for leaving everything they knew in Taiwan to start a better life for me and my brother in America. They told me since I was a young child that I can do whatever I want with the talents that I had, and I think this propelled me to always reach for the stars. I hope that I have done them proud and will continue to do so. Finally, I have to thank my fiancé, John, who really stepped up to the plate in supporting me in the rollercoaster ride that is graduate school, especially in the midst of a global pandemic. His unwavering love for and belief in me made every other aspect of my life that much easier. I feel so fortunate to have a partner who continues to encourage me, learn with me, and have fun with me when I need a break.

With regard to the work presented herein, I would like to acknowledge that Chapter 2 consists of a manuscript published in *The Journal of Neuroscience* in 2017 entitled, 'Mapping 22q11.2 Gene Dosage Effects on Brain Morphometry'. The work was co-authored by Christopher R.K. Ching, Ariana Vajdi, Daqiang Sun, Rachel K. Jonas, Maria Jalbrzikowski, Leila Kushan-Wells, Laura Pacheco Hansen, Emma Krikorian, Boris Gutman, Deepika Dokoru, Gerhard Helleman, Paul M. Thompson and Carrie E. Bearden, all of whom have consented to the inclusion of the work in this thesis. Chapter 3 includes a manuscript published in *Biological Psychiatry* in 2020 entitled, 'Reciprocal Copy Number Variations at 22q11.2 Produce Distinct and Convergent Neurobehavioral Impairments Relevant for Schizophrenia and Autism Spectrum Disorder'. The work could not have been possible without contributions from the co-authors: Leila Kushan-Wells, Gerhard Helleman, Laura Pacheco Hansen, Rachel K. Jonas, Maria Jalbrzikowski, Lyle Kingsbury, Armin Raznahan, and Carrie E. Bearden—whom all also consented to the inclusion of this work. Finally, Chapter 4 consists of a manuscript that will shortly be submitted to *Brain, Behavior, and Immunity* entitled, 'Transcriptomic profiling of whole blood in 22q11.2 reciprocal copy number variants reveals that cell proportion highly impacts gene expression'. The co-first authors, Jen Forsyth and Gil Hoftman, and co-last author to Carrie Bearden, Dan Nachun, made substantial contributions to the design, data processing,

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SELECTED PUBLICATIONS

Lin, A., Forsyth, J., Hoftman, G….Nachun., D., & Bearden, C. E. (in preparation for *Brain, Behavior, and Immunity*) Transcriptomic profiling of whole blood in 22q11.2 reciprocal copy number variants reveals that cell proportion highly impacts gene expression.

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Lin, A., Forsyth, J.K., Nachun, D., Sun, D., Kushan, L., Jalbrzikowski, M., Coppola, G., and Bearden, C.E. (2019) Characterizing Peripheral Blood Transcriptome Dysregulation Associated with Recurrent Copy Number Variations at the 22q11.2 Locus. UCLA Brain Research Institute 31st Annual Neuroscience Poster Session, Grand Ballroom Ackerman Union, UCLA, Los Angeles, CA.

Lin, A., Forsyth, J.K., Nachun, D., Sun, D., Kushan, L., Jalbrzikowski, M., Coppola, G., and Bearden, C.E. (2019) Characterizing peripheral blood transcriptome dysregulation associated with recurrent copy number variations at the 22q11.2 locus. 26th World Congress of Psychiatric Genetics. Anaheim, CA.

Lin, A., Forsyth, J.K., Nachun, D., Sun, D., Kushan, L., Jalbrzikowski, M., Coppola, G., and Bearden, C.E. (2019) Characterizing the dysregulation of peripheral blood gene expression associated with a 22q11.2 deletion or duplication compared to healthy individuals. 2019 Annual Society of Biological Psychiatry Meeting. Chicago, IL.

Lin, A.,* Forsyth*, J., Mennigen*, E., Sun, D., Vajdi, A., Kushan-Wells, L., 22q11.2 ENIGMA Consortium, Bearden, C.E. (2019) Multi-modal integration of transcriptomic and sMRI in a common neurogenetic developmental disorder. Organization of Human Brain Mapping Annual Conference. Rome, Italy. *co-first authors

Lin, A., Vajdi A., Kushan-Wells, L., Pacheco-Hansen, L., Jonas R.K., Jalbrzikowski, M., Bearden, C.E. (2018). An integrative approach to linking genes, brain, and behavior in 22q11.2 copy number variations (CNVs). Molecular Psychiatry Meeting, Kauai, Hawaii.

Lin, A., Forsyth J., Vajdi A., Jonas R.K., Jalbrzikowski, M., Kushan-Wells, L., Pacheco-Hansen, L., Coppola, G., Dokoru, D. Helleman, G. Bearden, C.E. (2017). Bridging the gap between genes, brain, and behavior using multi-modal phenotyping data from 22q11.2 copy number variants. Molecular Psychiatry Meeting, San Francisco, Ca.

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Lin, A. Ching, C., Vajdi, A., Sun, D., Jonas, RK., Jalbrzikowski, M., Kushan-Wells, L., Pacheco-Hansen, L., Kriokorian, E., Gutman, B., Dokoru, D., Helleman, G., Thompson, P., Bearden, C.E. (2017). Elucidating genetic underpinnings of brain development using copy number variation at the 22q11.2 locus. Organization of Human Brain Mapping Meeting, Vancouver, Canada.

Lin, A., Sun, F.,…,Bearden, C.E. (2016). 22q11.2 Gene Dosage Effects on Cortical Thickness and Surface Area. Society of Biological Psychiatry 2016 Annual Meeting, Atlanta, Georgia.

CHAPTER ONE

An integrative approach to linking genes, brain, and behavior in 22q11.2 copy number variations

1.1: The challenge of understanding the etiology of developmental neuropsychiatric disorders

Developmental neuropsychiatric disorders remain among the most intractable areas of medicine, the study of which has produced frustratingly little progress compared to other non-central nervous system diseases (Kapur et al., 2012; Papassotiropoulos & de Quervain, 2015). One paramount impediment is their incredible genetic and phenotypic complexity (Gelernter, 2015; Lee et al., 2021; Sullivan et al., 2012). Not only are these disorders highly polygenic, but there is also substantial overlap in genetic contribution between disorders (Gandal et al., 2019; Martin et al., 2019; Wendt et al., 2020). Current approaches in psychiatric nosology are subjective, without biologically-based laboratory assays that help determine diagnoses (Hyman, 2007; Kapur et al., 2012). Symptomatology can vary greatly between individuals with the same diagnosis when underlying pathogenesis is unknown. All of these factors have created barriers in uncovering the basic biology of these disorders and, in turn, has hindered the development of effective, mechanistically-informed treatments. However, major gains in understanding are starting to be made, aided by insights yielded from the study of highly-penetrant, disease-associated rare genetic mutations such as genomic copy number variants (CNVs) (Girirajan et al., 2011; McCarroll & Altshuler, 2007; Wain et al., 2009). This 'genetics-first' approach has shown great potential in mitigating some of these biological complexities to elucidating disease etiology and pathophysiology.

1.2: How disease-associated CNVs can mitigate biological complexities

CNVs are one type of rare, genetic mutation in which DNA segments of at least 50 base pairs are lost or gained, creating varying dosages of genetic material (Feuk et al., 2006; Lupski & Stankiewicz, 2005). One mechanism by which these structural mutations may arise is via non-allelic homologous recombination (NAHR), mediated by low copy repeats (LCRs). LCRs act as substrates for nonallelic pairing of paralogous sequences and crossover, leading to

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chromosomal rearrangements that can have deleterious effects (Carvalho & Lupski, 2016; Liu et al., 2011). CNVs have emerged as important risk factors for multiple neuropsychiatric disorders and offer a unique opportunity for elucidating underlying pathophysiology. As compared to common variants identified by genome-wide association studies (GWAS), which tend to have quite small effects on disease risk, CNVs are highly penetrant for developmental neuropsychiatric disorders (Sanders et al., 2019). Evidence that CNVs tend to confer larger effect sizes for functional impairment compared to common variants also make CNVs more biologically tractable for identifying biological pathways relevant to neuropsychiatric phenotypes (Kirov et al., 2014; Malhotra & Sebat, 2012; Moreno-De-Luca et al., 2013). More specifically, reciprocal CNVs at the same genetic locus enable a quasi-experimental, 'reverse-genetics' approach to revealing how gene dosage impacts downstream phenotypes (Hiroi et al., 2013). Human studies are typically restricted to genetic association frameworks, as gene dosage cannot be experimentally manipulated in human participants as it can be for animal or *in vitro* experiments. However, human genetic variations in the form of reciprocal deletions and duplications provide a naturally occurring alternative. In addition, as opposed to relying on behaviorally-defined animal models of neurodevelopmental disease, CNVs enable translational studies because the same genetic mutations can be modeled in lower-order systems (Dolmetsch & Geschwind, 2011; Khan et al., 2020; Meechan et al., 2015). Lastly, CNVs can be identified very early in development, even in utero, thus presenting opportunities for early identification of CNV carriers and the possibility of prospective studies where disease trajectories can be tracked (Bouwkamp et al., 2017). This allows investigators to monitor disease progression before overt onset of illness so that intermediate stages of disease development can be better discerned.

1.3: 22q11.2 CNVs as a compelling model

22q11.2 CNVs provide an ideal model to study the connection between genetic perturbation and downstream effects on various neurodevelopmental phenotypes. The locus is dense with highly conserved, brain-expressed, protein-coding genes, a number of which are crucial for brain and cognitive development (Guna et al., 2015; N. Hiroi et al., 2013). Some of these genes are implicated in cortical development, early neuronal migration, dopaminergic neurotransmission, mitochondrial function, myelination, and microRNA processing (Forsyth et al., 2020; Jonas et al., 2014; McDonald-McGinn et al., 2015). Murine models of 22q11.2 CNVs also provide a valuable means to experimentally test and validate novel hypotheses based on human studies (Boku et al., 2018; Drew et al., 2011; Forsingdal et al., 2019; Hiroi & Yamauchi, 2019; Karayiorgou et al., 2010; Saito et al., 2020). The phenotypes are fairly well-characterized and tend to recapitulate deficits in human 22q11.2 CNV carriers, including social and cognitive impairments, synaptic defects, and cortical circuit dysfunction (Donegan et al., 2020; Fenelon et al., 2013; Meechan et al., 2015; Mukai et al., 2015; Sigurdsson et al., 2010).

It is no surprise then that the clinical profiles of 22q11.2 CNV carriers predict major functional consequences of these genetic perturbations with regard to the development of neuropsychiatric disorders. In fact, 22q11.2 CNVs confer some of the greatest known genetic risk for developmental neuropsychiatric disorders (Drew et al., 2011; Wenger et al., 2016). In particular, the deletion is well known for its high rate of schizophrenia (SCZ), with up to 25-30-fold increased risk compared to population base rates (Chow et al., 2006; Green et al., 2009; Malhotra & Sebat, 2012; Marshall et al., 2017; Rees et al., 2016). 22q11.2 deletions are found in approximately 0.3% of SCZ cases in the general population (Kirov et al., 2014; Marshall et al., 2017; Rees et al., 2014). Interestingly, evidence from large-scale studies suggest that 22q11.2 duplications have diminished occurrence in SCZ cases compared to the general population, suggesting that 22q11.2 duplications are the first putative protective mutation for SCZ (Li et al., 2016; Rees et al., 2014, 2016). Although statistical significance varies depending on sample

size (Marshall et al., 2017), the overall pattern offers consistent evidence that SCZ risk is gene-dosage specific with respect to the 22q11.2 locus. Recent studies also suggest that both 22q11.2 deletion and duplication carriers have elevated risk for other developmental disorders such as Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD), and intellectual disability (Olsen et al., 2018; Schneider et al., 2014). This intriguing gene-dosage distinction suggests that there are both shared and unique effects of 22q11.2 genes on disease etiology. Altogether, 22q11.2 CNVs provide a promising avenue for teasing out relevant biological mechanisms of complex, highly polygenic disorders.

1.4: Mapping the functional consequences of 22q11.2 CNVs across modalities
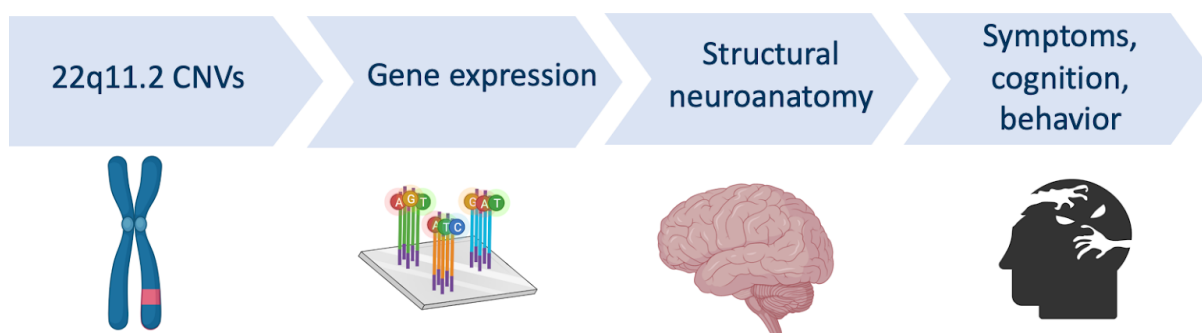
Figure 1.1: An integrative approach to linking genes, brain, and behavior in 22q11.2 copy number variants (CNVs). A "bottom-up" approach starting with the identification of genetically-defined individuals allows for the progression of genetic perturbation to macroscopic brain and behavioral alterations that lead to psychiatric diagnoses.

The work described herein explores how an integrative, multimodal model can bridge the gap between genes, brain, and behavior within this rare disease framework. While the 22q11.2 deletion has been investigated to some extent across these intermediate phenotypes, this work represents the first direct comparison of 22q11.2 reciprocal deletion and duplication carriers across these domains. A systematic characterization of molecular, cortical, and clinical

phenotypes between reciprocal 22q11.2 CNVs is necessary to establish clinical context and

functional relevance for how gene dosage contributes to brain dysfunction and downstream

clinical effects. Insights generated from this framework have the potential to improve patient

care and inform targeted, effective therapeutics by clarifying specific risks, improving early

detection, and elucidating pathophysiology.

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CHAPTER TWO

Mapping 22q11.2 Gene Dosage Effects on Brain Morphometry

2.1: Abstract

Reciprocal chromosomal rearrangements at the 22q11.2 locus are associated with elevated risk of neurodevelopmental disorders. The 22q11.2 deletion confers the highest known genetic risk for schizophrenia, but a duplication in the same region is strongly associated with autism and is less common in schizophrenia cases than in the general population. Here we conducted the first study of 22q11.2 gene dosage effects on brain structure in a sample of 143 human subjects: 66 with 22q11.2 deletions (22q-del; 32 males), 21 with 22q11.2 duplications (22q-dup; 14 males), and 56 age- and sex-matched controls (31 males). 22q11.2 gene dosage varied positively with intracranial volume, gray and white matter volume, and cortical surface area (deletion < control< duplication). In contrast, gene dosage varied negatively with mean cortical thickness (deletion > control > duplication). Widespread differences were observed for cortical surface area with more localized effects on cortical thickness. These diametric patterns extended into subcortical regions: 22q-dup carriers had a significantly larger right hippocampus, on average, but lower right caudate and corpus callosum volume, relative to 22q-del carriers. Novel subcortical shape analysis revealed greater radial distance (thickness) of the right amygdala and left thalamus, and localized increases and decreases in sub-regions of the caudate, putamen, and hippocampus in 22q-dup relative to 22q-del carriers. This study provides the first evidence that 22q11.2 is a genomic region associated with gene-dose-dependent brain phenotypes. Pervasive effects on cortical surface area imply that this copy number variant affects brain structure early in the course of development.

2.2: Introduction

Reciprocal chromosomal rearrangements represent powerful models to assess effects of copy number variation (CNVs) on brain morphology and associated neuropsychiatric outcomes. Gene dosage cannot be experimentally manipulated in humans as it can in animal or in vitro models, but a similar framework emerges via naturally-occurring genetic variation. Such

genomic imbalances confer some of the highest genetic risk factors for prevalent developmental

neuropsychiatric disorders (Malhotra & Sebat, 2012, Hoeffding et al., 2017), and offer a quasi-

experimental "reverse genetics" approach to elucidate how genes may impact

neurodevelopmental phenotypes (Hiroi et al., 2013).

The 22q11.2 locus is a valuable region to investigate gene dosage effects on brain

development, as it is particularly susceptible to chromosomal rearrangements due to non-allelic

homologous recombination (Stankiewicz and Lupski, 2002). Occurring at nearly 1 in 2,000 live

births (Grati et al., 2015), the 22q11.2 deletion (22q-del), also known as DiGeorge or

Velocardiofacial syndrome (OMIM #188400, #192430), results from a 1.5-3 Mb hemizygous

deletion on the long arm of chromosome 22 (Shaikh et al., 2007). 22q-del is the largest known

genetic risk factor for psychotic illness, associated with a ~30-fold increase in risk relative to

population base rates (Bassett & Chow, 2008; Green et al., 2009; Schneider et al., 2014). It is

also associated with heightened risk for other developmental neuropsychiatric disorders:

attention deficit hyperactivity disorder (ADHD), anxiety disorder, and autism spectrum disorders

(ASD; Girirajan et al., 2011; Niklasson et al., 2001, 2009; Vorstman et al., 2006).

Duplications at the same locus (22q-dup) were first reported clinically in 2003

(Ensenauer et al., 2003). Unlike 22q-del, which tends to occur de novo, the duplication is

frequently inherited (Ou et al., 2008). Less is known about the 22q-dup phenotype, which is

highly variable (Wentzel et al., 2008), but appears to be associated with elevated rates of ASD

and delays in language and psychomotor development (Wenger et al., 2016). In an analysis of

over 47,000 individuals, the 22q-dup was significantly less common in schizophrenia cases than

in the general population (0.014% compared to 0.085%, OR=0.17), suggesting the first putative

protective mutation for schizophrenia (Rees et al., 2014). This finding of lower schizophrenia

incidence in 22q-dup carriers compared to non-carriers has now been replicated in independent

studies (Li et al., 2016; CNV and PGC, 2016; Rees et al., 2016).

Genes within the 22q11.2 locus are essential for cortical circuit formation (Meechan et al., 2015a), so it is not surprising that 22q-del carriers show aberrations in cortical anatomy. These abnormalities include widespread reductions in cortical volume, particularly in midline regions, relative to typically developing controls (Bearden et al., 2007; Jalbrzikowski et al., 2013; Schmitt et al., 2015). Mouse models of 22q-del show diminished frequency of projection neurons in layers II/III of the medial prefrontal cortex, which was in turn associated with the severity of executive function deficits (Meechan et al., 2015b).

While no study has yet characterized how a 22q11.2 duplication affects brain morphometry, dose-dependent effects on human brain structure have recently been discovered for other reciprocal CNVs associated with neuropsychiatric phenotypes. Stefansson and colleagues (2014) first demonstrated dose-dependent effects of genes within the 15q11.2 locus for measures of regional brain volume that overlap with regions affected in idiopathic psychosis. Similarly, reciprocal 16p11.2 deletions and duplications were found to have global, 'mirror image' effects on brain structure, in which cortical surface area was differentially affected (Qureshi et al, 2014; Maillard et al., 2015).

We investigated cortical and subcortical anatomic variation at the 22q11.2 locus to investigate the hypothesis that reciprocal 22q11.2 deletions and duplications confer opposing effects on brain structure. We decomposed cortical volume into its constituent parts, cortical thickness (CT) and surface area (SA), which are believed to have distinct neurodevelopmental origins (Panizzon et al., 2009; Rakic, 1988; Winkler et al., 2010). Any differential effect of 22q11.2 variants on these measures may point to developmental processes that are disrupted during corticogenesis in distinct brain regions as a result of 22q11.2 gene dosage.

2.3: Materials and Methods

2.3.1: Participants

The sample consisted of 143 individuals: 66 with molecularly confirmed 22q11.2 deletions (32 males; 34 females), 21 with confirmed 22q11.2 duplications (14 males; 7 females), and 56 demographically-matched, unrelated controls (31 males; 25 females; see Table 2.1 for demographics). Approximately 25% of the deletion carriers and controls were included in a prior publication (Jalbrzikowski et al., 2013). As such, the current study includes a substantially larger sample of 22q11.2 deletion carriers and controls, as well as a novel cohort of 22q11.2 duplication carriers. Patients were ascertained from either (1) the UCLA or Children's Hospital, Los Angeles (CHLA) Pediatric Genetics, Allergy/Immunology and/or Craniofacial Clinics, or (2) local support groups and websites. Demographically comparable typically developing comparison subjects were recruited from the same communities as patients via web-based advertisements and by posting flyers and brochures at local schools, pediatric clinics, and other community sites.

	22q11.2 deletion participants ($N = 66$)	Healthy control participants ($N = 56$)	22q11.2 duplication participants ($N = 21$)
Scanner	34 BMC, 32 CCN	27 BMC, 29 CCN	21 CCN
Age (SD)	15.7 (7.55)	14.6 (6.93)	16.8 (12.00)
Males (% male)	32 (48.5%)	31 (55.4%)	14 (66.7%)
Race*,† (%)	59 white (89.4%), 1 black (1.5%), 6 multirace (9.1%)	33 white (58.9%), 7 black (12.5%), 5 Asian (8.9%), 11 multirace (19.6%)	21 white (100%)
Full-Scale IQ*,**,† (SD)	78.68 (12.53)	111.5 (18.98)	96.15 (20.42)
Verbal IQ*,**,† (SD)	76.2 (8.99)	113.3 (13.15)	93.3 (13.96)
Nonverbal IQ**,† (SD)	80.6 (10.91)	105 (10.11)	98.7 (14.41)
Highest parental education, years** (SD)	16.26 (2.52)	15.7 (3.18)	15.0 (2.25)
ASD (%)*,†	29 (43.9%)	0	13 (61.9%)
Psychotic disorder (%)**,†	4 (6.1%)	0	0
ADHD (%)*,†	27 (40.9%)	2 (3.6%)	6 (28.6%)
Social Responsiveness Scale*,† (SD)	70.07 (14.84)	49.29 (13.58)	72.31 (16.89)
Repetitive Behavioral Scale*,† (SD)	16.84 (22.77)	2.88 (7.16)	16.11 (19.44)
Current medication			
Psychostimulant*,** (%)	6 (9.1%)	1 (1.8%)	6 (28.6%)
Antipsychotic† (%)	7 (10.6%)	0	1 (4.8%)
Antidepressant (SSRI)**,† (%)	11 (16.7%)	0	1 (4.8%)
Other (%)	4 (6.1%)	1 (1.8%)	2 (9.52%)
None*,† (%)	38 (57.6%)	52 (92.9%)	12 (57.1%)
CNV breakpoints			
A-B (%)	5 (7.6%)	—	5 (23.8%)
A-C (%)	1 (1.5%)	—	—
A-D (%)	56 (84.8%)	—	10 (47.6%)
B-D (%)	—	—	3 (14.3%)
C-E (%)	1 (1.5%)	—	1 (4.8%)
Other (%)	3 (4.5%)	—	2 (9.5%)

[a]BMC, Brain Mapping Center; CCN, Center for Cognitive Neuroscience. One 22q-dup carrier was taking both an antipsychotic and psychostimulant. Family relatedness of the 22q-dup cohort: 4 singletons, 5 families with 2 members (3 parent-child pairs, 2 sibling pairs), 1 family with 3 members (siblings), 1 family with 4 members (1 parent, 3 children). CNV breakpoints: A-C deletion has additional C-D duplication, 3 Other deletions include D-F, D-G, and PRODH/DGCR8, 2 Other duplications include F-H and TOP3B. Data not available for the following: Full-Scale IQ/Verbal IQ: 1 22q-del, 2 controls, and 1 22q-dup; Nonverbal IQ: 2 controls and 1 22q-dup; Parental Education: 5 22q-del; Social Responsiveness Scale: 5 22q-dup, 6 22q-del, and 18 controls; Repetitive Behavioral Scale: 3 22q-del, 4 controls, and 2 22q-dup; Medication information for 2 controls.

*22q-dup/control difference (pairwise significance at uncorrected $p < 0.05$).

**22q-dup/22q-del difference (pairwise significance at uncorrected $p < 0.05$).

†22q-del/control difference (pairwise significance at uncorrected $p < 0.05$).

Table 2.1: Participant Demographics

Exclusion criteria for all study participants included significant neurological or medical conditions (unrelated to 22q11.2 mutation) that might affect brain structure, history of head injury with loss of consciousness, insufficient fluency in English, and/or substance or alcohol abuse or dependence within the past six months. Healthy controls additionally could not have significant intellectual disability or meet criteria for any major mental disorder with the exception of attention deficit–hyperactivity disorder (ADHD) or a past episode of depression, based on information gathered during the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (SCID; First & Gibbon, 2004) and/or Computerized Diagnostic Interview for Children (C-DISC; Shaffer et al., 2000). All participants underwent a verbal and written informed consent process. Participants under the age of 18

years provided written assent, while their parent or guardian completed written consent. The UCLA Institutional Review Board (IRB) approved all study procedures and informed consent documents.

2.3.2: Psychiatric and cognitive assessment

Supervised clinical psychology doctoral students administered neurocognitive and psychodiagnostic evaluations (SCID/C-DISC, as described above) to study participants. Estimates of general intellectual functioning were obtained for all participants using the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) or WAIS-IV (Wechsler et al., 2008). Diagnosis of ASD was based on the Autism Diagnostic Observation Schedule (Lord et al., 2000) and the Autism Diagnostic Interview-Revised (Lord et al., 1994). To obtain dimensional measures of ASD-relevant behavior, parents of study participants also completed the Social Responsiveness Scale [SRS; (Constantino and Gruber, 2007)], a quantitative measure of reciprocal social behavior that has been extensively validated in both clinically ascertained and population-based samples and the Repetitive Behavioral Scale (RBS; Lam and Aman, 2007) to capture patterns of restricted repetitive behavior often observed in ASD. All diagnoses were determined by trained clinicians who participated in an ongoing quality assurance program (Ventura et al., 1998). Training, reliability and ongoing quality assurance procedures for psychodiagnostic assessments are detailed in prior publications (Jalbrzikowski et al., 2013; Jalbrzikowski et al., 2016).

2.3.3: qRT-PCR

As an initial proof of principle to determine whether duplication and deletion carriers showed the expected increases or decreases, respectively, in gene dosage, we first investigated gene expression levels within three key genes in the 22q11.2 locus. Peripheral blood samples were drawn in two PAXgene tubes and were stored at 4°C. RNA was extracted using the PAXgene blood RNA kit (PreAnalytix GmbH, QIAGEN, Germany). We assessed RNA

quantity using Nanodrop ND-1000 spectrophotometer (Nanodrop Technologies, Wilmington, DE) and also quality with Agilent Bioanalyzer Nanochips.

Real time-quantitative polymerase chain reaction (RT-qPCR) was conducted using TaqMan assays, as described in Coppola et al., 2006. Total RNA was converted into cDNA by SuperScript II kit (Invitrogen). The reactions were performed with a TaqMan Master Mix (BioRad) in a 25 µl volume. Assays were performed in triplicate and analyzed using a Roche Lightcycler. qPCR analyses were carried out using the 2(-Delta Delta C(T)) method (2-ΔΔCt). We assayed three genes within the 22q11.2 locus: catechol-O-methyltransferase (COMT), DiGeorge Syndrome Critical Region Gene 8 (DGCR8), and Zinc Finger DHHC-Type Containing 8 (ZDHHC8), using Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) as a reference gene. Additionally, all 22q11.2 CNV carriers underwent multiplex ligation-dependent probe amplification (MLPA; (Sørensen et al., 2010) to determine specific breakpoint locations (see Table 1).

2.3.4: MRI acquisition and preprocessing

Measures of brain structure were obtained with high-resolution structural MRI. Scanning was conducted on an identical 3 Tesla Siemens Trio MRI scanner with a 12-channel head coil at the UCLA Brain Mapping Center or at the Center for Cognitive Neuroscience (Table 1). Each scan began with a 10-min acquisition of standard images used for determining regional anatomy, including a sagittal localizer image (TR/TE = 500/33 ms, 192 × 256 matrix), a high-resolution T2-weighted axial image (TR/TE = 5000/33 ms, 128 × 128 matrix, FOV = 200 × 200mm), and a sagittal 1 mm^3 T1-weighted image. We used FreeSurfer to process 1 mm^3 T1-weighted anatomical images acquired with an MPRAGE sequence. The parameters for the MPRAGE were the following: TR = 2.3 s, TE = 2.91 ms, FOV = 256 mm, matrix = 240 × 256, flip angle = 9°, slice thickness = 1.20 mm, 160 slices. The FreeSurfer image analysis suite (version 5.3.0, http://surfer.nmr.mgh.harvard.edu) surface-based processing pipeline was used to derive measures of volume, cortical thickness, and surface area. FreeSurfer is a well-validated

processing package that has been previously described in detail (Dale et al., 1999; Fischl et al., 1999). We extracted cortical measures based on the Desikan FreeSurfer atlas (Desikan et al., 2006).

2.3.5: Quality assessment of MRI

Structural T1-weighted MRI brain scans were analyzed in an unbiased, whole-brain approach using well-validated analysis and quality control protocols developed for the ENIGMA consortium (Enhancing Neuroimaging Genetics through Meta-Analysis; Thompson et al., 2014), that have previously been applied in large-scale studies of major depression (Schmaal et al., 2016), bipolar disorder (Hibar et al., 2016) and schizophrenia (van Erp et al., 2016). We used the ENIGMA quality assessment pipeline (Thompson et al., 2015) to determine scan quality. Segmented regions were visually inspected and statistically evaluated for outliers following standardized ENIGMA protocols (http://enigma.ini.usc.edu/protocols/imaging-protocols). Briefly, the pipeline includes 3 major steps: (1) extracting and organizing brain measures from FreeSurfer, (2) quality checking the outputs wherein a set of representative cross-sections from each subject are displayed with colored FreeSurfer segmentations, and (3) calculating population summary statistics of the cortical traits and related histograms. Visual inspections of ENIGMA snapshots were completed by 3 separate individuals who were blind to diagnostic status. Scans of 4 22q-dup participants, 3 control participants, and 5 22q-del participants failed the initial quality control assessment. The 22q-dup participant scans were then manually edited using standard procedures (detailed in Jalbrzikowski et al., 2013), after which they passed QC assessment.

2.3.6: Subcortical shape analysis

As conventional subcortical volume analysis may obscure fine-grained differences in anatomical changes, a novel surface-based high-resolution parametric mapping technique was used to investigate shape differences across subjects for all subcortical ROIs (Mamah et al., 2016). This technique is sensitive to subtle volumetric variations (Gutman et al., 2012; Gutman

et al., 2015) that may represent underlying subfield organization (Wang et al., 2008). It has recently shown high vertex-wise heritability, suggesting that shape indexes a biologically valid phenotype (Roshupkin et al., 2016). A growing body of evidence indicates that different diseases have distinct effects on hippocampal subfields (Small et al., 2011); these localized patterns of disease effects may extend to other subcortical structures as well.

Using FreeSurfer segmentations as an initial input for creating the shape models, shape registration was based on existing shape templates and template "medial" models. The shape template was made by registering all subjects to a representative subject. The Euclidean average of these shapes served as the template surface, from which the template medial curve was computed. A point-wise measure of shape morphometry, *radial distance*, was derived for all 14 subcortical ROIs for each subject, using a medial model approach (Gutman et al., 2012; Gutman et al., 2015). For each point $p \in \mathcal{M}$ on the surface, and given a medial curve $c: [0,1] \rightarrow \mathbb{R}^3$, the radial distance is defined by

$$D(p) = \min\{\|c(t) - p\| \,|\, t \in [0,1]\}$$

In this way, radial distance (termed *thickness* henceforth) was calculated in native space for up to 2,500 homologous points across each subcortical structure, providing a detailed index of regional shape differences across subjects. We included only those shape models that passed visual inspection and conformed to T1-weighted MRI anatomical boundaries using the ENIGMA Shape Analysis Quality Assessment Protocol (http://enigma.ini.usc.edu/protocols/imaging-protocols/).

2.3.7: Statistical analysis

The primary statistical analyses were performed in SPSS software version 24 (Chicago, Illinois; RRID: SCR_002865). Additional demographic comparisons and effect size calculations were done in either Matlab version R2015a (Mathworks, Natick, MA; RRID: SCR_001622) or R 3.0.2 (R Core Team, 2016; RRID: SCR_000432). Statistical modeling for shape analyses was carried out using the R stats package (https://stat.ethz.ch/R-manual/R-

devel/library/stats/html/lm.html). We conducted independent samples t-tests for continuous variables and chi-squared tests for categorical variables. For the analyses of relative gene expression differences, we conducted separate univariate analysis of covariance (ANCOVAs) with gene expression level as the dependent variable, CNV status as the independent variable, and age, gender, and RT-qPCR batch as covariates.

Significance testing for our primary analyses was conducted in two steps. First, we determined whether 22q11.2 CNVs had an effect on standard FreeSurfer regions of interest (ROIs) for CT and SA, as well as volumes of subcortical structures and global brain metrics (total intracranial volume, total gray and white matter volume, total SA, and average CT). For this omnibus test, we performed an analysis of covariance (ANCOVA) and false discovery rate (FDR) correction at q = 0.05 (Benjamini & Hochberg, 1995) for the number of regions, for each brain metric. Group (22q-dup, 22q-del, or control) was used as the independent variable, and each ROI was included as the dependent variable with age, sex, and scanner location as covariates. Analyses of cortical and subcortical volume included intracranial volume (ICV) as an additional covariate. Given the considerable variance across different brain structures, we performed an ANCOVA for each ROI independently. Secondly, for regions that passed the FDR-corrected omnibus test, we conducted post-hoc tests for each pairwise comparison, applying the same correction used for the initial omnibus test.

For subcortical shape analyses, a multiple linear regression model was used to assess surface-based thickness differences between 22q-del carriers, 22q-dup carriers, and controls after correcting for age, sex, intracranial volume (ICV), and scanner location. The model was fitted at each point across the surface of each subcortical structure. As these values were calculated in native space, ICV was included as a covariate to regress out effects of head size. To correct for multiple comparisons, a standard FDR correction was again applied at q = 0.05. Statistical models were fitted for the following comparisons of interest: 22q-del carriers vs.

controls; 22q-dup carriers vs. controls; and 22q-dup carriers vs. 22q-del carriers. All results described below are FDR-corrected unless otherwise indicated.

2.3.8: Sensitivity analyses

To determine whether group differences in brain structure are attributable to familial relationships between 22q-dup patients, a sensitivity analysis was conducted on a subset of the duplication cohort comprising only unrelated individuals (N=11), in which we determined whether the parameter estimates for this subset differed from those obtained on the full cohort. Specifically, we tested whether the adjusted means calculated for unrelated subjects were within 2 standard errors of the adjusted means of the full cohort. 22q-dup patients in the subset were selected with the aim of maintaining similar mean age and sex ratios to the control and 22q-del group.

We conducted a similar secondary analysis to rule out the effect of antipsychotic medication on brain structure, in which 8 participants (7 22q-del carriers and 1 22q-dup carrier) who were taking antipsychotic medication at the time of visit were excluded. This approach was chosen as the small sample size of the subgroup precluded a mixed model analysis that explicitly accounted for family structure. Similarly, the confounding of medication use and group made a direct analysis of the effects of antipsychotic medication difficult to interpret. These sensitivity analyses are designed to show that the inclusion/exclusion of these participants does not bias the results.

Additionally, we conducted secondary analyses in which we covaried for: 1) race and 2) global brain metrics (mean cortical thickness and total cortical surface area).

2.4: Results

2.4.1: Neuropsychiatric and cognitive findings

There were significant differences in Full Scale IQ between groups: 22q-del carriers had the lowest IQ scores, followed by 22q-dup carriers, then control participants had the highest IQ

scores (Table 1). The same pattern persisted for the Verbal IQ domain; however, for Nonverbal

IQ (as measured by Matrix Reasoning), 22q-del carriers performed significantly more poorly

than 22q-dup carriers and controls, who did not differ from each other. Four 22q-del carriers and

no 22q-dup carriers were diagnosed with a psychotic disorder, but rates of ASD were elevated

in both groups. 22q-del and 22q-dup carriers had similarly elevated scores on dimensional

measures of autism-relevant symptomatology (SRS and RBS scales) relative to control

participants.

2.4.2: mRNA expression

   As shown in Figure 2.1, RT-qPCR analyses revealed a linear effect of gene dosage on

mRNA expression levels of COMT and ZDHHC8, but not DGCR8 (Figure 1).
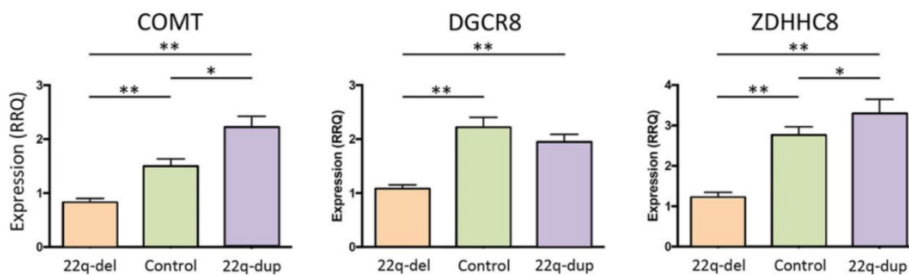
Figure 2.1: Gene Expression. Relative Quantification (RQ) levels of COMT, DGCR8, and

ZDHHC8. COMT and ZDHHC8 expression levels were significantly different between all 3

cohorts, whereas DGCR8 expression only showed significant differences between 22q-del

carriers and controls as well as 22q-del carriers and 22q-dup carriers. * denotes $p < 0.03$. **

denotes $p < 0.001$.

2.4.3: Gene dosage effects on global brain metrics

   There were no significant main effects of scanner location, but significant effects of

group were found for total intracranial volume $(F(2,137)= 7.12$, $p = 0.001)$, total gray matter

volume $(F(2, 136) = 5.43$, $p = 0.005)$, cortical white matter volume $(F(2,136) = 11.88$, $p = 1.76e$-

5), total cortical SA ($F(2,137)$ = 35.37, p = 4.1e-13), mean CT ($F(2,137)$ = 4.60, p = 0.01), and

the corpus callosum ($F(2,136)$ = 7.32, p = 9.6e-4; Figures 2A-2F). Effects of gene dosage

appeared generally proportional in magnitude relative to controls for callosal volume and cortical

thickness, although for total intracranial, gray and white matter volume and SA, the percent

reduction in deletion carriers was more substantial than the relative increase seen in duplication

carriers (Figure 2.2 and Table 2.2). Further, as shown in Figure 2, the effects of this CNV on

brain structure did not appear to be accounted for by a subset of severely affected individuals,

but rather, the entire distribution was shifted, suggesting a highly penetrant effect (Quereshi et

al., 2014). Post-hoc pairwise contrasts revealed that the significant effect of group was driven by

patterns of differences between 22q-del and 22q-dup carriers, as well as 22q-del carriers and

controls.
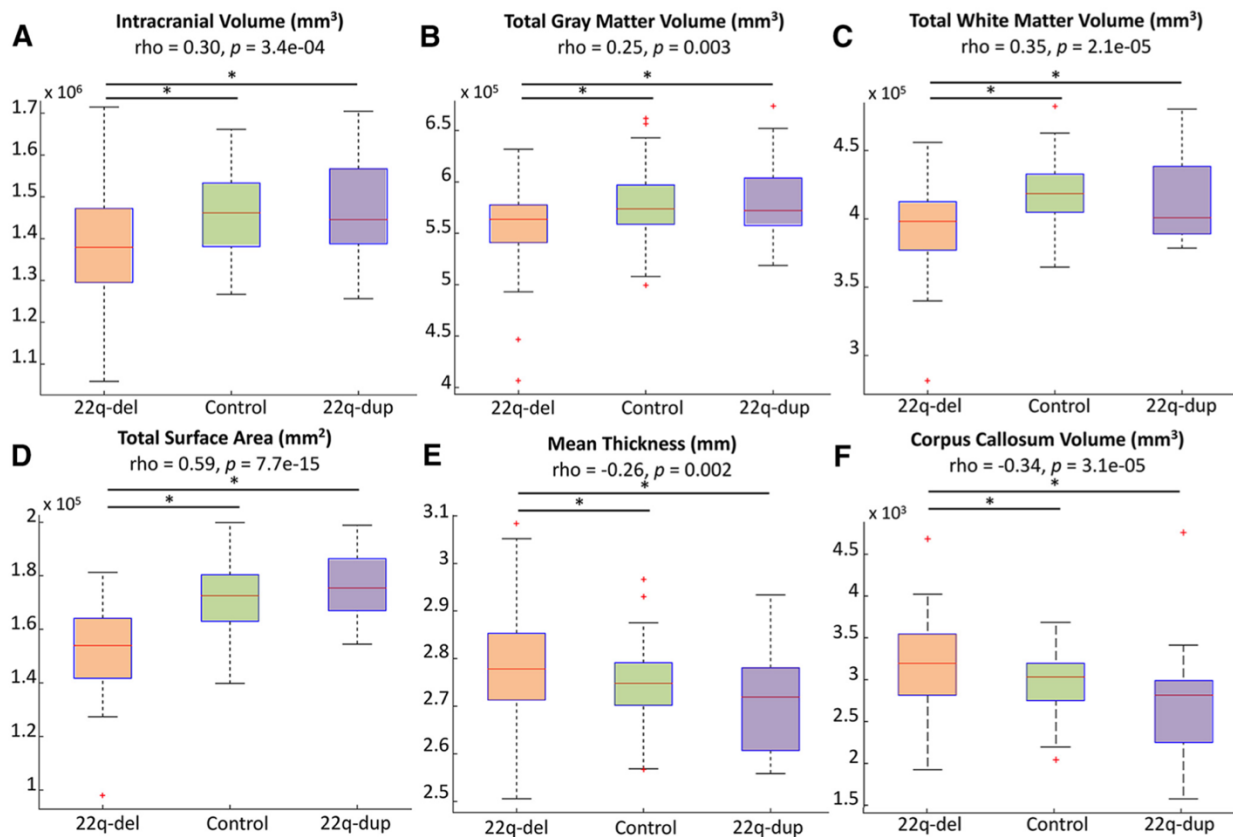
Figure 2.2: Global Brain Metrics. Boxplots of global brain metrics for each individual across

groups adjusted for sex, age, and scanner location (as well as intracranial volume for volumetric

measures). Spearman non-parametric correlations were performed for each measure, indicating

significant gene dosage effects. For all measures, there were significant pairwise differences

between 22q-del and controls that survive post-hoc correction at $p < 0.05$, as denoted by the

asterisks.

Region	F	22q-del Mean (SE)	22q-del % difference from controls	Control, mean (SE)	22q-dup, mean (SE)	22q-dup % difference from controls	dupN
Corpus callosum volume**,†,††	7.3	3195.5 (60.7)	7.6%	2969.3 (64.4)	2723.9 (113.5)	−8.3%	216
Cortical white matter volume**,†,††	11.9	395,129.2 (3381.3)	−5.7%	418,977.0 (3587.9)	415,362.7 (6319.3)	−0.9%	695
Total gray matter**,†,††	5.4	556,341.5 (4785.5)	−3.7%	577,545.6 (5080.0)	581,072.5 (8947.3)	0.6%	>1000
Mean thickness**,†,††	4.6	2.78 (0.01)	1.5%	2.74 (0.01)	2.71 (0.02)	−1.1%	140
Total intracranial volume**,†,††	7.1	1385812.3 (14058.4)	−4.9%	1,456,843.0 (15317.2)	1,466,356.0 (27086.6)	0.7%	403
Total area**,†,††	35.4	152,415.5 (1760.0)	−11.1%	171,524.8 (1917.5)	176,466.1 (3390.9)	2.9%	208

[a]Adjusted means are covaried for age, sex, and scanner location, as well as intracranial volume for volumetric measures.

**Survives FDR correction ($p < 0.05$ threshold) at post hoc level for 22q-dup versus 22q-del.

†Survives FDR correction ($p < 0.05$ threshold) at post hoc level for 22q-del versus control.

††Survives FDR correction ($p < 0.05$ threshold) at omnibus level.

Table 2.2: Global Metrics. Adjusted Means, Standard Errors, Percent Difference from Controls,

and Estimated samples size of 22q11.2 duplication carriers**.**

2.4.4: Effects of reciprocal 22q11.2 variation on cortical thickness.

Omnibus ANCOVA revealed a significant effect of group for 20 ROIs (Table 3). Across

cortical regions, 22q-dup tended to show lower thickness compared to 22q-del with controls

showing an intermediate pattern (Figure 3). Post-hoc pairwise t-tests revealed that compared to

controls, 22q-del showed significantly greater thickness in 8 ROI's and significantly lower

thickness in 1 ROI. In contrast, 22q-dup carriers had significantly lower CT relative to controls,

specifically in 3 lateral frontal and parietal ROIs: the left caudal and superior frontal gyrus, and

the right precuneus (Table 2.3). 22q-dup carriers also showed cortical thinning relative to

controls at a nominal uncorrected $p<0.05$ level in predominantly frontal and sensorimotor

regions (Figure 2.4A). As shown in Figure 3, the decreases in 22q-dup carriers in regional

cortical thickness measures are proportional to the increases observed in 22q-del carriers, albeit

in somewhat different cortical regions; specifically, increased CT in 22q-del carriers was

greatest in the insula and inferior frontal regions, while reductions of CT in 22q-dup were greatest in fronto-parietal regions.

Region	F	22q-del, mean (SE)	Control, mean (SE)	22q-dup, mean (SE)	Region	F	22q-del, mean (SE)	Control, mean (SE)	22q-dup, mean (SE)
Left hemisphere					**Right hemisphere**				
Bank of superior temporal sulcus	2.4	2.65 (0.02)	2.70 (0.02)	2.75 (0.04)	Bank of superior temporal sulcus	0.8	2.83 (0.02)	2.85 (0.03)	2.89 (0.04)
Caudal anterior cingulate gyrus	4.8	2.83 (0.03)	2.95 (0.04)	3.03 (0.07)	Caudal anterior cingulate gyrus	2.7	2.70 (0.03)	2.82 (0.04)	2.78 (0.07)
Caudal middle frontal gyrus*,**,††	18.2	2.82 (0.02)	2.74 (0.02)	2.58 (0.04)	Caudal middle frontal gyrus**,††	12.7	2.75 (0.02)	2.66 (0.02)	2.55 (0.04)
Cuneus	3.3	2.13 (0.02)	2.05 (0.03)	2.04 (0.04)	Cuneus	3.6	2.17 (0.02)	2.11 (0.02)	2.05 (0.04)
Entorhinal cortex	1.6	3.48 (0.04)	3.55 (0.05)	3.38 (0.09)	Entorhinal cortex	1.5	3.81 (0.05)	3.80 (0.05)	3.63 (0.09)
Frontal pole	0.4	2.84 (0.04)	2.89 (0.05)	2.88 (0.09)	Frontal pole	0.8	2.83 (0.04)	2.76 (0.05)	2.84 (0.08)
Fusiform gyrus	0.2	2.90 (0.02)	2.90 (0.02)	2.88 (0.03)	Fusiform gyrus	2.2	3.00 (0.02)	2.95 (0.02)	2.98 (0.03)
Inferior parietal cortex	1.7	2.70 (0.02)	2.69 (0.02)	2.64 (0.03)	Inferior parietal cortex	3.4	2.74 (0.02)	2.70 (0.02)	2.64 (0.03)
Inferior temporal gyrus	0.0	2.88 (0.02)	2.88 (0.03)	2.88 (0.05)	Inferior temporal gyrus	1.0	3.05 (0.02)	3.01 (0.02)	3.03 (0.04)
Insula**,†,††	23.3	3.42 (0.02)	3.25 (0.02)	3.21 (0.04)	Insula†,††	7.5	3.42 (0.02)	3.30 (0.02)	3.29 (0.04)
Isthmus cingulate	1.7	2.78 (0.03)	2.76 (0.04)	2.67 (0.05)	Isthmus cingulate gyrus	0.8	2.65 (0.02)	2.68 (0.03)	2.61 (0.05)
Lateral occipital cortex	0.8	2.35 (0.02)	2.33 (0.02)	2.30 (0.03)	Lateral occipital cortex	1.4	2.42 (0.02)	2.41 (0.02)	2.36 (0.03)
Lateral orbitofrontal cortex	2.8	2.91 (0.02)	2.83 (0.03)	2.86 (0.04)	Lateral orbitofrontal cortex	2.1	2.76 (0.02)	2.70 (0.03)	2.80 (0.05)
Lingual gyrus**,††	9.9	2.30 (0.02)	2.23 (0.02)	2.16 (0.03)	Lingual gyrus**,††	8.3	2.38 (0.02)	2.29 (0.02)	2.24 (0.04)
Medial orbitofrontal cortex	6.7	2.70 (0.03)	2.57 (0.03)	2.52 (0.06)	Medial orbitofrontal cortex	6.1	2.55 (0.03)	2.43 (0.03)	2.39 (0.05)
Middle temporal gyrus	0.7	3.05 (0.02)	3.02 (0.02)	3.04 (0.04)	Middle temporal gyrus	2.3	3.15 (0.02)	3.08 (0.03)	3.09 (0.05)
Paracentral cortex†,††	7.6	2.66 (0.02)	2.55 (0.02)	2.53 (0.04)	Paracentral gyrus**,††	8.9	2.70 (0.02)	2.62 (0.02)	2.51 (0.04)
Parahippocampal gyrus**,†,††	13.0	2.70 (0.04)	2.94 (0.04)	3.02 (0.07)	Parahippocampal gyrus	0.7	2.95 (0.04)	3.01 (0.04)	2.99 (0.07)
Pars opercularis**,†,††	15.2	2.89 (0.02)	2.77 (0.02)	2.75 (0.03)	Pars opercularis	3.3	2.82 (0.02)	2.73 (0.03)	2.73 (0.04)
Pars orbitalis	5.4	3.00 (0.03)	2.90 (0.03)	2.81 (0.06)	Pars orbitalis	2.1	2.83 (0.03)	2.73 (0.04)	2.78 (0.07)
Pars triangularis**,†,††	14.2	2.76 (0.02)	2.61 (0.02)	2.56 (0.04)	Pars triangularis	2.9	2.64 (0.03)	2.53 (0.03)	2.55 (0.06)
Pericalcarine gyrus	5.4	1.85 (0.02)	1.78 (0.02)	1.71 (0.04)	Pericalcarine gyrus†,††	9.7	1.87 (0.02)	1.75 (0.02)	1.72 (0.04)
Postcentral gyrus	6.8	2.28 (0.02)	2.19 (0.02)	2.17 (0.04)	Postcentral gyrus	5.3	2.28 (0.02)	2.20 (0.02)	2.14 (0.04)
Posterior cingulate gyrus	0.0	2.79 (0.02)	2.79 (0.02)	2.79 (0.04)	Posterior cingulate gyrus	2.9	2.72 (0.02)	2.78 (0.02)	2.72 (0.04)
Precentral gyrus**,††	9.9	2.76 (0.02)	2.70 (0.02)	2.61 (0.03)	Precentral gyrus	6.2	2.73 (0.02)	2.65 (0.02)	2.60 (0.04)
Precuneus	4.4	2.67 (0.02)	2.63 (0.02)	2.56 (0.03)	Precuneus*,**,††	11.3	2.70 (0.02)	2.66 (0.02)	2.50 (0.04)
Rostral anterior cingulate gyrus	0.6	3.18 (0.04)	3.14 (0.04)	3.10 (0.07)	Rostral anterior cingulate gyrus	1.9	2.83 (0.03)	2.92 (0.03)	2.92 (0.06)
Rostral middle frontal gyrus**,††	10.3	2.64 (0.02)	2.54 (0.02)	2.46 (0.04)	Rostral middle frontal gyrus**,†,††	9.4	2.46 (0.02)	2.35 (0.02)	2.29 (0.04)
Superior frontal gyrus*,**,††	14.7	3.05 (0.02)	3.00 (0.02)	2.84 (0.04)	Superior frontal gyrus**,††	10.1	2.93 (0.02)	2.88 (0.02)	2.74 (0.04)
Superior parietal cortex	2.7	2.41 (0.02)	2.37 (0.02)	2.32 (0.04)	Superior parietal cortex	3.4	2.40 (0.02)	2.34 (0.02)	2.30 (0.04)
Superior temporal gyrus	5.9	2.90 (0.02)	3.00 (0.02)	2.97 (0.04)	Superior temporal gyrus	0.2	2.99 (0.02)	2.99 (0.02)	3.02 (0.04)
Supramarginal gyrus**,††	9.0	2.86 (0.02)	2.77 (0.02)	2.71 (0.04)	Supramarginal gyrus**,†,††	15.0	2.90 (0.02)	2.79 (0.02)	2.70 (0.04)
Temporal pole	0.3	3.70 (0.04)	3.68 (0.05)	3.74 (0.08)	Temporal pole	0.3	3.92 (0.04)	3.91 (0.05)	3.84 (0.08)
Transverse temporal gyrus	0.5	2.58 (0.03)	2.62 (0.03)	2.57 (0.05)	Transverse temporal gyrus	1.8	2.68 (0.03)	2.60 (0.03)	2.68 (0.06)

[a]Adjusted means are covaried for age, sex, and scanner location.

*Survives FDR correction ($p < 0.05$ threshold) at post hoc level for 22q-dup versus control.

**Survives FDR correction ($p < 0.05$ threshold) at post hoc level for 22q-dup versus 22q-del.

†Survives FDR correction ($p < 0.05$ threshold) at post hoc level for 22q-del versus control.

††Survives FDR correction ($p < 0.05$ threshold) at omnibus level.

Table 2.3: Cortical Thickness. Adjusted Means and Standard Errors.
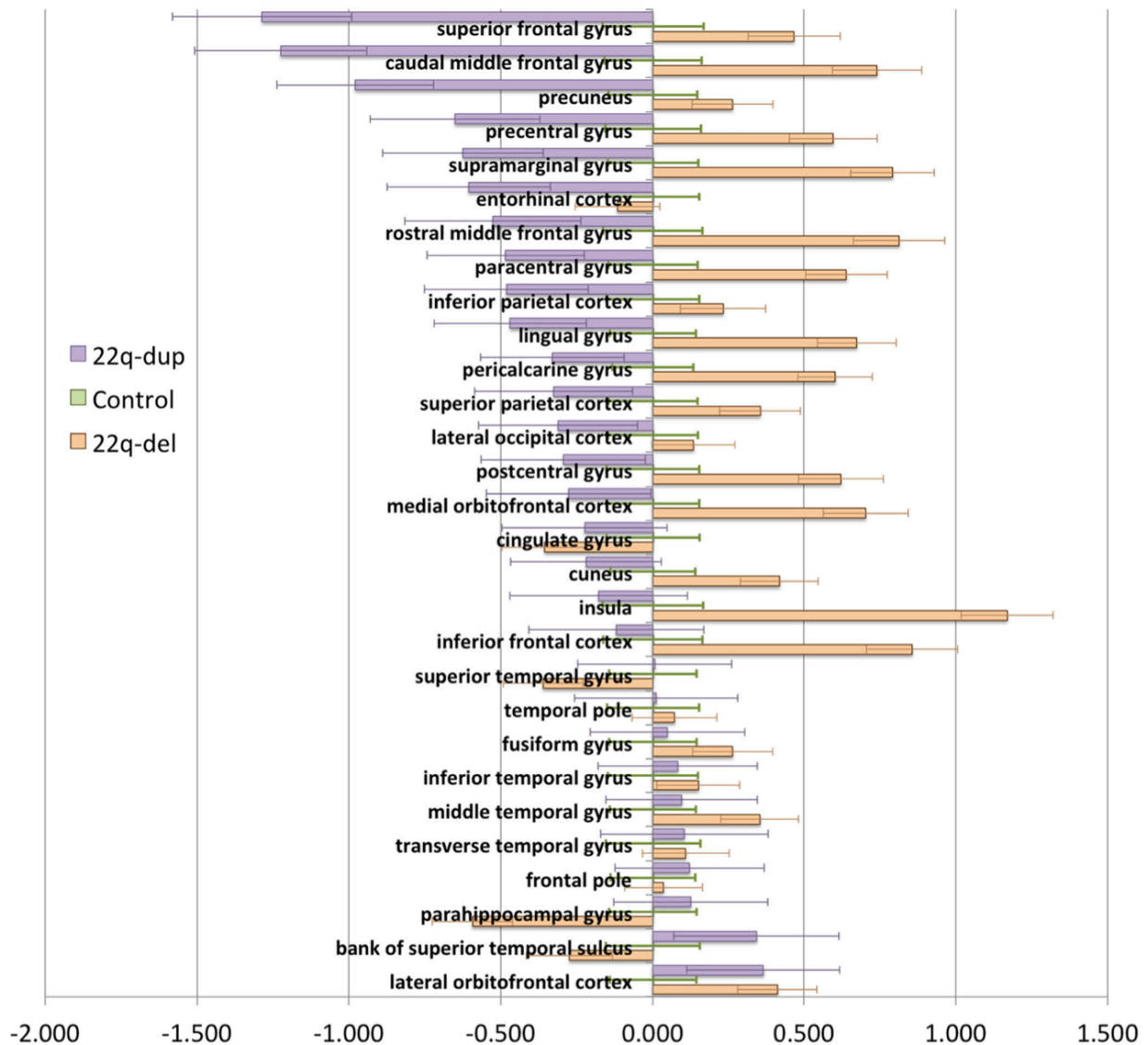
Figure 2.3: Cortical Thickness. Z-score Plots of Estimated Marginal Means and Standard Errors. Z-scores are derived from individual subject means adjusted for sex, age, and scanner location using control mean and standard deviation for each region. Then, Z-scores were submitted to the same primary statistical analysis to generate estimated marginal means and standard errors. 22q-dup showed lower thickness relative to 22q-del patients in predominantly medial frontal and parietal regions, with controls showing an intermediate pattern.
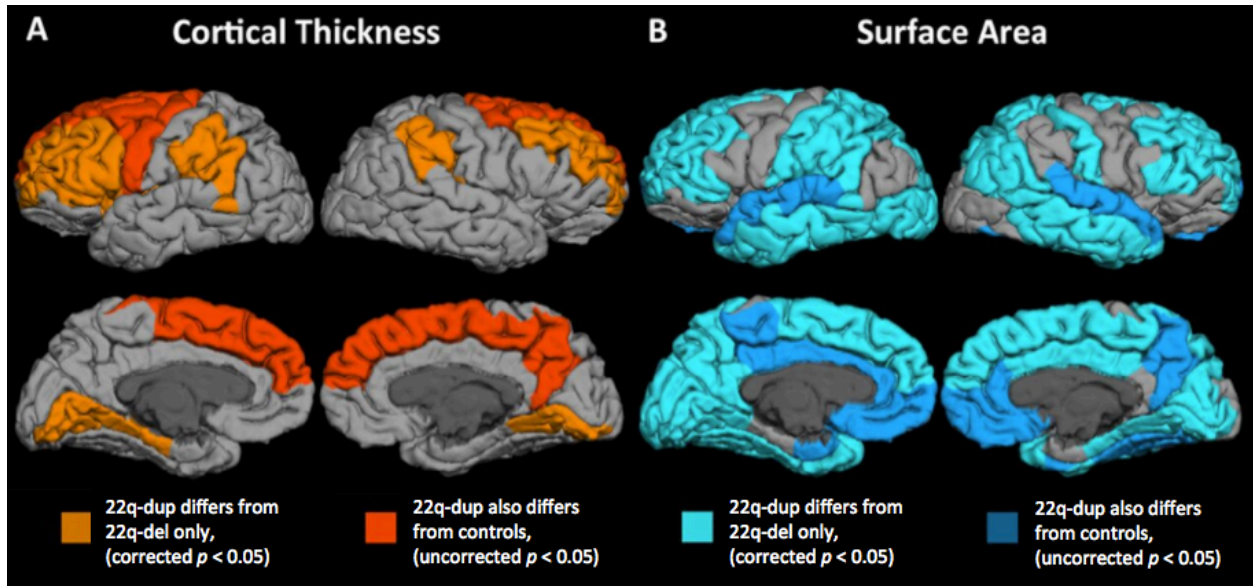
Figure 2.4: **Neuroanatomic differences between 22q-dup carriers, 22q-del carriers and controls: Cortical thickness and surface area.** A. The light orange color indicates regions in which 22q-dup show significant differences in cortical thickness relative to 22q-del (FDR-corrected, $q < 0.05$). Dark orange colors indicate regions in which 22q-dup significantly differs from both 22q-del (corrected) and controls (uncorrected, nominal $p < 0.05$), with 22q-dup showing lower thickness relative to 22q-del and controls in frontal, inferior parietal and parahippocampal regions. B. The light blue color indicates regions in which 22q-dup carriers differ in surface area from 22q-del carriers (FDR-corrected, $q < 0.05$). Dark blue colors indicate regions where 22q-dup differs significantly from both 22q-del (corrected) and controls (uncorrected, nominal $p < 0.05$). 22q-dup carriers show greater surface area relative to 22q-del carriers and controls throughout most of the cortex, except for lateral orbitofrontal, middle frontal, inferior parietal, and right occipital regions.

2.4.5: Opposing effects on cortical surface area.

Pervasive effects of gene dosage were observed for cortical SA with significant effects of group for 52 ROIs (Table 2.4). Cortical SA showed a pattern opposite to that observed for CT:

32

22q-dup carriers largely showed greater SA compared to 22q-del carriers and controls mostly

intermediate (Figure 2.5). No differences between 22q-dup and controls survived correction, but

16 ROIs showed nominally significant differences at an uncorrected $p < 0.05$ level (Figure 2.4B).

These regions included most of the cortex with differences of greatest magnitude observed in

medial frontal cortex, the cingulate, superior temporal gyrus and bank of the superior temporal

sulcus (Figure 5); notably, key components of social cognitive neural circuitry (Lieberman,

2007).

Region	F	22q-del, mean (SE)	Control, mean (SE)	22q-dup, mean (SE)	Region	F	22q-del, mean (SE)	Control, mean (SE)	22q-dup, mean (SE)
Left hemisphere					**Righthemisphere**				
Bank of superior temporal sulcus**,†,††	16.1	941.0 (19.9)	1049.5 (21.7)	1169.4 (38.3)	Bank of superior temporal sulcus**,†,††	24.6	882.7 (16.2)	1031.1 (17.6)	1062.8 (31.2)
Caudal anterior cingulate gyrus**,†,††	37.5	511.8 (15.4)	665.7 (16.8)	756.9 (29.6)	Caudal anterior Cingulate**,†,††	18.2	626.0 (19.5)	785.1 (21.3)	800.5 (37.6)
Caudal middle frontal gyrus	4.5	2172.4 (47.1)	2342.8 (51.3)	2422.2 (90.7)	Caudal middle frontal gyrus	3.4	1936.7 (49.6)	2103.6 (54.1)	2143.2 (95.6)
Cuneus**,†,††	59.7	1139.3 (23.8)	1479.2 (25.9)	1550.7 (45.8)	Cuneus**,†,††	43.6	1213.9 (24.5)	1522.3 (26.6)	1553.4 (47.1)
Entorhinal cortex**,††	6.2	340.5 (10)	369.6 (10.9)	414.1 (19.2)	Entorhinal cortex	5.1	288.0 (8.8)	326.8 (9.6)	328.0 (17)
Frontal pole**,††	6.9	203.2 (3.9)	212.8 (4.3)	234.6 (7.5)	Frontal pole**,††	11.6	270.9 (5.4)	292.4 (5.9)	325.5 (10.4)
Fusiform gyrus**,†,††	28.8	2909.4 (46.1)	3386.8 (50.3)	3416.9 (88.9)	Fusiform gyrus**,†,††	29.0	2807.8 (48.4)	3298.0 (52.7)	3374.1 (93.2)
Inferior parietal cortex	5.5	4415.6 (70.2)	4758.2 (76.5)	4621.3 (135.3)	Inferior parietal cortex**,†,††	13.1	5129.4 (86)	5715.1 (93.7)	5808.7 (165.6)
Inferior temporal gyrus**,†,††	32.0	2832.7 (50.7)	3402.2 (55.3)	3371.4 (97.7)	Inferior temporal gyrus**,†,††	19.0	2746.9 (57)	3237.9 (62.1)	3223.3 (109.9)
Insula	2.5	2020.5 (28.2)	2056.6 (30.7)	2156.5 (54.2)	Insula	0.7	2070.9 (32.7)	2032.4 (35.6)	2112.2 (63)
Isthmus cingulate**,††	8.8	960.2 (19.9)	1012.1 (21.7)	1140.5 (38.3)	Isthmus cingulate	4.4	904.4 (19.5)	920.9 (21.3)	1030.1 (37.7)
Lateral occipital cortex**,†,††	21.5	4315.6 (67)	4851.8 (73)	5082.6 (129.1)	Lateral occipital cortex†,††	13.5	4155.7 (76.2)	4708.4 (83)	4688.1 (146.8)
Lateral orbitofrontal cortex	4.2	2403.1 (38.2)	2551.7 (41.6)	2571.2 (73.6)	Lateral orbitofrontal cortex	3.2	2310.9 (40.6)	2444.1 (44.2)	2475.3 (78.2)
Lingual gyrus**,†,††	43.5	2497.2 (49.2)	3090.4 (53.6)	3238.2 (94.7)	Lingual gyrus**,†,††	57.2	2478.1 (45.7)	3121.8 (49.8)	3246.1 (88.1)
Medial orbitofrontal cortex**,††	9.9	1599.7 (28.5)	1715.3 (31.1)	1860.7 (54.9)	Medial orbitofrontal cortex**,†,††	11.8	1656.8 (25.3)	1783.0 (27.6)	1898.7 (48.7)
Middle temporal gyrus**,†,††	22.3	2719.2 (46.5)	3131.5 (50.7)	3198.6 (89.6)	Middle temporal gyrus**,†,††	15.1	3070.4 (52.6)	3448.2 (57.3)	3531.6 (101.4)
Paracentral gyrus**,†,††	18.1	1222.9 (22.3)	1369.4 (24.3)	1479.8 (42.9)	Paracentral gyrus**,†,††	14.8	1343.5 (29.5)	1559.0 (32.1)	1585.4 (56.8)
Parahippocampal gyrus	4.6	696.3 (14.6)	730.4 (15.9)	790.9 (28.2)	Parahippocampal gyrus**,††	7.3	633.2 (11)	683.1 (12)	708.9 (21.3)
Pars opercularis	1.8	1634.4 (32.7)	1715.0 (35.6)	1731.9 (63)	Pars opercularis	0.3	1348.7 (27.7)	1381.2 (30.2)	1367.4 (53.3)
Pars orbitalis	1.7	602.8 (10.6)	623.2 (11.5)	641.1 (20.4)	Pars orbitalis	3.4	731.5 (12.7)	777.0 (13.8)	777.3 (24.4)
Pars triangularis**,†,††	10.0	1201.2 (25.3)	1345.2 (27.5)	1388.8 (48.7)	Pars triangularis**,†,††	15.5	1328.8 (28.4)	1536.1 (30.9)	1578.3 (54.7)
Pericalcarine gyrus**,†,††	35.5	1070.8 (25.7)	1361.9 (28)	1398.2 (49.6)	Pericalcarine gyrus**,†,††	38.4	1193.6 (26.1)	1514.1 (28.4)	1499.0 (50.3)
Postcentral gyrus**,†,††	17.4	3819.5 (55.9)	4260.0 (61)	4323.3 (107.8)	Postcentral gyrus**,†,††	28.8	3576.2 (58.4)	4170.3 (63.7)	4247.1 (112.6)
Posterior cingulate**,†,††	14.0	1108.8 (21.1)	1226.8 (23)	1326.2 (40.7)	Posteriorcingulate gyrus**,†,††	14.1	1093.6 (23.7)	1256.2 (25.8)	1297.5 (45.6)
Precentral gyrus	1.3	4737.2 (63.4)	4795.0 (69.1)	4960.8 (122.1)	Precentral gyrus	1.4	4722.6 (63.7)	4878.9 (69.4)	4820.4 (122.8)
Precuneus**,†,††	36.3	3296.2 (53.3)	3893.8 (58.1)	4009.7 (102.7)	Precuneus**,†,††	30.6	3427.1 (60.4)	3990.3 (65.8)	4273.1 (116.4)
Rostral anterior cingulate**,†,††	33.7	641.6 (19)	807.5 (20.6)	942.8 (36.5)	Rostral anterior cingulate gyrus**,†,††	15.7	580.8 (16.1)	670.0 (17.5)	761.4 (31)
Rostral middle frontal gyrus**,†,††	26.3	4919.1 (88.9)	5784.2 (96.8)	5892.9 (171.2)	Rostral middle frontal gyrus**,†,††	34.6	5009.6 (88.6)	6005.9 (96.5)	6101.4 (170.6)
Superior frontal cortex**,†,††	15.2	6670.0 (95.9)	7369.3 (104.5)	7495.3 (184.9)	Superior frontal gyrus**,†,††	11.4	6533.1 (98.5)	7113.8 (107.4)	7344.0 (189.9)
Superior parietal cortex**,†,††	47.0	4657.2 (72.2)	5651.2 (78.6)	5539.0 (139)	Superior parietal cortex**,†,††	45.2	4696.4 (66.5)	5536.5 (72.4)	5670.4 (128.1)
Superior temporal gyrus**,††	11.8	3512.4 (51.6)	3756.9 (56.2)	4017.4 (99.4)	Superior temporal gyrus**,†,††	20.8	3241.9 (44.1)	3569.5 (48)	3765.9 (84.9)
Supramarginal gyrus**,††	7.1	3684.9 (60.5)	3958.8 (65.9)	4089.0 (116.5)	Supramarginal gyrus†,††	12.7	3414.5 (61.4)	3671.1 (66.9)	4063.7 (118.3)
Temporal pole**,†,††	18.6	426.2 (7)	483.3 (7.6)	490.2 (13.4)	Temporal pole**,†,††	10.8	381.3 (7.3)	427.2 (8)	432.5 (14.1)
Transverse temporal gyrus**,††	10.6	424.6 (8.6)	463.9 (9.4)	504.0 (16.6)	Transverse temporal gyrus†,††	9.1	302.3 (6.7)	341.2 (7.3)	344.2 (12.9)

[a]Adjusted means are covaried for age, sex, and scanner location.

**Survives FDR correction ($p < 0.05$ threshold) at post hoc level for 22q-dup versus 22q-del.

†Survives FDR correction ($p < 0.05$ threshold) at post hoc level for 22q-del versus control.

††Survives FDR correction ($p < 0.05$ threshold) at omnibus level.

Table 2.4: Surface Area: Adjusted Means and Standard Errors.
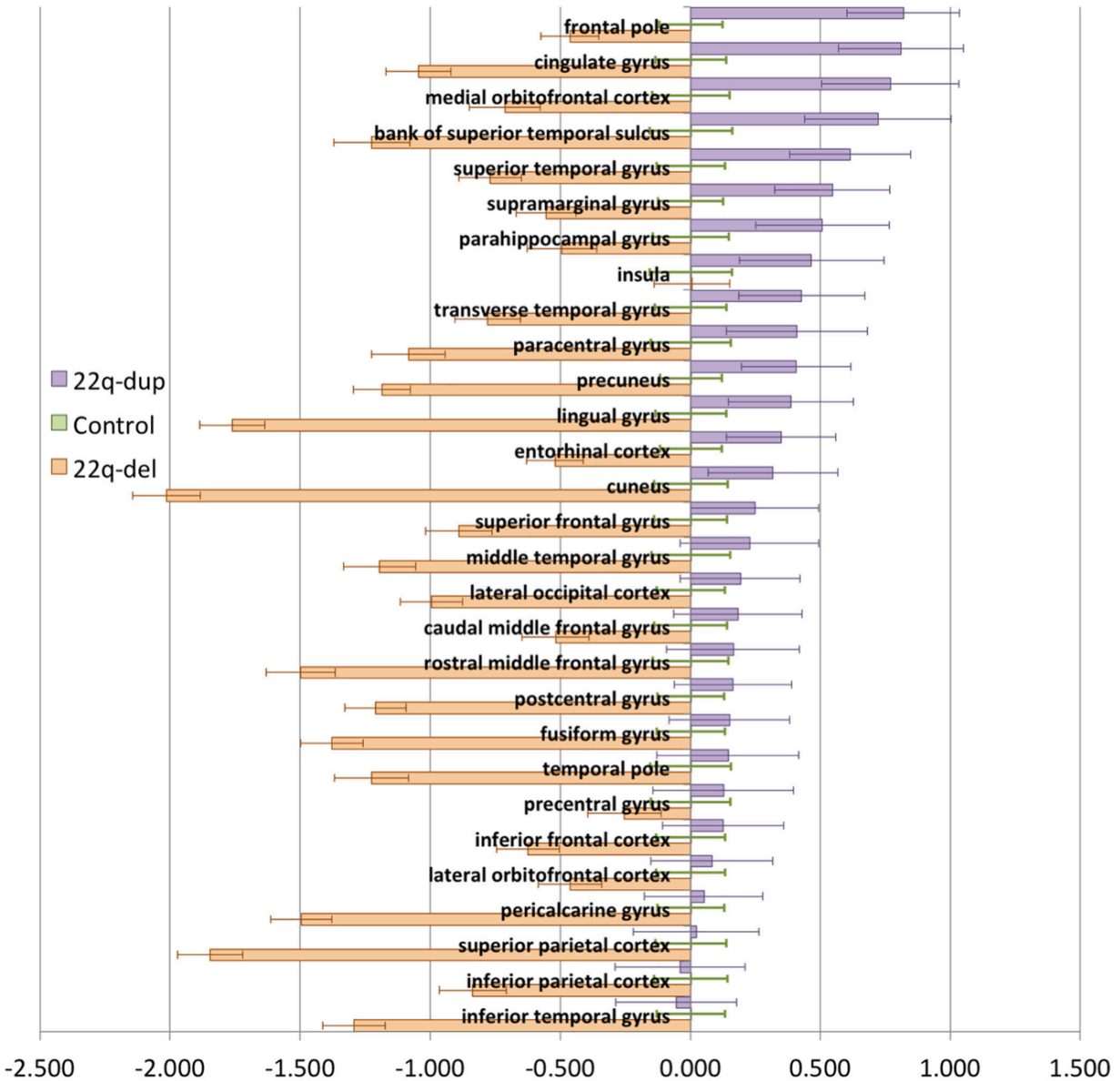
Figure 2.5: Cortical Surface Area: Z-score Plots of Estimated Marginal Means and Standard Errors. Z-scores are derived from individual subject means adjusted for sex, age, and scanner location using control mean and standard deviation for each region. Then, Z-scores were submitted to the same primary statistical analysis to generate estimated marginal means and standard errors. 22q-dup showed greater surface area relative to 22q-del patients in predominantly medial frontal and superior temporal regions, with controls showing an intermediate pattern.

Moreover, there was a notable divergence in the brain regions predominantly affected by the deletion versus duplication. While reductions of cortical SA were of greatest magnitude in parietal regions for 22q-del carriers, SA increases in the duplication group were greatest in fronto-temporal and midline regions (i.e., cingulate cortex).

Effect size plots for 22q-dup carriers vs. controls confirmed a global divergent pattern between CT and SA: SA was larger in 22q-dup carriers relative to controls (median effect size: Cohen's *d*= -0.22) with a negative value indicating larger cortical SA in 22q-dup carriers (Figure 2.6B). Effects on CT, although more localized, were generally in the opposite direction. 22q-dup carriers showed lower thickness relative to controls (median effect size: Cohen's *d*= 0.20), most notably in superior frontal regions (Figure 6A).
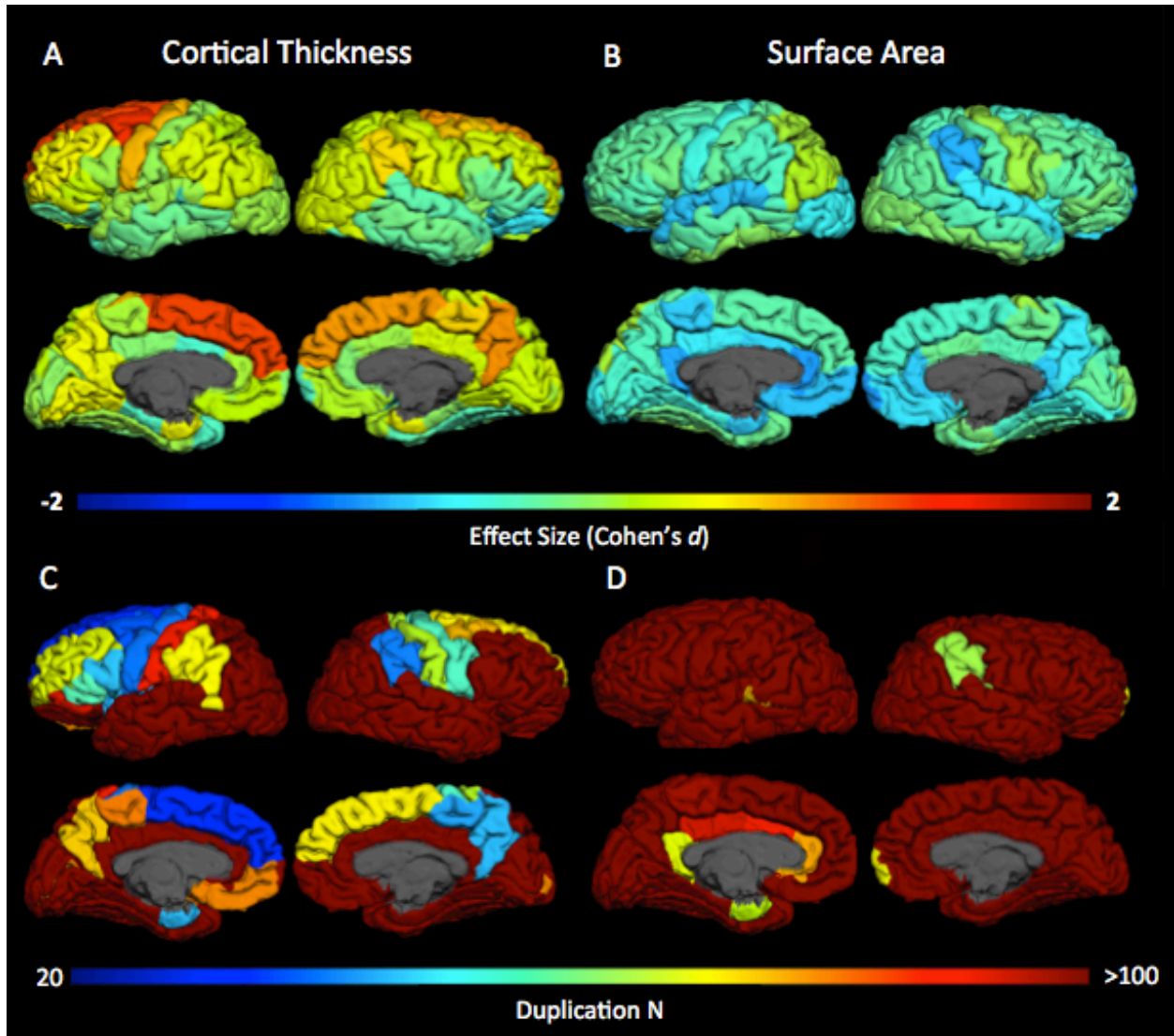
Figure 2.6: Effect size maps for 22q-dup carriers vs. controls. In panels 6a and 6b, Cohen's *d* is displayed for each ROI adjusted for age, sex, and scanner for 22q-dup carriers and controls. Cooler colors indicate regions in which 22q-dup carriers show greater thickness or area, and warmer colors indicate regions in which controls show greater thickness or area. For thickness, effect sizes ranged from -0.5 to 1.4 (median: 0.2), with controls showing greater thickness particularly in medial frontal regions. 22q-dup carriers showed widespread increases in surface area relative to controls, across multiple cortical regions (median effect size: -0.22; range -0.82 – 0.24). Panels 6c and 6d display the estimated number of 22q-dup carriers needed to achieve a statistically significant difference from controls with 80% power, for each ROI. Raw

values (not adjusted for any covariates) and Bonferroni correction for the number of regions were used to reduce model assumptions, resulting in conservative estimates.

2.4.6: Posthoc power analysis for regional cortical thickness and surface area

Maps of post-hoc power calculations, estimating the sample size needed to achieve a significant group difference in 22q-dup carriers vs. controls across cortical regions (Figures 2.6C and 2.6D), indicate that there is substantial regional variability in the effects of the 22q11.2 duplication on brain structure. With a sample size roughly equivalent to that of our deletion and control groups, we would also be likely to find significant thickness differences in additional fronto-parietal regions in the duplication cohort (i.e., the bilateral supramarginal, pre- and post-central gyrus, and left entorhinal cortex and insula). However, much larger samples would be required to observe thickness differences in temporal structures, as indicated by the smaller effect sizes in these regions. The regional distribution of effect sizes differs somewhat for cortical SA (Figure 2.6D). With comparable sample sizes to our deletion and control groups, we would likely identify significant differences in SA in midline and right lateral parietal regions, as well as the frontal pole and left temporal regions (entorhinal cortex, bank of the superior temporal sulcus) in duplication carriers versus controls. However, in other regions the effects were quite small, likely requiring several hundred subjects to detect a significant group difference.

2.4.7: Patterns extend to subcortical structures: volume and morphometry

Significant effects of group extended into subcortical structures. While pairwise differences between 22q-duplication carriers and controls did not survive multiple comparison correction for global subcortical volumes or local shape metrics, there were significant differences between 22q-dup and 22q-del carriers. Pairwise significant differences, indicating lower volume in 22q-del carriers compared to 22q-dup carriers, were found for the right hippocampus (Table 2.5). In contrast, the right caudate displayed an opposite pattern: 22q-del

carriers showed greater volume while 22q-dup showed a decrease in volume compared to controls.

Region	F	22q-del, mean (SE)	Control, mean (SE)	22q-dup, mean (SE)	dupN	Region	F	22q-del, mean (SE)	Control, mean (SE)	22q-dup, mean (SE)	dupN
Left hemisphere						**Right hemisphere**					
Accumbens	2.7	852.7 (15.0)	803.6 (15.9)	807.2 (28.0)	>1000	Accumbens	5.8	815.7 (13.1)	749.6 (13.9)	774.3 (24.5)	>1000
Caudate	4.9	4058.0 (54.2)	3872.5 (57.5)	3729.0 (101.2)	363	Caudate**,†,††	10.5	4423.3 (55.8)	4091.8 (59.3)	3997.7 (104.4)	435
Hippocampus†,††	8.6	3790.8 (56.3)	4132.8 (59.8)	4054.5 (105.3)	>1000	Hippocampus**,†,††	8.2	3789.8 (53.9)	4074.8 (57.2)	4147.3 (100.7)	155
Inferior lateral ventricle**,†,††	17.6	505.4 (26.2)	295.9 (27.8)	263.8 (48.9)	>1000	Inferior lateral ventricle**,†,††	19.0	483.9 (27.7)	239.1 (29.4)	265.1 (51.7)	417
Lateral ventricle†,††	9.4	8339.6 (510.4)	5042.0 (541.6)	6534.2 (953.9)	189	Lateral ventricle†,††	15.0	7967.4 (475.7)	4094.3 (504.7)	6062.3 (888.9)	80
Pallidum	0.4	1787.5 (35.4)	1834.2 (37.5)	1817.2 (66.1)	>1000	Pallidum	0.4	1654.4 (25.0)	1670.5 (26.5)	1704.9 (46.6)	>1000
Putamen	1.0	6468.2 (87.2)	6558.3 (92.5)	6302.9 (162.9)	465	Putamen	1.6	6053.1 (75.0)	6247.9 (79.5)	6092.9 (140.1)	384
Thalamus	1.3	7269.6 (75.4)	7421.2 (80.0)	7484.6 (141.0)	658	Thalamus	1.8	7325.2 (73.2)	7295.5 (77.7)	7033.2 (136.8)	892

[a]Adjusted means are covaried for age, sex, scanner location, and intracranial volume.

**Survives FDR correction ($p < 0.05$ threshold) at post hoc level for 22q-dup versus 22q-del.

†Survives FDR correction ($p < 0.05$ threshold) at post hoc level for 22q-del versus control.

††Survives FDR correction ($p < 0.05$ threshold) at omnibus level.

Table 2.5: Subcortical Volume: Adjusted Means, Standard Errors, and Estimated 22q-dup N

Novel shape analysis methods revealed a widespread and complex pattern of differences in local thickness measures between 22q-del and 22q-dup carriers in subcortical regions (Figure 2.7). Compared to 22q-del carriers, 22q-dup carriers had predominantly greater local thickness in bilateral hippocampal, left thalamus, and right amygdala structures. However, some smaller sub-regions of the hippocampi showed the opposite effect. Based on prior surface-based mapping of hippocampal subfields (Mamah et al., 2016), regions of greater thickness in the 22q-dup carriers approximately correspond to subiculum and CA1 regions, whereas decreased thickness in 22q-dup carriers roughly corresponds to CA2-4/dentate subfield regions. In contrast, largely lower local thickness measures were found in bilateral putamen and caudate structures in 22q-dup relative to 22q-del carriers with small localized

regions of greater thickness.
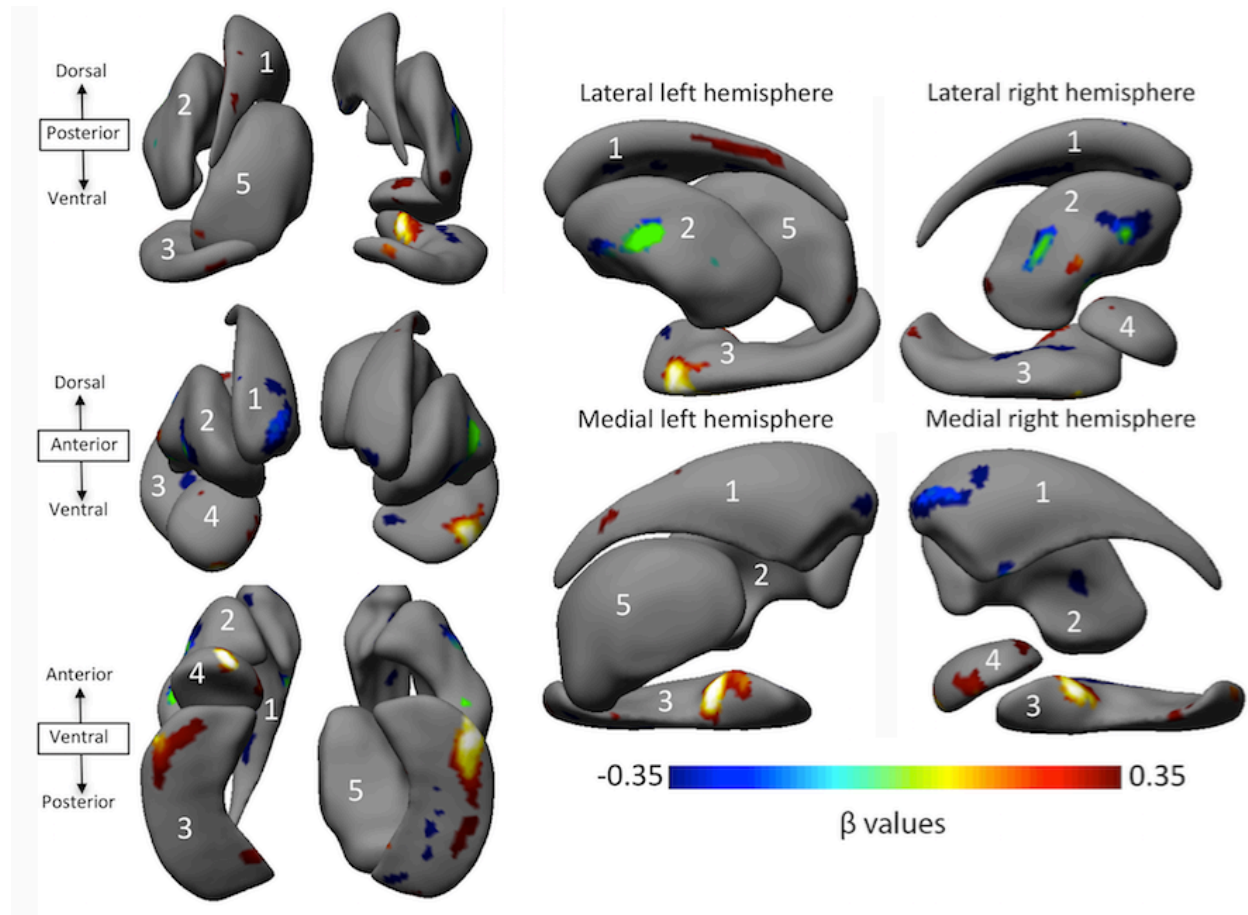
Figure 2.7: Subcortical Shape Differences. Radial distance maps for 22q-dup vs 22q-del carriers, showing β values, adjusted for sex, age, scanner and ICV, for regions passing correction for multiple comparisons at q < 0.05. Cooler colors indicate negative β values (regions of lower local thickness or volume in 22q-dup vs. 22q-del). Warmer colors indicate positive β values (regions of greater local thickness or volume in 22q-dup vs. 22q-del). Only structures which showed differences between 22q-dup and 22q-del that survive correction are displayed, as no significant differences were found between 22q-dup and controls. 1. Caudate; 2. Putamen; 3. Hippocampus; 4. Amygdala; 5. Thalamus.

Sensitivity analyses revealed that neither familial relatedness nor antipsychotic medication generally influenced the parameter estimates of interest. For the subsample of unrelated individuals, the estimated effects for all global metrics, as well as the ROIs showing significant 22q-dup vs. control differences, were all within 2 standard errors of the estimated effects in the primary analyses (Table 2.6). Similarly, the results of the analyses excluding participants on antipsychotics were within 2 standard errors of the estimates obtained in the primary analyses for all ROIs.

Measure	Full dataset 22q-dup adjusted, mean (SE)	Unrelated 22q-dup adjusted, mean (SE)	Within 2 SEs?
Corpus callosum volume	2723.9 (113.5)	2737.4 (149.7)	Yes
Cortical white matter volume	415,362.7 (6319.3)	411,210.5 (8372.5)	Yes
Total gray matter	581,072.5 (8947.3)	5738,25.4 (11956.8)	Yes
Mean thickness	2.71 (0.02)	2.70 (0.03)	Yes
Total intracranial volume	1,466,356.0 (27086.6)	1,466,689.9 (35730.6)	Yes
Total area	176,466.1 (3390.9)	174,713.5 (4522.6)	Yes
Left caudal middle frontal gyrus	2.58 (0.04)	2.56 (0.05)	Yes
Left superior frontal gyrus	2.84 (0.04)	2.83 (0.05)	Yes
Right precuneus	2.50 (0.04)	2.49 (0.05)	Yes

Table 2.6: Full Dataset vs Unrelated 22q-dup patients: Adjusted Means and Standard Errors.

Moreover, covarying for race did not alter our overall pattern of findings. Specifically, significant 22q-dup versus control differences in cortical thickness in all previously identified ROIs (the left caudal and superior frontal gyrus, and the right precuneus) remained significant, and an additional region, the right superior frontal gyrus, was also found to be significantly different.

Finally, after adjusting for mean thickness (Table 2.7), 7 of the 17 ROIs remained significant for 22q-del versus 22q-dup differences. The 3 ROI's in which we observed 22q-dup versus control differences remained significant, regardless of whether average cortical thickness was

included as a covariate or not, indicating localized effects of the 22q11.2 CNV on thickness. In contrast, covarying for total SA reduced the magnitude of deletion–duplication differences in regional SA measures. Specifically, only 8 of the 50 previously identified ROIs remained significantly different for 22q-del versus 22q-dup comparisons (Table 2.8), suggesting that our SA results should be interpreted as a diffuse, global surface deficit in 22q11.2 deletion carriers with additional regional accentuation in occipito-parietal and cingulate regions.

| Region	F	22q-del, mean (SE)	Control, mean (SE)	22q-dup, mean (SE)	Region	F	22q-del, mean (SE)	Control, mean (SE)	22q-dup, mean (SE)
Left hemisphere					**Right hemisphere**				
Bank of superior temporal sulcus**,††	9.3	2.63 (0.02)	2.72 (0.02)	2.8 (0.04)	Bank of superior temporal sulcus	4.9	2.81 (0.02)	2.87 (0.02)	2.94 (0.04)
Caudal anterior cingulate gyrus**,††	9.1	2.81 (0.03)	2.97 (0.04)	3.08 (0.06)	Caudal anterior cingulate gyrus	6.4	2.68 (0.03)	2.84 (0.03)	2.84 (0.06)
Caudal middle frontal gyrus*,**,††,‡	14.4	2.8 (0.01)	2.76 (0.02)	2.63 (0.03)	Caudal middle frontal gyrus**,††,‡	7.7	2.73 (0.02)	2.68 (0.02)	2.6 (0.03)
Cuneus	1.0	2.11 (0.02)	2.07 (0.02)	2.09 (0.04)	Cuneus	0.8	2.15 (0.02)	2.12 (0.02)	2.1 (0.04)
Entorhinal cortex	1.9	3.46 (0.04)	3.57 (0.05)	3.44 (0.08)	Entorhinal cortex	0.8	3.78 (0.05)	3.82 (0.05)	3.69 (0.09)
Frontal pole	2.3	2.81 (0.04)	2.92 (0.04)	2.96 (0.08)	Frontal pole	1.1	2.8 (0.04)	2.78 (0.04)	2.92 (0.08)
Fusiform gyrus	1.1	2.89 (0.01)	2.91 (0.02)	2.93 (0.03)	Fusiform gyrus	1.9	2.99 (0.01)	2.97 (0.01)	3.03 (0.03)
Inferior parietal cortex	0.9	2.69 (0.01)	2.71 (0.01)	2.69 (0.02)	Inferior parietal cortex	0.4	2.72 (0.01)	2.71 (0.01)	2.69 (0.02)
Inferior temporal gyrus	1.7	2.86 (0.02)	2.9 (0.02)	2.94 (0.04)	Inferior temporal gyrus	1.4	3.03 (0.02)	3.03 (0.02)	3.09 (0.03)
Insula**,†,††,‡	18.6	3.4 (0.02)	3.26 (0.02)	3.26 (0.03)	Insula	3.9	3.4 (0.02)	3.32 (0.02)	3.35 (0.04)
Isthmus cingulate	0.7	2.77 (0.03)	2.78 (0.03)	2.71 (0.05)	Isthmus cingulate	1.5	2.64 (0.02)	2.69 (0.02)	2.66 (0.04)
Lateral occipital cortex	0.2	2.33 (0.01)	2.34 (0.02)	2.35 (0.03)	Lateral occipital cortex	0.6	2.4 (0.02)	2.43 (0.02)	2.4 (0.03)
Lateral orbitofrontal cortex	2.1	2.89 (0.02)	2.86 (0.02)	2.93 (0.03)	Lateral orbitofrontal cortex	6.2	2.73 (0.02)	2.73 (0.02)	2.86 (0.04)
Lingual gyrus	5.3	2.29 (0.02)	2.24 (0.02)	2.2 (0.03)	Lingual gyrus	4.0	2.37 (0.02)	2.31 (0.02)	2.29 (0.03)
Medial orbitofrontal cortex	3.2	2.67 (0.03)	2.59 (0.03)	2.57 (0.05)	Medial orbitofrontal cortex	2.3	2.52 (0.02)	2.46 (0.02)	2.45 (0.04)
Middle temporal gyrus	0.8	3.03 (0.02)	3.03 (0.02)	3.08 (0.04)	Middle temporal gyrus	0.9	3.12 (0.02)	3.1 (0.02)	3.15 (0.04)
Paracentral gyrus	3.9	2.65 (0.02)	2.57 (0.02)	2.58 (0.04)	Paracentral gyrus	4.8	2.68 (0.02)	2.64 (0.02)	2.55 (0.04)
Parahippocampal gyrus**,†,††,‡	17.5	2.68 (0.04)	2.95 (0.04)	3.06 (0.07)	Parahippocampal gyrus	2.0	2.93 (0.04)	3.02 (0.04)	3.04 (0.07)
Pars opercularis†,††,‡	11.4	2.87 (0.01)	2.78 (0.01)	2.8 (0.02)	Pars opercularis	1.1	2.79 (0.02)	2.76 (0.02)	2.8 (0.04)
Pars orbitalis	2.0	2.98 (0.03)	2.93 (0.03)	2.88 (0.05)	Pars orbitalis	1.4	2.8 (0.03)	2.75 (0.03)	2.86 (0.06)
Pars triangularis†,††,‡	9.6	2.74 (0.02)	2.63 (0.02)	2.63 (0.03)	Pars triangularis	1.2	2.61 (0.03)	2.56 (0.03)	2.62 (0.05)
Pericalcarine gyrus	2.6	1.84 (0.02)	1.79 (0.02)	1.75 (0.04)	Pericalcarine gyrus	6.5	1.86 (0.02)	1.76 (0.02)	1.74 (0.04)
Postcentral gyrus	3.0	2.26 (0.02)	2.21 (0.02)	2.23 (0.03)	Postcentral gyrus	1.6	2.26 (0.02)	2.22 (0.02)	2.19 (0.04)
Posterior cingulate	0.8	2.78 (0.02)	2.81 (0.02)	2.82 (0.04)	Posterior cingulate	3.9	2.71 (0.02)	2.79 (0.02)	2.75 (0.04)
Precentral gyrus	5.3	2.74 (0.01)	2.72 (0.01)	2.65 (0.02)	Precentral gyrus	2.0	2.71 (0.02)	2.67 (0.02)	2.65 (0.03)
Precuneus	1.3	2.65 (0.01)	2.65 (0.01)	2.61 (0.02)	Precuneus*,**,††,‡	8.5	2.68 (0.02)	2.68 (0.02)	2.56 (0.03)
Rostral anterior cingulate	0.2	3.15 (0.03)	3.17 (0.03)	3.18 (0.06)	Rostral anterior cingulate	6.2	2.81 (0.03)	2.94 (0.03)	2.98 (0.06)
Rostral middle frontal gyrus	5.3	2.62 (0.02)	2.56 (0.02)	2.53 (0.03)	Rostral middle frontal gyrus	4.6	2.44 (0.02)	2.37 (0.02)	2.36 (0.03)
Superior frontal cortex*,**,††,‡	12.1	3.03 (0.01)	3.02 (0.01)	2.89 (0.03)	Superior frontal cortex	6.3	2.91 (0.01)	2.9 (0.02)	2.8 (0.03)
Superior parietal cortex	0.1	2.39 (0.02)	2.39 (0.02)	2.38 (0.03)	Superior parietal cortex	0.3	2.38 (0.02)	2.36 (0.02)	2.35 (0.03)
Superior temporal gyrus†,††,‡	23.0	2.87 (0.02)	3.01 (0.02)	3.03 (0.03)	Superior temporal gyrus	4.2	2.97 (0.02)	3.01 (0.02)	3.08 (0.03)
Supramarginal gyrus	4.1	2.84 (0.01)	2.79 (0.02)	2.76 (0.03)	Supramarginal gyrus**,†,††,‡	11.1	2.87 (0.01)	2.81 (0.01)	2.76 (0.02)
Temporal pole	1.1	3.67 (0.04)	3.69 (0.05)	3.8 (0.08)	Temporal pole	0.1	3.9 (0.04)	3.92 (0.05)	3.89 (0.08)
Transverse temporal gyrus	2.8	2.55 (0.03)	2.64 (0.03)	2.63 (0.05)	Transverse temporal gyrus	1.9	2.66 (0.03)	2.62 (0.03)	2.73 (0.05)

[a]Adjusted means are covaried for age, sex, scanner location, and mean thickness.

**Survives FDR correction ($p < 0.05$ threshold) at post hoc level for 22q-dup versus 22q-del.

†Survives FDR correction ($p < 0.05$ threshold) at post hoc level for 22q-del versus control.

††Survives FDR correction ($p < 0.05$ threshold) at omnibus level.

‡FDR-corrected omnibus effect as well as FDR-corrected del-dup or dup-con difference that remain significant with inclusion of mean thickness covariate.

Table 2.7: Cortical Thickness with Additional Mean Thickness Covariate: Adjusted Means and Standard Errors.

Region	F	22q-del, mean (SE)	Control, mean (SE)	22q-dup, mean (SE)	Region	F	22q-del, mean (SE)	Control, mean (SE)	22q-dup, mean (SE)
Left hemisphere					**Right hemisphere**				
Bank of superior temporal sulcus	3.0	1012.1 (19.2)	1003.3 (19.2)	1092.9 (33.8)	Bank of superior temporal sulcus	2.3	944 (15.2)	991.3 (15.3)	996.9 (26.8)
Caudal anterior cingulate gyrus**,††,‡	9.5	562.7 (15.3)	632.6 (15.3)	702.1 (26.9)	Caudal anterior cingulate gyrus	3.2	674.4 (20.8)	753.7 (20.8)	748.4 (36.6)
Caudal middle frontal gyrus	1.6	2347.8 (44.7)	2229 (44.8)	2233.6 (78.7)	Caudal middle frontal gyrus	2.3	2122.7 (47)	1982.9 (47.1)	1943.2 (82.7)
Cuneus**,†,††,‡	21.4	1207.1 (24.6)	1435.2 (24.7)	1477.9 (43.4)	Cuneus†,††,‡	9.2	1315.4 (21.9)	1456.4 (21.9)	1444.3 (38.5)
Entorhinal cortex	1.4	361 (10.9)	356.3 (10.9)	392 (19.2)	Entorhinal cortex	1.1	298.1 (10)	320.3 (10)	317.1 (17.6)
Frontal pole	3.0	208 (4.4)	209.6 (4.4)	229.4 (7.8)	Frontal pole	4.0	280.2 (6)	286.3 (6)	315.4 (10.5)
Fusiform gyrus	3.8	3089.4 (42.8)	3269.9 (42.8)	3223.2 (75.3)	Fusiform gyrus	1.7	3039.8 (38.2)	3147.4 (38.3)	3124.6 (67.2)
Inferior parietal cortex**,††	8.9	4753.7 (55.1)	4539.3 (55.2)	4257.6 (97)	Inferior parietal cortex	0.4	5522.2 (71.2)	5460 (71.4)	5386.2 (125.4)
Inferior temporal gyrus	4.8	3060.1 (42.8)	3254.6 (42.8)	3126.8 (75.3)	Inferior temporal gyrus	1.1	3016.1 (45.8)	3063.2 (45.8)	2933.7 (80.6)
Insula†,††	12.9	2150.5 (23.1)	1972.2 (23.1)	2016.7 (40.7)	Insula†,††	12.0	2188.7 (31.5)	1955.9 (31.6)	1985.6 (55.5)
Isthmus cingulate	5.5	1035.8 (18.7)	962.9 (18.7)	1059.1 (32.9)	Isthmus cingulate†,††	11.2	987.4 (17.2)	867.1 (17.2)	940.8 (30.3)
Lateral occipital cortex	0.9	4603.4 (58.5)	4665 (58.6)	4773 (102.9)	Lateral occipital cortex	1.4	4513.9 (61.4)	4475.9 (61.5)	4302.8 (108.1)
Lateral orbitofrontal cortex**,†,††	12.7	2602.7 (26.8)	2422.1 (26.8)	2356.5 (47.1)	Lateral orbitofrontal cortex**,†,††	8.7	2504 (32.2)	2318.7 (32.3)	2267.5 (56.8)
Lingual gyrus**,†,††,‡	9.3	2691.7 (45.2)	2964.1 (45.3)	3028.9 (79.6)	Lingual gyrus**,†,††	16.1	2663.8 (41.4)	3001.2 (41.5)	3046.4 (72.9)
Medial orbitofrontal cortex	2.7	1712.5 (26.2)	1642 (26.3)	1739.3 (46.2)	Medial orbitofrontal cortex	2.2	1767.2 (21.8)	1711.4 (21.8)	1779.9 (38.4)
Middle temporal gyrus	0.3	2947.1 (35.8)	2983.6 (35.8)	2953.5 (62.9)	Middle temporal gyrus	1.5	3349.2 (36)	3267.2 (36)	3231.7 (63.3)
Paracentral gyrus	1.8	1311.3 (20.5)	1312 (20.5)	1384.8 (36.1)	Paracentral gyrus	0.2	1466.5 (26.3)	1479.2 (26.3)	1453.1 (46.2)
Parahippocampal gyrus	1.6	735.3 (15.4)	705 (15.4)	748.9 (27.1)	Parahippocampal gyrus	0.4	672.3 (10.7)	657.8 (10.7)	666.9 (18.9)
Pars opercularis	3.3	1750.8 (31.7)	1639.5 (31.7)	1606.7 (55.7)	Pars opercularis**,†,††	9.8	1458.5 (25.4)	1309.9 (25.5)	1249.2 (44.8)
Pars orbitalis	4.1	641.3 (10.1)	598.3 (10.2)	599.6 (17.8)	Pars orbitalis	2.1	777.3 (12.2)	747.3 (12.2)	728.1 (21.5)
Pars triangularis	0.0	1290.9 (24.5)	1287 (24.6)	1292.4 (43.2)	Pars triangularis	0.7	1425.3 (28)	1473.4 (28)	1474.5 (49.2)
Pericalcarine gyrus†,††,‡	8.3	1153.1 (25.9)	1308.5 (25.9)	1309.6 (45.6)	Pericalcarine gyrus†,††,‡	10.2	1279.5 (26)	1458.4 (26.1)	1406.7 (45.8)
Postcentral gyrus	0.1	4075.6 (46.3)	4093.8 (46.4)	4047.8 (81.5)	Postcentral gyrus	2.1	3845.7 (48)	3995.4 (48.1)	3957.2 (84.5)
Posterior cingulate	1.5	1190 (19.7)	1174.1 (19.8)	1238.9 (34.7)	Posterior cingulate	0.0	1196.4 (20.5)	1189.4 (20.5)	1186.8 (36)
Precentral gyrus†,††	14.8	5030.1 (52)	4604.7 (52.1)	4645.7 (91.5)	Precentral gyrus**,†,††	21.7	5049.7 (45.9)	4666.6 (46)	4468.5 (80.8)
Precuneus	4.5	3542.2 (43.8)	3734 (43.9)	3745 (77.1)	Precuneus	2.5	3733.5 (44.3)	3791.4 (44.4)	3943.5 (78)
Rostral anterior cingulate	6.8	729.4 (15.5)	750.5 (15.5)	848.3 (27.2)	Rostral anterior cingulate	2.5	638.4 (15.5)	632.6 (15.6)	699.4 (27.3)
Rostral middle frontal gyrus	0.6	5387.4 (61.3)	5480.1 (61.4)	5389.1 (108)	Rostral middle frontal gyrus	3.1	5473.6 (61.8)	5704.7 (61.9)	5602.3 (108.7)
Superior frontal cortex	2.3	7192.6 (62)	7030 (62.1)	6933.1 (109.2)	Superior frontal cortex	5.6	7073.8 (62.7)	6762.8 (62.8)	6762.4 (110.4)
Superior parietal cortex†,††,‡	13.6	4941.4 (66.6)	5466.6 (66.7)	5233.2 (117.2)	Superior parietal cortex†,††,‡	10.6	4952 (62.1)	5370.5 (62.2)	5395.4 (109.4)
Superior temporal gyrus	6.4	3776 (37.4)	3585.7 (37.5)	3733.8 (65.9)	Superior temporal gyrus	1.3	3457.6 (33.9)	3429.4 (34)	3533.8 (59.7)
Supramarginal gyrus	1.3	3933 (54.4)	3797.7 (54.5)	3822.2 (95.8)	Supramarginal gyrus	5.2	3682.6 (52.9)	3497 (53)	3775.3 (93.1)
Temporal pole	3.7	442.6 (7.5)	472.7 (7.5)	472.6 (13.2)	Temporal pole	2.9	391.3 (8.3)	420.7 (8.3)	421.8 (14.6)
Transverse temporal gyrus	1.5	451.3 (8.7)	446.5 (8.7)	475.2 (15.4)	Transverse temporal gyrus	0.3	321.5 (7)	328.7 (7)	323.6 (12.2)

^{a}Adjusted means are covaried for age, sex, scanner location, and total area.

**Survives FDR correction ($p < 0.05$ threshold) at post hoc level for 22q-dup versus 22q-del.

†Survives FDR correction ($p < 0.05$ threshold) at post hoc level for 22q-del versus control.

††Survives FDR correction ($p < 0.05$ threshold) at omnibus level.

‡FDR-corrected omnibus effect as well as FDR-corrected del-dup or dup-con difference that remain significant with inclusion of total area covariate.

Table 2.8: Surface Area with Additional Total Area Covariate: Adjusted Means and Standard Errors.

2.5: Discussion

22q11.2 copy number variation was associated with global opposing effects on brain structure, involving widespread cortical SA reductions in deletion carriers with corresponding enlargement in duplication carriers. CT showed an opposite, more localized pattern. These findings were not accounted for by a subset of individuals, but rather the entire distribution was shifted, suggesting a highly penetrant effect of gene dosage.

2.5.1: 22q11.2 gene dosage implications for neuropsychiatric disorders

There is now replicated evidence that duplications at 22q11.2 are substantially less common in schizophrenia cases than in the general population, but reciprocal deletions are an established strong risk factor for schizophrenia (Rees et al., 2014, 2016). Our findings suggest a possible underlying neurobiological basis for these divergent behavioral phenotypes. We found opposing effects of CT and SA in in 22q-del vs. 22q-dup in medial temporal and frontal brain regions strongly implicated in idiopathic schizophrenia (Shepherd et al., 2012; Palaniyappan et al., 2011), suggesting relevant underlying brain mechanisms that may be selective for schizophrenia. Alternatively, since both 22q-del and 22q-dup confer increased risk for ASD, opposing effects in common brain regions implicated in autism (e.g., decreased vs. increased SA in medial frontal regions in 22q-del and 22q-dup, respectively; Ecker et al., 2013; Ohta et al., 2016, Wallace et al., 2015) may result in similar downstream phenotypic effects on traits such as language delay and reciprocal social behavior deficits. Future, prospective longitudinal brain-behavior investigations in these two groups are necessary to test these hypotheses.

2.5.2: 22q11.2 gene dosage effects on brain structure

Critical to our study framework, we separately measured CT and SA, two cortical measures that likely have different phylogenetic and ontogenetic origins (Rakic, 1995; Panizzon et al., 2009) and distinct developmental trajectories (Raznahan et al., 2011; Wierenga et al., 2014). Our findings of opposing directions of effect, as well as more pervasive effects of the 22q1l CNV on SA relative to CT, suggest that different mechanisms may be involved. In particular, increased progenitor cell production during early embryonic development predominantly influences SA expansion (Rakic, 1988); thus, widespread SA decreases in 22q-del may reflect reduced production of progenitor cells in multiple cortical areas, implying that these divergent phenotypes arise early in the course of development. Nevertheless, these effects were not entirely proportional in magnitude, as deletions conferred a relatively larger "hit" to SA and to global brain volume metrics than did duplications. This pattern is consistent with

the relatively milder effect of 22q-dup on cognition, which aligns with epidemiologic findings that duplication CNVs tend to have less deleterious effects on cognition (Männik et al., 2015). Widespread SA reductions in 22q-del, with more subtle increases for 22q-dup, may be a potential mechanism underlying differential deficits in cognition associated with deletions at this locus. However, regional CT decreases in 22q-dup were proportional to the increases observed in deletion carriers, albeit in somewhat different cortical regions.

While deletion-duplication differences in SA were widespread throughout the cortex, including fronto-temporal regions critical for language (Friederici & Gierhan, 2013) and medial and lateral frontal and parietal regions implicated in self-referential thought and social perception (Kennedy & Adolphs, 2012), effects on CT were more localized. Despite the notable divergence in the specific brain regions predominantly affected by the deletion versus duplication, regions with the greatest magnitude of effects are notable in their shared role in social–cognitive neural circuitry (Adolphs, 2009; Lieberman, 2007).

The overall patterns detected in the cortex persisted into subcortical regions, previously shown to be affected by 22q-del (Bish et al., 2004; Kates et al., 2004), suggesting global effects of 22q11.2 CNV on brain development. Our novel shape analysis revealed localized patterns of subcortical alteration, which may correspond to underlying anatomic subfields that cannot be resolved by conventional volumetric approaches (Mamah et al., 2016). We found largely higher local thickness in 22q-dup relative to 22q-del carriers in bilateral hippocampal, left thalamus, and right amygdala structures; the opposite pattern was observed for bilateral putamen and caudate structures, which together form the dorsal striatum and importantly contain the same types of neurons and circuits (Alexander & Crutcher, 1990). Local and global hippocampal reductions in 22q-del are consistent with findings in a mouse model, indicating decreased density of dendritic spines and glutamatergic synapses as well as impaired dendritic growth, in primary hippocampal neurons (Mukai et al., 2008). To our knowledge, no pre-clinical models of the reciprocal duplication have yet been developed; thus, it is unclear the extent to which our

human findings are recapitulated in animal models. Future work aims to map known subfields to subcortical surface models so that stronger inferences may be made regarding the underlying compartmental effects detected by this shape analysis technique.

2.5.3: Genes critical for cortical circuit formation in the 22q11.2 locus

The 22q11.2 region houses many genes highly conserved in model organisms and expressed in the developing brain. Some 22q11.2 genes are selectively expressed in cortical progenitors in the ventricular/subventricular zones (e.g., *Ranbp1* and *Cdc45l*), whereas others, including *Dgcr8*, a microRNA processing co-factor, are more broadly expressed in cortical neurons (Meechan et al., 2015). As many of these genes are expressed early in development, diminished dosage of multiple 22q11.2 genes may lead to compromised proliferative and neurogenic capacity of neuronal precursors.

While the function of individual 22q11.2 genes in the developing cortex remains poorly understood, *Ranbp1* gene dosage remains a candidate mechanism as a regulator of early nervous system development (Paronett et al., 2015). *Ranbp1* homozygous null mouse embryos are either exencephalic or microcephalic at early stages. *Ranbp1* plays a role in rapidly dividing precursors in the developing cortex, loss of which may compromise the overall pool of cortical radial glial progenitors, resulting in a smaller brain. *Ranbp1−/−* embryos were found to have selectively disrupted layer 2/3 cortical projection neuron generation, suggesting an important role in cortical circuit development. In addition, a haplotype block including the *RANBP1* and *DGCR8* genes was associated with idiopathic schizophrenia (Liu et al., 2002). Thus, targeted studies of the effects of over- and under-expression of *Ranbp1* and other key neurodevelopmental genes in the locus are warranted.

2.5.4: Gene-dosage effects in other reciprocal CNVs

Notably, dose-dependent effects of two other neuropsychiatric CNVs (15q11.2 BP1-BP2 and 16p11.2) on brain structure have recently been discovered. Our findings of similar diametric patterns in the 22q11.2 locus suggest that this anthropometric variation may be regulated by

multiple, distinct genomic regions. Consistent with our 22q11.2 findings, in the Icelandic population Stefansson and colleagues (2014) found a positive gene dosage effect of 15q11.2 on gray matter volume, whereas corpus callosum size was lower in 15q11.2 duplication relative to deletion carriers. Further, convergent findings across 16p11.2 mouse and human studies indicate pervasive effects of gene dosage across cortical and subcortical structures, suggesting the role of genes important in early development (Horev et al., 2011; Quereshi et al., 2014). Similar to our results, reciprocal variation at 16p11.2 revealed widespread alterations in SA (Quereshi et al., 2014); intriguingly, however, the pattern of findings was in the opposite direction (deletion> control>duplication). Thus, while gene dosage is associated with opposing brain phenotypes across these "neuropsychiatric" CNVs, deletion or duplication of genomic material does not consistently determine the direction of effect. Finally, in a zebrafish model, Golzio and colleagues (2012) identified a single gene at the 16p11.2 locus, *KCTD13*, that is likely responsible for the opposing brain phenotypes, as it causes microcephaly when overexpressed and macrocephaly when suppressed. It is not yet known whether the patterns observed for 22q11.2 are attributable to a single gene or an oligogenic effect.

2.5.5: Study limitations

Several limitations of our study must be noted, such as the modest sample size of our 22q-dup group. As the first study to investigate effects of reciprocal genomic variation in this region, these results should be confirmed in subsequent, larger investigations. Additionally, given the duplication's inheritance pattern (Wentzel et al., 2008), many participants in this group were related. Although effect sizes for our main findings did not substantively change when removing related individuals, we could not entirely disentangle familial effects from those of the duplication itself. Additionally, the two CNV groups contained a greater proportion of subjects of European ancestry than the control group; nevertheless, covarying for race did not alter the significant findings. Further, although 22q-dup carriers did not differ in nonverbal IQ from controls, it was not possible to match nonverbal IQ of duplication to deletion carriers. Crucially,

however, our sample was highly representative of the phenotypic spectrum of 22q11.2 disorders in the broader population (McDonald-McGinn et al., 2015; Tang et al., 2016).

2.5.6: Concluding remarks

Elucidating the pathophysiology of developmental neuropsychiatric disorders remains a major challenge, due to considerable heterogeneity at both the genetic and phenotypic level (Geschwind & Flint, 2015). The robust, opposing effects on brain structure described here highlight the utility of investigating the influence of reciprocal chromosomal imbalances on neural processes and how these may ultimately contribute to disease pathogenesis. Prospective longitudinal studies are underway to track divergent neurodevelopmental trajectories over time in CNV carriers. Finally, in vitro modeling of reciprocal CNVs at the 22q11.2 locus offers an avenue to directly characterize associated cellular phenotypes.

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CHAPTER THREE

Reciprocal Copy Number Variations at 22q11.2 Produce Distinct and Convergent

Neurobehavioral Impairments Relevant for Schizophrenia and Autism Spectrum Disorder

3.1: Abstract

22q11.2 deletions and duplications are copy number variations (CNVs) that predispose to developmental neuropsychiatric disorders. Both CNVs are associated with autism spectrum disorder (ASD), while the deletion confers disproportionate risk for schizophrenia. Neurobehavioral profiles associated with these reciprocal CNVs in conjunction with brain imaging measures have not been reported. We profiled the impact of 22q11.2 CNVs on neurobehavioral measures relevant to ASD and psychosis in 106 22q11.2 deletion carriers, 38 22q11.2 duplication carriers, and 82 demographically-matched controls. To determine whether brain-behavior relationships were altered in CNV carriers, we further tested for interactions between group and regional brain structure on neurobehavioral domains. Cognitive deficits were observed in both CNV groups, with the lowest IQs in deletion carriers. ASD and dimensionally-measured ASD traits were elevated in both CNV groups; however, duplication carriers exhibited increased stereotypies compared to deletion carriers. Moreover, discriminant analysis using ASD sub-domains distinguished between CNV cases with 76% accuracy. Both psychotic disorder diagnosis and dimensionally-measured positive and negative symptoms were elevated in deletion carriers. Finally, control participants showed an inverse relationship between processing speed and cortical thickness in heteromodal association areas, which was absent in both CNV groups. 22q11.2 CNVs differentially modulate intellectual functioning and psychosis-related symptomatology but converge on broad ASD-related symptomatology. However, subtle differences in ASD profiles distinguish CNV groups. Processing speed impairments, coupled with the lack of normative relationship between processing speed and cortical thickness in CNV carriers, implicate aberrant development of the cortical mantle in the pathology underlying impaired processing speed ability.

3.2: Introduction

Developmental neuropsychiatric disorders such as schizophrenia (SCZ) and autism spectrum disorders (ASD) have remarkable genetic and phenotypic heterogeneity. These biological complexities have impeded efforts to elucidate disease pathophysiology. One potential strategy to overcome this challenge is to adopt a reverse-genetics approach to characterize brain and behavioral patterns in individuals that carry defined genetic mutations that predispose toward neuropsychiatric illness. Further, variation in specific symptoms and dimensional traits may more precisely represent underlying biological variation than does diagnostic category (Casey et al., 2013; Cuthbert, 2014). Thus, dimensional phenotyping of these high-impact mutations offers a window to elucidating neurobiological mechanisms underlying major neuropsychiatric disorders (Malhotra & Sebat, 2012; Simons Vip, 2012).

22q11.2 copy number variants (i.e. deletions or duplications, CNVs) confer some of the greatest known genetic risks for psychiatric disorders (Monks et al., 2014; Niarchou et al., 2014; Schneider et al., 2014). As such, they represent a particularly powerful model to yield biological insights into how 22q11.2 gene dosage may influence downstream brain and behavioral consequences (Hiroi et al., 2013; Hiroi & Yamauchi, 2019). The 22q11.2 locus is a genetic hotspot that harbors highly-conserved genes critical for brain and cognitive development (Guna et al., 2015; Meechan et al., 2015). A 1.5-3 megabase deletion at this locus results in the most commonly-known microdeletion disorder, 22q11.2 Deletion Syndrome (also known as DiGeorge or Velocardiofacial syndrome; OMIM #188400, #192430). It has an estimated prevalence of 1 in ~4,000 live births and has been extensively characterized for associated congenital malformations and neurodevelopmental comorbidities, including Autism Spectrum Disorder (ASD), intellectual disability (ID), and developmental delay (DD) (Hoeffding et al., 2017; McDonald-McGinn et al., 2015; Olsen et al., 2018; Schneider et al., 2014). Most notably, the deletion is one of the greatest known genetic risk factors for schizophrenia, with up to 20-fold increased risk compared to population-base rates (Chow et al., 2006; Green et al., 2009;

Malhotra & Sebat, 2012; Marshall et al., 2017; Rees et al., 2016). Moreover, 22q11.2 deletions are found in approximately 0.3% of schizophrenia cases in the general population (Kirov et al., 2014; Marshall et al., 2017; Rees, Walters, et al., 2014).

In contrast, data on the neurobehavioral phenotype of the 22q11.2 duplication is just starting to emerge, in part due to its more recent discovery as a recurrent CNV (Ensenauer et al., 2003; Firth, 1993; Portnoi, 2009). A recent population-based study found that 22q11.2 duplications occur ~2.5 times as often as the deletion and confer elevated risk for neurodevelopmental and psychiatric conditions (Olsen et al., 2018). However, most available clinical knowledge to date comes from case reports (Bassett et al., 2008; Ou et al., 2008; Wentzel et al., 2008; Woodward et al., 2019; Yu et al., 2008) and recent studies that assayed multiple CNVs across the genome (Chawner et al., 2019; Kendall et al., 2019; Stefansson et al., 2014). These studies indicate incomplete penetrance and variable expressivity of the duplication, including mild to severe forms of dysmorphia and ID/DD.

Interestingly, multiple large-scale studies have recently shown 22q11.2 duplications to be significantly *less* common in schizophrenia cases than in the general population, suggesting the first putative protective mutation for schizophrenia (Li et al., 2016; Marshall et al., 2017; Rees et al., 2016; Rees, Kirov, et al., 2014). While statistical significance varies depending on sample size (Marshall et al., 2017), the overall pattern across such large studies offers consistent evidence that SCZ risk is gene dosage-specific with respect to the 22q11.2 locus. Thus, while preliminary, this intriguing distinction indicates copy-number dependency for risk or putative protective factors for schizophrenia versus copy-number irrelevance for risk of ASD and ID, and suggests that there may be both general and specific effects of gene dosage on disease evolution.

No study has yet directly compared reciprocal 22q11.2 CNVs to each other and to typically developing controls across multiple neurobehavioral traits relevant to schizophrenia, ASD, and neurocognitive functioning, in conjunction with brain imaging measures. This 'deep-

phenotyping' approach is crucial to establishing clinical context and functional relevance for how variable gene dosage may contribute to shared or distinct effects on brain and behavioral traits. Here, we sought to obtain a finer granularity of dimensional neurobehavioral traits to capture intermediate phenotypes of cognitive and behavioral dysfunction associated with these CNVs. Moreover, while 22q11.2 gene dosage is associated with global opposing effects on brain structure (Lin et al., 2017), it is unknown whether these opposing effects are associated with similar or distinct neurobehavioral impairments. Integration of brain and high-dimensional cognitive and behavioral assays may help elucidate common or discrete brain biomarkers and biological pathways that lead to cognitive and/or psychiatric dysfunction.

Here, in the largest known cohort of phenotypically well-characterized 22q11.2 reciprocal CNV carriers, we first compared the impact of 22q11.2 deletions and duplications on 15 dimensional traits relevant to intellectual functioning, ASD, and SCZ. Next, given evidence that both 22q11.2 deletions and duplications predispose to ASD, we assessed whether there are differences in specific aspects of the ASD profile between CNV carrier groups. Finally, we asked whether the relationship between brain structure and neurobehavioral traits differed between these genetically-defined groups and controls, which would inform neuroanatomic substrates of neurocognitive and behavioral impairment in 22q11.2 CNVs.

3.3: Materials and Methods

3.3.1: Participants

The sample consisted of 226 individuals: 106 with molecularly confirmed 22q11.2 deletions (52 males; 54 females), 38 with confirmed 22q11.2 duplications (22 males; 16 females), and 82 demographically-matched typically developing controls (42 males; 40 females; see Table 3.1 for participant demographics). Patients were ascertained as part of an ongoing longitudinal study at the University of California at Los Angeles, and were ascertained from local medical or genetics clinics, or from national or local support groups and websites.

Demographically comparable, typically-developing participants were recruited from local communities via web-based advertisements and flyers/brochures in local schools, pediatric clinics, and other community sites.

Demographics	22q11.2 Deletion Carriers	Typically Developing Healthy Control Subjects	22q11.2 Duplication Carriers
N	106	82	38
Age, Years (SD)	15.94 (10.3)	14.61 (7.5)	15.87 (12.4)
Age Range, Years	6–61	6–45	5–49
Male, n (%)	52 (49.1)	41 (50.0)	22 (57.9)
White, n (%)[a,b,c]	92 (86.8)	52 (63.4)	37 (97.4)
Other: Asian and Black, n (%)[a,b]	2 (1.9)	18 (16.8)	1 (2.7)
Multiracial, n (%)[b,c]	12 (11.2)	12 (14.6)	0 (0)
Highest Parental Education, Years (SD)	16.1 (2.7)	16.0 (3.3)	15.8 (2.5)
ASD, n (%)[a,b]	49 (46.2)	0 (0)	17 (44.7)
Psychosis, n (%)[a,c]	13 (12.3)	0 (0)	0 (0)
ADHD, n (%)[a,b]	47 (44.4)	5 (6.1)	15 (39.4)

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder.
[a]Corrected difference between 22q11.2 deletion carriers and healthy control subjects.
[b]Corrected difference between 22q11.2 duplication carriers and healthy control subjects.
[c]Corrected difference between 22q11.2 deletion carriers and 22q11.2 duplication carriers.

Table 3.1: Demographic information between groups at baseline. [a]corrected 22qDEL-CON difference; [b]corrected 22qDUP-CON differences; [c]corrected 22qDEL-22qDUP difference.

Exclusion criteria for all study participants included significant neurological or medical conditions (unrelated to 22q11.2 CNV) that might affect brain structure or function, history of head injury with loss of consciousness, insufficient fluency in English, and/or substance or alcohol use disorder within the past 6 months (see Supplement for details). All participants underwent a verbal and written informed consent process. Participants under the age of 18 years provided written assent, while their parent or guardian completed written consent. The UCLA Institutional Review Board approved all study procedures and informed consent documents.

3.3.2: Neurobehavioral Phenotyping Assessment

Cognitive and behavioral traits were chosen based on their relevance for developmental psychiatric disorders, with emphasis on ASD and SCZ (Green et al., 2009; Lord et al., 2013; Morgan et al., 2008; Vorstman et al., 2015). Age-appropriate, gold-standard psychiatric and

cognitive assessments were administered to all participants and included a battery of structured interviews, self-reports, and cognitive tests, spanning several neuropsychological domains. Behavioral questionnaires were also given to parents (see Table 3.2 for assessment descriptions). Supervised clinical psychology doctoral students administered neurocognitive and psychodiagnostic evaluations to participants to assess for DSM diagnoses (SCID/C-DISC). To assess for ASD, the Autism Diagnostic Observation Schedule (ADOS) was administered to participants (Lord et al., 2000), and the Autism Diagnostic Interview-Revised (ADI-R) was administered to participant's parent/primary caretaker (Rutter et al., 2003).

All diagnoses were determined by trained clinicians who participated in an ongoing quality assurance program. Training, reliability, and ongoing quality assurance procedures for psychodiagnostic assessments and clinical rating scales are detailed in prior publications (Jalbrzikowski et al., 2017; Jalbrzikowski et al., 2013).

Domain	Test	Trait	Measure
Neurocognition	Wechsler Abbreviated Scale of Intelligence or Wechsler Adult Intelligence Scale, 4th edition	Full-scale IQ	Standard score
		Nonverbal IQ	Standard score
		Verbal IQ	Standard score
	Letter Number Sequencing, WISC-IV	Working memory	Percent correct
	California Verbal Learning Test	Verbal memory	Sum of raw scores
	Brief Assessment of Cognition Symbol Coding/WISC-IV Coding A or B	Processing speed	Percent correct
Social Cognition	The Awareness of Social Inference Test A: Part 3	Lie detection	Sum of scores
		Sarcasm detection	Sum of scores
	Penn Computerized Neurocognitive Battery	Emotion recognition	Sum of scores
		Emotion differentiation	Sum of scores
ASD-Related	Short Sensory Profile, Adolescent/Adult Sensory Profile	Sensory insensitivity	Sum of scores
	Repetitive Behavior Scale	Restrictive and repetitive behavior	Sum of scores
	Social Responsiveness Scale	Reciprocal social behavior	Summary T-score
Psychosis-Related	Structured Interview for Prodromal Syndromes	Positive symptoms	Sum of P1–P5
		Negative symptoms	Sum of N1–N6

WISC-IV, Wechsler Intelligence Scale for Children, 4th edition.

Table 3.2: Cognitive and behavioral trait descriptions.

3.3.2.1: Cognitive Functioning

We assessed cognition using measures of global cognitive function, including: full-scale, verbal IQ, and nonverbal IQ (i.e., Matrix Reasoning (Wechsler, 1999; Wechsler, 2008)), working memory, processing speed (Wechsler, 2008), and verbal memory (Delis et al., 1987).

3.3.2.2: Social Cognition Measures

Social cognition impairments are hallmark features of both idiopathic ASD and SCZ (Couture et al., 2010; Pilowsky et al., 2000; Pinkham et al., 2003). Thus, four measures were analyzed to capture different aspects of social cognition. To assess theory of mind, we analyzed participants' ability to ascertain sarcasm or 'white lies' from conversational exchanges in video vignettes (McDonald et al., 2006). In addition, we used the Penn-CNB to test ability to recognize different facial expressions of emotion and to differentiate the intensity of facial expressions of emotion (Gur et al., 2010).

3.3.2.3: Autism Spectrum Measures

Because ASD diagnosis is prevalent in both CNV groups (Schneider et al., 2014; Wenger et al., 2016), we aimed to assess three cardinal dimensions of ASD-relevant symptomatology, including: sensory sensitivity (Dunn, 1999), restrictive/repetitive behavior (Lam & Aman, 2007), and social responsiveness (Constantino & Gruber, 2007). Within each of those composite measures, we additionally investigated sub-scale traits. For the Short Sensory Profile, we looked at subdomains of tactile sensitivity, taste/smell sensitivity, movement sensitivity, under-responsivity/seeking sensation, auditory filtering, low energy/weakness and visual/auditory sensitivity. Restrictive/repetitive behavior was further subdivided into categories of stereotyped behavior, self-injurious behavior; compulsive behavior, ritualistic behavior, sameness behavior, and restricted behavior. The Social Responsiveness Scale was subdivided into social awareness, social cognition, social communication, social motivation, and autistic mannerisms.

3.3.2.4: Psychosis-Relevant Measures

The Structured Interview for Prodromal Syndromes (SIPS; (McGlashan et al., 2001)) was used to capture dimensional psychosis-relevant traits by quantifying positive symptoms (e.g. unusual thought content/delusional ideas, suspiciousness/persecutory ideas, perceptual abnormalities/hallucinations, grandiosity, and disorganized communication) as well as negative symptoms (social anhedonia, avolition, decreased emotional expression or experience, decreased ideational richness, and occupational impairments).

3.3.3: Structural MRI

Measures of brain structure were obtained with high-resolution structural MRI. Scanning was conducted on an identical 3 Tesla Siemens Trio MRI scanner with a 12-channel head coil at the UCLA Brain Mapping Center or at the Center for Cognitive Neuroscience. T1-weighted structural scans were analyzed in an unbiased, whole-brain approach using well-validated analysis and quality control protocols (Thompson et al., 2014), previously applied by our group and others (Hibar et al., 2018; Schmaal et al., 2016; Sun et al., 2018; van Erp et al., 2016). Details of the scanning protocol, image pre-processing, and quality control procedures are included in Supplemental Material.

3.3.4: Statistical Analysis

All statistical analyses were performed using R 3.5.2 (Core Team, 2013) except for the discriminant analyses which were conducted in Matlab version 2017a (MathWorks, 2017). First, we tested the extent to which 22q11.2 CNVs influenced neurobehavioral domains relevant to intellectual functioning, ASD, and SCZ by comparing group differences across 15 measures (see Figure 1, Table 2). Toward this end, we performed an omnibus analysis of covariance (ANCOVA) to test the effect of group on each measure, adjusting for age and sex. Given the number of measures analyzed, we took a conservative approach to ensure standardized removal of potential age and sex biases by applying the same covariate adjustments for each univariate model. Post-hoc pairwise comparisons between groups were conducted using Tukey contrasts. Multiple comparisons correction using false discovery rate (FDR) was applied to

account for the number of traits and group comparisons (Benjamini & Hochberg, 1995). FDR-adjusted q-values ≤ 0.05 were considered significant.

Second, within CNV carriers, we asked whether ASD profiles between deletion and duplication carriers differed across subscale measures using a mass univariate as well as multivariate approach. The univariate model directly assessed group differences for each subscale measure by modeling the effect of group, while correcting for age and sex. FDR correction was performed for the number of subscale measures within each composite trait. The multivariate model used Fisher's linear discriminant analysis to distinguish between CNV carriers, based on all 18 ASD subscale measures. Model performance was assessed using leave one out cross-validation. To account for differences in sample size between the groups and equalize class representation, data from the duplication cohort was uniformly oversampled. "Control" models were constructed by randomly shuffling class identities within the training set prior to model construction and cross-validation. Mean and standard deviations of model accuracy represent statistics that were computed over 100 simulations of model construction and testing over all subjects. The p-value was generated based on the fraction of the shuffled simulations in which performance exceeded the observed value (see Figure 2).

Finally, we asked whether the relationship between regional brain structure and each of the cognitive/behavioral traits differed as a function of group. To reduce the number of comparisons, measures of cortical thickness (CT) and surface area (SA) were averaged across homologous regions-of-interest (ROIs) between each hemisphere, generating 34 total ROIs, for which 2 brain metrics (CT or SA) were assessed. First, as before, each neurobehavioral trait score was adjusted for effects of age and sex. Then, the main effect of group, brain metric, and group-by-brain metric interaction term were included as predictors in separate linear models for each residualized neurobehavioral score. Because we were interested in relationships between brain and behavior that differed between groups, we focused on the interaction effect (see Figure 3, Figure S3.4). Finally, for traits in which there was a significant, corrected interaction

effect, post-hoc comparisons were performed to test pairwise differences. Also, for those traits

and ROIs which showed a significant group-by-brain interaction effect, within-group linear

models were conducted to directly characterize the relationships between brain structure and

trait (see Table 4). FDR correction at $q < 0.05$ was used to account for the number of ROIs,

neurobehavioral traits, and brain metrics in the omnibus test, while correction of the post-hoc

tests accounted for the number of pairwise comparisons.

We further explored whether ASD-related impairments correlated with cognitive function

in deletion and duplication carriers. As these results were beyond the main scope of this paper,

they are included in Supplementary Material (Figure S2).

Secondary analyses of group differences in measures of social-emotional behavior and

real-world function not specific to ASD or SCZ are included in Supplemental Material, as these

were also beyond the main scope of this paper (Figure S3, Tables S1 and S2).

3.5: Results

3.5.1: 22q11.2 CNVs produce convergent phenotypes relevant for ID and ASD

but divergent psychosis-relevant phenotypes

At $q < 0.05$, 22q11.2 deletion carriers exhibited the lowest Full-Scale IQ, control participants

displayed the highest IQ, while duplication carriers were intermediate (del<dup<con; see Figure

3.1, Table 3.3). The same pattern remained when Full-Scale IQ was broken down into its

constituent parts, verbal and non-verbal IQ. Regarding specific cognitive domains, deletion and

duplication carriers exhibited significant impairments in working memory, verbal memory, and

processing speed compared to controls, but did not significantly differ from each other.
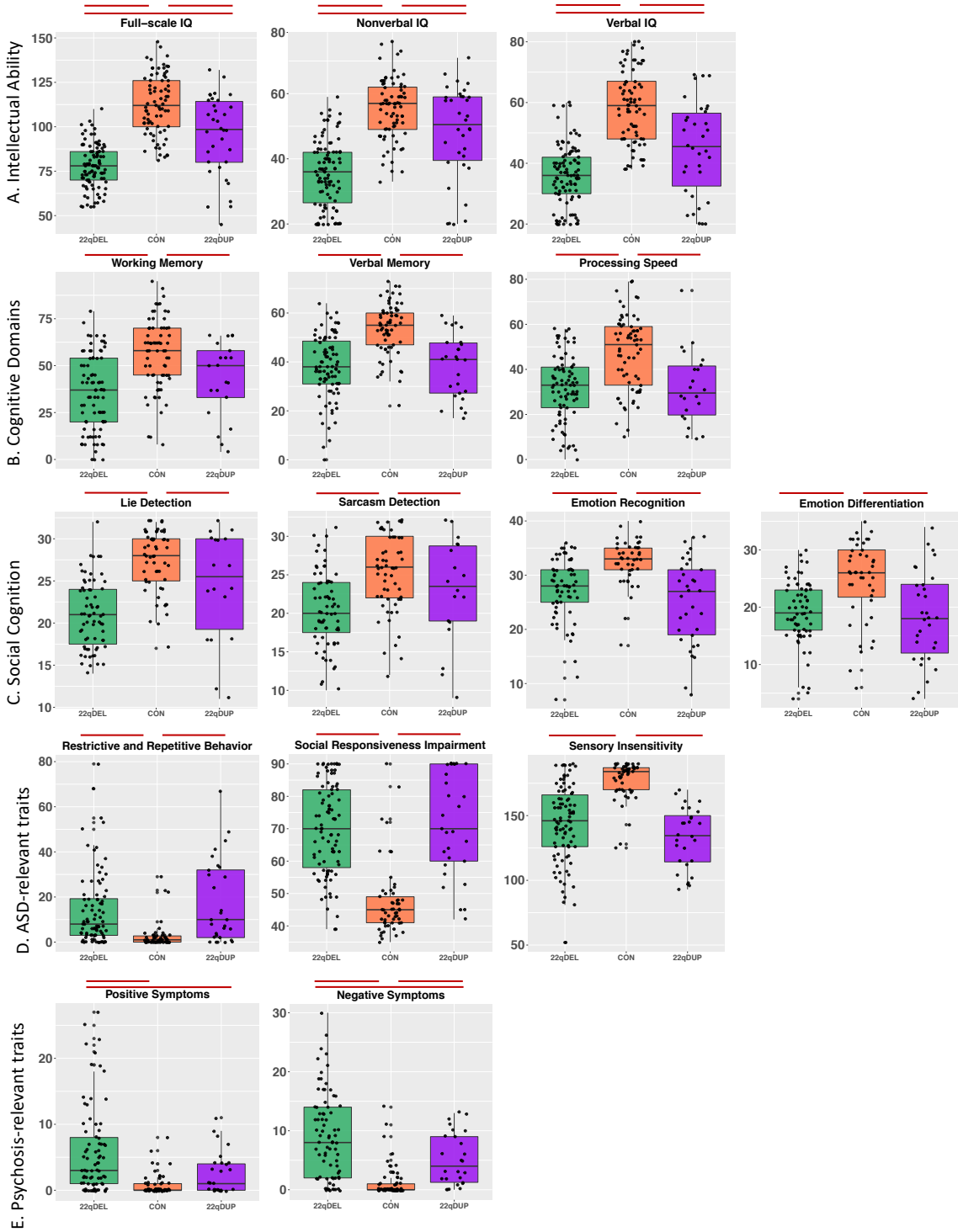
Figure 3.1: Combined box- and scatterplots of average group scores for 15 traits relevant for intellectual ability, ASD, and SCZ, adjusted for sex and age. Red, horizontal lines indicate FDR-corrected pairwise differences at the post-hoc level. For all measures, there was a significant omnibus effect of group ($q < 0.05$). At the post-hoc pairwise level, 22q11.2 deletion carriers exhibited significantly elevated positive symptoms compared to duplication carriers and controls. There were significant pairwise differences between all three groups for Full-scale, Nonverbal, and Verbal IQ as well as for negative symptoms. For the remaining cognitive, social cognitive, and ASD-related measures, both the CNV groups were impaired compared to controls, but did not significantly differ from each other.

Trait	F Statistic	22qDEL–CON Estimate (SE)	22qDUP–CON Estimate (SE)	22qDUP–22qDEL Estimate (SE)
Nonverbal IQ[a,b,c]	75.68	−19.93 (−1.64)	−7.25 (−2.22)	12.68 (−2.14)
Full-Scale IQ[a,b,c]	105.82	−35.52 (−2.45)	−17.38 (−3.29)	18.14 (−3.19)
Verbal IQ[a,b,c]	87.05	−23.29 (−1.77)	−13.86 (−2.38)	9.43 (−2.3)
Working Memory[a,b]	31.73	−21.86 (−2.8)	−18.99 (−4.41)	2.87 (−4.3)
Verbal Memory[a,b]	44.27	−16.1 (−1.78)	−15.28 (−2.56)	0.82 (−2.48)
Processing Speed[a,b]	38.66	−16.49 (−2.02)	−18.74 (−3.12)	−2.24 (−3.04)
Lie Detection[a,b]	42.05	−6.71 (−0.73)	−3.94 (−1.12)	2.77 (−1.08)
Sarcasm Detection[a,b]	16	−4.95 (−0.88)	−3.58 (−1.34)	1.37 (−1.3)
Emotion Recognition[a,b]	17.35	−5.08 (−1.07)	−6.89 (−1.27)	−1.81 (−1.12)
Emotion Differentiation[a,b]	13.65	−5.64 (−1.19)	−6.22 (−1.45)	−0.57 (−1.34)
Sensory Insensitivity[a,b]	44.12	−36.19 (−4.45)	−44.58 (−5.77)	−8.39 (−5.58)
Restrictive and Repetitive Behavior[a,b]	14.6	11.9 (−2.59)	14.8 (−3.3)	2.92 (−3.2)
Social Responsiveness Impairment[a,b]	48.91	21.7 (−2.45)	24.48 (−3.14)	2.79 (−3.03)
Positive Symptoms[a,c]	19.53	5.19 (−0.84)	2.02 (−1.15)	−3.18 (−1.11)
Negative Symptoms[a,b,c]	33.79	7.77 (−0.95)	3.69 (−1.3)	−4.08 (−1.26)

22qDEL, 22q11.2 deletion carriers; 22qDUP, duplication carriers; CON, healthy control subjects.
[a]Corrected difference between 22q11.2 deletion carriers and healthy control subjects.
[b]Corrected difference between 22q11.2 duplication carriers and healthy control subjects.
[c]Corrected difference between 22q11.2 deletion carriers and 22q11.2 duplication carriers.

Table 3.3: ANCOVA results including all 15 measures, covarying for age and sex.

[a]corrected 22qDEL-CON difference; [b]corrected 22qDUP-CON differences; [c] corrected 22qDEL-22qDUP difference.

Both CNV groups had significantly higher rates of ASD diagnosis compared to controls (see Table 3.1). Dimensionally, as expected compared to controls, both 22q11.2 CNV groups

showed significantly poorer social cognition (e.g. emotion differentiation, emotion recognition, lie detection, sarcasm detection), as well as elevated scores on reciprocal social behavior, sensory sensitivity, and restrictive, repetitive behavior, which were not significantly different from each other. In contrast, deletion carriers diverged from duplication carriers in the psychosis domain, with higher rates of psychotic disorder diagnosis (12.1%; Table 3.1), as well as significantly elevated positive and negative symptom scores (Table 3.3).

Deletion and duplication carriers did not differ from each other in rates of ADHD diagnosis, but both groups had significantly elevated rates of ADHD relative to controls (see Table 1). Further, compared to controls, both CNV groups had significant impairments in dimensional measures of executive and daily life functioning (i.e. somatic complaints, thought problems, withdrawn/depressed, attention problems, anxious/depressed, aggression, role functioning, social functioning, and global functioning). CNV groups did not significantly differ from each other except in terms of role functioning, for which deletion carriers were more impaired (Figure S3.3, Tables S3.1 and S3.2).

3.5.2: 22q11.2 CNVs involve subtle differences in ASD profile, despite similar
rates of ASD diagnosis

Assessments on the subdomains of the 3 composite ASD measures of social responsiveness, sensory sensitivity, and restrictive/repetitive behavior revealed differences in ASD-relevant symptom profiles between the CNV groups (See Figure 3.2). Specifically, the univariate model revealed significantly increased stereotyped behaviors in duplication relative to deletion carriers ($q < 0.05$). No corrected differences between the deletion and duplication groups were found for any of the other individual subscale measures at $q < 0.05$ (see Figure S3.1). However, the multivariate model that incorporated all 18 subscale features correctly classified deletion versus duplication carriers 76.6% of the time ($p < 10^{-3}$.), suggesting distinctiveness in the overall picture of ASD symptomatology between deletion and duplication

carriers. Further, verbal IQ was correlated with social cognition traits in both CNV groups, with

larger effects in duplication carriers ($q<0.05$; Figure S3.2).
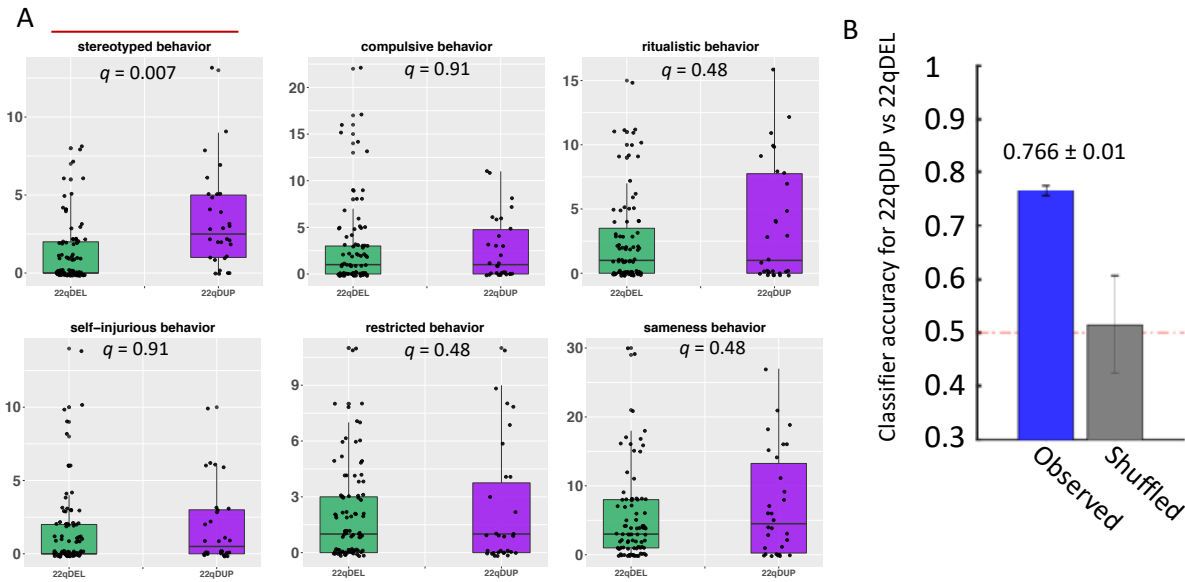
**Figure 3.2: Modeling subdomains of ASD traits reveals distinct profiles between 22q11.2
deletion and duplication carriers**. A. The univariate model showed that duplication carriers
exhibited significantly more stereotyped behaviors compared to deletion carriers (indicated by
red, horizontal line) after adjusting for age and sex, at a corrected $q < 0.05$. B. The multivariate
model using discriminant analysis of all 18 subscales correctly classified deletion versus
duplication carriers 76.6% of the time, suggesting distinct characteristics of ASD-relevant
symptomatology in deletion versus duplication carriers.

*3.5.3: Healthy control subjects showed an inverse relationship between CT in
heteromodal association areas and processing speed that was absent in CNV carriers*

Lastly, CT in frontal, medial, and inferior parietal regions differentially explained

processing speed, depending on group (see Figure 3.3). Table 4 includes ROIs that showed a

significant, FDR-corrected group-by-brain interaction effect on processing speed. Specifically,

processing speed was inversely correlated with CT in controls in frontal, inferior parietal, and

medial regions (anterior cingulate and insula), but not in either CNV group. No significant group-

dependent relationships between surface area and any cognitive/behavioral trait survived

correction. See Figure S3.4 for uncorrected p-values across all ROIs for both CT and SA.
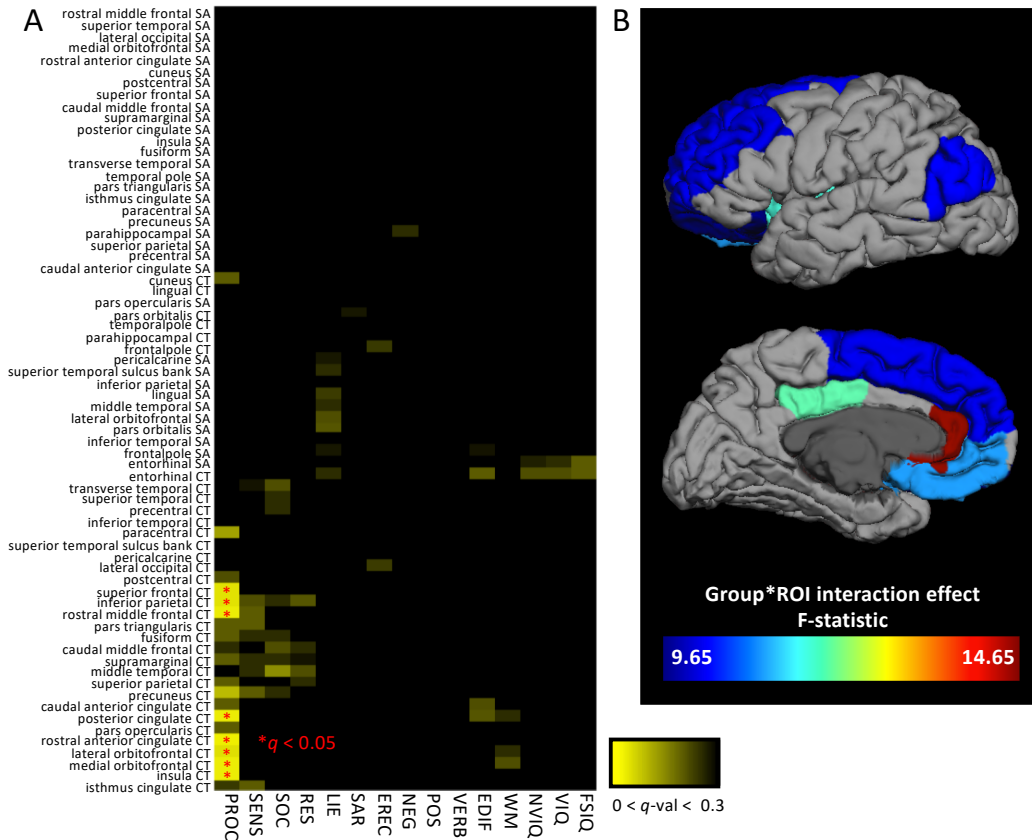
Figure 3.3: Regional cortical thickness (CT) of frontal, inferior parietal, and medial regions differentially explains processing speed depending on group. After regressing out age and sex from cognitive measures, a linear model was applied to estimate the interaction effect of brain and group for each of the 15 traits using measures of CT or SA. False discovery rate correction was applied for 34 ROIs,15 traits, and each brain metric (SA or CT). Panel A depicts a heatmap of the q-values for the significance of the interaction term associated with each test, from $q = 0$ to $q = 0.30$. Panel B depicts the ROIs for which there was a corrected interaction effect, plotting the associated F-statistic. Panel C displays the within-group correlation between processing speed and CT for each of the 8 regions that showed a significant interaction effect. The control group showed a consistent negative correlation between CT and processing speed that was not found in either CNV group.

3.6: Discussion

This study revealed several novel findings regarding the impact of 22q11.2 CNVs on neurobehavioral function, in that they: (i) produce comparable impairments in traits relevant for ASD and intellectual functioning but differential impairments in psychosis-related traits; (ii) comprise distinct differences in ASD profile at the subdomain level; and (iii) both lack the normative relationships between processing speed and cortical thickness in higher-order brain regions.

Notably, these reciprocal CNVs conferred broad 'hits' across multiple neuropsychiatric domains, with shared as well as unique effects on dimensional traits of ASD and psychosis. Specifically, we found convergent effects of both CNVs on intellectual abilities, specific cognitive domains, and social cognition, with greater impairment in intellectual abilities in the deletion group, consistent with elevated rates of ID in 22q11.2 deletion versus duplication (Hoeffding et al., 2017; Niarchou et al., 2014; Olsen et al., 2018). Rates of ASD were similar in deletion and

duplication carriers (45.8% and 44.7%, respectively), whereas 12.1% of deletion carriers (and no duplication carriers) had a psychotic disorder diagnosis.

Both CNV groups also exhibited elevations in dimensional, ASD-related traits compared to controls, consistent with the significantly higher rates of ASD diagnosis across both CNV groups (Olsen et al., 2018; Schneider et al., 2014; Wenger et al., 2016). These findings suggest that both over and under-expression of genes within the 22q11.2 locus may result in downstream pathogenic effects on cognition and social behavior. Considering only our 22q11.2 deletion participants who have mostly passed the risk period for schizophrenia onset (≥ 25 years old; (Gur et al., 2017)), the rate of schizophrenia increases to 25%, which is more comparable to rates reported in other studies that typically include adults. Further, deletion carriers exhibited greater positive and negative symptoms compared to the other two groups. This specific association of both categorically- and dimensionally-measured SCZ-related symptoms with the deletion suggests that under-expression of 22q11.2 genes may represent a specific biological mechanism predisposing toward psychotic symptomatology.

Although mean global IQ in deletion carriers was significantly lower than duplication cases, the CNV groups showed similar impairments in other cognitive and behavioral domains. Dimensionally, these include working memory, verbal memory, processing speed, social cognition (e.g. lie/sarcasm detection and emotion differentiation/recognition), and composite ASD-related traits (e.g. restrictive/repetitive behavior, social responsiveness, and sensory sensitivity) compared to controls. These findings are compatible with results from the population-based registry study on the cumulative incidence of psychiatric diagnoses in 22q11.2 CNV carriers in the Danish population, which found greater ID in 22q11.2 deletion carriers but increased rates of developmental neuropsychiatric disorders in both deletion and duplication carriers (Hoeffding et al., 2017; Olsen et al., 2018). The comorbidity of ID and psychiatric disorders, namely for ASD and SCZ, has been extensively discussed in the literature, particularly with regard to CNVs (Kendall et al., 2019; Rees et al., 2016; Stefansson et al., 2014;

Thygesen et al., 2018). However, the mechanisms by which reciprocal deletions and duplications at the same locus can have divergent effects on intellectual dysfunction and psychosis-related traits (Li et al., 2016; Marshall et al., 2017; Rees et al., 2016; Rees, Kirov, et al., 2014) but converge on similar impairments for specific cognitive domains and social cognition remain unknown. Notably, ASD diagnosis does not appear to increase risk of subsequent development of schizophrenia in 22q11.2 deletion carriers, suggesting pleiotropic effects of 22q11.2 gene dosage, at least with regard to these neurobehavioral outcomes (Fiksinski et al., 2017; Vorstman et al., 2013).

Animal models of 22q11.2 CNVs involving over or under-expression of specific genes within the homologous 22q11.2 locus offer crucial insight into potential mechanisms that underlie brain and behavioral dysfunction in human CNV carriers. Such experimental paradigms can elucidate the ways in which reciprocal gene dosage contributes to impairment in the same cognitive domain at single-gene resolution. For example, transgenic mice constitutively overexpressing a 190 kb human chromosomal 22q11.2 segment, including TXNRD2, COMT, and ARVCF, showed impairments in prolonged maintenance of working memory during a delay task (Suzuki et al., 2009). In another murine model, region-specific overexpression of COMT and Tbx1 in the hippocampal dentate gyrus resulted in reduced developmental maturation of working memory capacity, as well as reduced proliferation and migration of adult neural stem/progenitor cells (Boku et al., 2018). Working memory impairments using a T-maze paradigm (Hiramoto et al., 2011) have also been observed in mice heterozygous for Tbx1. Because the authors found Tbx1 expression in postnatally generated neurons and in cells that differentiate into glial cells, they posit altered neurogenesis or reactive glial proliferation as potential mechanisms that may underlie working memory impairment. Moreover, mouse studies of Dgcr8 deficiency have also implicated potential mechanisms of working memory impairment in the form of reduced adult hippocampal neurogenesis (Ouchi et al., 2013), as well as perturbed short-term synaptic plasticity in prefrontal cortex (Fenelon et al., 2013). Whether

similar mechanisms explain convergent effects on other cognitive domains such as verbal memory and processing speed is unknown, as a remaining challenge will be overcoming the animal to human translation to test these and other human-specific traits.

One important implication of these findings is that lack of genetic material is more broadly deleterious than excess of the same genetic material, suggesting that certain 22q11.2 genes are sensitive to haploinsufficiency. This is consistent with the prediction that deletion carriers would be more severely affected than duplication carriers (Mannik et al., 2015), given that the deletion is more likely to arise *de novo (Bassett et al., 2008)*, whereas the duplication is more frequently inherited (Ou et al., 2008). In the context of other reciprocal CNVs, 16p11.2 deletion has been associated with a 2 standard deviation decrease in IQ relative to controls, while the duplication was associated with only a 1 standard deviation decrease (D'Angelo et al., 2016; Hanson et al., 2015; Hippolyte et al., 2016). Also similar to our findings, there were no differences in the prevalence of ASD between 16p11.2 CNV groups, suggesting multiple pathways to ASD that include over and under-expression of genes implicated in neurodevelopment across multiple genomic locations. However, divergent from our findings, 16p11.2 duplication carriers showed increased frequency of psychotic symptoms and severe psychiatric disorders relative to 16p11.2 deletion carriers, further demonstrating increased specificity for copy number and genomic location in mediating psychosis risk, compared to ASD (Niarchou et al., 2019). More direct and targeted genomic assays are warranted to disentangle how deletions or duplications may lead to transcriptomic dysregulation to cause widespread, convergent as opposed to specific, divergent effects on downstream brain and behavioral impairments.

Despite global similarities in social cognitive and social behavioral impairments across 22q11.2 CNVs, at a more granular level, 22q11.2 duplication carriers exhibited more stereotyped behaviors than 22q11.2 deletion carriers. The only other in-depth investigation of ASD-related phenotypes in 22q11.2 CNV carriers to date also found elevated stereotypies in

duplication carriers, albeit in a smaller sample (Wenger et al., 2016). Murine models have implicated the nigrostriatal dopamine pathway in the mediation of stereotypies, where administration of indirect and direct dopamine agonists or selective dopamine uptake inhibitors have been shown to induce stereotypic behaviors (Lewis & Kim, 2009; Tanimura et al., 2010). These findings suggest neuroanatomical relevance and potential biochemical mechanisms for increased 22q11.2 gene dosage leading to greater stereotyped behaviors. However, ASD is notoriously heterogeneous and not diagnosable by a single behavioral scale. Thus, using a multivariate discriminant analyses, we showed that a collection of ASD-associated traits was informative in classifying deletion versus duplication carriers with 76.6% accuracy. This significantly above-chance performance indicates that the overall manifestation of ASD-relevant traits is complex and differs between reciprocal 22q11.2 CNVs in a way that was not captured by traditional univariate methods. Thus, while rates of ASD diagnosis and composite dimensional measures may not statistically differ between groups, subtle and meaningful differences in clinical profile exist. Other studies have also used multivariate approaches and found ASD-related behavioral signatures of ASD cases who carry 22q11.2 deletions compared to ASD cases with different genetically-defined syndromes (e.g., Down's syndrome, Prader-Willi, tuberous sclerosis complex (Bruining et al., 2010; Bruining et al., 2014)). Collectively, these findings emphasize the utility of a "genetics-first" approach for disentangling the heterogeneity and revealing biological underpinnings of ASD. In sum, our findings suggest a need for more comprehensive clinical screening of 22q11.2 duplication carriers, as well as informed guidance in genetic counseling, optimization of health care, and clinical follow-up.

We also found that thickness of heteromodal association regions explained processing speed ability in typical development, but not in either CNV group. More specifically, cortical thinning in these regions within the control group was associated with better processing speed, suggesting that developmental thinning within the cortical mantle underlies the neural circuitry that supports processing speed ability. Processing speed refers to the efficiency of information

transfer and manipulation (Kail & Salthouse, 1994) and is a complex, multidimensional ability, which improves over adolescent development and constrains other higher-order cognitive processes in health and disease (Fry & Hale, 2000; Ojeda et al., 2012; Rodríguez-Sánchez et al., 2007; Span et al., 2004). Not surprisingly, impairments in processing speed have also been implicated in various complex neuropsychiatric disorders. In high-functioning ASD, processing speed task performance has been correlated with communication abilities, indicating its importance to functional outcomes in ASD (Haigh et al., 2018; Oliveras-Rentas et al., 2012). In patients with schizophrenia, processing speed ability is strongly associated with illness risk (Glahn et al., 2007; Niendam et al., 2003; Reichenberg et al., 2009), illness severity (Dickinson et al., 2007) and functional disability (Brekke et al., 2007). The specific association with cortical thickness as opposed to surface area suggests that developmentally-mediated, normative cortical thinning (for circuit refinement via white matter expansion from increasing myelination and/or pruning of inefficient synaptic connections (Glasser & Van Essen, 2011; Paus, 2005; Tamnes et al., 2010) may underlie processing speed ability. As such, distributed neural network operations supported by myelinated axonal fibers are likely relevant to processing speed (Bells et al., 2017; Madden et al., 2004). White matter alterations have been consistently observed in schizophrenia (Kelly et al., 2018), ASD (Keller et al., 2007), and 22q11.2 Deletion syndrome via human post-mortem and in-vivo imaging studies (Villalon-Reina et al., 2019). As specific genes within the 22q11.2 region are implicated in axonal development and myelination (Mukai et al., 2015; Perlstein et al., 2014), abnormal dosage of these genes may contribute to the underlying pathophysiology of processing speed deficits that cross many developmental psychiatric disorders (Kochunov et al., 2017; Kochunov et al., 2016). Thus, these findings highlighting the link between 22q11.2 gene dosage and cortical thickness provide opportunities to test novel mechanistic hypotheses regarding the interaction between under- or over-expression of 22q11.2 genes and processing speed on cortical development in cell cultures and animal models.

Several limitations to this study should be considered. As with any study involving a clinically-ascertained cohort, the possibility of ascertainment bias may influence representativeness of our cohort. As such, differences we observed between CNV carriers and controls may be attenuated in an epidemiologic cohort, particularly for 22q11.2 duplication carriers who are more likely under-diagnosed than deletion carriers due to the lack of associated congenital and medical issues that prompt genetic testing (Grati et al., 2015). Importantly, our rates of childhood psychiatric disorders are largely comparable to those observed in epidemiologically-based studies of 22q11.2 CNVs (Hoeffding et al., 2017; Olsen et al., 2018). Further, while some duplication carriers in our study were diagnosed based on developmental or medical concerns, our duplication cohort also includes relatives who were not clinically ascertained and are otherwise clinically unremarkable. In addition, CNV size/breakpoints may impact phenotypic severity (Sun et al., 2018); however, given variability in CNV breakpoints, the current study was under-powered to investigate these effects. As sample sizes increase, future multisite investigations should integrate information on CNV breakpoints to better characterize effects of specific genes within the locus. Finally, sample size limits our capability to model non-linear effects of age, particularly in the duplication cohort. However, our findings of both convergent and divergent 22q11.2 CNV effects motivate longitudinal assays of brain and behavioral development within these CNV groups to better delineate changes in developmental trajectories that result from these genetic perturbations.

This deep phenotyping approach offers a unique opportunity to characterize the functional consequences of high-impact genetic mutations such as 22q11.2 CNVs. Future directions include integrating genomic information to assess whether transcriptomic signatures of these genetic conditions explain differences in downstream brain and behavioral traits, as well as longitudinal studies to assess developmental trajectories. Finally, our findings demonstrate the utility of using 22q11.2 CNVs as a model for bridging the gap between genes, brain, and behavior. Crucially, these findings allow generation of hypothesis-driven, translational

experiments using in vivo or in vitro models to validate meaningful biological insights into molecular pathways and identification of relevant cell types and circuits.

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3.8: Supplement

3.8.1: Inclusion/exclusion criteria details

Our goal was to include as representative a cohort of CNV carriers as possible; as such,

we did not exclude participants for cardiac-related issues, as cardiac complications are a

hallmark of 22q11.2 Deletion Syndrome. Such exclusions would reduce power and create an

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unrepresentative sample. Control participants were excluded if they had intellectual disability, evidence of past or current major mental disorder, based on information gathered during the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, edition 4 (First & Gibbon, 2004) and/or Computerized Diagnostic Interview for Children (Shaffer et al., 2000), and/or first-degree relative with a psychotic disorder diagnosis. Because Attention-deficit/hyperactivity disorder (ADHD) is a common childhood behavioral disorder (Danielson et al., 2018), this was not exclusionary for controls.

3.8.2: Neuroimaging protocol

Each scan began with a 10 min acquisition of standard images used for determining regional anatomy, including a sagittal localizer image (TR/TE = 500/33 ms, 192 × 256 matrix), a high-resolution T2-weighted axial image (TR/TE = 5000/33 ms, 128 × 128 matrix, FOV = 200 × 200 mm), and a sagittal 1 mm3 T1-weighted image. We used FreeSurfer to process 1 mm3 T1-weighted anatomical images acquired with an MPRAGE sequence. The parameters for the MPRAGE were the following: TR = 2.3 s, TE = 2.91 ms, FOV = 256 mm, matrix = 240 × 256, flip angle = 9°, slice thickness = 1.20 mm, 160 slices. The FreeSurfer image analysis suite (version 5.3.0; http://surfer.nmr.mgh.harvard.edu) surface-based processing pipeline was used to derive measures of volume, cortical thickness, and surface area. FreeSurfer is a well-validated processing package that has been previously described in detail (Dale et al., 1999; Fischl et al., 1999). We extracted cortical measures based on the Desikan FreeSurfer atlas (Desikan et al., 2006). Quality assessment procedures were applied by 2 blind raters to determine scan quality. Segmented regions were visually inspected and statistically evaluated for outliers following standardized ENIGMA protocols (http://enigma.ini.usc.edu/protocols/imaging-protocols).

3.8.3: Analysis of sensory sensitivity and social responsiveness subdomains did

not show significant differences between 22q11.2 deletion and duplication carriers

A linear model was used to test for differences in ASD subscales of sensory sensitivity and social responsiveness between 22q11.2 deletion versus duplication carriers, while adjusting for age and sex. No corrected differences were found at $q < 0.05$ (see Figure S3.1).
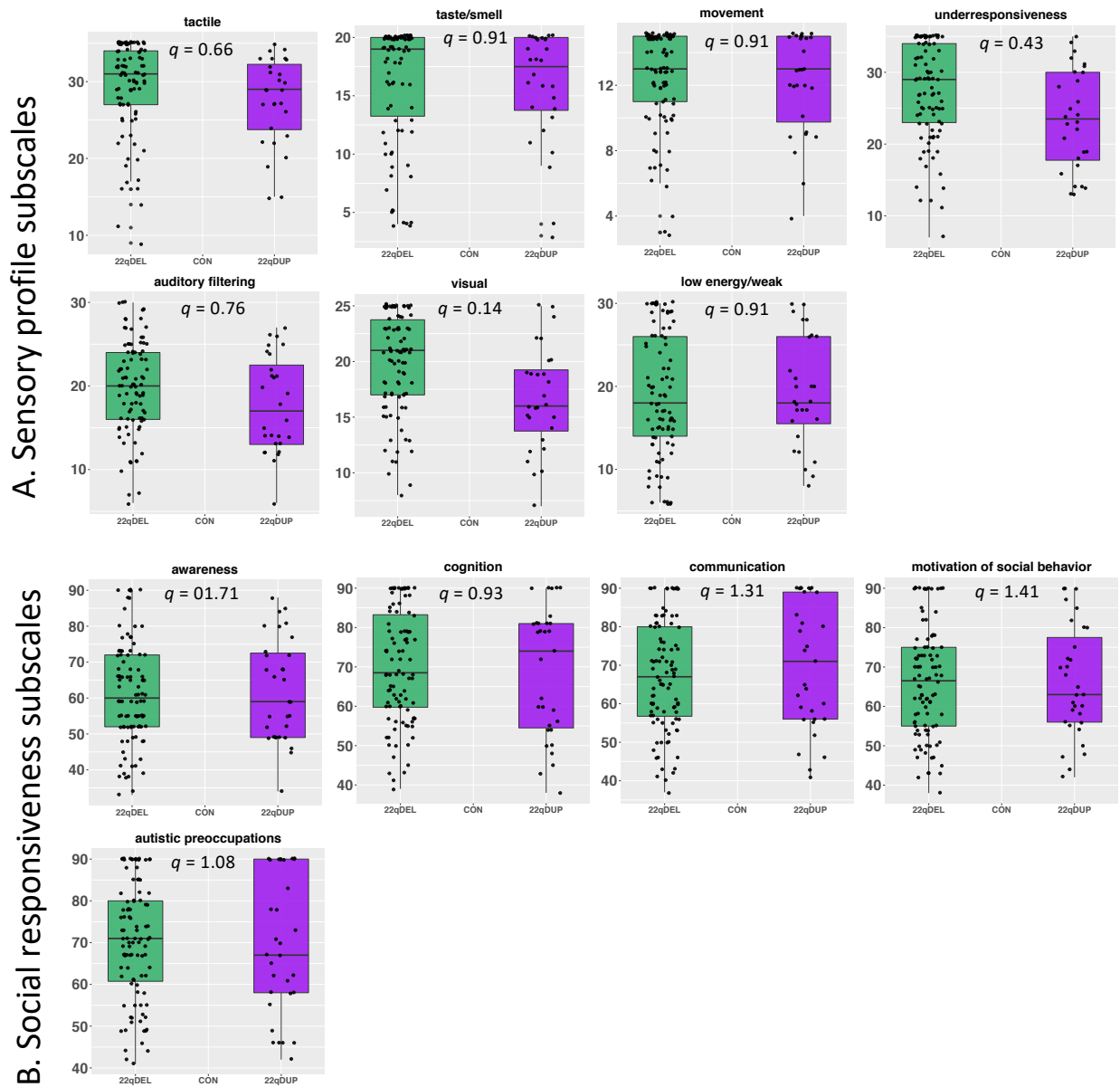
Figure S3.1: Combined box- and scatterplots of average group scores for ASD subdomain scales.

3.8.4: Investigating the relationship between ASD-related impairments and

cognitive abilities

We further explored whether ASD-related symptoms correlated with cognitive function, and to what extent the associations differed between deletion and duplication carriers (see Figure S3.2). To do so, we performed partial Spearman's correlation analyses, controlling for age, between each of 5 cognitive traits (i.e., Verbal IQ, Nonverbal IQ, working memory, processing speed, and verbal memory) and each of 7 dimensional ASD-related traits (i.e., social responsiveness impairment, sensory insensitivity, repetitive/restrictive behavior, lie detection, sarcasm detection, emotion recognition, and emotion differentiation), separately for deletion and duplication carriers. Because Full-Scale IQ is comprised of nonverbal and verbal IQ, it was not included to avoid redundant variables. After correcting for multiple comparisons using an FDR adjustment at $q<0.05$ across 35 tests within each group, 6 correlations survived. Within 22q11.2 deletion carriers, verbal IQ positively correlated with lie detection ($q=0.02$, rho = 0.42, Cohen's d = 0.92) and emotion recognition ($q=0.03$, rho = 0.37, Cohen's d = 0.78). Also, higher processing speed was associated with less sensory sensitivity ($q=0.03$, rho = 0.35, Cohen's d = 0.74). Within duplication carriers, verbal IQ was positively correlated with lie detection ($q=0.0006$, rho = 0.85, Cohen's d = 3.18), emotion recognition ($q=0.007$, rho = 0.60, Cohen's d = 1.48), and emotion differentiation ($q=0.03$, rho = 0.53, Cohen's d = 1.24). These results indicate that verbal IQ is positively correlated with social cognition in both duplication and deletion carriers, although effect sizes for these relationships were greater in the duplication group.
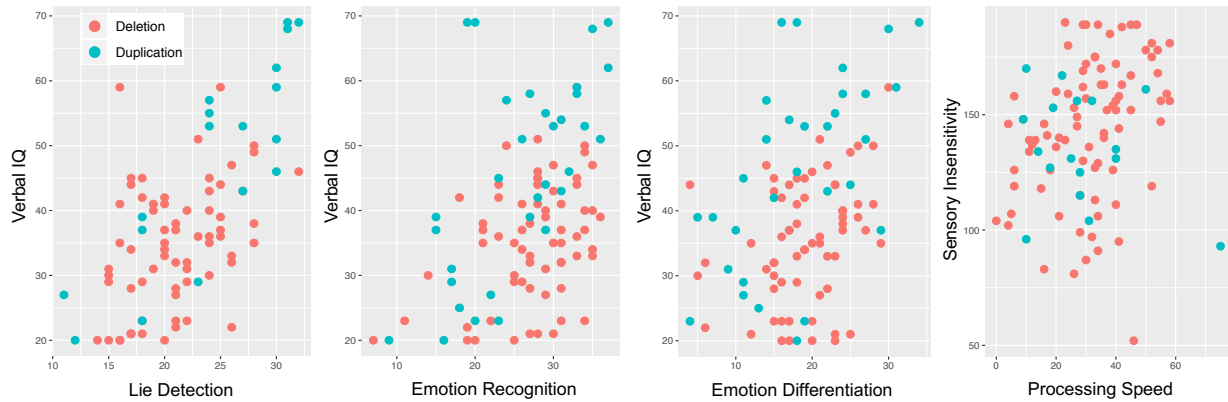
Figure S3.2. Correlations of ASD-related traits and cognitive abilities between deletion and duplication carriers that survived FDR correction. Within deletion carriers, verbal IQ was significantly correlated with lie detection and emotion recognition. Processing speed was also correlated with sensory insensitivity. Within duplication carriers, verbal IQ was significantly correlated with lie detection, emotion recognition, and emotion differentiation.

3.8.5: Analysis of additional measures of social-emotional behavior and real-world function

We extended our univariate analysis of group differences to include 10 additional neurobehavioral traits on a scale normalized to controls to determine whether there are specific areas of impairment or preservation (Tables S3.1 and S3.2, Figure S3.3). These traits are beyond the scope of the primary hypotheses of the main text and assess broader neuropsychological profiles spanning social-emotional behavior and real-world function, not specific to ASD or SCZ. Executive functioning was measured via the Behavior Rating Inventory of Executive Function (BRIEF) Global Executive Composite score (Gioia et al., 2000). Behavioral/emotional problems and competencies were assessed using overlapping domains of the Child or Young Adult Behavioral Checklist (CBCL/YABC), including: somatic complaints, anxious/ depressed, withdrawn/depressed, thought problems, attention problems, delinquent behavior, and aggressive behavior (Achenbach, 1993). Overall daily functioning was measured

using the Global Assessment of Functioning Scale (GAF; (Association, 2000)). Additionally, two specific measures of social and role functioning, specifically designed for assessment of youth, were obtained to more precisely capture real-life behavioral challenges independent of symptom severity (Global Functioning: Social; Global Functioning: Role scales (Cornblatt et al., 2007)).

We converted individual raw scores into standard scores, relative to control subjects (mean = 0, sd = 1). Each score was converted to a z-score by subtracting the group mean and then dividing by the standard deviation of the control group. Then, significance testing was conducted on the normalized scores as before, where an omnibus ANCOVA was first applied to test for the overall effect of group, followed by Tukey's post-hoc pairwise comparisons. FDR correction was applied for the number of traits within each panel.

For every trait analyzed, both CNV groups showed significant differences compared to controls at a corrected $q < 0.05$. There were significant, corrected differences between CNV groups for only one trait in which 22q11.2 deletion carriers showed significantly greater impairment in role functioning compared to duplication carriers. These findings highlight the pleiotropic effects of 22q11.2 genes and also suggest that both over and under-expression of genes within the locus can lead to convergent, complex neuropsychiatric deficits.

Domain	Test	Trait	Measure
Behavioral Functioning	Behavior Rating Inventory of Executive Function	Executive Functioning	global executive composite T-score
	Child Behavior Checklist, Young Adult Behavior Checklist	Anxious Depressed	T-score
		Withdrawn Depressed	T-score
		Somatic Complaints	T-score

		Thought Problems	T-score
		Attention Problems	T-score
		Aggression	T-score
Global Functioning	Global Functioning: Role Scale	Role Functioning	scale of 1-10
	Global Functioning: Social Scale	Social Functioning	scale of 1-10
	Global Assessment of Functioning	Global Functioning	scale of 1-100

Table S3.1: Description of additional measures of social-emotional behavior and real-world functioning.

Trait	Omnibus F-statistic	22qDEL-Control Estimate (SE)		22qDUP-Control Estimate (SE)		22qDUP-22qDEL Estimate (SE)	
Executive Functioning[a,b]	38.78	18.05	(-2.27)	19.85	(-2.92)	1.8	(-2.84)
Somatic Complaints[a,b]	23.34	9.73	(-1.48)	8.45	(-1.89)	-1.28	(-1.82)
Thought Problems[a,b]	15.64	8.87	(-1.62)	6.9	(-2.06)	-1.97	(-1.99)
Withdrawn Depressed[a,b]	20.82	8.45	(-1.39)	8.2	(-1.78)	-0.25	(-1.72)
Attention Problems[a,b]	29.51	12.15	(-1.69)	11.91	(-2.15)	-0.24	(-2.08)

Anxious Depressed[a,b]	25.63	8.93	(-1.39)	9.96	(-1.77)	1.04	(-1.71)
Aggression[a,b]	10.04	5.25	(-1.45)	7.41	(-1.92)	2.16	(-1.88)
Role Functioning[a,b,c]	78.48	-3.34	(-0.27)	-2.19	(-0.35)	1.16	(-0.34)
Social Functioning[a,b]	67.54	-2.53	(-0.22)	-1.87	(-0.29)	0.66	(-0.28)
Global Functioning[a,b]	83.14	-28.93	(-2.28)	-21.51	(-2.96)	7.41	(-2.9)

Table S3.2: ANCOVA results for additional measures of social-emotional behavior and real-world functioning, covarying for age and sex. [a]corrected 22qDEL-CON difference; [b]corrected 22qDUP-CON differences; [c] corrected 22qDEL-22qDUP difference.
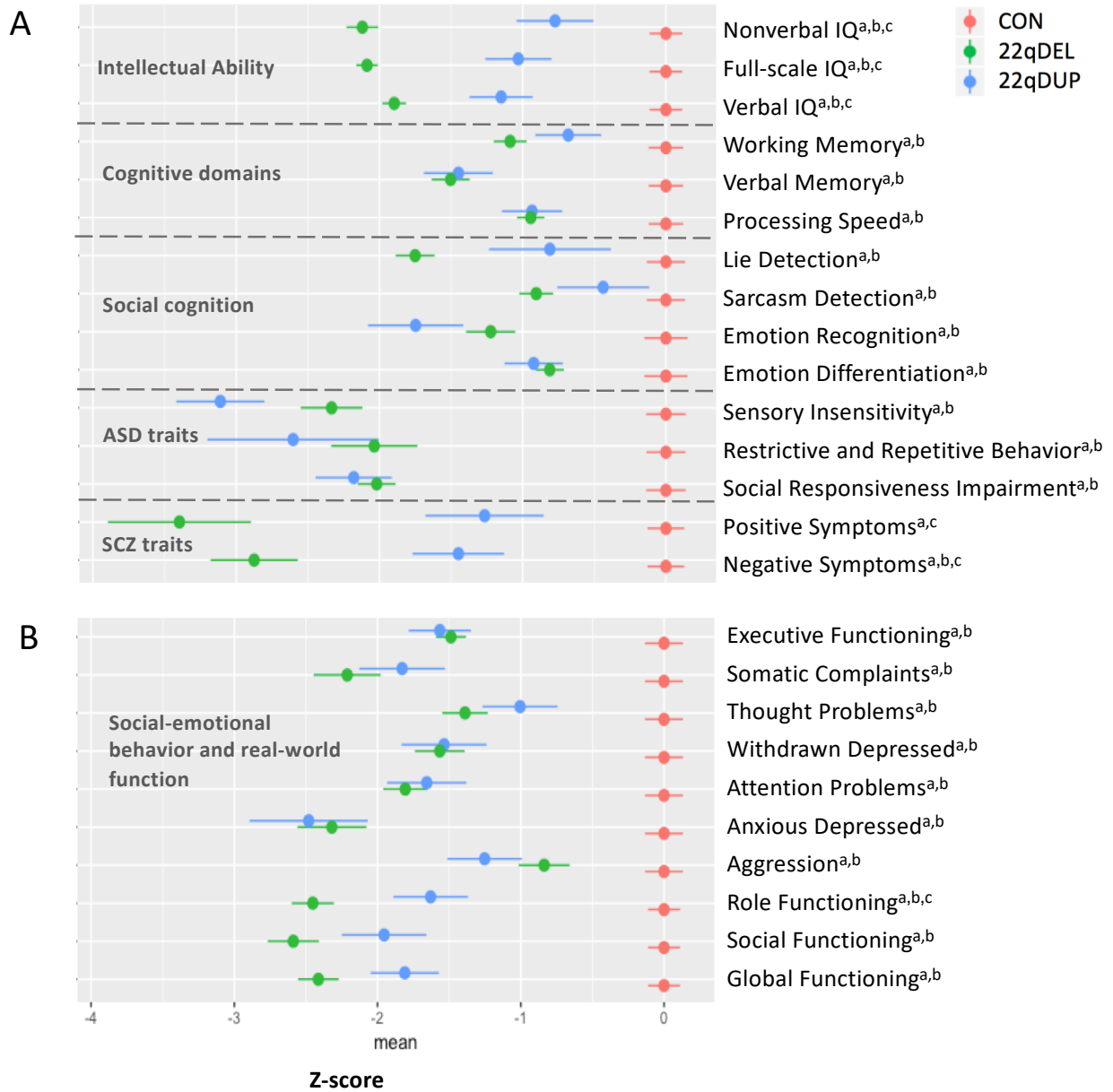
Figure S3.3: Z-scores and standard errors depicting effects of 22q11.2 CNVs across a wider neurocognitive profile with additional behavioral functioning measures, standardized to control mean and standard deviation. For comparability, panel A reproduces the z-scores of the cognitive/behavioral measures in the main text while panel B contains the additionally analyzed traits. For visualization purposes, scores are converted to absolute values and then multiplied by -1 to highlight impairments in CNV groups compared to controls. Dotted lines separate traits into neurocognitive and behavioral domains. Compared to

controls, 22q11.2 deletion and duplication carriers showed significant impairment across all traits with the exception of positive symptoms, for which duplication carriers did not differ from controls. In addition, 22q11.2 deletion carriers showed even greater impairment than duplication carriers for all three IQ measures, positive and negative symptoms, and role functioning but otherwise displayed no significant difference from duplication carriers for social cognition and ASD-relevant traits. At $q < 0.05$, [a]corrected 22qDEL-CON difference; [b]corrected 22qDUP-CON differences; [c] corrected 22qDEL-22qDUP difference.

raw *p*-value

0   0.4   0.8

pericalcarine area
bankssts area
cuneus area
parsorbitalis area
posteriorcingulate area
medialorbitofrontal area
inferiorparietal area
lateralorbitofrontal area
lingual area
middletemporal area
superiorparietal area
caudalmiddlefrontal area
precentral area
inferiortemporal area
frontalpole area
isthmuscingulate area
rostralmiddlefrontal area
superiortemporal area
rostralanteriorcingulate area
paracentral area
insula area
fusiform area
superiorfrontal area
supramarginal area
postcentral area
lateraloccipital area
precuneus area
paracentral thickness
parsopercularis thickness
isthmuscingulate thickness
parstriangularis area
parstriangularis thickness
rostralmiddlefrontal thickness
medialorbitofrontal thickness
lateralorbitofrontal thickness
insula thickness
fusiform thickness
caudalanteriorcingulate thickness
rostralanteriorcingulate thickness
posteriorcingulate thickness
frontalpole thickness
transversetemporal thickness
lingual thickness
caudalanteriorcingulate area
temporalpole thickness
transversetemporal area
parahippocampal area
parsopercularis area
temporalpole area
parahippocampal thickness
entorhinal thickness
entorhinal area
parsorbitalis thickness
superiortemporal thickness
caudalmiddlefrontal thickness
superiorfrontal thickness
bankssts thickness
middletemporal thickness
precentral thickness
inferiortemporal thickness
pericalcarine thickness
cuneus thickness
lateraloccipital thickness
supramarginal thickness
postcentral thickness
inferiorparietal thickness
superiorparietal thickness
precuneus thickness

SSP SRS RBS ER PS WM SAR ED LIE NVIQ VIQ FSIQ VM NEG POS

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Figure S3.4: Interaction between group and brain measure (regional cortical thickness/surface area) on processing speed (uncorrected *p*-values). After regressing out age and sex from cognitive measures, a linear model was applied to estimate the interaction effect of brain and group for each of the 15 traits using measures of CT or SA. Rows and columns are ordered by hierarchical clustering as annotated by the dendrograms. SSP = Sensory Sensitivity Profile, SRS = Social Responsiveness Scale, RBS = Restricted, Repetitive Behavior, ER = Emotion Recognition, PS = Processing Speed, WM = Working Memory, SAR = Sarcasm Detection, ED = Emotion Differentiation, LIE = Lie Detection, NVIQ = Nonverbal IQ, VIQ = Verbal IQ, FSIQ = Full-scale IQ, VM = Verbal Memory, NEG = Negative Symptoms, POS = Positive Symptoms.

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CHAPTER FOUR

Transcriptomic profiling of whole blood in 22q11.2 reciprocal copy number variants reveals that

cell proportion highly impacts gene expression

4.1: Abstract

22q11.2 reciprocal copy number variants (CNVs) offer a powerful quasi-experimental "reverse-genetics" paradigm to elucidate how gene dosage (i.e., deletions and duplications) disrupts the transcriptome to cause further downstream effects. Clinical profiles of 22q11.2 CNV carriers suggest that disrupted gene expression could underlie known alterations in neuroanatomy, cognitive function, and psychiatric disease risk. However, interpreting transcriptomic signal in blood tissue requires careful consideration of cell type heterogeneity. We characterized transcriptomic dysregulation of peripheral blood from reciprocal 22q11.2 CNV carriers using differential expression analysis and unsupervised weighted gene co-expression network analysis (WGCNA) to identify modules of co-expressed genes. We also accounted for the effect of cell type proportions and other potential confounders such as batch and medication usage. Finally, to explore whether CNV-related transcriptomic changes relate to downstream phenotypes associated with 22q11.2 CNVs, we tested for associations of gene expression with neuroimaging measures and behavioral traits, including IQ and psychosis or ASD diagnosis. 22q11.2 deletion (22qDel) significantly altered genome-wide expression at the individual gene as well as module eigengene level. In 22qDel carriers, modules showed significant upregulation for 2 modules and downregulation for 3 modules compared to 22q duplication carriers (22qDup) and controls, as well as significant upregulation in 1 module compared to only 22qDup carriers. However, 22qDup did not show any significant differential expression compared to 22qDel carriers or controls. Notably, differences in gene expression between groups were substantially attenuated after adjustment for cell type heterogeneity. Three modules showing group differences were highly enriched for specific cell types, including T-cell and macrophage subtypes, of which proportions also showed group differences. Mast cell subtypes were also found to significantly differ between CNV groups. While gene expression and cell type proportions largely did not associate with clinical phenotypes, WDR1 and FNBP1 genes were significantly underexpressed in 22qDel carriers with ASD compared to 22qDel

carriers without ASD, but overexpressed in 22qDup carriers with ASD compared to 22qDup carriers without ASD. Our findings highlight the importance of accounting for cell type heterogeneity when analyzing peripheral blood to study brain-related diseases. Nonetheless, the identification of several potentially novel cell type composition differences warrants future investigation in animal or in vitro models to test whether 22q11.2 CNV effects on macrophages may have implications for microglial function. In sum, provided key confounds are appropriately adjusted, blood tissue may shed light on immune mechanisms relevant to psychiatric disorders.

4.2: Introduction

Deletions and duplications at the 22q11.2 locus occur in 1 in ~3000-4000 and 1 in ~1600 live births, respectively (Hoeffding et al., 2017; Olsen et al., 2018). They span a gene-rich region of chromosome 22 that includes highly conserved, brain-expressed, protein-coding genes, many of which are crucial for brain and cognitive development (Guna et al., 2015; N. Hiroi et al., 2013). 22q11.2 deletions are associated with a multi-system phenotype that includes heart anomalies, immune dysfunction, and high rates of neuropsychiatric and neurodevelopmental disorders (McDonald-McGinn et al., 2015). Both of these copy number variants (CNVs) are associated with developmental delays and intellectual disability; however, cognitive deficits tend to be milder in 22q11.2 duplication carriers compared to deletion carriers (A. Lin et al., 2020). Notably, both convergent and divergent impairments are associated with these reciprocal chromosomal rearrangements (Hoeffding et al., 2017; A. Lin et al., 2020; Olsen et al., 2018). For example, both the 22q11.2 deletion and duplication are associated with elevated rates of autism spectrum disorder (ASD)(Olsen et al., 2018; Jacob A. S. Vorstman et al., 2006; Wenger et al., 2016), but only the 22q11.2 deletion confers elevated risk for psychosis (Z. Li et al., 2016; Marshall et al., 2017; Monks et al., 2014; Niarchou et al., 2014; Rees et al., 2016; Schneider et al., 2014). Moreover, the only structural neuroimaging study thus far to analyze both 22q11.2

CNV groups showed that brain morphology differed meaningfully as a function of reciprocal genomic variation, with 22q11.2 deletion carriers being more impacted (A. Lin et al., 2017). While understanding the biological mechanisms that lead to partially overlapping versus distinct phenotypes associated with reciprocal 22q11.2 CNVs remains a challenge, the advent of high throughput transcriptomics offers the potential to gain new mechanistic insights.

Intermediate to genetic variation and downstream traits (i.e. measures of neuroanatomy, cognition and behavior), gene expression represents the transcriptional activity that underlies biological mechanisms (Coppola, 2011). Characterizing how the transcriptome changes in 22q11.2 deletion versus duplication carriers can enhance our understanding of how biological systems are disrupted by these major genetic perturbations to yield partially overlapping versus distinct phenotypes. The identification of differential expression in individual genes or co-expression of multiple genes can implicate different cell-types or biological processes underlying disorder pathology. Moreover, whole-transcriptome profiling allows the unbiased interrogation of all genes in parallel, avoiding the limitations of targeted gene approaches (Zhang & Horvath, 2005). As cellular processes often affect many genes acting in concert, it is also crucial to analyze genomic information at the level of coexpression (Allen et al., 2012; Kadarmideen & Watson-Haigh, 2012). Finally, integrating orthogonal behavioral phenotype measures can aid in functional interpretation of genes of interest (Jalbrzikowski et al., 2015). This includes the incorporation of both quantitative and categorical measures of neurodevelopmentally relevant traits, such as those from brain imaging, cognitive assays, and psychiatric diagnoses.

Interpreting transcriptomic signal from heterogeneous bulk tissue like peripheral blood (Shen-Orr & Gaujoux, 2013) can be challenging because the measured expression levels of gene expression detected by microarray or RNA sequencing can be greatly influenced by variation in cell type composition (Farahbod & Pavlidis, 2020). In psychiatric genetics, most studies to date aim to identify dysregulated genes to uncover biological bases of disease using heterogeneous bulk tissue, either from the brain or blood. However, without accounting for

heterogeneity in the proportion of distinct cell types that comprise a given tissue, it is difficult to know whether disease-associated transcriptomic changes represent differences in the number of cells expressing certain genes, alterations in transcript levels within the cells themselves, or some combination of both. This may be particularly important in blood, where cell type variation is especially pronounced with over a dozen distinct cell types for which abundance can vary up to 10–20-fold, even in healthy individuals (Adalsteinsson et al., 2012; Chikina et al., 2015; Farahbod & Pavlidis, 2020; Shen-Orr et al., 2010). To address this issue, computational methods have been developed to estimate cell type-specific proportions based on expression patterns of known marker genes (Chikina et al., 2015; Newman et al., 2015; Xu et al., 2013). It is not yet routine practice to account for cell type heterogeneity in studies of CNS disorders. However, recent studies of bipolar disorder and schizophrenia (Toker et al., 2018) as well as Huntington's Disease (Kuhn et al., 2011) found that when there are cell type composition differences in bulk tissue samples, adjusting for it provided more accurate insights into disease pathology.

Here, we aimed to characterize transcriptomic dysregulation in peripheral blood from individuals with reciprocal 22q11.2 CNVs while carefully considering the effect of cell type proportions and other potential confounders such as batch and medication usage. While two prior studies profiled the peripheral blood transcriptome in 22q11.2 deletion carriers with smaller sample sizes (Jalbrzikowski et al., 2015; van Beveren et al., 2012), neither study included duplication carriers nor adjusted for cell type composition or medication usage. Therefore, we characterized CNV-associated differential expression of individual genes and co-expression of genes (i.e., eigengenes), before and after accounting for potential confounders, including cell type proportion and medication. To explore whether blood transcriptomic changes in the context of 22q11.2 deletions and duplications relate to phenotypes associated with the CNVs, we also tested for associations between gene and eigengene expression with neuroimaging measures and behavioral traits (IQ and diagnosis of psychosis or ASD). This comprehensive approach

aims to bridge the gap between transcriptomics, brain development, and behavioral outcomes to generate testable hypotheses about the molecular effects of 22q11.2 CNVs.

4.3: Materials and Methods

4.3.1: Participants

The sample consisted of 179 age and sex-matched individuals: 82 with molecularly confirmed 22q11.2 deletions (22qDel), 29 with confirmed 22q11.2 duplications (22qDup), and 68 demographically-matched controls (for demographics, see Table 4.1). CNVs were determined via multiplex ligation-dependent probe amplification (MLPA; (Schouten et al., 2002)) using the SALSA MLPA Probemix P250-B2 DiGeorge kit from MRC-Holland (J. A. S. Vorstman et al., 2006), a polymerase chain reaction (PCR)-based assay that is a gold standard method for determining copy number changes in humans. Patients were ascertained from a variety of sources, including the University of California at Los Angeles (UCLA) or Children's Hospital, Los Angeles Pediatric Genetics, Allergy/Immunology and Craniofacial Clinics, as well as local support groups and websites. Demographically comparable, typically developing comparison subjects were recruited from the same communities as patients via web-based advertisements, flyers and brochures at local schools, pediatric clinics, and other community sites. Approximately 25.6% of the deletion carriers and 42.6% of the controls were included in a prior publication (Jalbrzikowski et al., 2015). As such, the current study includes a substantially larger sample of both 22q11.2 deletion carriers and controls, as well as a novel cohort of 22q11.2 duplication carriers.

	22q11.2 Deletion Carriers	Typically-developing Controls	22q11.2 Duplication Carriers
Sample Size	82	68	29
Age (SD)	17 (8.4)	18.5 (12.6)	18.5 (12.6)
Age Range	5.5 to 41	6 to 49	6.7 to 49.5
N, females (%)	41 (50%)	34 (50%)	13 (44.8%)
Full-scale IQ (SD)	76.6 (11.8)	109.0 (19.3)	96.6 (23.6)
N, Autism Spectrum Disorder (%)	44 (53.7%)	0	12 (41.4%)
N, Psychotic Disorder (%)	11 (13.4%)	0	0
RIN[a,b] (SD)	8.52 (0.66)	8.86 (0.55)	8.43 (0.54)
N, Antidepressants[a,b]	24	4	9
N, Antiepileptics[b]	8	1	4
N, Benzodiazepines[a,c]	8	0	0
N, Antipsychotics[a,b]	10	1	3
N, Stimulants[b,c]	10	2	10

Table 4.1: Participant Demographics

[a] 22q-del ≠CTL (p<.05), [b] 22q-dup ≠ CTL (p<.05), [c] 22q-del ≠ 22q-dup (p<.05)

note: family relatedness of controls to 22qDel carriers: 8 brothers, 1 half-brother, 2 sisters, 1 half-sister, 1 mother, 1 aunt, 1 grandmother, 1 grandfather/father

Exclusion criteria for all study participants included significant neurological or medical conditions (unrelated to 22q11.2 CNVs) that might affect brain structure, history of head injury with loss of consciousness, insufficient fluency in English, and/or substance or alcohol abuse or dependence within the past 6 months. Healthy controls additionally could not have significant intellectual disability or meet criteria for any psychiatric disorder with the exception of attention deficit-hyperactivity disorder or a past episode of depression, due to their prevalence in childhood and adolescence (Ghandour et al., 2019; Sayal et al., 2018; Thapar et al., 2012). All participants underwent a verbal and written informed consent process. Participants under the age of 18 years provided written assent, while their parent or guardian completed written

consent. The University of California at Los Angeles Institutional Review Board approved all study procedures and informed consent documents.

4.3.2: *Peripheral Blood Sample Preparation*

RNA was extracted from whole blood using the PAXgene extraction kit (Qiagen) and stored at -80C for subsequent analysis. RNA quantity was assessed using Nanodrop (Nanodrop Technologies) and RNA quality was determined using the Agilent Bioanalyzer (Agilent Technologies) to quantify RNA fragmentation in each sample, creating an RNA integrity number (RIN) (Schroeder et al., 2006). Total RNA (200 ng) was amplified, biotinylated, and hybridized on Illumina HT12 v3 or v4 microarrays as per manufacturer protocol at the UCLA Neuroscience Genomics Core. Only probes shared between the 2 platforms were used in analyses. Slides were scanned using an Illumina BeadStation and signal was extracted using the Illumina BeadStudio software (Illumina, San Diego, CA).

4.3.3: *Structural Neuroimaging*

High-resolution structural magnetic resonance imaging (MRI) scans were acquired concurrently with blood measures for 49 22qDel carriers, 43 controls, and 21 22qDup carriers. Scanning was conducted on a 3T Siemens (Erlangen, Germany) TimTrio MRI scanner with a 12-channel head coil at the UCLA Brain Mapping Center or an identical 3T scanner, using identical acquisition parameters, at the UCLA Center for Cognitive Neuroscience. Details of scanning parameters have been described in prior publications (A. Lin et al., 2017); see Supplementary Methods for details). Quality assessment procedures were applied by 2 raters blind to group status. We extracted cortical measures based on the Desikan-Killiany FreeSurfer atlas (Desikan et al., 2006). Segmented regions were visually inspected and statistically evaluated for outliers following standardized ENIGMA protocols (http://enigma.ini.usc.edu/protocols/imaging-protocols).

4.3.4: *Clinical and Neurocognitive Assessments*

IQ estimates were obtained using the Vocabulary and Matrix Reasoning subtests in the Wechsler Abbreviated Scale of Intelligence (Wechsler, 2012) or Wechsler Adult Intelligence Scale, Ed 4 (Wechsler, 2008) for 82 22qDel carriers, 55 controls, and 27 22qDup carriers. Supervised clinical psychology doctoral students administered psychodiagnostic evaluations to all study participants to assess for DSM psychiatric diagnoses (Structured Clinical Interview for DSM [SCID] ((First & Gibbon, 2004; Shaffer et al., 2000)) and/or Computerized Diagnostic Interview Schedule for Children [C-DISC]; (First & Gibbon, 2004; Shaffer et al., 2000). To assess for ASD, the Autism Diagnostic Observation Schedule (ADOS) was administered to 22q11.2 CNV participants, and the Autism Diagnostic Interview-Revised (ADI-R) was administered to their parent/primary caretaker (Lord et al., 2000).

4.3.5: *STATISTICAL ANALYSES*

4.3.5.1: *Microarray-based Gene Expression Analysis Data: Pre-processing and Statistical Overview*

Raw data were processed with the lumi package (Du et al., 2008) in the R statistical environment (version 3.5.2; R Foundation for Statistical Computing, Vienna, Austria). Only samples with a RIN of 7 or greater were included (Gallego Romero et al., 2014) (refer to Table 4.1). Signal intensity was normalized with variance stabilizing transformation (S. M. Lin et al., 2008) and interarray normalization was done using robust spline regression normalization. Probes with a detection threshold of $p < .01$ or that were unannotated were dropped. Duplicated probes for the same transcript were also dropped using the collapseRows function (Miller et al., 2011) from the WGCNA package using the default maxMean approach, resulting in expression measurements for 14,013 unique genes. Finally, outliers (>|3| SD) were removed based on connectivity z-scores (Dong & Horvath, 2007).

As psychotropic medication usage is known to influence peripheral blood gene expression (Flanagan & Dunk, 2008; Stübner et al., 2004), we also included categories of psychotropic medications used by 22q11.2 CNV carriers in a subset of our analyses. Categories

included antidepressants, antiepileptics, antipsychotics, benzodiazepines and stimulants (refer to Table 4.1). Batch effects were controlled for using the 'removeBatchEffect' from limma (Ritchie et al., 2015). For analyses additionally controlling for cell type proportions and/or medication effects, these variables were modeled simultaneously with batch using 'removeBatchEffect', to avoid introducing biases that can occur when sequentially removing confounded variables which are associated with our variable of interest and each other (i.e., CNV group status (Aschard et al., 2017). Age, sex, and RIN were included as covariates for all statistical models involving gene expression data.

4.3.5.2: *Cell Type Proportion Estimation*

Cell-type estimation relies on the observation that variation in expression of cell type-specific marker genes is correlated with the abundance of the cell type in which they are expressed and has been validated in multiple studies (Kuhn et al., 2011; Mancarci et al., 2017; Newman et al., 2015; Patrick et al., 2020). Cell-type proportions were estimated using the LM22 reference dataset and CIBERSORT (Kuhn et al., 2011; Mancarci et al., 2017; Newman et al., 2015; Patrick et al., 2020). The LM22 reference dataset consists of 547 genes that discriminate between 22 mature human hematopoietic populations that were isolated from peripheral blood or in vitro cultures. It includes 7 T-cell types, naïve and memory B-cells, plasma cells, natural killer (NK) cells, and myeloid subsets. Proportions were logit-transformed after applying an adjustment for values of 0 (Smithson & Verkuilen, 2006). A linear model was used to test for associations between cell-type proportion and CNV status and brain and behavioral measures, with confounding covariates first removed using residualization.

4.3.5.3: *Differential Expression*

Genes with differential expression were assessed transcriptome-wide using linear models in the limma package (Ritchie et al., 2015). Pairwise contrasts compared controls vs 22qDel, controls vs. 22qDup, and 22qDup vs 22qDel. Empirical Bayes-moderated p-values generated by limma were used to adjust for multiple testing across all genes; genes with an

adjusted p-value < 0.05 were considered significantly differentially expressed (DE). Potential CNV group differences in gene expression were assessed prior to, and after adjusting expression data for differences in cell-type proportions. Genes with significant differential expression were functionally annotated using gene ontology (GO) with g:Profiler (Raudvere et al., 2019)

4.3.5.4: *Weighted Gene Co-expression Network Analyses (WGCNA) and enrichment of gene sets from WGCNA modules for cell-type specific expression*

WGCNA was used to identify modules of co-expressed genes using standard parameters (Langfelder & Horvath, 2008). Briefly, correlations were computed between all pairs of genes, and unsupervised clustering was used to identify modules of co-expressed genes. Modules were functionally annotated using GO with g:Profiler (Raudvere et al., 2019) as well as for cell-type specificity using the pSI package (Dougherty et al., 2010; Xu et al., 2013) and sorted reference datasets (Newman et al., 2015; Novershtern et al., 2011; see Supplementary Information for details). The first principal component of each module (i.e., module eigengene) was used to summarize the expression of each module. Co-expression modules were generated and tested for potential differences in expression by CNV group prior to, and after adjusting for, differences in cell-type proportions.

4.3.5.5: *Associations with neuroimaging, IQ, and psychiatric phenotypes*

We assessed potential interaction effects between gene expression and CNV group after accounting for effects of batch, cell-type proportion, and medication, on trait measures of mean cortical thickness, total cortical surface area, and IQ using linear models. The linear model included: trait ~ age + sex + CNV group*gene expression.

To assess for significant main effects of gene expression on CNV group-residualized outcomes, traits were residualized for CNV group status because the 22q11.2 CNV affects both gene expression and the clinical traits (A. Lin et al., 2017, 2020) and could thus drive spurious associations (Aschard et al., 2017). We use a linear model with cell type and medication-

adjusted expression measures, age, and sex as predictors and group-residualized clinical traits as the outcome measures. To assess the association between cell type proportion and the same 3 outcome measures, we applied the same model using medication- and batch-adjusted cell type proportion as predictors to assess interaction effects with CNV group on unadjusted outcomes and for main effects on CNV group-residualized outcomes. The linear model included: group residualized trait ~ age + sex + gene expression. The same linear models including the interaction effect or main effect were used to test for the association between clinical phenotypes and cell-type-adjusted WGCNA module expression or cell type proportions.

To test for potential associations between diagnoses of psychosis or ASD and the expression of each gene or WGCNA-derived module eigengene, we fit linear models with the limma package using batch, cell-type proportion, and medication adjusted gene expression data and WGCNA modules. Since psychosis is associated with 22qDel only (Z. Li et al., 2016; Marshall et al., 2017; Rees et al., 2016), the linear models testing for group differences in subjects with or without psychosis were restricted to 22qDel subjects. For ASD, which is associated both with 22qDel and 22qDup (Olsen et al., 2018; Wenger et al., 2016), the linear model included an interaction term between CNV status and ASD diagnosis, as well as the main effects of CNV status and ASD diagnosis. Potential group differences in medication- and batch-adjusted cell-type proportions were also assessed using linear models.

False discovery rate correction was used to correct for multiple comparisons and performed per analysis (i.e., across genes, eigengenes, cell-types, and clinical phenotype measures of IQ, cortical thickness, surface area, or ASD/psychosis diagnosis). All results were considered significant at an FDR-corrected $q <.05$.

4.4: Results

4.4.1: 22q11.2 deletion significantly alters genome-wide gene expression

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For gene expression that was unadjusted for cell type proportion or medication status, 22qDel carriers showed 312 genes with significant DE relative to controls (113 downregulated, 199 upregulated *Figure 4.1, Table 4.2*). This included 28 downregulated genes within the 22q11.2 locus, with the remaining DEgenes outside the locus. No genes were significantly DE between 22qDup carriers and controls. However, consistent with opposing gene dosage effects between 22q11Del versus 22q11Dup, differential expression was most pronounced between 22qDel and 22qDup carriers, with 477 DE genes (254 downregulated, 223 upregulated), including 29 22q11.2 genes. GO analysis of DE genes between 22qDel and 22qDup carriers, excluding genes found within the 22q11.2 locus, implicated immune related processes including leukocyte, lymphocyte, and T cell activation. Between 22qDel carriers and controls (again excluding genes within the 22q11.2 locus), GO analysis of DEgenes again implicated immune processes, particularly with regard to the activation of T cells, leukocytes, and lymphocytes.

Figure 4.1: Volcano plots of differential gene expression across the genome for each pairwise contrast. Panel A represents gene expression that is unadjusted for cell type or medication, while panel B represents gene expression that is adjusted for both cell type and medication. Red dots represent genome-corrected, significant 22q11.2 DE genes. Black dots represent genome-corrected, significant, non-22q11.2 DE genes. Light red dots represent

nonsignificant 22q11.2 DE genes. Light black dots represent nonsignificant, non-22q11.2 DE genes. Significant DE genes were submitted to gene ontology (GO) enrichment analysis, and the top 5 GO terms displayed.

Cell type and medication-unadjusted	22qDel vs Control	22qDel vs 22qDup
Total DE gene	312	477
Upregulated genes	113 (36.22%)	254 (53.25%)
Downregulated genes	199 (63.78%)	223 (46.75%)
22q11.2 genes	28 (8.98%), all downregulated	29 (6.08%), all downregulated
Outside 22q region	284 (91.03%)	448 (93.92%)

Cell type and medication-adjusted	22qDel vs Control	22qDel vs 22qDup
Total DE gene	24	29
Upregulated genes	1 (4.17%)	3 (10.34%)
Downregulated genes	23 (95.83%)	26 (89.66%)
22q11.2 genes	22 (91.67%), all downregulated	25 (86.21%), all downregulated
Outside 22q region	2 (8.33%)	4 (13.80%)

Table 4.2: Significant differentially-expressed (DE) genes before and after cell type and medication adjustment.

4.4.2: Module eigengenes show significant group differences for 22q11.2 deletion carriers

Without adjusting for cell type proportion, WGCNA identified 28 modules of co-expressed genes in the full dataset of 22qDel carriers, 22qDup carriers, and control subjects (see Supplementary Figure 4.1 for full module dendrogram). Six out of 28 modules showed significant differential expression between groups (see Figure 4.2). In 3 of these modules, 22qDel carriers showed significantly decreased expression compared to controls and 22qDup carriers. 22qDel carriers showed significantly increased expression in 2 modules,compared to controls and 22qDup carriers. In 1 module, 22qDel carriers showed significantly increased

expression compared to only 22qDup carriers. GO analysis of WGCNA modules that differed between groups implicated terms such as platelet activity (royal blue module), immune response (yellow module), vesicles (dark red module), and intracellular anatomical structures (light yellow module).
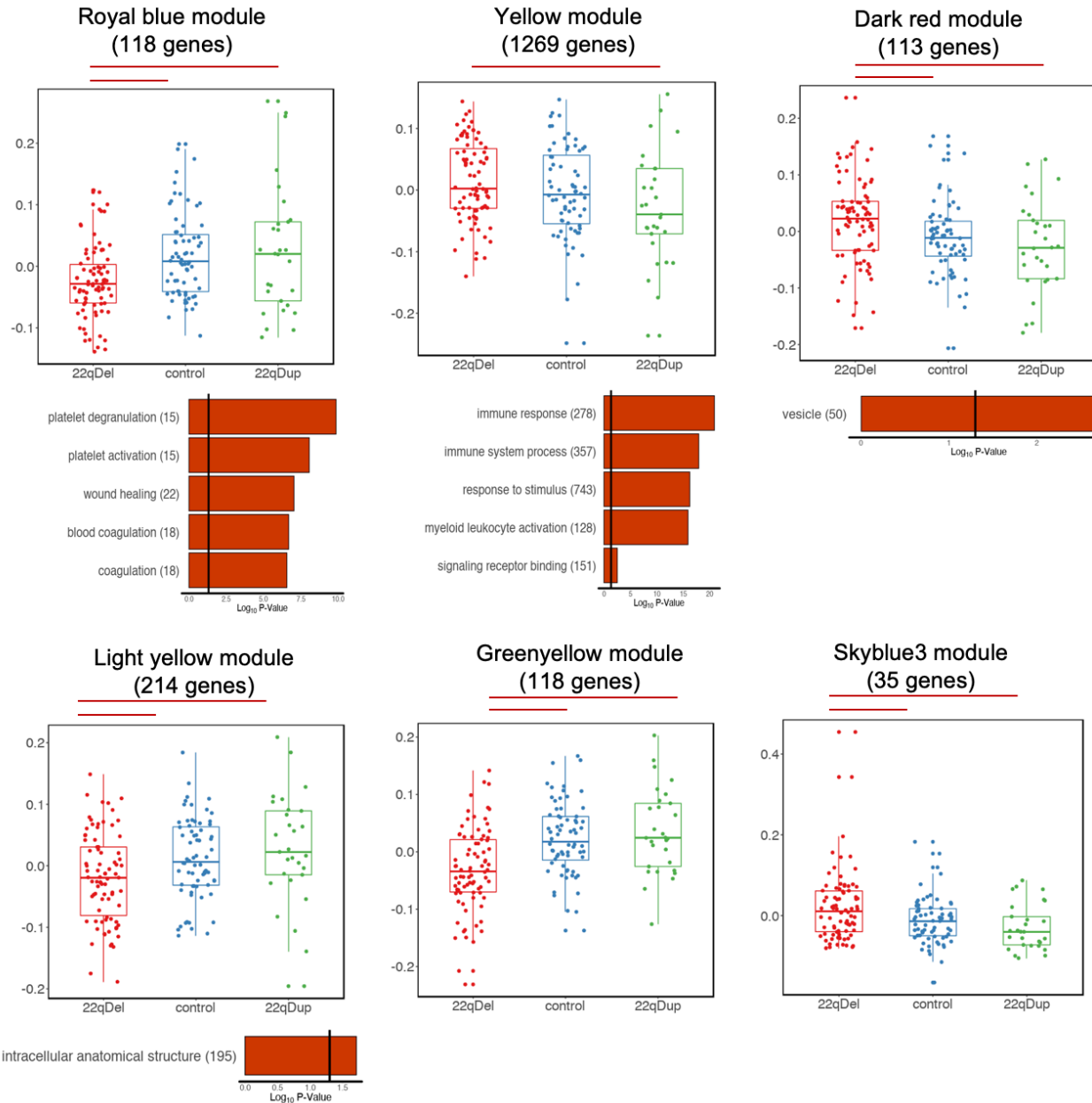
Figure 4.2: Module eigengene expression for the 6 modules (of 29 modules) that showed corrected group differences. These modules were from gene expression that was not

adjusted for cell type nor medication. Red lines indicate FDR-corrected significant difference at q < .05. Modules that were significantly different between groups were submitted to gene ontology (GO) enrichment analysis, and the top 5 GO terms are displayed.

As differential expression and WGCNA-identified genes and gene modules broadly related to immune processes, we also directly annotated the modules for cell type specificity and found strong enrichment for select immune cell types (Figure 4.3; Supplementary Figure 4.2). The pSI tool was used to estimate cell type specificity from the LM22 dataset (Newman et al., 2015), allowing us to test modules for cell type specificity enrichment in the cell types for which we already had proportion estimates. Three modules which showed group differences were highly enriched for similar classes of cell types. The green-yellow module was enriched for several types of T-cells (CD8 T cells, CD4 memory resting T cells, and CD4 naive T cells). The yellow module was enriched for neutrophils and monocytes, both of which are phagocytic cells involved in innate immunity (Kantari et al., 2008). The dark red module was enriched for macrophage-like cells (M0 macrophages, monocytes, and M2 macrophages). We observed some enrichment of the skyblue3 module for eosinophils, another type of white blood cell, despite predicting zero abundance of this cell type for all samples. This may indicate that eosinophils are present but at a level too low to be detected by CIBERSORT.
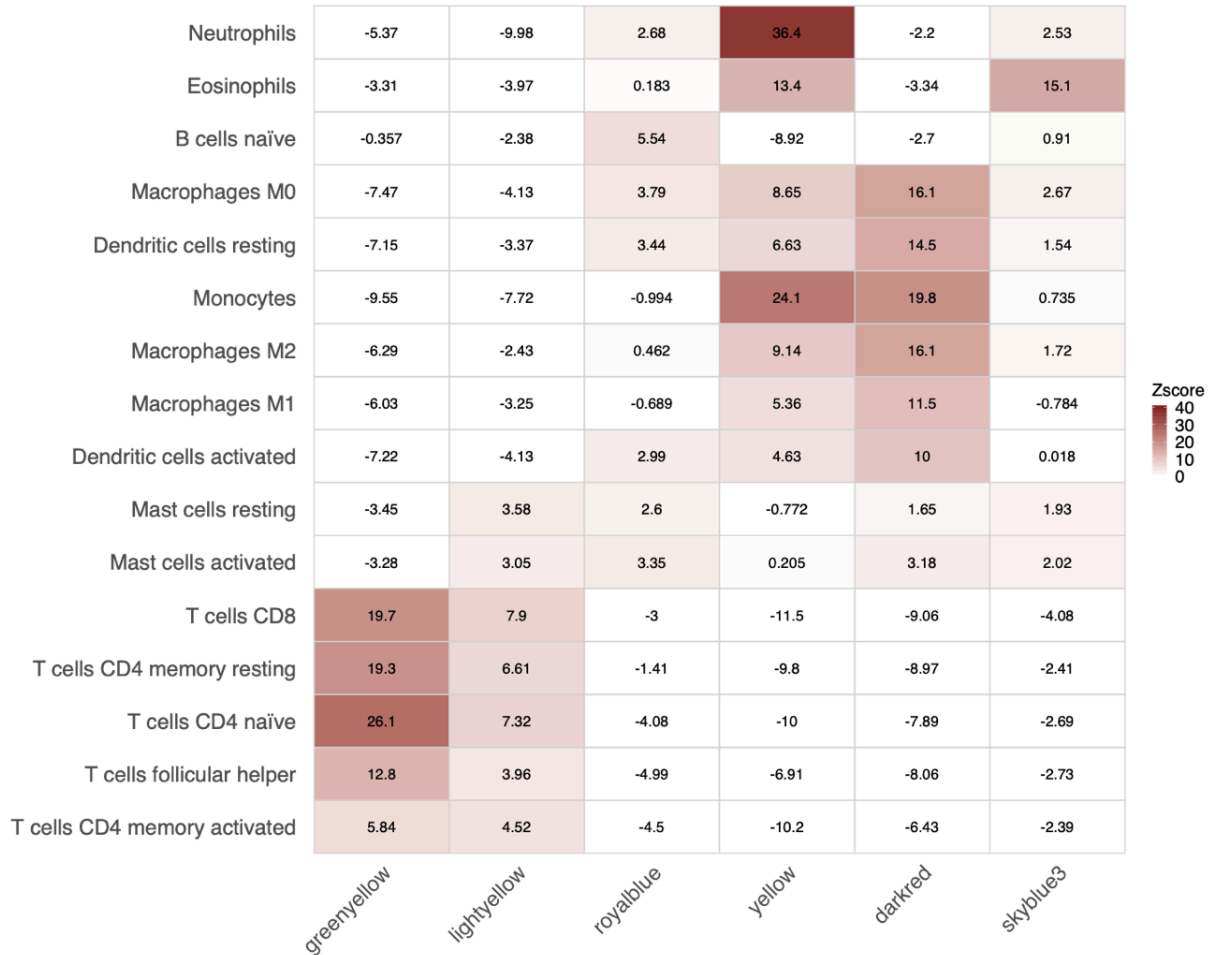
Figure 4.3: Cell type enrichment of the unadjusted module eigengenes that were significantly different between CNV groups. This heatmap displays the enrichment of the gene set for each module for cell type specificity. Cell types are ordered by hierarchical clustering of average expression profiles. Module are ordered by hierarchical clustering of eigenegene values. Only cell types that were enriched in a module or were found to have significant differences in cell type composition between CNV groups are shown. The full table can be found in Supplementary Figure 1.

Finally, we also tested cell type enrichment of modules using a different reference dataset from (Novershtern et al., 2011) to validate enrichment findings from the LM22 reference dataset (See Supplemental Results and Supplementary Figure 4.3). Enrichment results were consistent between the two reference datasets.

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4.4.3: *Proportions of T cell, mast cell, and macrophage subtypes significantly differed between CNV groups*

After finding differential expression in genes and module eigengenes that were related to immune cell types, we sought to directly assess any group differences in immune cell type composition. After residualizing cell type proportion for medication usage, there were significant groupwise differences in 5 cell types at a corrected $q \leq .05$: resting mast cells, activated mast cells, CD8 T cells, M0 macrophages, and M1 macrophages (refer to Table 4.3, Figure 4.4). 22qDel carriers had significantly decreased CD8 T cell proportions compared to controls, consistent with prior findings of T-cell dysfunction and thymic dysplasia in 22q11.2 Deletion Syndrome (McLean-Tooke et al., 2008; Morsheimer et al., 2017), as well as marginally decreased proportions compared to 22q11Dup carriers. Interestingly, 22qDel carriers showed increased activated mast cell proportions but decreased resting mast cells compared to 22qDup carriers and controls. In contrast, 22qDup carriers showed increased proportions of M0 macrophages relative to 22qDel carriers and controls, while 22qDel carriers showed increased M1 macrophage proportions compared to controls and 22qDup carriers. Because of these cell type proportion differences between groups, subsequent differential expression analysis and WGCNA were performed with cell type adjustment in order to assess: i) the extent to which differences in cell-type proportion accounts for the prior described differential gene and module eigengene expression findings, ii) any potential pan-cellular effects on differential expression.

Celltype	Omnibus adj.P.Val	22qDel vs control Coefficient	22qDel vs control adj.P.Val	22qDup vs control Coefficient	22qDup vs control adj.P.Val	22qDel vs 22qDup Coefficient	22qDel vs 22qDup adj.P.Val
Mast cells resting	0.00	-0.48	0.00	0.08	0.62	-0.56	0.00
Mast cells activated	0.01	0.44	0.00	0.14	0.33	0.31	0.04
T cells CD8	0.01	-0.64	0.00	-0.21	0.34	-0.42	0.08
Macrophages M1	0.02	0.25	0.00	0.06	0.57	0.19	0.08
Macrophages M0	0.05	-0.01	0.94	0.41	0.01	-0.42	0.01
T cells CD4 naive	0.05	-0.29	0.22	0.03	0.88	-0.33	0.22
Monocytes	0.12	0.17	0.05	0.02	0.85	0.15	0.15
T cells regulatory	0.13	-0.22	0.05	-0.06	0.63	-0.16	0.27
B cells memory	0.34	-0.03	0.81	0.22	0.28	-0.25	0.28
Dendritic cells activated	0.34	-0.13	0.51	-0.08	0.72	-0.04	0.72
Neutrophils	0.34	0.16	0.24	0.06	0.62	0.10	0.62
NK cells resting	0.34	0.37	0.21	-0.11	0.75	0.47	0.21
T cells CD4 memory activated	0.49	-0.08	0.63	-0.29	0.53	0.21	0.53
B cells naive	0.51	0.21	0.31	-0.02	0.92	0.22	0.31
NK cells activated	0.52	-0.20	0.50	-0.37	0.50	0.17	0.52
T cells gamma delta	0.53	0.20	0.50	-0.22	0.50	0.42	0.50
Macrophages M2	0.79	-0.14	0.82	-0.14	0.82	0.00	0.99
T cells CD4 memory resting	0.79	-0.04	0.82	0.14	0.82	-0.19	0.82
T cells follicular helper	0.79	-0.09	0.43	-0.10	0.43	0.00	0.96
Plasma cells	0.90	-0.05	0.90	-0.07	0.90	0.02	0.90

Table 4.3: Group differences in cell-type proportion that has been medication-adjusted
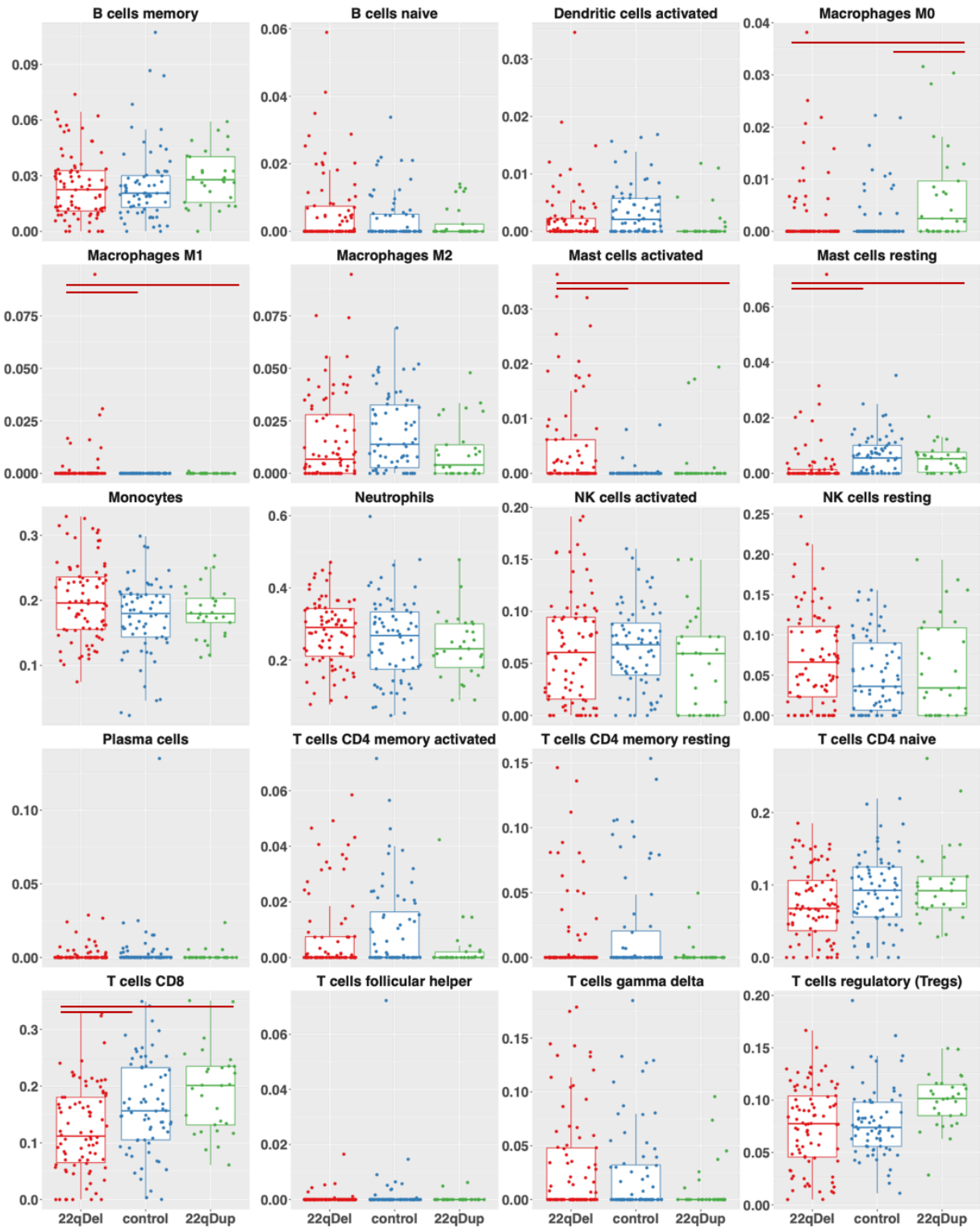
Figure 4.4: Blood cell type proportions across groups. Box plots overlaid with scatterplots of

cell-type proportion values that have been adjusted for medication usage for 20 cell types

across each group. Solid red horizontal lines indicate significant pairwise contrast at q ≤ .05, while dashed red horizontal line indicates marginally significant pairwise contrast at q = .08. Due to the low expression of some cell types, a linear model was applied to logit-transformed cell type percentages after residualizing for potential batch and medication confounds to handle non-normality of values and presence of zeroes.

4.4.4: Cell type proportion strongly impacts differential expression at the single-gene level

After adjusting gene expression for cell type proportion, differential expression was much less pronounced between groups in magnitude and number of genes. As described in the Methods, we simultaneously adjusted for batch, medication, and cell type proportions, as these variables were confounded with CNV status and each other (Table 4.1, Supplementary Table 4.1, Supplementary Figure 4.4, Supplementary Figure 4.5). While 22 and 25 genes within the 22q11.2 locus remained significantly downregulated in 22qDel compared to controls and 22qDup, respectively, the number of significantly DEgenes outside the 22q11.2 locus decreased from 284 to 2 for the 22qDel versus control comparison, and from 448 to 4 for the 22qDel vs. 22qDup comparison. Similarly, the average log-fold change (logFC) of genes with significant differential expression decreased from approximately -1 with unadjusted gene expression to -0.5 with adjusted gene expression across comparisons between 22qDel carriers, 22qDup carriers, and controls. 22qDup did not show any significant differential expression compared to controls, as in the prior analysis.

Six genes outside of the 22q11.2 locus that remained DE after cell type and medication adjustment (see Table 4.4 for all DE genes*)*. 22qDel carriers were significantly downregulated for FUT7 compared to controls and for CDH6 compared to 22qDup carriers. 22qDel carriers were significantly upregulated for HIST1H2BD compared to controls as well as significantly upregulated for SIGLEC10, MIR29B2CHG, and CHPF2 compared to 22qDup carriers.

22qDel vs Control

Symbol	Definition	Chromosome	logFC	adj.P.Val	t	B	AveExpr
HIST1H2BD	H2B Clustered Histone 5	6	0.27	2.0E-03	4.83	4.30	11.27
FUT7	fucosyltransferase 7	9	-0.11	2.3E-02	-4.23	1.94	8.78
CRKL	CRK like proto-oncogene, adaptor protein	22	-0.40	3.1E-09	-7.91	19.64	10.76
ZDHHC8	zinc finger DHHC-type palmitoyltransferase 8	22	-0.37	3.1E-09	-7.83	19.22	9.31
COMT	catechol-O-methyltransferase	22	-0.39	9.2E-09	-7.57	17.78	9.56
KLHL22	kelch like family member 22	22	-0.34	2.2E-08	-7.31	16.35	9.14
LZTR1	leucine zipper like transcription regulator 1	22	-0.32	2.2E-08	-7.31	16.32	8.50
RANBP1	RAN binding protein 1	22	-0.33	2.2E-08	-7.30	16.28	8.33
DGCR6	DiGeorge syndrome critical region gene 6	22	-0.36	2.8E-08	-7.23	15.90	8.50
TXNRD2	thioredoxin reductase 2	22	-0.25	7.5E-08	-7.03	14.85	8.21
PI4KA	phosphatidylinositol 4-kinase alpha	22	-0.31	1.7E-07	-6.87	13.96	9.60
SNAP29	synaptosome associated protein 29	22	-0.22	9.6E-07	-6.53	12.21	8.53
DGCR2	DiGeorge syndrome critical region gene 2	22	-0.24	1.2E-06	-6.47	11.89	9.38
SLC25A1	solute carrier family 25 member 1	22	-0.20	4.9E-06	-6.17	10.42	8.09
RTL10	retrotransposon Gag like 10	22	-0.16	4.9E-06	-6.17	10.41	7.82
ZNF74	zinc finger protein 74	22	-0.15	3.1E-05	-5.78	8.54	7.38
MED15	mediator complex subunit 15	22	-0.15	3.1E-05	-5.78	8.54	7.84
TANGO2	transport and golgi organization 2 homolog	22	-0.29	5.0E-05	-5.67	8.02	9.51
ESS2	ess-2 splicing factor homolog	22	-0.14	5.7E-05	-5.63	7.84	8.21
THAP7	THAP domain containing 7	22	-0.13	5.7E-04	-5.14	5.61	7.76
C22orf39	chromosome 22 open reading frame 39	22	-0.12	6.0E-04	-5.12	5.52	7.70
UFD1	ubiquitin recognition factor in ER associated degradation 1	22	-0.08	1.0E-03	-4.99	4.97	7.63

Symbol	Definition	Chromosome	logFC	adj.P.Val	t	B	AveExpr
SEPTIN5	septin 5	22	-0.47	1.3E-02	-4.38	2.49	12.99
GNB1L	G protein subunit beta 1 like	22	-0.13	3.3E-02	-4.12	1.54	7.66

22qDel vs 22qDup

Symbol	Definition	Chromosome	logFC	adj.P.Val	t	B	AveExpr
CDH6	cadherin 6	5	-0.12	3.7E-04	-5.19	5.85	7.55
SIGLEC10	sialic acid binding Ig like lectin 10	19	0.42	2.0E-03	4.80	4.23	11.79
MIR29B2CHG	MIR29B2 and MIR29C host gene	1	0.15	3.1E-02	4.11	1.59	9.19
CHPF2	chondroitin polymerizing factor 2	7	0.09	3.1E-02	4.09	1.52	8.38
ZDHHC8	zinc finger DHHC-type palmitoyltransferase 8	22	-0.54	3.7E-12	-9.05	25.83	9.31
CRKL	CRK like proto-oncogene, adaptor protein	22	-0.54	1.3E-10	-8.34	21.79	10.76
RANBP1	RAN binding protein 1	22	-0.48	1.3E-10	-8.29	21.52	8.33
LZTR1	leucine zipper like transcription regulator 1	22	-0.45	6.7E-10	-7.94	19.53	8.50
TXNRD2	thioredoxin reductase 2	22	-0.37	6.7E-10	-7.93	19.50	8.21
RTL10	retrotransposon Gag like 10	22	-0.25	1.4E-09	-7.78	18.66	7.82
C22orf39	chromosome 22 open reading frame 39	22	-0.23	2.3E-09	-7.66	18.03	7.70
DGCR6	DiGeorge syndrome critical region gene 6	22	-0.48	3.0E-09	-7.60	17.65	8.50
COMT	catechol-O-methyltransferase	22	-0.50	3.0E-09	-7.58	17.57	9.56
KLHL22	kelch like family member 22	22	-0.44	6.7E-09	-7.42	16.72	9.14
ZNF74	zinc finger protein 74	22	-0.24	1.4E-08	-7.28	15.95	7.38
PI4KA	phosphatidylinositol 4-kinase alpha	22	-0.41	4.2E-08	-7.07	14.84	9.60
SNAP29	synaptosome associated protein 29	22	-0.29	2.7E-07	-6.72	13.04	8.53
DGCR2	DiGeorge syndrome critical region gene 2	22	-0.32	4.2E-07	-6.62	12.55	9.38
THAP7	THAP domain containing 7	22	-0.21	5.1E-07	-6.57	12.31	7.76
SLC25A1	solute carrier family 25 member 1	22	-0.25	3.6E-06	-6.19	10.44	8.09
TANGO2	transport and golgi organization 2 homolog	22	-0.40	6.5E-06	-6.06	9.82	9.51
ESS2	ess-2 splicing factor homolog	22	-0.19	1.4E-05	-5.91	9.07	8.21

MED15	mediator complex subunit 15	22	-0.19	2.4E-05	-5.79	8.52	7.84
UFD1	ubiquitin recognition factor in ER associated degradation 1	22	-0.11	6.6E-05	-5.57	7.53	7.63
CLDN5	claudin 5	22	-0.35	2.8E-04	-5.26	6.15	8.04
TRMT2A	tRNA methyltransferase 2 homolog A	22	-0.08	4.1E-03	-4.63	3.54	7.45
RTN4R	reticulon 4 receptor	22	-0.09	5.3E-03	-4.56	3.28	7.35
TMEM191A	transmembrane protein 191A (pseudogene)	22	-0.11	7.4E-03	-4.48	2.94	7.36
SEPTIN5	septin 5	22	-0.56	3.1E-02	-4.11	1.57	12.99

Table 4.4: Significant differentially-expressed genes after cell type and medication adjustment

4.4.5: No group differences in WGCNA module eigengene expression were observed after adjusting for cell-type proportion and medication usage

Applying WGCNA to cell-type proportion and medication-adjusted gene expression data identified 28 modules of co-expressed genes in the full dataset of 22qDel carriers, 22qDup carriers, and control subjects; however, modules were not significantly different between groups (Supplementary Table 4.2). Taken together, these findings indicate that cell type proportion drives the bulk of the differential expression signal for 22qDel carriers.

4.4.6: Expression of WDR1 and FNBP1 are differentially associated with ASD in 22qDel and 22qDup carriers

Differential expression analyses for ASD status across 22qDel and 22qDup carriers, after accounting for cell-type proportions and medication, revealed significant interactions of CNV group by ASD status for two genes, formin binding protein 1 (FNBP1) and WD repeat domain 1 (WDR1). There were also significant main effects of CNV carrier status for FNBP1 and WDR1 and a significant main effect of ASD status for FNBP1 (Figure 4.5). Follow-up

pairwise comparisons indicated that 22qDel carriers with ASD had lower levels of FNBP1 and WDR1 than 22qDel carriers without ASD, and 22qDup carriers with ASD have higher levels of FNBP1 and WDR1 than those without ASD. Conversely, for psychosis status in 22qDel carriers, cell-type- and medication-adjusted expression did not significantly differ between groups for any genes, although this may partially reflect reduced statistical power due to the small sample of 22qDel patients with a psychosis history (N=11).
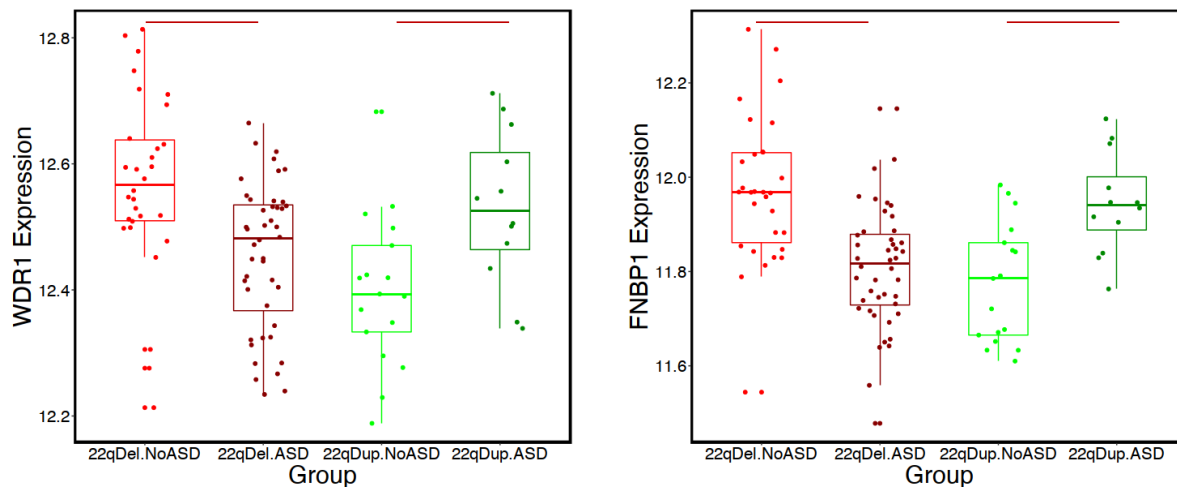
Figure 4.5: Expression of WDR1 and FNBP1 differs across 22qDel and 22qDup carriers with and without ASD. There was a significant interaction effect (group * ASD status) as well as a significant main effect of group on gene expression at an adjusted $p \leq 0.05$. Red horizontal lines indicate significant pairwise differences at nominal $p < 0.006$.

No significant main effects or interactions were found between 22qDel and 22qDup carriers with and without ASD for cell-type proportions (Supplementary Figure 4.6), nor in cell-type- and medication-adjusted WGCNA module eigengene expression, (Supplementary Table 4.3; Supplementary Figure 4.7). Similarly, no significant differences were found in cell-type proportion (Supplementary Figure 4.8), nor cell-type- and medication-adjusted module eigenene

expression for 22qDel carriers with and without psychosis (Supplementary Table 4.3; Supplementary Figure 4.9).

4.4.7: *No associations between IQ or structural MRI characteristics and adjusted expression of DE genes, module eigengenes, or cell type proportions*

There were no significant interaction effects between cell-type-adjusted gene expression and CNV group on IQ, mean cortical thickness, or total cortical surface area (Supplementary Table 4.4). There was also no main effect of DE genes on group-residualized IQ, mean cortical thickness, or total cortical surface area (Supplementary Table 4.5).

There were no interaction effects of adjusted module expression with group on IQ, mean cortical thickness, or total cortical surface area (Supplementary Table 4.6). There was also no main effect of adjusted module expression on group-residualized IQ, mean cortical thickness, or total cortical surface area (Supplementary Table 4.7).

Finally, there were no significant interaction effects of cell type proportion with group on IQ, mean cortical thickness, or total cortical surface area (Supplementary Table 4.8). There was also no main effect of cell type proportion on group-residualized IQ, mean cortical thickness, or total cortical surface area (Supplementary Table 4.9).

4.5: Discussion

This study is the first, to our knowledge, to comprehensively characterize transcriptome-wide gene dosage effects of peripheral blood gene expression derived from 22q11.2 reciprocal CNV carriers. While we observed robust differential expression in 22q11.2 deletion carriers compared to both controls, as previously reported (Jalbrzikowski et al., 2015; van Beveren et al., 2012), and to 22q11.2 duplication carriers, differences in expression were substantially reduced after adjustment for differences in cell type proportion. The strongest remaining

differences between deletion carriers and controls were decreased expression of genes within the 22q11.2 locus, with few significant differences seen outside the locus. We did not observe any significant differential expression of genes within or outside the 22q11.2 locus in duplication carriers compared to the other two groups, which may relate to the more severe phenotype associated with the 22q11.2 deletion. This directional effect is consistent with behavioral studies showing copy number deletions to be more deleterious than duplications (Douard et al., 2021; Girirajan et al., 2012; Rosenfeld et al., 2013). Moreover, while the impact of deletions is thought to be mediated by loss of genes within the locus, the molecular consequences of duplications are more variable and context-dependent (Hurles et al., 2008). Taken together, our findings strongly imply that most differential expression of genes outside the 22q11.2 locus are the result of differences in cell type composition associated with 22q11.2 deletion rather than direct effects on gene expression across cell-types. Genes within the 22q11.2 locus which still showed significantly decreased expression after adjusting for cell type proportion likely reflect pan-cellular effects of the deletion, which are believed to underlie the broad systemic pathology of 22q11.2 deletion syndrome.

A small number of genes outside the 22q11.2 locus still showed differential expression after adjusting for cell type proportion. These findings may reflect genuine effects that are non-tissue-specific, which would be consistent with the regulatory function of some genes within the locus, such as DGCR8, that have been hypothesized to play an important role in the 22q11.2 Deletion Syndrome phenotype (Forsyth et al., 2020; Merico et al., 2014; Stark et al., 2008). However, we cannot definitively rule out the possibility that they represent residual effects of cell type composition, batch, or other unaccounted for confounding variables. Cell-type specific effects of 22q11.2 deletion can only be definitively resolved by analyzing purified cell populations obtained through sorting approaches such as fluorescence activated cell sorting (FACS) or magnetic activated cell sorting (MACS; (Sutermaster & Darling, 2019)). In lieu of such data, future development of "digital sorting" methods for gene expression may allow us to

impute cell-type specific expression from bulk tissue. Such methods are well developed for methylation (TCA, (Rahmani et al., 2019)) but remain challenging to apply to gene expression data.

We observed several differences in cell type composition that are supported by a rich literature showing mild-to-moderate T cell deficits in 22qDel carriers (Crowley et al., 2018; Gennery, 2012), resulting in a spectrum of immune dysfunction, including infection and autoimmunity issues (Derfalvi et al., 2016; Jawad et al., 2001). To our knowledge, differences between 22q11.2 CNV carriers in macrophage and mast cell abundance have not yet been reported. These low abundance cell populations can only be identified using flow cytometry, making them more challenging to study than more abundant cell populations. Notably, macrophages in peripheral blood share many properties with microglia, the resident macrophages of the brain, which may imply speculatively that 22q11.2 deletion also affects microglia function. Microglia interact with virtually all CNS components, are critical for brain development, tissue integrity, and neuronal activity, and also refine cortical circuits by regulating synaptic pruning (Q. Li & Barres, 2018; Paolicelli et al., 2011). Mounting evidence implicates microglial dysfunction leading to chronic neuroinflammation in the pathogenesis of schizophrenia as well as ASD (De Picker et al., 2017; Koyama & Ikegaya, 2015; Laskaris et al., 2016; Petrelli et al., 2016; Takano, 2015). Although our results were limited by the heterogeneity of whole blood, our identification of several potentially novel cell type composition differences warrants future investigation. Recent work has established in vitro organoid models of 22q11.2 deletion and found evidence of neuronal defects (Khan et al., 2020). This experimental context would provide an ideal environment to test whether and to what extent microglial dysfunction, particularly in synaptic pruning, is observed in the 22q11.2 deletion

. Alternatively, the same phenotype could be tested in a mouse model of the deletion, in which neuronal/synaptic deficits have already been identified (Fénelon et al., 2013; Guna et al., 2015; Noboru Hiroi & Yamauchi, 2019; Meechan et al., 2015; Saito et al., 2020; Stark et al.,

2008; Sun et al., 2018). Although mast cells have no analogue in the central nervous system, like macrophages they are also derived from the myeloid lineage (Valent et al., 2020). Moreover, mast cells are multi-functional master cells involved with maintenance of many physiological functions along with disease pathophysiology, such as for cardiovascular diseases (Krystel-Whittemore et al., 2015). The differences observed in predicted composition of mast cells may indicate a broader effect of 22q11.2 deletion on myeloid differentiation, which also warrants future experimental validation.

Within 22qDel and 22qDup carriers, there was a significant interaction of ASD diagnosis and CNV carrier status for 2 genes, after adjusting for cell type proportion and medication effects. Specifically, expression of FNBP1 and WDR1 was lower in 22qDel carriers with ASD compared to 22qDel carriers without ASD. Conversely, for 22qDup carriers, FNBP1 and WDR1 levels were higher in those with ASD compared to subjects without ASD. FNBP1 forms a protein-protein interaction network with vesicle-mediated transport and cytoskeletal proteins like SHANK2, AP1S2, and BIN1, which are dysregulated in ASD and associated with ASD risk (Irimia et al., 2014). In addition, WDR1 was previously found to be differentially expressed in postmortem temporal cortex in ASD subjects (Ander et al., 2015) and is important for cytoskeletal functions (Ono, 2018). It is possible that dysregulated expression of FNBP1 and/or WDR1 in 22q11.2 CNV carriers could contribute to aberrant vesicle-mediated transport or cytoskeletal function and increase ASD risk. However, further molecular studies are needed to exclude technical artifacts and parse out molecular consequences that occur as a result of opposing directions of association of ASD with FNBP1 and WDR1, both broadly-expressed genes (GTEx Consortium, 2020), between 22q11.2 CNV carriers. Furthermore, we did not find any other significant associations between cell type proportion, cell-type-adjusted gene expression, or cell-type-adjusted module expression with clinical phenotypes, including IQ, average cortical thickness, and total surface area. It is possible that previous reports of clinical associations with module expression have been confounded by cell type composition

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(Jalbrzikowski et al., 2015; van Beveren et al., 2012). The 22q11.2 CNV can act as a latent variable affecting both cell composition and brain/behavioral measures independently, which may lead to spurious correlations between both affected phenotypes. Thus, while the association between ASD with FNBP1 and WDR1 expression among 22q CNV carriers may represent a novel finding, it will need to be validated in larger samples. Importantly, further studies are needed to clarify whether differential expression of these genes is mechanistically linked to the development of ASD.

Our study has some parallels to expression quantitative trait loci (eQTL) studies, which inform one of our most significant limitations in connecting CNV-associated gene expression changes in blood to potential effects in the brain, especially regarding DE of genes outside the 22q11.2 locus. Like analyses of the transcriptomic effects of CNVs, eQTL studies seek to identify the effects of genetic variation on gene expression. While our focus is on rare pathogenic genetic variants, eQTL studies examine the effects of many common variants. The significant differences that we observe in expression of genes within the 22q11.2 locus are comparable to *cis*-eQTLs, which identify variants that affect expression of proximal genes. Conversely, the significant but sparse differences that we observe in expression of genes outside the 22q11.2 locus are analogous to *trans*-eQTLs, which identify variants that affect distal gene expression. eQTL studies have shown that while *cis*-eQTLs are often conserved across many cell types and tissues, *trans*-eQTLs are more tissue- and cell-type-specific (GTEx Consortium, 2020). This suggests that the molecular effects of 22q11.2 deletions are also conserved across many cell types and tissues, which is consistent with the broad, multi-systemic clinical phenotype associated with 22q11.2 Deletion Syndrome. Thus, given these insights from eQTL studies, that a subset of 22q11.2 genes are known to be highly-conserved and broadly-expressed (Guna et al., 2015), and that 22q11.2 deletion confers a multisystemic phenotype (McDonald-McGinn et al., 2015), we believe this limits our ability to extrapolate

tissue and cell-type specific *trans*-effects of the 22q11.2 CNVs, even if we were able to obtain these findings from purified blood cell populations.

However, given that broadly-expressed genes are an important class of genes for neurodevelopmental disorders like ID or ASD (Courchesne et al., 2020; Kasherman et al., 2020), and that there is correspondence between brain and blood tissues (Qi et al., 2018; Sullivan et al., 2006; Tylee et al., 2013), investigating blood expression pattern can still prove valuable. For example, leukocyte expression has been found to relate to large-scale functional neural system response to speech in youth with ASD (Lombardo et al., 2018). Associated coexpression modules were enriched for genes that were broadly expressed in the brain as well as many other tissues. Another study found that leukocyte expression identified a perturbed gene network that correlated with symptom severity and contained genes involved in conserved pathways linked to ASD genetics (Gazestani et al., 2019). Lastly, as immune dysfunction is becoming increasingly relevant in the pathology of psychiatric disorders (Capuron & Miller, 2011; Irwin & Miller, 2007; Jones & Thomsen, 2013; Misiak et al., 2019), studying blood tissue which carries strong immune signals, still remains a critical avenue of research. This is especially important as blood tissue is often the most widely-accessible tissue of study.

Our findings reveal challenges that are inherent in using peripheral blood to study brain-related diseases. However, analyzing blood tissue, which contains a wealth of information regarding the immune system still offers important insights into immune dysfunction in psychiatric disorders, provided cell type proportion is properly addressed. The methodology established here demonstrates how information can be extracted from existing blood "omics" datasets to generate testable hypotheses with the ultimate goal of advancing our understanding of the pathophysiology of psychiatric and neurodevelopmental disorders.

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4.7: Supplement

4.7.1: Demographic Information

We aimed to include a representative cohort of CNV carriers. Therefore, there was no exclusion of participants with cardiac-related issues, a hallmark of 22q11.2 Deletion Syndrome. A subset of controls was related to other controls (9 brothers, 3 sisters) or deletion carriers (1 aunt, 8 brothers, 1 half-brother, 1 grandfather, 1 grandmother, 1 mother, 2 sisters).

4.7.2: *MRI acquisition and preprocessing*

T1- weighted structural scans were analyzed in an unbiased, whole-brain approach using well-validated analysis and quality control protocols (Thompson et al., 2014, 2017) , previously applied by our group and others (Ching et al., 2020; Schmaal et al., 2016; Sun et al., 2018; van Erp et al., 2016). Each scan began with a 10 min acquisition of standard images used for determining regional anatomy, including a sagittal localizer image (TR/TE = 500/33 ms, 192 × 256 matrix), a high-resolution T2-weighted axial image (TR/TE = 5000/33 ms, 128 × 128 matrix, FOV = 200 × 200 mm), and a sagittal 1 mm3 T1-weighted image. We used FreeSurfer to process 1 mm3 T1-weighted anatomical images acquired with an MPRAGE. The parameters for the MPRAGE were the following: TR = 2.3 s, TE = 2.91 ms, FOV = 256 mm, matrix = 240 × 256, flip angle = 9°, slice thickness = 1.20 mm, 160 slices. The FreeSurfer image analysis suite (version 5.3.0; http://surfer.nmr.mgh.harvard.edu) surface-based processing pipeline was used to derive measures of volume, cortical thickness, and surface area.

4.7.3: *Weighted gene co-expression network analysis (WGCNA) parameters*

We used WGCNA to identify modules of co-expressed genes using an approach similar to previous studies which have applied this method (Oldham et al., 2008; Stuart et al., 2003) using the WGCNA package (Langfelder et al., 2008). Signed adjacency matrices were computed using the lowest soft power with a scale-free topology fit of $R^2 > 0.8$ and a scale-free topology coefficient < -2. Correlation coefficients were estimated using biweight midcorrelation

(Song et al., 2012), converted to topological overlap matrices (Dong & Horvath, 2007), and

clustered using the default average-linked hierarchical clustering. Modules were identified using

dynamic tree cutting of the hierarchical clustering tree (Langfelder et al., 2008) with a cut height

of 0.995 and a deepSplit parameter of 3. Module eigengenes were computed from the first

principal component of the expression values of the genes in each module, and correlated

modules were merged using a dissimilarity threshold of 0.2. We then fit a linear model for group

effect on module eigengene with age, sex, and RIN as covariates to assess group differences

and then corrected for the number of modules tested using false discovery rate. For eigengenes

that were DE between groups at q <0.05, post-hoc pairwise contrasts were calculated using the

RMS package.

4.7.4: *Enrichment of gene sets from WGCNA modules for cell type specific expression*

We used the pSI package (Dougherty et al., 2010; Xu et al., 2014) to estimate a cell type

specificity index for genes expressed in a sorted reference LM22 dataset in peripheral blood

(Newman et al., 2015). The specificity index is a rank-based method computed for every gene

and cell type in a sorted dataset where lower values indicate higher specificity of a gene for a

cell type. We subsetted the specificity indices to the genes shared between our data and the

reference data. We then tested the enrichment of the gene set obtained from each WGCNA

module using a linear model to determine if genes in the gene set had significantly lower

specificity indices than the rest of the genes. For large WGCNA modules, we only used the top

500 genes ranked by scaled connectivity to make gene sets for those modules.

The alternate reference dataset was not used to estimate cell type proportion and included

slightly different cell types (Novershtern et al., 2011, Supplementary Figure 4.3). Enrichment

results were consistent between the two reference datasets. We observed that the royal blue

module was highly enriched in the alternate dataset for megakaryocytes/ thrombocytes, a cell

type not included in the LM22 reference dataset.
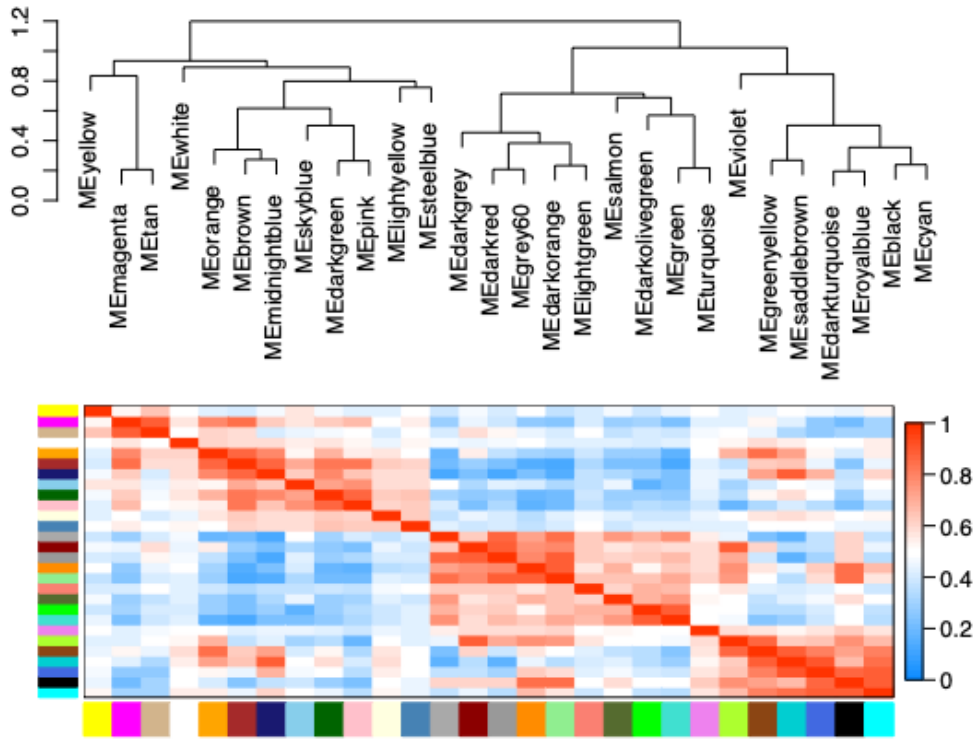
Supplementary Figure 4.1: Dendrogram of eigenegene expression for 28 modules showing hierarchical clustering. Modules were constructed from gene expression data that was adjusted for cell type proportion and medication usage. No modules showed corrected group differences in expression.
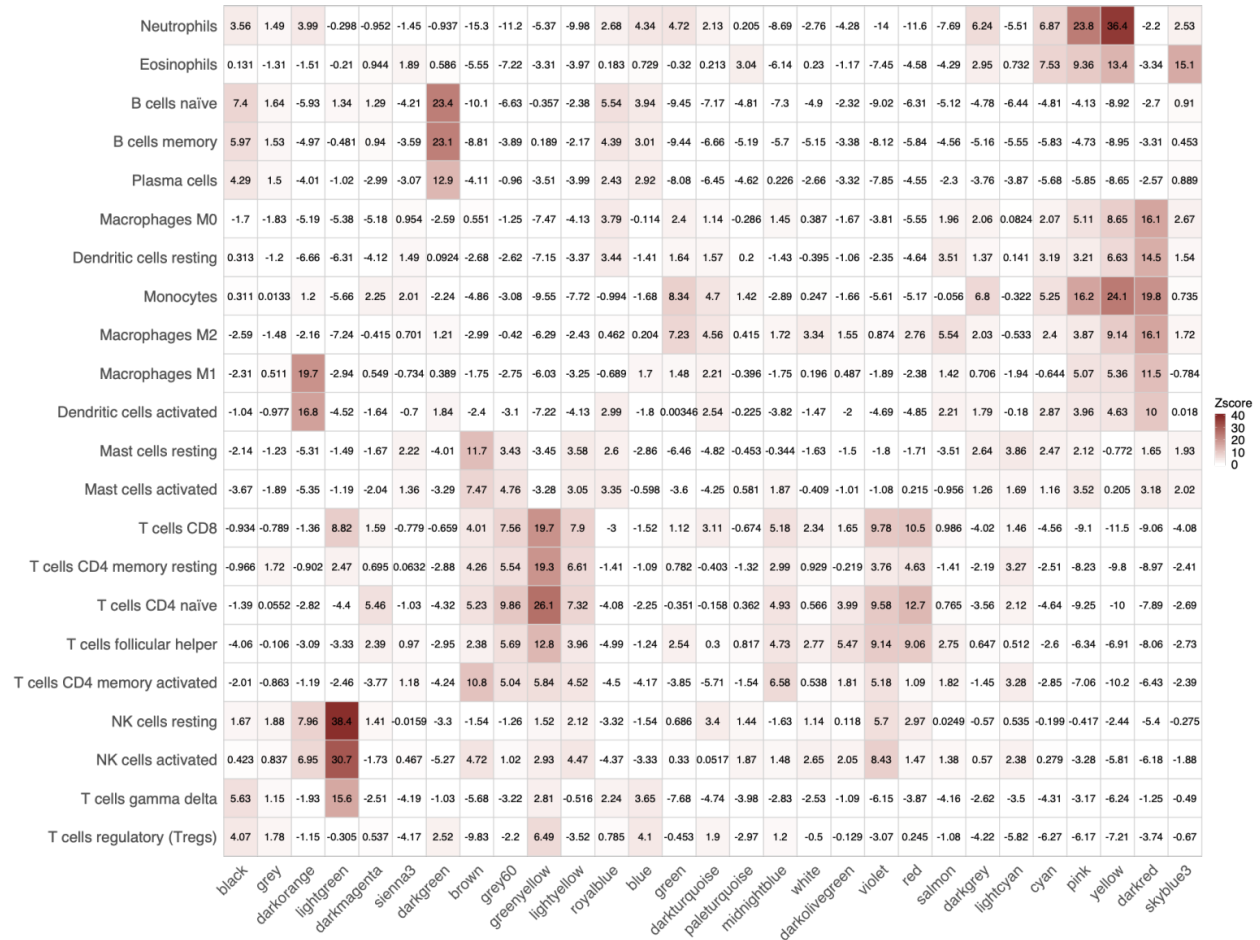
Supplementary Figure 4.2: Cell type enrichment of all unadjusted module eigengenes using LM22 reference data. This heatmap displays the degree of overlap between cell type using the LM22 reference dataset and module eigengenes which have been adjusted for cell type and medication status. Modules are ordered by clustering of cell types whose expression profiles are most similar.
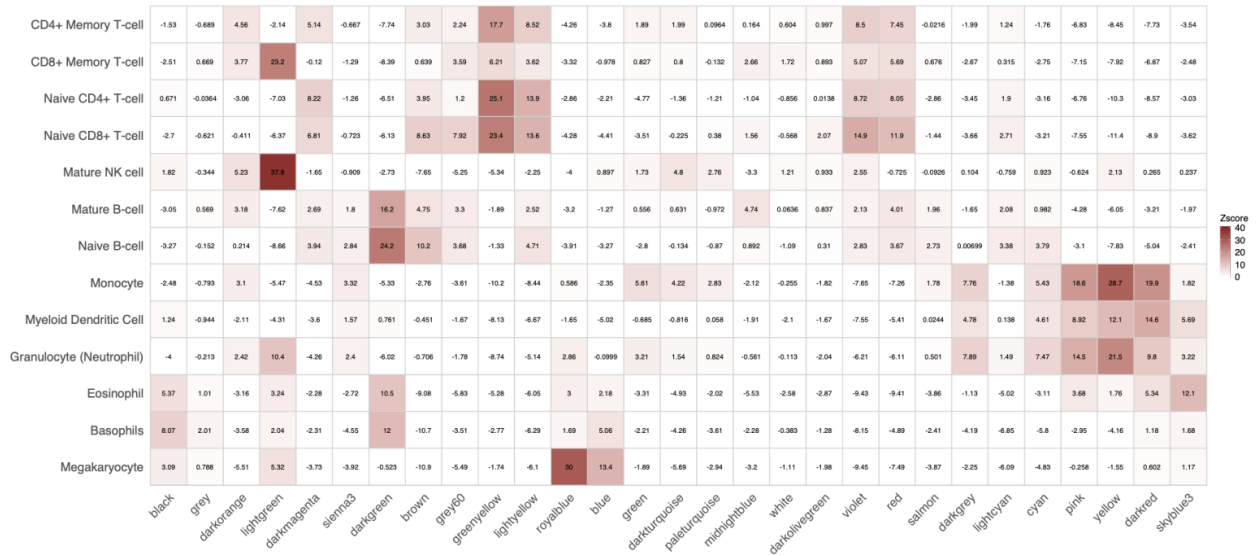
Supplementary Figure 4.3: Cell type enrichment of unadjusted module eigengenes using the alternate reference data. This heatmap displays the degree of overlap between cell type markers from Novershtern et al., 2011 and module eigengenes which have been adjusted for cell type and medication status. Modules are ordered by clustering of cell types whose expression profiles are most similar. No modules showed corrected group differences.

Batch	N, antidepressants	N, antiepileptics	N, benzodiazepines	N, antipsychotics	N, stimulants
1	2	0	0	0	1
2	3	1	1	1	1
3	0	0	0	1	0
4	10	4	2	6	7
5	15	5	4	3	8
6	7	3	1	3	5

Supplementary Table 4.1A: Number of subjects on each type of medication by batch.

N, medications taken	N, Subjects
0	123
1	29
2	18
3	7
4	2

Supplementary Table 4.1B: Number of subjects who are unmedicated, on a single type of medication, or on multiple types of medication.
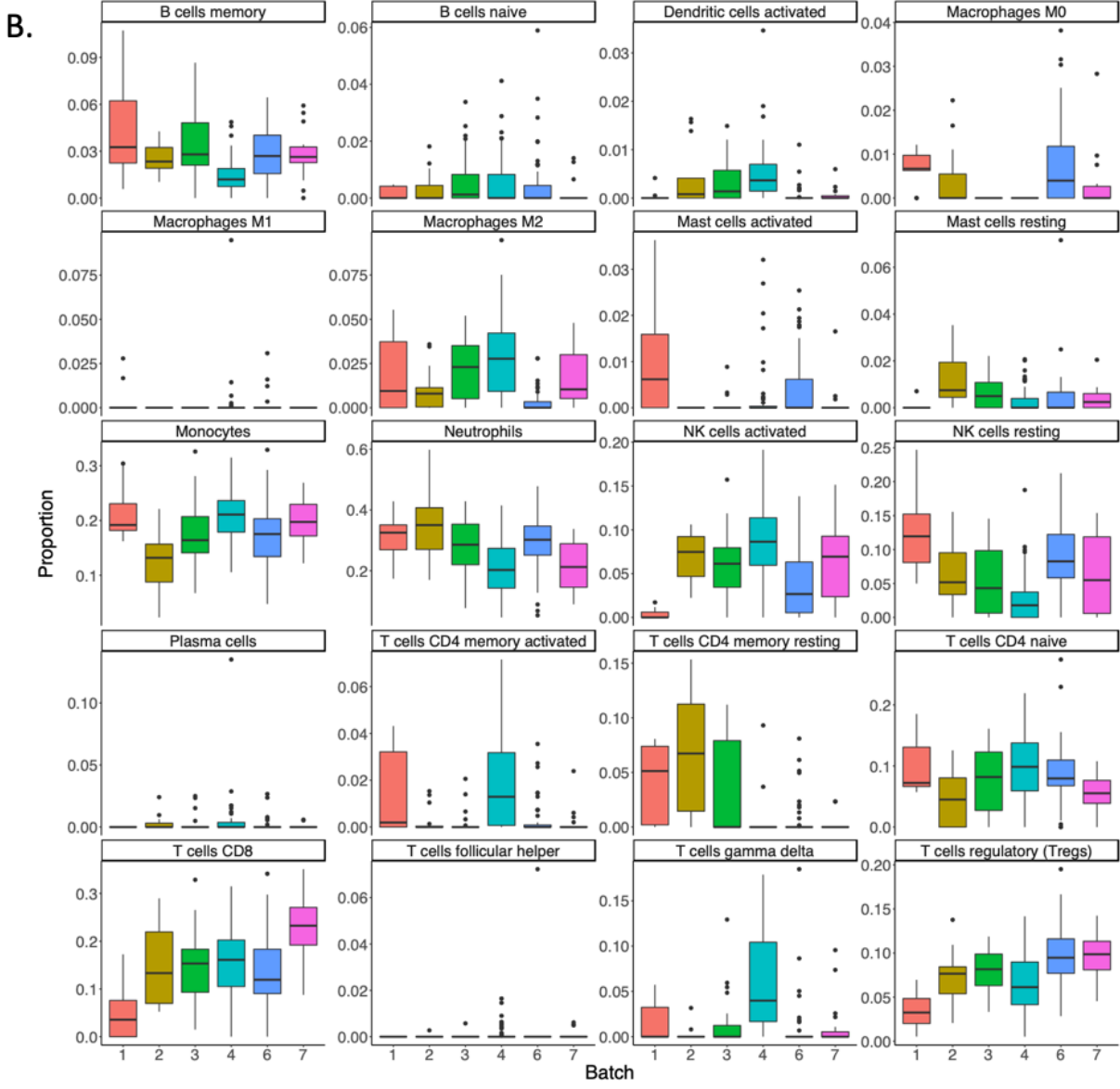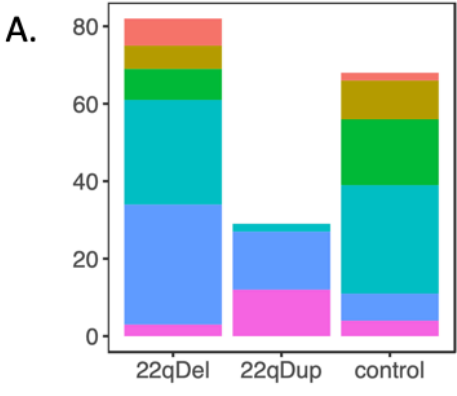
Supplementary Figure 4.4: Batch and cell type proportion confounds in samples. Panel A shows the number of subjects in each color-coded batch by group. Panel B shows the number of subjects in each color-coded batch by cell type proportion.

	AD	ST	AP	AED	BZ
Neutrophils	-0.731	-0.123	-0.0383	0.287	0.517
B cells naive	-0.276	0.17	1.4	-0.0903	0.0941
B cells memory	0.213	0.101	0.846	0.0525	0.225
Plasma cells	0.787	0.0779	-0.293	-0.543	-0.907
Macrophages M0	-1.79	1.98	2.25	0.539	-0.14
Monocytes	1.04	-0.696	-0.576	-0.317	0.187
Macrophages M2	1.41	-0.682	0.0144	-0.154	0.758
Macrophages M1	1.48	0.358	1.19	-1.98	-0.294
Dendritic cells activated	0.657	1.55	-0.409	0.196	0.0104
Mast cells resting	-0.45	0.468	0.0515	1.31	-3.52e-05
Mast cells activated	-2.2	0.874	-0.463	-0.171	-0.161
T cells CD8	-1.31	-0.991	-0.925	0.216	-0.227
T cells CD4 memory resting	0.453	-0.435	-1.04	0.0421	-0.515
T cells CD4 naive	-0.978	-1.17	2.15	0.61	2.33
T cells follicular helper	0.874	1.16	-0.319	-0.505	-0.373
T cells CD4 memory activated	0.458	0.188	-0.0286	1.09	0.906
NK cells resting	-0.229	0.337	0.917	0.847	0.907
NK cells activated	1.51	0.897	-1.6	0.384	-1.76
T cells gamma delta	-0.0345	-0.163	-1.32	-1.64	-0.646
T cells regulatory (Tregs)	-0.112	-0.722	-0.25	-0.635	-0.907

Zscore
5
4
3
2
1
0

Supplementary Figure 4.5: Medication usage shows modest effects on cell type proportion. Heat map displays Z-score of the effects of medication usage on cell type proportion. Cell type proportions were logit transformed and residualized for batch and

diagnosis with age and sex included as covariates. Cell types are ordered by similarity of

average expression. Medications are ordered by overlap in usage. AD = antidepressants, ST =

stimulants AP = antipsychotics, AED = antiepileptics, BZ = benzodiazepines.

Module	Sum of Square	Mean Square	F-statistic	FDR q-val
yellow	0.01	0.00	0.89	6.3E-01
magenta	0.01	0.01	0.94	6.3E-01
tan	0.01	0.00	0.55	7.2E-01
white	0.02	0.01	1.79	4.1E-01
orange	0.01	0.01	0.93	6.3E-01
brown	0.02	0.01	1.69	4.2E-01
midnightblue	0.03	0.02	3.06	2.9E-01
skyblue	0.01	0.00	0.45	7.2E-01
darkgreen	0.04	0.02	3.24	2.9E-01
pink	0.01	0.00	0.61	7.2E-01
lightyellow	0.00	0.00	0.26	8.0E-01
steelblue	0.01	0.00	0.46	7.2E-01
darkgrey	0.02	0.01	1.92	4.0E-01
darkred	0.02	0.01	1.91	4.0E-01
grey60	0.03	0.02	3.08	2.9E-01
darkorange	0.03	0.01	2.29	3.8E-01
lightgreen	0.04	0.02	3.56	2.9E-01
salmon	0.02	0.01	2.09	4.0E-01
darkolivegreen	0.02	0.01	1.40	5.2E-01
green	0.00	0.00	0.43	7.2E-01
turquoise	0.01	0.01	0.96	6.3E-01
violet	0.05	0.03	5.16	1.9E-01
greenyellow	0.01	0.00	0.67	7.2E-01
saddlebrown	0.00	0.00	0.08	9.2E-01
darkturquoise	0.01	0.01	1.17	6.1E-01
royalblue	0.00	0.00	0.38	7.4E-01
black	0.03	0.01	2.29	3.8E-01
cyan	0.01	0.00	0.65	7.2E-01

Supplementary Table 4.2: Effect of group status on the expression of each cell type and medication-adjusted module eigengene

Supplementary Figure 4.6: Cell type proportions across 22qDel and 22qDup carriers with and without ASD. There were no significant main effects or interactions for ASD and CNV group for any cell type.

Module	Main effect of ASD FDR q-val	ASD by CNV group interaction effect FDR q-val	Main effect of psychotic disorder FDR q-val
MEblack	8.4E-01	2.9E-01	9.8E-01
MEblue	9.2E-01	7.9E-01	8.6E-01
MEbrown	8.5E-01	9.4E-01	8.6E-01
MEcyan	8.5E-01	4.5E-01	8.6E-01
MEdarkgreen	8.5E-01	2.9E-01	8.6E-01
MEdarkgrey	5.6E-01	2.9E-01	8.6E-01
MEdarkorange	9.2E-01	8.9E-01	8.8E-01
MEdarkred	8.5E-01	1.4E-01	8.8E-01
MEdarkturquoise	5.6E-01	5.6E-01	7.9E-01
MEgreen	8.5E-01	9.7E-01	8.6E-01
MEgreenyellow	9.2E-01	9.7E-01	9.7E-01
MEgrey60	8.5E-01	2.9E-01	8.6E-01
MElightcyan	8.5E-01	8.6E-01	8.8E-01
MElightgreen	9.9E-01	9.7E-01	8.6E-01
MElightyellow	8.7E-01	9.5E-01	8.6E-01
MEmagenta	9.2E-01	8.9E-01	8.6E-01
MEmidnightblue	5.6E-01	2.9E-01	8.6E-01
MEorange	8.5E-01	5.4E-01	9.8E-01
MEpink	5.6E-01	3.1E-01	8.6E-01
MEred	9.2E-01	7.8E-01	8.6E-01
MEsaddlebrown	5.6E-01	8.6E-01	8.8E-01
MEsalmon	5.6E-01	1.4E-01	7.9E-01
MEskyblue	8.5E-01	5.6E-01	7.9E-01
MEtan	8.5E-01	5.6E-01	8.6E-01
MEturquoise	8.5E-01	9.7E-01	8.6E-01
MEwhite	9.2E-01	9.5E-01	8.6E-01
MEyellow	7.1E-01	4.8E-01	8.6E-01

Supplementary Table 4.3: Effects of disease status on module eigengene expression.
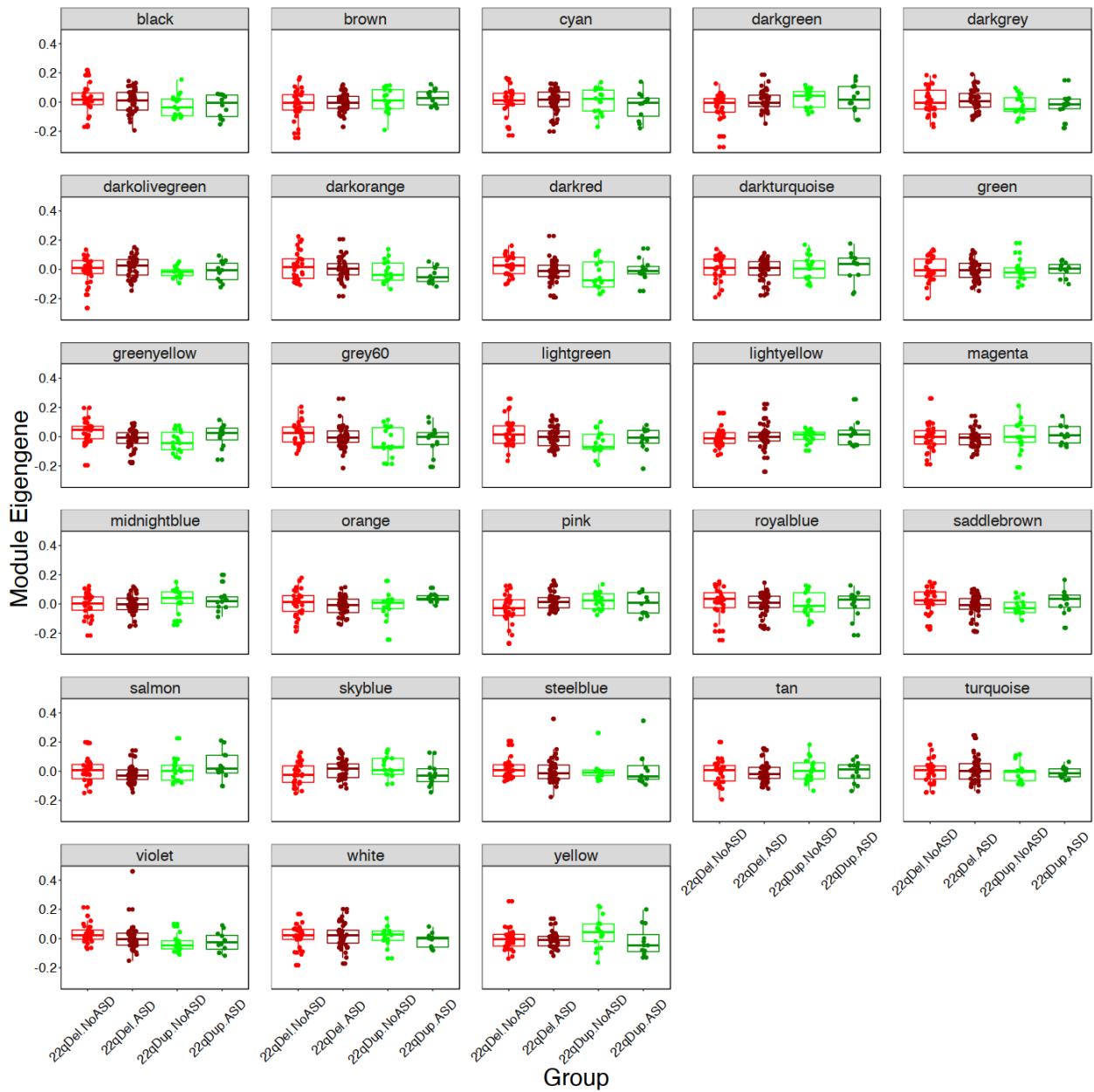
Supplementary Figure 4.7: Cell-type proportion and medication-adjusted module eigengene expression across 22qDel and 22qDup carriers with and without ASD. There were no significant main effects or interactions for ASD and CNV group for any module.
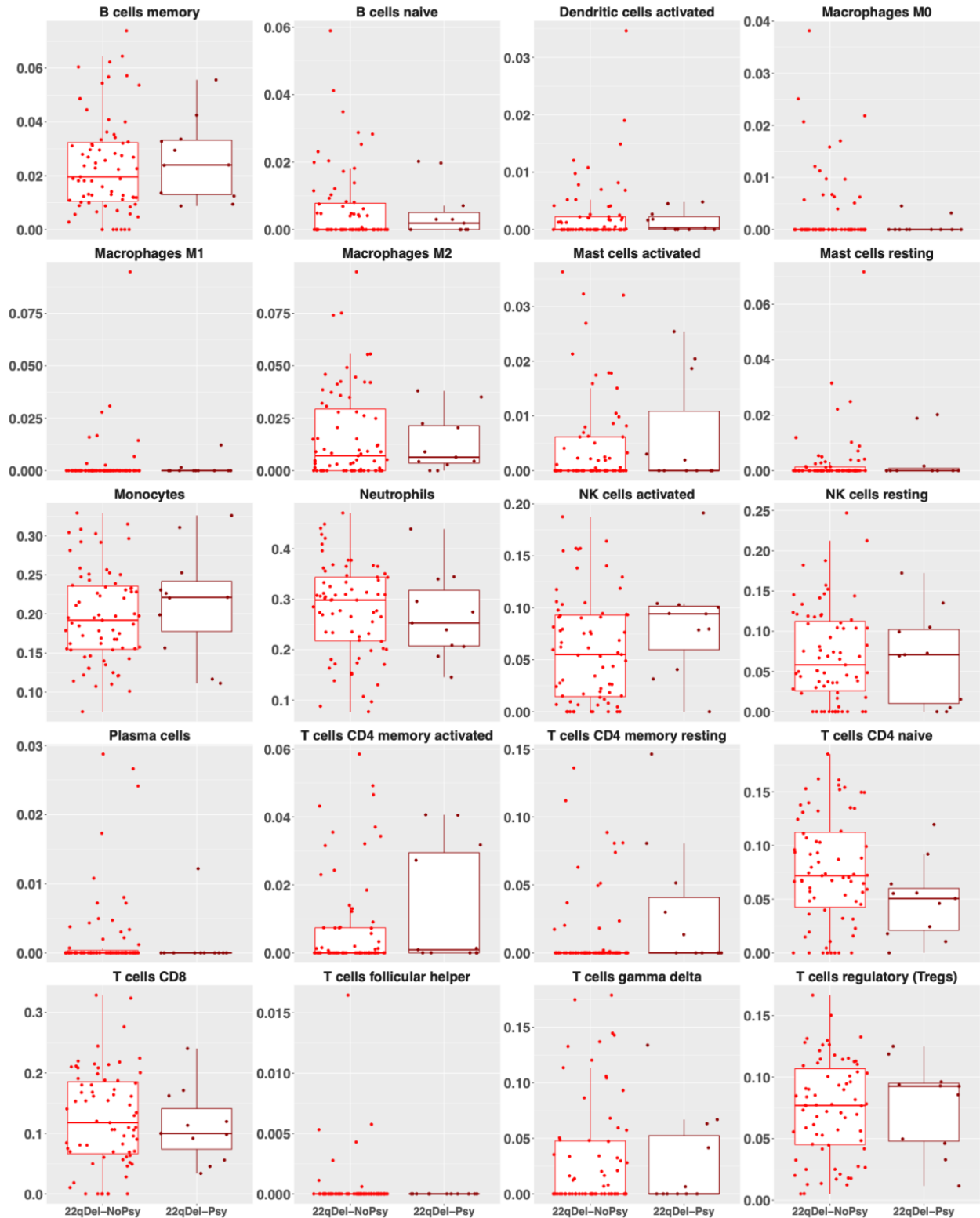
Supplementary Figure 4.8: Cell type proportions across 22qDel carriers with and without psychosis. There were no significant group differences for any cell type.

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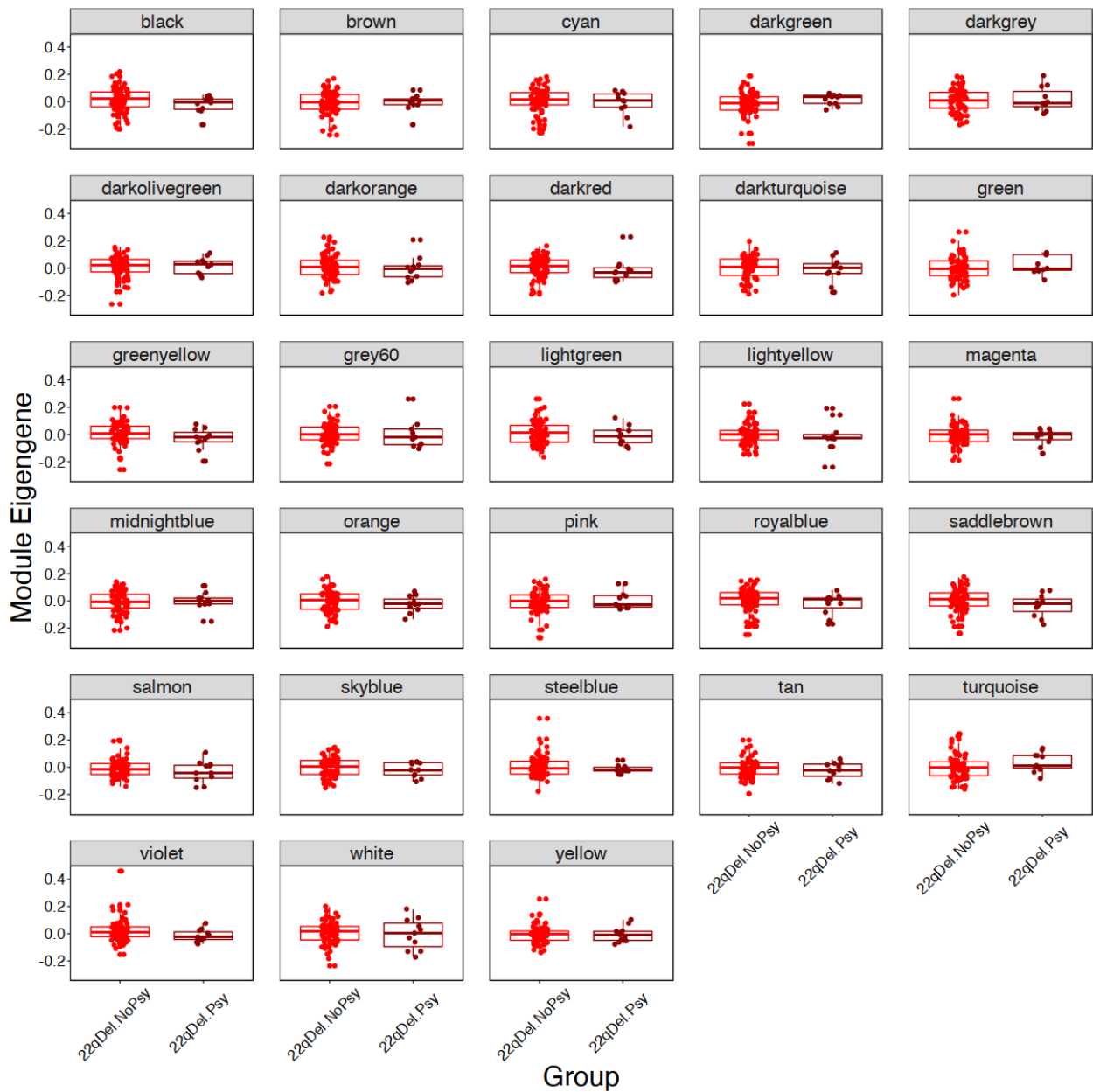
Supplementary Figure 4.9: Cell-type proportion and medication-adjusted module eigengene expression across 22qDel carriers with and without psychosis. There were no significant differences between 22qDel carriers with and without psychosis for any module.

Gene	Outcome measure	Sum of Squares	Mean Square	F-statistic	FDR q-val
C22orf39	cortical thickness	0.019952	0.009976	0.89	7.0E-01
	IQ	2418.481	1209.24	4.38	4.5E-01
	surface area	84822146	42411073	0.21	9.2E-01
CDH6	cortical thickness	0.065052	0.032526	2.97	5.1E-01
	IQ	506.0822	253.0411	0.89	7.0E-01
	surface area	222000000	111000000	0.55	7.9E-01
CHPF2	cortical thickness	0.044951	0.022475	2.01	5.5E-01
	IQ	127.7167	63.85835	0.22	9.2E-01
	surface area	368000000	184000000	0.92	7.0E-01
CLDN5	cortical thickness	0.068377	0.034189	3.13	5.1E-01
	IQ	32.42398	16.21199	0.06	9.7E-01
	surface area	892000000	446000000	2.30	5.3E-01
COMT	cortical thickness	0.061389	0.030694	2.84	5.1E-01
	IQ	62.49263	31.24631	0.11	9.5E-01
	surface area	594000000	297000000	1.51	5.6E-01
CRKL	cortical thickness	0.041697	0.020849	1.92	5.6E-01
	IQ	408.7089	204.3545	0.71	7.7E-01
	surface area	91575526	45787763	0.23	9.2E-01
DGCR2	cortical thickness	0.026257	0.013129	1.18	6.2E-01
	IQ	250.8361	125.418	0.44	8.4E-01
	surface area	2230000000	1110000000	6.10	3.0E-01
DGCR6	cortical thickness	0.029784	0.014892	1.34	6.1E-01
	IQ	710.2455	355.1228	1.27	6.2E-01
	surface area	51589688	25794844	0.13	9.5E-01
ESS2	cortical thickness	0.069445	0.034723	3.20	5.1E-01
	IQ	319.1911	159.5955	0.55	7.9E-01
	surface area	483000000	241000000	1.22	6.2E-01
FUT7	cortical thickness	0.000827	0.000414	0.04	9.7E-01
	IQ	1337.044	668.5221	2.43	5.1E-01
	surface area	217000000	109000000	0.56	7.9E-01
GNB1L	cortical thickness	0.02237	0.011185	1.00	7.0E-01
	IQ	2436.341	1218.17	4.47	4.5E-01
	surface area	183000000	91577948	0.45	8.4E-01
HIST1H2BD	cortical thickness	0.006445	0.003222	0.28	9.2E-01
	IQ	365.4951	182.7475	0.63	7.9E-01
	surface area	86997064	43498532	0.21	9.2E-01
KLHL22	cortical thickness	0.05862	0.02931	2.84	5.1E-01
	IQ	1024.089	512.0445	1.80	5.6E-01
	surface area	75999466	37999733	0.19	9.2E-01
LZTR1	cortical thickness	0.047229	0.023614	2.19	5.4E-01
	IQ	827.8715	413.9357	1.44	5.6E-01
	surface area	259000000	130000000	0.66	7.8E-01
MED15	cortical thickness	0.07103	0.035515	3.41	5.1E-01
	IQ	62.65265	31.32633	0.11	9.5E-01
	surface area	14430824	7215412	0.04	9.7E-01
MIR29B2CHG	cortical thickness	0.009351	0.004675	0.41	8.5E-01
	IQ	698.9055	349.4528	1.22	6.2E-01
	surface area	488000000	244000000	1.23	6.2E-01
PI4KA	cortical thickness	0.049006	0.024503	2.31	5.3E-01
	IQ	441.0809	220.5405	0.76	7.5E-01
	surface area	90674901	45337450	0.23	9.2E-01
RANBP1	cortical thickness	0.019897	0.009949	0.91	7.0E-01
	IQ	329.5509	164.7755	0.58	7.9E-01
	surface area	72207312	36103656	0.18	9.2E-01

RTL10	cortical thickness	0.008196	0.004098	0.36	8.8E-01
	IQ	1223.115	611.5577	2.16	5.4E-01
	surface area	1370000000	683000000	3.64	5.1E-01
RTN4R	cortical thickness	0.026789	0.013394	1.19	6.2E-01
	IQ	1017.988	508.9942	1.79	5.6E-01
	surface area	971000000	486000000	2.50	5.1E-01
SEPTIN5	cortical thickness	0.03731	0.018655	1.67	5.6E-01
	IQ	37.78498	18.89249	0.07	9.7E-01
	surface area	1030000000	514000000	2.71	5.1E-01
SIGLEC10	cortical thickness	0.001075	0.000537	0.05	9.7E-01
	IQ	1615.193	807.5966	2.87	5.1E-01
	surface area	623000000	311000000	1.57	5.6E-01
SLC25A1	cortical thickness	0.021336	0.010668	0.94	7.0E-01
	IQ	1163.982	581.991	2.05	5.5E-01
	surface area	137000000	68641136	0.34	8.9E-01
SNAP29	cortical thickness	0.038426	0.019213	1.74	5.6E-01
	IQ	656.4613	328.2306	1.14	6.3E-01
	surface area	105000000	52670230	0.26	9.2E-01
TANGO2	cortical thickness	0.032246	0.016123	1.44	5.6E-01
	IQ	321.3355	160.6677	0.58	7.9E-01
	surface area	311000000	156000000	0.79	7.5E-01
THAP7	cortical thickness	0.036388	0.018194	1.62	5.6E-01
	IQ	594.146	297.073	1.03	6.9E-01
	surface area	326000000	163000000	0.81	7.4E-01
TMEM191A	cortical thickness	0.003749	0.001874	0.16	9.3E-01
	IQ	383.3613	191.6806	0.66	7.8E-01
	surface area	586000000	293000000	1.49	5.6E-01
TRMT2A	cortical thickness	0.016167	0.008084	0.71	7.7E-01
	IQ	939.2427	469.6214	1.64	5.6E-01
	surface area	621000000	311000000	1.57	5.6E-01
TXNRD2	cortical thickness	0.036035	0.018017	1.61	5.6E-01
	IQ	309.958	154.979	0.54	7.9E-01
	surface area	957000000	478000000	2.50	5.1E-01
UFD1	cortical thickness	0.020353	0.010176	0.91	7.0E-01
	IQ	244.8963	122.4481	0.43	8.4E-01
	surface area	687000000	343000000	1.74	5.6E-01
ZDHHC8	cortical thickness	0.046244	0.023122	2.12	5.5E-01
	IQ	871.6847	435.8424	1.53	5.6E-01
	surface area	611000000	305000000	1.54	5.6E-01
ZNF74	cortical thickness	0.058833	0.029416	2.69	5.1E-01
	IQ	130.9815	65.49076	0.23	9.2E-01
	surface area	987000000	493000000	2.54	5.1E-01

Supplementary Table 4.4: Interaction effect of gene expression and group status on cortical thickness, total surface area, and Full Scale IQ

Gene	Outcome measure	Sum of Squares	Mean Square	F-statistic	FDR q-val
C22orf39	cortical thickness	0.014306	0.014306	1.25	6.8E-01
	IQ	19.40808	19.40808	0.07	9.9E-01
	surface area	257000000	257000000	1.31	6.8E-01
CDH6	cortical thickness	0.000366	0.000366	0.03	9.9E-01
	IQ	425.3028	425.3028	1.51	6.8E-01
	surface area	286000000	286000000	1.46	6.8E-01
CHPF2	cortical thickness	0.000201	0.000201	0.02	9.9E-01
	IQ	14.00001	14.00001	0.05	9.9E-01
	surface area	11546404	11546404	0.06	9.9E-01
CLDN5	cortical thickness	0.001238	0.001238	0.11	9.9E-01
	IQ	365.1437	365.1437	1.29	6.8E-01
	surface area	252000000	252000000	1.29	6.8E-01
COMT	cortical thickness	0.019816	0.019816	1.74	6.8E-01
	IQ	645.5401	645.5401	2.30	6.8E-01
	surface area	261000000	261000000	1.34	6.8E-01
CRKL	cortical thickness	0.030371	0.030371	2.69	6.8E-01
	IQ	28.19473	28.19473	0.10	9.9E-01
	surface area	260000000	260000000	1.33	6.8E-01
DGCR2	cortical thickness	0.022593	0.022593	1.99	6.8E-01
	IQ	348.0647	348.0647	1.23	6.8E-01
	surface area	678105.8	678105.8	0.00	9.9E-01
DGCR6	cortical thickness	0.02271	0.02271	2.00	6.8E-01
	IQ	747.1936	747.1936	2.67	6.8E-01
	surface area	135000000	135000000	0.69	7.7E-01
ESS2	cortical thickness	0.009383	0.009383	0.82	7.7E-01
	IQ	61.68711	61.68711	0.22	9.1E-01
	surface area	315000000	315000000	1.61	6.8E-01
FUT7	cortical thickness	0.007621	0.007621	0.66	7.7E-01
	IQ	1219.605	1219.605	4.40	6.8E-01
	surface area	533000000	533000000	2.76	6.8E-01
GNB1L	cortical thickness	0.021685	0.021685	1.91	6.8E-01
	IQ	541.2304	541.2304	1.92	6.8E-01
	surface area	87139.45	87139.45	0.00	9.9E-01
HIST1H2BD	cortical thickness	0.0000357	0.0000357	0.00	9.9E-01
	IQ	15.47767	15.47767	0.05	9.9E-01
	surface area	118000000	118000000	0.60	7.8E-01
KLHL22	cortical thickness	0.06916	0.06916	6.32	6.4E-01
	IQ	62.26273	62.26273	0.22	9.1E-01
	surface area	15987.17	15987.17	0.00	9.9E-01
LZTR1	cortical thickness	0.036482	0.036482	3.25	6.8E-01
	IQ	1.321463	1.321463	0.00	9.9E-01
	surface area	192000000	192000000	0.98	7.6E-01
MED15	cortical thickness	0.051025	0.051025	4.60	6.8E-01
	IQ	0.368506	0.368506	0.00	9.9E-01
	surface area	93847.73	93847.73	0.00	9.9E-01
MIR29B2CHG	cortical thickness	0.004459	0.004459	0.39	8.7E-01
	IQ	303.0783	303.0783	1.07	7.3E-01
	surface area	7786988	7786988	0.04	9.9E-01
PI4KA	cortical thickness	0.054036	0.054036	4.88	6.8E-01
	IQ	78.80458	78.80458	0.28	9.0E-01
	surface area	165000000	165000000	0.84	7.7E-01
RANBP1	cortical thickness	0.036749	0.036749	3.27	6.8E-01
	IQ	513.7703	513.7703	1.82	6.8E-01
	surface area	216000000	216000000	1.10	7.3E-01

RTL10	cortical thickness	0.00942	0.00942	0.82	7.7E-01
	IQ	175.6385	175.6385	0.62	7.8E-01
	surface area	473000000	473000000	2.44	6.8E-01
RTN4R	cortical thickness	0.000329	0.000329	0.03	9.9E-01
	IQ	92.67416	92.67416	0.33	8.8E-01
	surface area	93020569	93020569	0.47	8.5E-01
SEPTIN5	cortical thickness	0.009457	0.009457	0.82	7.7E-01
	IQ	627.9029	627.9029	2.24	6.8E-01
	surface area	570000000	570000000	2.96	6.8E-01
SIGLEC10	cortical thickness	0.002664	0.002664	0.23	9.1E-01
	IQ	3.648585	3.648585	0.01	9.9E-01
	surface area	1534791	1534791	0.01	9.9E-01
SLC25A1	cortical thickness	0.004562	0.004562	0.40	8.7E-01
	IQ	100.5208	100.5208	0.35	8.8E-01
	surface area	35032568	35032568	0.18	9.4E-01
SNAP29	cortical thickness	0.019657	0.019657	1.73	6.8E-01
	IQ	21.08809	21.08809	0.07	9.9E-01
	surface area	148000000	148000000	0.75	7.7E-01
TANGO2	cortical thickness	0.005079	0.005079	0.44	8.6E-01
	IQ	1766.241	1766.241	6.45	6.4E-01
	surface area	385000000	385000000	1.98	6.8E-01
THAP7	cortical thickness	0.006703	0.006703	0.58	7.8E-01
	IQ	0.578998	0.578998	0.00	9.9E-01
	surface area	1400143	1400143	0.01	9.9E-01
TMEM191A	cortical thickness	0.00393	0.00393	0.34	8.8E-01
	IQ	6.572305	6.572305	0.02	9.9E-01
	surface area	152000000	152000000	0.77	7.7E-01
TRMT2A	cortical thickness	0.001427	0.001427	0.12	9.9E-01
	IQ	11.17041	11.17041	0.04	9.9E-01
	surface area	10482.37	10482.37	0.00	9.9E-01
TXNRD2	cortical thickness	0.007833	0.007833	0.68	7.7E-01
	IQ	536.8741	536.8741	1.91	6.8E-01
	surface area	471000000	471000000	2.43	6.8E-01
UFD1	cortical thickness	0.024953	0.024953	2.20	6.8E-01
	IQ	822.6568	822.6568	2.94	6.8E-01
	surface area	54957229	54957229	0.28	9.0E-01
ZDHHC8	cortical thickness	0.018542	0.018542	1.63	6.8E-01
	IQ	71.30603	71.30603	0.25	9.1E-01
	surface area	144000000	144000000	0.73	7.7E-01
ZNF74	cortical thickness	0.010165	0.010165	0.89	7.7E-01
	IQ	410.566	410.566	1.45	6.8E-01
	surface area	2789197	2789197	0.01	9.9E-01

Supplementary Table 4.5: Main effect of gene expression on group-residualized cortical thickness, total surface area, and Full Scale IQ

Module	Outcome measure	Sum of Squares	Mean Square	F-statistic	FDR q-val
MEblack	IQ	620.3474	310.1737	1.08	7.3E-01
	surface area	175000000	87496859	0.44	9.0E-01
	cortical thickness	0.005543	0.002772	0.24	9.0E-01
MEbrown	IQ	741.961	370.9805	1.29	6.9E-01
	surface area	489000000	244000000	1.23	6.9E-01
	cortical thickness	0.008695	0.004348	0.38	9.0E-01
MEcyan	IQ	1542.162	771.0809	2.74	5.7E-01
	surface area	246000000	123000000	0.61	8.5E-01
	cortical thickness	0.009284	0.004642	0.41	9.0E-01
MEdarkgreen	surface area	823000000	412000000	2.10	5.7E-01
	IQ	539.9381	269.969	0.95	7.4E-01
	cortical thickness	0.006415	0.003208	0.28	9.0E-01
MEdarkgrey	IQ	841.3884	420.6942	1.48	6.5E-01
	surface area	345000000	173000000	0.86	7.6E-01
	cortical thickness	0.010102	0.005051	0.44	9.0E-01
MEdarkolivegreen	IQ	600.9965	300.4982	1.04	7.3E-01
	cortical thickness	0.005647	0.002823	0.24	9.0E-01
	surface area	29510722	14755361	0.07	9.3E-01
MEdarkorange	surface area	336000000	168000000	0.86	7.6E-01
	cortical thickness	0.009569	0.004784	0.43	9.0E-01
	IQ	195.6639	97.83197	0.34	9.0E-01
MEdarkred	IQ	2066.262	1033.131	3.71	5.7E-01
	surface area	347000000	173000000	0.88	7.6E-01
	cortical thickness	0.007583	0.003792	0.33	9.0E-01
MEdarkturquoise	IQ	953.8003	476.9002	1.68	6.3E-01
	surface area	668000000	334000000	1.69	6.3E-01
	cortical thickness	0.02726	0.01363	1.21	6.9E-01
MEgreen	IQ	1887.29	943.6452	3.43	5.7E-01
	cortical thickness	0.052045	0.026023	2.38	5.7E-01
	surface area	246000000	123000000	0.61	8.5E-01
MEgreenyellow	IQ	967.2038	483.6019	1.70	6.3E-01
	surface area	197000000	98368083	0.50	9.0E-01
	cortical thickness	0.002583	0.001291	0.11	9.3E-01
MEgrey60	IQ	1338.03	669.015	2.37	5.7E-01
	surface area	587000000	293000000	1.48	6.5E-01
	cortical thickness	0.001855	0.000928	0.08	9.3E-01
MElightgreen	IQ	1288.342	644.1711	2.27	5.7E-01
	surface area	196000000	97920909	0.49	9.0E-01
	cortical thickness	0.001662	0.000831	0.07	9.3E-01
MElightyellow	IQ	1779.687	889.8435	3.19	5.7E-01
	surface area	448000000	224000000	1.12	7.3E-01
	cortical thickness	0.011804	0.005902	0.52	9.0E-01
MEmagenta	surface area	1260000000	628000000	3.27	5.7E-01
	cortical thickness	0.047079	0.023539	2.12	5.7E-01
	IQ	402.7882	201.3941	0.70	8.4E-01

MEmidnightblue	IQ	921.5953	460.7976	1.62	6.3E-01
	surface area	535000000	268000000	1.35	6.9E-01
	cortical thickness	0.016871	0.008436	0.75	8.2E-01
MEorange	surface area	138000000	68857235	0.34	9.0E-01
	cortical thickness	0.00584	0.00292	0.25	9.0E-01
	IQ	50.01916	25.00958	0.09	9.3E-01
MEpink	IQ	994.5147	497.2574	1.76	6.3E-01
	cortical thickness	0.02724	0.01362	1.21	6.9E-01
	surface area	313000000	157000000	0.78	8.0E-01
MEroyalblue	IQ	1297.573	648.7866	2.29	5.7E-01
	surface area	679000000	339000000	1.72	6.3E-01
	cortical thickness	0.02933	0.014665	1.30	6.9E-01
MEsaddlebrown	surface area	411000000	206000000	1.03	7.3E-01
	cortical thickness	0.009686	0.004843	0.42	9.0E-01
	IQ	111.7871	55.89353	0.19	9.3E-01
MEsalmon	surface area	1220000000	611000000	3.23	5.7E-01
	cortical thickness	0.050441	0.02522	2.27	5.7E-01
	IQ	67.37634	33.68817	0.12	9.3E-01
MEskyblue	IQ	926.1191	463.0596	1.62	6.3E-01
	cortical thickness	0.031579	0.015789	1.40	6.8E-01
	surface area	118000000	59194793	0.29	9.0E-01
MEsteelblue	IQ	1719.79	859.8952	3.10	5.7E-01
	surface area	856000000	428000000	2.19	5.7E-01
	cortical thickness	0.001849	0.000925	0.08	9.3E-01
MEtan	surface area	1590000000	795000000	4.22	5.7E-01
	cortical thickness	0.052065	0.026033	2.36	5.7E-01
	IQ	585.0534	292.5267	1.02	7.3E-01
MEturquoise	IQ	1574.854	787.4269	2.81	5.7E-01
	surface area	642000000	321000000	1.62	6.3E-01
	cortical thickness	0.015257	0.007629	0.67	8.5E-01
MEviolet	surface area	257000000	128000000	0.64	8.5E-01
	cortical thickness	0.008216	0.004108	0.36	9.0E-01
	IQ	167.8923	83.94616	0.29	9.0E-01
MEwhite	cortical thickness	0.059726	0.029863	2.72	5.7E-01
	IQ	846.789	423.3945	1.48	6.5E-01
	surface area	40335863	20167931	0.10	9.3E-01
MEyellow	IQ	550.9985	275.4993	0.97	7.4E-01
	surface area	31993093	15996547	0.08	9.3E-01
	cortical thickness	0.001733	0.000867	0.08	9.3E-01

Supplementary Table 4.6: Interaction effect of module eigengene expression and CNV group on cortical thickness, total surface area, and Full Scale IQ

Module	Outcome measure	Sum of Squares	Mean Square	F-statistic	FDR q-val
MEblack	cortical thickness	0.002772	0.244902	0.78	9.0E-01
	IQ	310.1737	1.077374	0.34	7.3E-01
	surface area	87496859	0.435357	0.65	9.0E-01
MEbrown	cortical thickness	0.004348	0.381361	0.68	9.0E-01
	IQ	370.9805	1.291755	0.28	6.9E-01
	surface area	244000000	1.228304	0.30	6.9E-01
MEcyan	cortical thickness	0.004642	0.407596	0.67	9.0E-01
	IQ	771.0809	2.744182	0.07	5.7E-01
	surface area	123000000	0.611862	0.54	8.5E-01
MEdarkgreen	cortical thickness	0.003208	0.279208	0.76	9.0E-01
	IQ	269.969	0.948437	0.39	7.4E-01
	surface area	412000000	2.096864	0.13	5.7E-01
MEdarkgrey	cortical thickness	0.005051	0.441282	0.64	9.0E-01
	IQ	420.6942	1.478873	0.23	6.5E-01
	surface area	173000000	0.858957	0.43	7.6E-01
MEdarkolivegreen	cortical thickness	0.002823	0.244854	0.78	9.0E-01
	IQ	300.4982	1.042852	0.35	7.3E-01
	surface area	14755361	0.072756	0.93	9.3E-01
MEdarkorange	cortical thickness	0.004784	0.428171	0.65	9.0E-01
	IQ	97.83197	0.337201	0.71	9.0E-01
	surface area	168000000	0.859065	0.43	7.6E-01
MEdarkred	cortical thickness	0.003792	0.330077	0.72	9.0E-01
	IQ	1033.131	3.705164	0.03	5.7E-01
	surface area	173000000	0.879542	0.42	7.6E-01
MEdarkturquoise	cortical thickness	0.01363	1.206079	0.30	6.9E-01
	IQ	476.9002	1.684596	0.19	6.3E-01
	surface area	334000000	1.688826	0.19	6.3E-01
MEgreen	cortical thickness	0.026023	2.375016	0.10	5.7E-01
	IQ	943.6452	3.427408	0.03	5.7E-01
	surface area	123000000	0.611371	0.54	8.5E-01
MEgreenyellow	cortical thickness	0.001291	0.112402	0.89	9.3E-01
	IQ	483.6019	1.697635	0.19	6.3E-01
	surface area	98368083	0.496583	0.61	9.0E-01
MEgrey60	cortical thickness	0.000928	0.080881	0.92	9.3E-01
	IQ	669.015	2.36894	0.10	5.7E-01
	surface area	293000000	1.483331	0.23	6.5E-01
MElightgreen	cortical thickness	0.000831	0.072876	0.93	9.3E-01
	IQ	644.1711	2.272975	0.11	5.7E-01
	surface area	97920909	0.486151	0.62	9.0E-01
MElightyellow	cortical thickness	0.005902	0.515571	0.60	9.0E-01
	IQ	889.8435	3.190306	0.04	5.7E-01
	surface area	224000000	1.120799	0.33	7.3E-01
MEmagenta	cortical thickness	0.023539	2.116365	0.13	5.7E-01
	IQ	201.3941	0.698666	0.50	8.4E-01
	surface area	628000000	3.268106	0.04	5.7E-01
MEmidnightblue	cortical thickness	0.008436	0.748329	0.48	8.2E-01
	IQ	460.7976	1.617892	0.20	6.3E-01
	surface area	268000000	1.347722	0.26	6.9E-01
MEorange	cortical thickness	0.00292	0.253657	0.78	9.0E-01
	IQ	25.00958	0.085819	0.92	9.3E-01
	surface area	68857235	0.33964	0.71	9.0E-01
MEpink	cortical thickness	0.01362	1.207464	0.30	6.9E-01
	IQ	497.2574	1.762362	0.18	6.3E-01
	surface area	157000000	0.782805	0.46	8.0E-01
MEroyalblue	cortical thickness	0.014665	1.298375	0.28	6.9E-01

	IQ	648.7866	2.293394	0.10	5.7E-01
	surface area	339000000	1.716738	0.18	6.3E-01
MEsaddlebrown	cortical thickness	0.004843	0.422056	0.66	9.0E-01
	IQ	55.89353	0.19275	0.82	9.3E-01
	surface area	206000000	1.029442	0.36	7.3E-01
MEsalmon	cortical thickness	0.02522	2.271419	0.11	5.7E-01
	IQ	33.68817	0.116247	0.89	9.3E-01
	surface area	611000000	3.228215	0.04	5.7E-01
MEskyblue	cortical thickness	0.015789	1.399772	0.25	6.8E-01
	IQ	463.0596	1.624967	0.20	6.3E-01
	surface area	59194793	0.291668	0.75	9.0E-01
MEsteelblue	cortical thickness	0.000925	0.079951	0.92	9.3E-01
	IQ	859.8952	3.096645	0.05	5.7E-01
	surface area	428000000	2.190869	0.12	5.7E-01
MEtan	cortical thickness	0.026033	2.358212	0.10	5.7E-01
	IQ	292.5267	1.019958	0.36	7.3E-01
	surface area	795000000	4.218718	0.02	5.7E-01
MEturquoise	cortical thickness	0.007629	0.666924	0.52	8.5E-01
	IQ	787.4269	2.813754	0.06	5.7E-01
	surface area	321000000	1.622241	0.20	6.3E-01
MEviolet	cortical thickness	0.004108	0.362967	0.70	9.0E-01
	IQ	83.94616	0.292402	0.75	9.0E-01
	surface area	128000000	0.637254	0.53	8.5E-01
MEwhite	cortical thickness	0.029863	2.71605	0.07	5.7E-01
	IQ	423.3945	1.477241	0.23	6.5E-01
	surface area	20167931	0.099235	0.91	9.3E-01
MEyellow	cortical thickness	0.000867	0.07507	0.93	9.3E-01
	IQ	275.4993	0.966113	0.38	7.4E-01

Supplementary Table 4.7: Main effect of module eigengene expression on group-residualized cortical thickness, total surface area, and Full Scale IQ

Celltype	Outcome measure	Sum of Squares	Mean Square	F-statistic	FDR q-val
B cells memory	cortical thickness	0.011984	0.005992	0.53	1.0E+00
	IQ	638.7655	319.3828	1.11	9.9E-01
	surface area	16081857	8040929	0.04	1.0E+00
B cells naive	cortical thickness	0.005172	0.002586	0.23	1.0E+00
	IQ	1668.097	834.0487	2.97	3.8E-01
	surface area	238000000	119000000	0.60	1.0E+00
Dendritic cells activated	cortical thickness	0.019775	0.009888	0.87	1.0E+00
	IQ	82.57532	41.28766	0.14	1.0E+00
	surface area	220000000	110000000	0.55	1.0E+00
Macrophages M0	cortical thickness	0.046337	0.023169	2.11	5.8E-01
	IQ	281.3063	140.6532	0.49	1.0E+00
	surface area	125000000	62292495	0.31	1.0E+00
Macrophages M1	cortical thickness	0.006104	0.006104	0.54	1.0E+00
	IQ	1780.496	1780.496	6.39	3.7E-01
	surface area	342000000	342000000	1.74	7.6E-01
Macrophages M2	cortical thickness	0.112874	0.056437	5.38	3.6E-01
	IQ	14.48139	7.240693	0.02	1.0E+00
	surface area	106000000	52972739	0.27	1.0E+00
Mast cells activated	cortical thickness	0.081069	0.040535	3.83	3.8E-01
	IQ	1030.832	515.4158	1.85	6.9E-01
	surface area	178000000	89120970	0.46	1.0E+00
Mast cells resting	cortical thickness	0.015565	0.007783	0.68	1.0E+00
	IQ	597.85	298.925	1.05	1.0E+00
	surface area	263000000	132000000	0.65	1.0E+00
Monocytes	cortical thickness	0.028264	0.014132	1.27	9.5E-01
	IQ	463.4238	231.7119	0.82	1.0E+00
	surface area	14858816	7429408	0.04	1.0E+00
Neutrophils	cortical thickness	0.057121	0.02856	2.59	4.5E-01
	IQ	61.27486	30.63743	0.11	1.0E+00
	surface area	624000000	312000000	1.59	7.9E-01
NK cells activated	cortical thickness	0.076574	0.038287	3.53	3.8E-01
	IQ	6.311145	3.155572	0.01	1.0E+00
	surface area	25480884	12740442	0.06	1.0E+00
NK cells resting	cortical thickness	0.003473	0.001736	0.15	1.0E+00
	IQ	136.6315	68.31573	0.23	1.0E+00
	surface area	3327390	1663695	0.01	1.0E+00
Plasma cells	cortical thickness	0.0000573	0.0000287	0.00	1.0E+00
	IQ	117.322	58.66098	0.21	1.0E+00
	surface area	135000000	67551425	0.34	1.0E+00
T cells CD4 memory activated	cortical thickness	0.000812	0.000406	0.04	1.0E+00
	IQ	91.52826	45.76413	0.16	1.0E+00
	surface area	163000000	81552203	0.41	1.0E+00
T cells CD4 memory resting	cortical thickness	0.012417	0.006209	0.54	1.0E+00
	IQ	1367.517	683.7585	2.41	4.6E-01
	surface area	233000000	116000000	0.58	1.0E+00

T cells CD4 naive	cortical thickness	0.08015	0.040075	3.74	3.8E-01
	IQ	420.1587	210.0794	0.73	1.0E+00
	surface area	468000000	234000000	1.17	9.9E-01
T cells CD8	cortical thickness	0.068497	0.034248	3.13	3.8E-01
	IQ	39.62784	19.81392	0.07	1.0E+00
	surface area	91547725	45773862	0.24	1.0E+00
T cells follicular helper	cortical thickness	0.056026	0.028013	2.54	4.5E-01
	IQ	286.9273	143.4637	0.50	1.0E+00
	surface area	524000000	262000000	1.32	9.5E-01
T cells gamma delta	cortical thickness	0.001239	0.000619	0.05	1.0E+00
	IQ	1722.689	861.3447	3.08	3.8E-01
	surface area	353000000	177000000	0.89	1.0E+00
T cells regulatory (Tregs)	cortical thickness	0.012226	0.006113	0.53	1.0E+00
	IQ	15.23473	7.617367	0.03	1.0E+00
	surface area	1130000000	567000000	2.94	3.8E-01

Supplementary Table 4.8: Interaction effect of gene expression and group status on cortical thickness, total surface area, and Full Scale IQ

Celltype	Outcome measure	Sum of Squares	Mean Square	F-statistic	FDR q-val
B cells memory	cortical thickness	0.012558695	0.012558695	1.02	0.96
	IQ	61.09149273	61.09149273	0.23	0.99
	surface area	7668137.857	7668137.857	0.04	0.99
B cells naive	cortical thickness	0.038237771	0.038237771	3.17	0.67
	IQ	6.479261015	6.479261015	0.02	0.99
	surface area	397182170	397182170	2.01	0.96
Dendritic cells activated	cortical thickness	9.69E-03	9.69E-03	0.79	0.98
	IQ	9.663696185	9.663696185	0.04	0.99
	surface area	269435279.3	269435279.3	1.36	0.96
Macrophages M0	cortical thickness	4.06E-02	4.06E-02	3.37	0.67
	IQ	10.38263681	10.38263681	0.04	0.99
	surface area	13028.29065	13028.29065	0	0.99
Macrophages M1	cortical thickness	0.000314352	0.000314352	0.03	0.99
	IQ	0.073704868	0.073704868	0	0.99
	surface area	1.04E+08	1.04E+08	0.52	0.98
Macrophages M2	cortical thickness	1.43E-02	1.43E-02	1.16	0.96
	IQ	28.21160782	28.21160782	0.1	0.99
	surface area	955885244.6	955885244.6	4.97	0.63
Mast cells activated	cortical thickness	6.23E-06	6.23E-06	0	0.99
	IQ	762.8533111	762.8533111	2.89	0.68
	surface area	913083235.6	913083235.6	4.74	0.63
Mast cells resting	cortical thickness	1.08E-02	1.08E-02	0.88	0.96
	IQ	381.1308385	381.1308385	1.43	0.96
	surface area	42276.92217	42276.92217	0	0.99
Monocytes	cortical thickness	0.011117986	0.011117986	0.9	0.96
	IQ	850.4410129	850.4410129	3.22	0.67
	surface area	316324934.7	316324934.7	1.6	0.96
Neutrophils	cortical thickness	1.09E-04	1.09E-04	0.01	0.99
	IQ	41.09321562	41.09321562	0.15	0.99
	surface area	199437510.8	199437510.8	1	0.96
NK cells activated	cortical thickness	1.87E-03	1.87E-03	0.15	0.99
	IQ	313.5525538	313.5525538	1.17	0.96
	surface area	109223949	109223949	0.55	0.98
NK cells resting	cortical thickness	0.000677155	0.000677155	0.05	0.99
	IQ	89.76861378	89.76861378	0.33	0.98
	surface area	91040637.04	91040637.04	0.45	0.98
Plasma cells	cortical thickness	3.97E-06	3.97E-06	0	0.99
	IQ	910.9197471	910.9197471	3.46	0.67
	surface area	132299171.9	132299171.9	0.66	0.98
T cells CD4 memory activated	cortical thickness	1.13E-03	1.13E-03	0.09	0.99
	IQ	107.9111888	107.9111888	0.4	0.98
	surface area	276867989.8	276867989.8	1.39	0.96
T cells CD4 memory resting	cortical thickness	2.93E-03	2.93E-03	0.24	0.99
	IQ	4.998174104	4.998174104	0.02	0.99
	surface area	276387838.8	276387838.8	1.39	0.96
T cells CD4 naive	cortical thickness	0.007165129	0.007165129	0.58	0.98
	IQ	191.5581161	191.5581161	0.72	0.98
	surface area	4031988.244	4031988.244	0.02	0.99
T cells CD8	cortical thickness	2.45E-03	2.45E-03	0.2	0.99
	IQ	263.6606557	263.6606557	0.99	0.96

	surface area	1205168729	1205168729	6.34	0.63
T cells follicular helper	cortical thickness	0.001429997	0.001429997	0.12	0.99
	IQ	94.78289197	94.78289197	0.35	0.98
	surface area	16121009.72	16121009.72	0.08	0.99
T cells gamma delta	cortical thickness	4.84E-04	4.84E-04	0.04	0.99
	IQ	161.2183942	161.2183942	0.6	0.98
	surface area	379418307.2	379418307.2	1.92	0.96
T cells regulatory (Tregs)	cortical thickness	0.004029288	0.004029288	0.33	0.98
	IQ	3.517604291	3.517604291	0.01	0.99
	surface area	89272127.42	89272127.42	0.45	0.98

Supplementary Table 4.9: Main effect of cell type proportion on group-residualized cortical thickness, total surface area, and Full Scale IQ

4.7.5: Supplementary References

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CHAPTER FIVE

Conclusions and Future Directions

5.1: Conclusions

In this body of work, I leveraged multimodal datasets and complementary analyses to yield insights about how genes may disrupt the brain and contribute to downstream cognitive and behavioral impairments using a "genetics-first" approach. In Chapter 1, I laid out the framework for how the study of reciprocal 22q11.2 copy number variants (CNVs) can offer mechanistic insights regarding the development of neuropsychiatric disorders. Chapter 2 provided the first evidence that the 22q11.2 locus confers reciprocal gene-dose-dependent cortical and subcortical phenotypes. Findings of opposing directions of effect for cortical thickness (CT) versus surface area (SA) along with more pervasive effects for SA relative to CT, suggest that distinct neurodevelopmental mechanisms may be perturbed. Widespread SA decreases in 22q11.2 deletion (22qDel) carriers may reflect reduced production of progenitor cells across multiple cortical regions, indicating a cortical phenotype that arises during early brain development. Although there was divergence in the specific brain areas most impacted by 22qDel vs 22qDup, areas most significantly impacted across CNVs were noteworthy as neural substrates relevant for social-cognitive circuitry (Lieberman, 2007; Pinkham et al., 2003). This suggests that both over- and under-expression of 22q11.2 genes may lead to cortical perturbations that give rise to the social cognitive deficits observed in both groups, perhaps through different mechanisms. Finally, subcortical regions also displayed complex, localized patterns of shape differences between 22qDel and 22qDup carriers, indicating global effects of the 22q11.2 CNV on brain development.

Chapter 3 illustrated how 22q11.2 CNVs influenced neurobehavioral function across multiple domains relevant to developmental neuropsychiatric disorders. First, these reciprocal imbalances were associated with similar deficits in traits related to Autism Spectrum Disorder (ASD) as well as cognitive function. In contrast, 22qDel was uniquely associated with dimensionally-measured positive and negative psychotic symptomology, consistent with the increased risk of a categorical diagnosis of psychotic disorder, for which 22qDel is well-known

(Gur et al., 2017; Monks et al., 2014; Schneider et al., 2014; Stefansson et al., 2014). The comparably high rates of ASD diagnoses for both CNV groups, however, belied subtle differences in ASD profile when the broad disease phenotype was carved into subdomain traits. Finally, the absence of the normative association between processing speed and cortical thickness of higher-order brain regions in both CNV groups suggests that typical cortical thinning during development may underlie processing speed ability. The specific association with thickness, but not surface area, additionally suggests compromised myelinated axonal fibers leading to disruptions in distributed neural networks in the context of a 22q11.2 CNV. Thus, these findings provide opportunities to test novel mechanistic hypotheses regarding the connection between 22q11.2 gene dosage, cortical thickness, and white matter aberrations in shaping processing speed impairments. Taken together, these discoveries indicate that both decreased and increased expression of genes within the 22q11.2 locus can result in convergent downstream pathogenic effects on cognition and social behavior. On the other hand, under-expression of genes within the locus may indicate a unique biological etiology influencing psychotic symptomatology. Moreover, the mechanisms by which reciprocal deletions and duplications at the same locus can have divergent effects on intellectual function and psychosis-related traits but converge on similar impairments for specific cognitive domains and social cognition remain unknown. Future studies are needed to elucidate the ways in which reciprocal gene dosage can lead to impairments in the same cognitive domain.

Chapter 4 demonstrated that the significant genome-wide transcriptomic dysregulation seen in peripheral blood of 22qDel carriers compared to 22qDup carriers and controls was likely driven by differences in blood cell type proportion, as opposed to direct effects of 22qDel on gene expression across cell types. However, it is possible that genes within the 22q11.2 locus which still exhibited significantly decreased expression after adjusting for cell type heterogeneity reflect pan-cellular or tissue-non-specific effects of 22qDel. This may, in turn, underlie the systemic, multi-organ pathology seen in 22q11.2 Deletion Syndrome. Finally, expression of two

ASD-associated and cytoskeletal-relevant genes, FNBP1 and WDR1, were found to differ between 22q11.2 CNV carriers with and without ASD, albeit in opposing directions. This suggests that FNBP1 and WDR1 contributions to ASD risk may be mechanistically distinct and depend on 22q11.2 CNV status. Further replication of these findings and experimental studies will be important for parsing out the role of abnormal expression of these genes in conferring ASD risk in the context of 22q11.2 CNVs.

5.2: Future Directions

In all three studies, 22q11.2 deletion showed a more robust impact on intermediate phenotypes (gene expression, cortical indices, and neurobehavioral traits) compared to the duplication. This is consistent with epidemiological findings that duplication CNVs generally tend to have less deleterious effects than deletions (Douard et al., 2021; Mannik et al., 2015). Future studies with larger sample sizes of 22qDup carriers should validate and extend these disparate effect size findings across multiple endophenotypes. Power analyses from Study 2 demonstrated that with sample sizes comparable to the number of deletion carriers and controls in that study, additional differences in cortical thickness and area could likely be identified. It will be important to assess whether additional effects on neurobehavioral traits and gene expression measures could be revealed when assessing more duplication carriers as well. A larger sample of CNV carriers would also provide greater power to detect potential variable impacts of CNV breakpoints. The studies described herein lacked the ability to delineate how breakpoint locations may impact downstream phenotypes, but such analyses will be important to parse haplo- or triplosensitivity across different 22q11.2 genes (Collins et al., 2021).

Moreover, common genetic variation may also influence the phenotypic expression of 22q11.2 CNVs, thereby modulating clinical presentation (Davies et al., 2020). Thus, the additive contribution of polygenic, common risk should also be investigated (Huguet et al., 2018; Weiner

et al., 2017). With sufficient sample sizes, future investigations should be conducted to hone in on genetic background contributions to phenotypic variability and expression between reciprocal 22q11.2 CNV carriers. Studies leveraging population-based birth cohorts of 22q11.2 CNV carriers, such as those identified by iPSYCH study in Denmark (Olsen et al., 2018), as well as including first-degree relatives as controls for genetic background, will be important to account for additional genetic and environmental factors (D'Angelo et al., 2016; A. Moreno-De-Luca et al., 2015).

Improved *in vitro* and *in vivo* models of 22q11.2 CNVs are also required to elucidate the contribution of particular genes, cell types, and biological pathways implicated in this body of work. Organoid models of both 22q11.2 CNVs could test whether experimental manipulation of one or more genes in the locus drives aberrant brain development within developmentally critical windows. Although such *in vitro* approaches are necessary to identify biochemical and cellular consequences of genetic mutations, a more intact system such as an animal model enables identification of perturbed neural circuit properties during behavior that lead to dysfunction. While mouse models and cerebral cortical organoids have already been developed for 22qDel (Fenelon et al., 2013; Hiramoto et al., 2011; Mukai et al., 2015; Ouchi et al., 2013; Saito et al., 2020; Khan et al. 2020), there are far fewer model systems for 22qDup. In fact, only 1 (partial) mouse model of the duplication has currently been developed, which includes overexpression of only the COMT and Tbx1 genes (Boku et al., 2018). Murine models of the 22q11.2 critical region or even cortical organoids of 22q11.2 duplication would be a boon to testing some of the gene dosage hypotheses born out of the insights generated from the aforementioned studies.

Finally, as there are other reciprocal CNVs that confer high risk for neuropsychiatric disorders, some of which show similar opposing effects on downstream phenotypes (e.g. Hippolyte et al., 2016; Jacquemont et al., 2011; Qureshi et al., 2014), it will be important to compare findings across CNVs to generate further insights and share methodologies (Collins et

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al., 2021; D. Moreno-De-Luca et al., 2014; Sanders et al., 2019). In fact, studies of other disease-associated genomic imbalances have already begun to pave the way towards developing novel, genetically-informed interventions. For example, a promising strategy has recently been developed to treat Angelman's syndrome, a genetic disorder caused by a deletion or mutation of the maternally inherited UBE3A gene (in the imprinted 15q11-13 region) that leads to loss of its function (Elgersma & Sonzogni, 2021). UBE3A is an E3-ubiquitin ligase known to be critical for typical postnatal brain development and thought to be a driver of the clinical phenotype through affecting multiple convergent pathways (Williams, 2010). The strategy uses an antisense oligonucleotide (ASO) to activate the silenced paternal UBE3A gene and restore UBE3A protein levels. Due to successes observed in treating spinal muscular atrophy (Singh et al., 2017; Wood et al., 2017), ASO therapy holds great potential for Angelman syndrome as well as other genetically-defined, neurodevelopmental disorders. This kind of precision medicine approach developed as a result of genetic insights garnered from human association studies, animal models, and other *in vitro* assays, represent future avenues for potential treatments of CNV disorders. Knowledge gathered across these highly-penetrant CNVs will be critical to developing other pharmacologic or gene-editing therapies, ideally with further insights about which critical periods may be optimal for intervention. Collectively, this work demonstrates how systematic investigation of the effects of reciprocal 22q11.2 imbalances on underlying biological processes offers a window into how these CNVs disrupt the brain and contribute to disease pathogenesis. The hope is that the study of such high-penetrance genetic mutations can also provide key insights into the underlying biology of idiopathic developmental neuropsychiatric disorders which share downstream phenotypic characteristics.

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