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Neurocorrelates of the Mirror Neuron System in Children with Chromosome 22q11.2 Deletion Syndrome

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Abbreviations

Attention Deficit Hyperactivity Disorder ..... ADHD
Autism Spectrum Disorder ..... ASD
Basal Ganglia ..... BG
Bipolar Disorder ..... BPD
Blood Oxygenated Level Dependent ..... BOLD
Chromosome 22q11.2 Deletion Syndrome 22q11.2DS
Corpus Callosum CC
Fixed Effects Analysis ..... FFX
Functional Magnetic Resonance Imaging ..... fMRI
Fuzzy Clustering Analysis ..... FCA
Diffusion Tensor Imaging ..... DTI
Gamma Aminobutyric Acid ..... GABA
Globus Pallidus ..... GP
High Functioning Autism ..... HFA
Inferior Frontal Gyrus ..... IFG
Intellectual Disability ..... ID
Middle Frontal Gyrus ..... MFG
Middle Occipital Gyrus ..... MOG
Mirror Neuron System ..... MNS
Random Effects Analysis ..... RFX
Superior Temporal Gyrus ..... STG
Typically Developing ..... TD
Theory of Mind ..... ToM
Statistical Threshold Estimator ..... STE
Voxel Count VC
Working Memory ..... WM

Abstract

Activation of brain regions that make up the mirror neuron system (MNS) is thought to reflect processing and perceiving behavior, action, and intentionality of other organisms. Sensing and perceiving motor behavior in others is an important component of understanding and participating in social interactions. Children with chromosome 22q11.2 deletion syndrome (22q11.2DS) are diagnosed with serious medical, cognitive, and socio-emotional symptoms. Atypical development and function of the MNS may underpin some aspects of socio-emotional impairment and autism spectrum disorder (ASD)-like symptomology reported. This study of the MNS investigates differences in activation in the operculum, sensorimotor areas, and basal ganglia (BG) in children with 22q11.2DS compared to typically-developing (TD) controls. Twenty-nine children (22q11.2DS: n=15; TD: n=16) between ages 7-16 viewed videos of a human hand manipulating various household objects during a functional magnetic resonance imaging (fMRI) scan. In Analysis 1, children with 22q11.2DS had less extensive brain activation than TD children in the operculum, sensorimotor areas, and BG. In Analysis 2, children with 22q11.2DS had the same results as Analysis 1 with the exception of sensorimotor areas not being highly active in either group. In both analyses, fMRI signal change from baseline to video did not differ significantly between groups. Processing efficiency in children with 22q11.2DS may be lower or more variable when compared to TD peers. This is the first study comparing children with 22q11.2DS to TD peers specifically looking at MNS activation within the operculum region to assess higher cognitive functioning, somatosensory cortex for sensory interpretation, and basal ganglia for gross motor activity. Future studies should compare brain activation between children with ASD and those with 22q11.2DS during an MNS task as the next step to further clarify the origin of ASD symptoms reported in this population.

Keywords: Attentional Processes; Cognitive Impairments; Functional Magnetic Resonance Imaging; Mirror Neurons; 22q11.2DS; DiGeorge Syndrome; Velocardiofacial Syndrome

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Introduction

Chromosome 22q11.2 Deletion Syndrome

Chromosome 22q11.2 Deletion Syndrome (22q11.2DS), also known as DiGeorge syndrome and velocardiofacial syndrome (VCFS), occurs in 1:2000 to 1:4,000 live births. 22q11.2DS is caused by a 1.5 to 3 megabase deletion on the long arm of chromosome 22. Along with serious medical, psychological, cognitive, and social challenges, this syndrome is associated with elevated risk of serious neuropsychiatric disorders in late adolescence to early adulthood. The affliction also results in abnormal organ formation in utero as well as medical complications in infancy (Badcock, 2013; Bassett et al., 2003; Gothelf et al., 2005; Gothelf, Schaer, & Eliez, 2008; Hall & Owen, 2015; Karayiorgou, Simon, & Gogos, 2010; McDonald-McGinn et al., 2015; Simon et al., 2005). They are also at greater risk for developing neuropsychiatric issues such as developmental delay and risk for psychosis (Wenger et al., 2016). Children with 22q11.2DS have an increased prevalence of comorbid diagnoses including attention deficit hyperactivity disorder (ADHD: 3-46%), generalized anxiety disorder (GAD: 17-29%), obsessive compulsive disorder (OCD: 4-33%) and bipolar affective disorder (BPD: 52%) (Bassett et al., 2003; Bish, Ferrante, McDonald-McGinn, Zackai, & Simon, 2005; Karayiorgou et al., 2010; Vorstman et al., 2006). Rates of autism spectrum disorder (ASD) range from 14% to 50% in children with 22q11.2DS (Bassett et al., 2003; Bish et al., 2005; Gothelf et al., 2008; Kates et al., 2007; Vorstman et al., 2006; Wenger et al., 2016).

Origins of Socio-emotional Impairment

Individuals with 22q11.2DS often have difficulty with social interactions and demonstrate elevated levels of anxiety and shyness (Ho et al., 2012; Niklasson, Rasmussen, Óskarsdóttir, & Gillberg, 2005; Swillen et al., 1999; Wenger et al., 2016). Their understanding of social context is often poor with a tendency for literal interpretations of others' words and actions. Individuals with 22q11.2DS also have notable circumscribed interests, evident in their limited spectrum of subjects with the desire to direct others' attention to their interests (Kates et al., 2007). These interests may interfere with their desire to have friends, however, they may have a poor understanding about what it means to have or be a friend in terms of reciprocal interactions in communication and activities (Ho et al., 2012).

Poor communication is a strong contributor to poor social interactions. In 22q11.2DS, some congenital malformations such as cleft palate and facial dysmorphisms could contribute to their social and communication impairment. For example, cleft palate malformation may result in feeding problems, excessive drooling, dysphagia, dysphonia, nasal speech, and speech delays (Bingham et al., 1997; Zur, 2013) that could contribute to both verbal and non-verbal communication deficits. Some children also have hearing loss, with mild loss related to inattentiveness (Wenger et al., 2016). Given the high rate of medical complications in children with 22q11.2DS, prolonged physiological and psychological stress could also exacerbate existing anxiety and hamper social development (Beaton & Simon, 2010).

Atypical brain development could also contribute to aspects of commonly reported socio-emotional difficulties seen in those with 22q11.2DS. For example, symptoms common to both 22q11.2DS and ASD, such as difficulty understanding the behavior of others, can arise in part from differences in brain processing of visual stimuli in faces versus objects or symbols

(Campbell et al., 2010). Eye-tracking in individuals with 22q11.2DS tends to be more erratic, demonstrated by shorter scanning length and fewer fixations overall. Reduced eye contact in ASD was not shown to be the result of social discomfort, nor did it vary by differences in emotional expression. In fact, it is difficult to establish if people with ASD are actively avoiding eye contact (Kliemann, Dziobek, Hatri, Steimke, & Heekeren, 2010). In 22q11.2DS, however, there is a paucity of research about the extent and purpose of actual avoidance of faces, particularly the eyes (Karagoz Uzel, 2013). In individuals with 22q11.2DS, lack of eye contact is often a result of social anxiety or lack of interest. Problems with attention regulation and initiating conversation are present in children with 22q.11.2DS regardless of a comorbid ASD diagnosis (Kates et al., 2007; Simon, 2008; Tang et al., 2014). To date, studies involving 22q11.2DS and eye gaze are limited to tasks investigating cognitive impairment but not social impairment (Andersson et al., 2008; Campbell et al., 2010; Swillen et al., 1999; Tang et al., 2014).

Campbell and colleagues (2010) found that children with 22q11.2DS spend significantly less time looking at the entire face or at the eyes and more time looking at mouths. This could be a result of less time attending to faces or to differences in associative brain regions involved in processing social stimuli. Functional MRI studies demonstrate that children with 22q11.2DS have less activation in the fusiform face area relative to TD controls when looking at faces compared to houses (Andersson et al., 2008). During tasks with facial stimuli, less activation in frontal cortex and right insula, but greater activation in the occipital lobe was found (Van Amelsvoort et al., 2006). Less activation in the fusiform area may be a result of less time spent looking at faces, as a result of atypical brain development, or both. However, the fusiform face area is not solely attuned to faces but is also an associative brain region combining information

from the larger visuoperceptual system. Complex cognition and social interaction arises from the coordinated action of associative brain regions that are dependent on efficient functioning of a network of modules. The efficient function (and development) of one module is dependent upon the function (and development) of the other modules it is connected to. For example, if a brain region is processing and associating information from four modules but one of those models is not working well, the efficiency of the association region is reduced. Consequently, repairing the impaired module or compensating for it should lead to improvement in higher-order dependent brain processes.

Atypical brain structure may affect the quality of social experiences, but it is also possible that poor social experiences earlier in life may determine atypical brain development. An important difference between children with 22q11.2DS as a group and those with ASD is that social competence appears to be more readily trainable in children with 22q11.2DS compared to children with ASD. For example, *Vis A Vis*, a socio-emotional computer-based training program, has been shown to improve ASD-like behaviors such as eye contact and recognition of emotional states of others in children with ID and 22q11.2DS (Angkustsiri et al., 2014; Glaser et al., 2012). These skills lasted beyond the training period and were reflected in pre- and post-training changes in brain activity in response to social stimuli measured using fMRI in children with 22q11.2DS (Karagoz Uzel, 2013). Furthermore, children with 22q11.2DS performed worse than TD controls in a video-based task designed to investigate the relationship between theory of mind (ToM) and reciprocal social behavior regardless of whether the children with 22q11.2DS had a comorbid diagnosis of ASD (Ho et al., 2012). Even in the absence of comorbidity with each other, 22q11.2DS and ASD share many neuropsychiatric and behavioral features that may contribute to several impairments like the presence of circumscribed interests, difficulties in

sharing attention, and initiating conversation (Kates et al., 2007). 22q11.2DS and ASD share visual features such as an abnormal scan path that may reduce activation in the fusiform gyrus and medial temporal lobes (Karagoz Uzel, 2013). Children with ASD also cannot shift thought and motor outputs on demand as a result of erratic executive function (Ito, 2004). Damage to the structure or functionality of the operculum region is tied to deficits in perception, attention, and awareness. For example, enlarged Sylvian fissures detected in a sample of infants with 22q.11.2DS are believed to demonstrate delayed growth in the opercular region, accounting for oromotor difficulties that contribute to communication deficits and subsequently, social deficits (Bingham et al., 1997; Rolland et al., 1995; Van Amelsvoort et al., 2001). This gives us more cause to suspect children with 22q11.2DS may have lower activation in the operculum region, fronto-temporal cortex, basal ganglia, and possibly sensorimotor cortices than their TD peers (Ho et al., 2012; Niklasson et al., 2005; Rolland et al., 1995; Sahyoun, 2009).

The direct link between perception and action is a basic mechanism for social interactions (Jackson & Decety, 2004). Understanding intentionality of motor movements, irrespective of theory of mind (ToM) processes, can demonstrate social competence (Enticott, Johnston, Herring, Hoy, & Fitzgerald, 2008). In early infancy, disruptions of core aspects of brain function related to motor control and planning are also likely to result in problematic behaviors like motor deficits and the inability to perceive and accurately imitate social interactions early in life (Hall & Owen, 2015).

Perceptual Problems in 22q11.2DS

Children with 22q11.2DS have demonstrated non-verbal cognitive disturbances in visual and spatial perception, learning, memory, attentional processes, and problem-solving skills in multiple studies (Bish et al., 2005; Simon, 2008; Swillen et al., 1999; Tang et al., 2014). While

there is consensus on visuospatial task performance deficits in children with 22q11.2DS, the deficit appears to vary by demands put on the participants. Howley and colleagues (2012) found that vigilance affects impairment on visual motor tasks and that children with 22q11.2DS were similar to TD participants in terms of accuracy. However, deficits in psychomotor speed in 22q11.2DS were due to poor fine motor coordination during timed tasks. Without being timed, speed for 22q11.2DS was comparable to TD in most cases (Howley, Prasad, Pender, & Murphy, 2012). Simon and colleagues (2008) used fMRI to assess the neural correlates of deficits processing spatial and temporal visual information. They posited that atypical brain development in children with 22q11.2DS contributes to less resolution and acuity leading to poorer foundational spatiotemporal competencies. In turn, this affects the development of cortical circuitry that supports efficient higher-order cognitive functions such as mathematics and abstract and relational reasoning (Simon, 2008). There are other indicators of atypical visual processing in people with 22q11.2DS as well. Bearden et al. (2001) found deficits in spatial memory, object memory and general visuospatial cognition in children with 22q11.2DS. Other studies found object speed did not appear to affect their performance. Instead, increasing cognitive demands, such as distraction from introducing multiple objects, tends to reduce performance accuracy and acuity in children with 22q11.2DS, but not TD children (Bish et al., 2005; Cabaral, Beaton, Stoddard, & Simon, 2012; Simon et al., 2005; Swillen et al., 1999; Villalon-Reina et al., 2013). Although there are measurable differences in attention and memory as well as performance abilities comparing individuals with 22q11.2DS and TD controls (particularly in spatial and visuospatial skills) verbal abilities are often comparable to TD children, and task performance differences may reflect subtle differences in observable behavior that shape brain development. For example, cognitive abilities like time-keeping and distance are

thought to build on visuospatial abilities (Hubbard, Piazza, Pinel, & Dehaene, 2005). Specific reduction in volumes of the parahippocampal gyrus, fusiform gyrus, lingual gyrus, posterior cingulate, cerebellum, cuneus, and precuneus were all noted to contribute to poor visuospatial task performance in 22q11.2DS (Sahyoun, 2009; Simon, 2007, 2008).

Overall demands on executive function and use of fine motor skills may account for poorer results in perceptual processing in special populations like 22q11.2DS. In addition to integration issues in the visual system, some motor systems may also be impaired in 22q11.2DS and ASD as a result of poor modeling of others' motor movement in their brain (Bish et al., 2005; Courchesne et al., 1994; Howley et al., 2012; Ito, 2004; Simon et al., 2005; Swillen et al., 1999; Tang et al., 2014). For example, demands on executive function like selectivity in attentional processes tend to slow down reaction times in children with 22q11.2DS. However, unlike individuals with ASD (excluding HFA), only poor fine motor skills accounted for the decline in reaction time in less demanding tasks in 22q11.2DS, indicating children with 22q11.2DS have specific deficits not completely mediated by intellectual disability (Howley et al., 2012). Atypical brain structure, such as partial absence of the corpus callosum (CC) and volume reduction in the posterior CC, is suggestive of low interhemispheric connectivity that likely result in lower neural activity in 22q11.2DS (Bingham et al., 1997). In contrast, other studies found larger volumes are found in the midsagittal CC, posterior CC, and the anterior (rostral) portion of the CC that sometimes appears larger with a bending angle. Response time in task was found to be inversely related to the size of the genu of the CC, but the direct involvement of the size and morphology was not definitive about its effects on cognitive abilities (Machado et al., 2007; Simon et al., 2005; Van Amelsvoort et al., 2001). The cerebellum also plays a large role in cognition by its reciprocal connections with the basal ganglia, thalamus, and

brainstem. It affects cognition (attention shifting, spatial attention), motor control (coordination), and the ability to detect change. The overall volume in individuals with 22q11.2DS is reduced in the cerebellum including the vermis, albeit inconsistently (Casey, Tottenham, Liston, & Durston, 2005; Millan et al., 2012; Simon et al., 2005; Van Amelsvoort et al., 2001). Reduced topokinetic memory may also contribute to poorer motor control in 22q11.2DS. Believed to be a function in the limbic region including the hippocampal formation, insular region, dorsolateral frontal cortex, and the parietal cortex, topokinetic memory in spatial memory tasks requires a memory of a previously experienced movement in space to be accessed through self-generated eye movement or actual locomotor movement. Activation of these regions in 22q11.2DS and ASD is reduced, but the dorsolateral frontal cortex is completely inactive in ASD in spatial tasks (Berthoz, 1997; Ito, 2004).

The Mirror Neuron System

Building on Rizzolatti's 1988 study where researchers recorded the activation of three macaque monkeys' motor areas while performing several motor movements their arm, Di Pellegrino and colleagues used tungsten microelectrodes to record electrical microstimulation of the F5 to determine if a monkey would have similar activation in observing a hand movement without participation. Strikingly, results revealed the same activation occurred whether a monkey was performing the action or watching the action, irrespective of a change in grip (Di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992). Rizzolatti et al., (2001) later investigated the concept of the visual hypothesis of action, suggesting activation in the premotor cortex translates goals into action by visual stimuli while watching an object being manipulated. Heyes (2011) explained, however, that for activation to be truly of a mirrored nature, it has to be observed only and include no participation.

Vision occurs by the intake of light in the retina, which translates it into neural signals via visual transduction. Neural signals enter the visual cortex via retinal geniculate striate in the primary motor cortex and end in of cortical layer IV. Information enters the thalamus, visual cortex (striate and prestriate), and then the association cortex (Kandel, Schwartz, Jessell, Siegelbaum, & Hudspeth, 2000). The visual system responds to change in the form of movement, and spatial organization is dependent on simple edge detection. Deficits in hierarchical organization such as detecting and understanding a stimulus are exhibited in impaired individuals. As visual input is the precursor to activating the mirror neuron system, atypical scanning (or possibly erratic saccadic movement) may contribute to decreased activation or be indicative of other structural and functional issues. This may affect eye field activation as well as regions of the brain associated in mirror tasks. Impairment to visual processes alone may inhibit mirror neuron activation (which can occur without higher cognitive processes) and subsequently, the understanding of movements and intention in others (Heyes, 2010; Kandel et al., 2000; Lang et al., 1998). MNS is created from action and perception cycles that can be mediated by internal representation of a movement, allowing us to create an internal representation of that action automatically generated in the premotor cortex. This helps us react to our environment and anticipate consequences. These representations may be used to interpret the movement and behaviors of others; however interpreting is dependent on individual cognitive abilities (Buccino et al., 2001; Jackson & Decety, 2004).

Visuospatial, motor planning/control, and executive processes are involved in sensing and perceiving actions in others. These systems are the foundation of higher order cognitive processes such as understanding intentionality and theory of mind (ToM). However, deficits in basic visual and motor systems as well as visuospatial attention have been found in 22q11.2DS

that may explain some of the perceptual issues affecting social interactions and literal interpretation these children have in understanding the behavior of others in social interactions (Campbell et al., 2010; Courchesne et al., 1994; Howley et al., 2012; Ito, 2004; Niklasson et al., 2005; Simon, 2007, 2008; Simon et al., 2005; Swillen et al., 1999; Villalon-Reina et al., 2013). Activation of mirror neurons, also called canonical neurons, reflects motor, social, and cognitive processes. The mirror neuron system (MNS) is implicated in understanding action behavior by creating an internal account of an action and using it to organize future behavior (Rizzolatti, Fogassi, & Gallese, 2001). Deficits in motor, social, and cognitive processes like those present in 22q11.2DS and ASD are likely to show decreased activation in the MNS.

Mirror neurons have been a source of studying theory of mind (ToM), associated learning, and imitation in humans. The ToM concept explains meta-cognitive abilities such as intentions, beliefs, and desires of others as well as the ability to anticipate consequences. To accomplish this, an individual must make the distinction between self and others; the ability to make this distinction supports the idea that perception and production of an action means the interpretation of other person's actions are functionally connected (Jackson & Decety, 2004; Kaplan & Iacoboni, 2006; Rizzolatti et al., 2001; Schulte-Rüther, Markowitsch, Fink, & Piefke, 2007). Furthermore, functional and structural changes over time in populations with various cognitive or psychiatric disorders have helped shed light on specific impairments that have aided (and continue to aid) in the treatments of disorders such as ASD, HFA, and ADHD (Heeger & Ress, 2002; Iacoboni et al., 2005; Ito, 2004; Kaplan & Iacoboni, 2006; Rizzolatti et al., 2001; Schulte-Rüther et al., 2007).

The 1992 hallmark study propelled future publications suggesting that activation during mirror neuron tasks may also be implicated in ToM, intention, and empathy (Dapretto et al.,

2006; Iacoboni et al., 2001; Iacoboni et al., 2005). Using mirror neurons to assess ToM has also been assessed in special populations having intellectual disabilities (ID), other cognitive impairments, brain damage from head injuries, and brain lesions (Fisch, 2013; Ito, 2004; Schulte-Rüther et al., 2007; Spengler, von Cramon, & Brass, 2010). While many studies focused on children with ASD (particularly empathy), no mirror neuron tasks have been performed on children with 22q11.2DS. Assessing theory of mind, intention, and basic mirror and motor systems could cite evidence of cognitive impairments as well as neural impairments in children with 22q11.2DS.

In one meta-analysis, human and non-human animal studies appear to have robust, "mirror-like" activation when watching object manipulation from others. In whole brain analysis, the largest areas of activation occurred in the fronto-temporal regions, parietal lobes, frontal lobes, and temporal lobes in humans (Molenberghs, Cunnington, & Mattingley, 2012). According to Kandel et al. (2000), the operculum region covers the insula and encompasses parts of the frontal, temporal, and parietal lobes, integrating the inferior frontal gyrus (BA 44), superior temporal gyrus (BA 22, 41, 42, 45), and transverse gyrus (BA 41, 42). In other studies, these regions are known to demonstrate executive functioning such as behavior inhibition and motor inhibition (Seitz, Gaebel, & Zielasek, 2011). The inferior frontal gyrus integrates executive function and working memory (WM) to contribute to decision-making and response inhibition (Millan et al., 2012). Superior temporal gyri activation is expected for TD participants and is thought to be active during ToM processing and making associations. Outside of mentalizing an action while observing it, ToM is theorized to give people the ability to be successful in their social interactions when they are able to understand in desires of others (Buccino et al., 2001; Lyons, Caldwell, & Shultz, 2010; Schulte-Rüther et al., 2007). Language

systems such as comprehension are also involved in MNS and support the visual hypothesis of understanding action through visual analysis (Rizzolatti et al., 2001); but activation in areas of language expression during an MNS manual manipulation is not clear (Molenberghs et al., 2012).

Brain networks are activated by stimuli presented in mirror neuron experiments include parts of the somatosensory and motor cortices when observing movement; therefore activation in these areas are expected in the present experiment. While residing in the parietal lobe, these regions also share simultaneous activation from parts of the frontal (premotor cortex) and temporal lobes. Robust activation in TD individuals is found in the postcentral gyrus (BA 3, BA 7, BA 40), superior parietal lobule (BA 7), inferior parietal lobule (BA 40), precuneus (BA 7), precentral gyrus (BA 9, BA 44), inferior frontal gyrus (BA 9, BA 44), superior frontal gyrus (BA 9), medial frontal gyrus (BA 9), insula (BA 13), superior temporal gyrus (BA 45), and supramarginal gyrus (BA40) (Buccino et al., 2001; Iacoboni et al., 2001; Kandel et al., 2000; Lombardo et al., 2010). Activity in the inferior parietal lobule is associated with conceptualizing motor acts (Rizzolatti, Fabbri-Destro, & Cattaneo, 2009) while medial frontal gyrus (MFG) activation is associated with fast top-down modulation of sensory activity in sensory cortical areas. The MFG also collaborates with supplementary motor area important for subjective experience of contextualizing sensory processing in valenced and non-valenced tasks (Lombardo et al., 2010; Seitz et al., 2011). In prior studies, the postcentral gyrus of the primary motor cortex was found to be active in motor planning, motor learning, motor imagery, and saccadic movements (Casey et al., 2005; Kandel et al., 2000).

In studies of TD humans, working memory, spatial memory, retrieval, and memory encoding are involved in MNS sensory-perception (Berthoz, 1997; Cole & Paillard, 1995; Millan

et al., 2012; Seitz et al., 2011). Executive functions related to planning are thought to create an image of an action coupled with the inhibition to not mimic the movement (Buccino et al., 2001; Lombardo et al., 2010; Spengler et al., 2010; Wang, Ramsey, & Hamilton, 2011). Activation pertaining to behavior and motor inhibition in these regions appear to be a result of cooperating during the task. Pertinent to the present study, attentional processes involving visuospatial and visuomotor attention was also active in the precentral gyrus in other studies for TD individuals (Berthoz, 1997; Casey et al., 2005; Hubbard et al., 2005; Schreiner et al., 2014). Insula (and claustrum) activation in BA 13 is often attributed to fear or disgust, but in other studies, the insula also appears active during neutral conditions involving motor control, perception, and general cognitive functioning. However, this information from the latter conditions was gathered by studying individuals with brain damage in that region (Kamphaus & Reynolds, 2007; Spengler et al., 2010). Activation in the insula region is likely to occur as well.

Activation in the basal ganglia, specifically the bilateral caudate, globus pallidus, and substantia nigra (SN) was common in TD individuals during mirror tasks, but usually to a lesser degree than operculum and sensorimotor regions (Molenberghs et al., 2012). While rarely addressed in MNS tasks, the basal ganglia is thought to be involved in cortico-subcortical mirror neuron networks and appears active in response to movement in other tasks (Bonini, 2017; Molenberghs et al., 2012). In fMRI mirror tasks, the caudate is implicated in WM integration and detecting change, which is likely to occur during changing conditions in a task (Casey et al., 2005; Millan et al., 2012).

The Current Study

This study investigates differences in functional magnetic resonance (fMRI) activation in children with 22q11.2DS and typically developing children while observing hand-object

manipulation in others. This is the first study comparing children with 22q11.2 with age-matched TD peers specifically looking at mirror neuron system activation within the operculum region to assess higher cognitive functioning, somatosensory/motor cortex (SI & SII) for sensory interpretation, and basal ganglia for gross motor activity. As MNS activation has never been studied in this population, our expectations about the amount and location of activation differs from previous studies in typical and ASD populations. Due to their differences with visuospatial attention, social abilities, and motor skills, it is likely that children with 22q11.2DS will show less activation that their TD peers.

Hypothesis

Aim: To compare motor neuron system function in children with 22q11.2DS to an age-matched group of TD children while watching motor action in others. Focal brain regions will include canonical somatosensory and premotor cortex and the basal ganglia. These regions are involved in processing, integrating, and perceiving motor, sensory, and visual information of action in the self and in others.

Hypothesis: Children with 22q11.2DS will show less functional activation than TD children in brain regions considered part of the mirror neuron system while watching videos of others' motor actions during an fMRI scan. More specifically, children and adolescents with 22q11.2DS will have less functional brain activation in sensorimotor areas, the opercular region, and in the basal ganglia compared to TD children and adolescents when observing video of others' motor action.

Method

Participants

Analysis 1

A sample of 36 children and adolescents with 22q11.2DS (n =16) and TD (n = 20) between the ages of 7 and 16 years were recruited for this study. Two participants (one from each group) were dismissed from analysis due to excessive movement artifacts in the MRI scans. A diagnosis of 22q11.2DS was confirmed by fluorescence in-situ hybridization. Participants with 22q11.2DS were excluded if they were below 6 years of age, had a head injury, focal neurological abnormalities, or had a central nervous system infection. TD participants were excluded if they had a genetic disorder, psychiatric diagnosis, a learning disability or behavioral disorder.

Analysis 2

A sample of 29 children and adolescents with 22q11.2DS (n =15) and TD (n = 16) between the ages of 7 and 16 years were recruited for this study. Five participants from the TD group and four from the 22q11.21DS group were removed due to excessive movement in the MRI scanner. Three participants were added to the 22q11.2DS group that were acquired since the first analysis. The inclusion and exclusion requirements of the groups remained the same (see Figure 2).

Table 1: Demographics

	22q11.2DS (n=15)	**TD** (n=16)
	M	M
Age	13.18 (.73)	10.94 (.67)
Gender (Male)	8	7
Gender (Female)	7	9

Procedure

All data collection methods were approved by the Institutional Review Board at the University of New Orleans (UNO). As part of a larger on-going study, participants were recruited through national and state-level 22q11.2DS support networks, flyers, social media, and word of mouth. Visits lasted between 2-3 days where they completed computer-based tasks, questionnaires, intelligence testing, and structural and functional magnetic resonance imaging.

Intelligence Measures

Wechsler Intelligence Scales for Children (WISC-IV) was administered to all subjects to assess subscales domains in verbal comprehension, working memory, processing speed, perceptual reasoning and full-scale IQ (FSIQ) (Wechsler, 2003).

Brain Imaging Measures

Structural magnetic resonance imaging (sMRI) was conducted at the Touro Imaging Center in New Orleans, Louisiana, USA. Images were acquired on a three Tesla Siemens MAGNETOM Verio system and a 10 channel head coil. Brain structures were obtained using a T1-weighted anatomical images using a MPRAGE sequence with the following acquisition parameters: TR =1900; TE = 2.48; TI = 900; flip angle = 9º; slice thickness = 1 mm, with a 256 x 256 acquisition matrix. Function data was collected using an EPI Blood Oxygen Level Dependent (BOLD) contrast with the following parameters: 31 slices, 70 volume, TR = 3000 msec; slice thickness = 4mm; interslice time = 96; pixel spacing = 3.75; repetitions = 3000. To reduce motion artifacts, participant heads were stabilized using head and ear pillows. Participants were excluded from the study if they had greater than 3 mm of head motion during the functional scans.

Neutral Motor Stimulus Video

A block design was used with a goal-directed action viewing task alternated with rest, in order to examine the MNS. During the action viewing task, subjects viewed clips of someone performing actions on objects. The clips consisted of the individual's arm and hand only to avoid any face or emotion processing. During rest, subjects were shown a fixation cross in the middle of the screen. Five blocks of action viewing were alternated with 5 blocks of rest (Stimulus: 21 seconds; Rest: 21 seconds) for a total of 3.5 minutes. The task was presented using EPrime 2.0 Pro (Psychology Tools, 2008, United Kingdom). See Figure 1.

Statistical Analyses

Analysis 1

Anatomical and functional data was analyzed using BrainVoyager QX 2.8 (BVQX; Brain Innovation, The Netherlands, Goebel et al., 2006). Preprocessing of functional scans were modified for motion correction, slice scan time correction, high frequency temporal filtering, and removal of linear trends. Functional and 3-D structural measurements were co-registered and transformed into Talairach space (Talairach & Tournoux, 1988). The resulting data sets (voxel size $2 \times 2 \times 2$ mm^3) were spatially smoothed with a 6 mm^3 full width at half-maximum Gaussian kernel for group analysis. Talairach scales were combined to form a template brain. A multistudy, multisubject general linear model was used to analyze the data. After retrieving clusters from regions of interest (ROI), coordinates were entered into Talairach Daemon (Lancaster et al., 2000) to identify the lobule, structure, voxel count, and Brodmann areas of activation. High voxel count is usually indicative of prominent activation in a specific area. Group differences in BOLD signal during the task were first compared using a fixed effects

general linear model (FFX GLM) and then using a random effects general linear model (RFX GLM). False discovery rate (FDR) correction was automatically applied to the statistical parametric maps to correct for multiple comparisons. The statistical threshold estimator (STE) plugin for BVQX also identified the number of voxels (47 voxel minimum) needed within a cluster to have a 5% FDR after noise reduction. Full width at half maximum (FWHM) was measured by identifying points on the signal curve that were half the maximum value, FWHM= 3.91. Significance value was set to (p = 0.001) to obtain stringent results (Genovese, Lazar, & Nichols, 2002). A fuzzy clustering algorithm (FCA) was applied to the statistical parametric maps generated from the RFX GLM to separate artifacts within the task. This method allow activated voxels to belong to two or more clusters by group where intracluster distances are minimized and intercluster distances are maximized (Tong, Zeng, Sang, & Zeng, 2010). The FCA is used when subjects within a group have significant heterogeneity; it manipulates activation around the centroid by merging clusters by temporal features (e.g. eliminating physiological data like cardiac action and breathing) (Windischberger et al., 2003). The merging factor is a threshold of z-scores calculated between two clusters at the end of each iteration. If their mutual z-scores are below the merging factor, the clusters are combined. FCA reduces noise from the signal-to-noise ratio at the expense of losing signal to gain accuracy of clustering with a more stringent false discovery rate of $p < 0.001$. After converting volumes of interest (VOIs) to voxels at a 300-voxel threshold, average signal change, cluster count, peak voxels, and values were calculated using BVQX. Coordinates of activation were then entered into Talairach Daemon to identify activation by hemisphere, lobule, structure, and cortices (Lancaster et al., 2000).

Analysis 2

After removing five scans from the TD group, and four scans from the 22q11.2DS group due to the lack of functional activation, we added another three scans to the 22q11.2DS group which changed the dynamic of the analysis. Anatomical and functional data was analyzed using BrainVoyager QX 2.8 (BVQX; Brain Innovation, The Netherlands, Goebel et al., 2006). Preprocessing of functional scans were modified for motion correction, slice scan time correction, high frequency temporal filtering, and removal of linear trends. Functional and 3-D structural measurements were co-registered and transformed into Talairach space (Talairach & Tournoux, 1988). The resulting data sets (voxel size $2 \times 2 \times 2$ mm^3) were spatially smoothed with a 6 mm^3 full width at half-maximum Gaussian kernel for group analysis. Talairach scales were combined to form a template brain. A multistudy, multisubject general linear model was used to analyze the data. After retrieving clusters from regions of interest (ROI), coordinates were entered into Talairach Daemon (Lancaster et al., 2000) to identify the lobule, structure, voxel count, and Brodmann areas of activation. High voxel count is usually indicative of prominent activation in a specific area. Group differences in BOLD signal during the task were first compared using a fixed effects general linear model (FFX GLM) and then using a random effects general linear model (RFX GLM). False discovery rate (FDR) correction was automatically applied to the statistical parametric maps to correct for multiple comparisons. The statistical threshold estimator (STE) plugin for BVQX also identified the number of voxels (37 voxel minimum) needed within a cluster to have a 5% FDR after noise reduction. Full width at half maximum (FWHM) was measured by identifying points on the signal curve that were half the maximum value, FWHM= 3.11. Significance value was set to ($p = 0.001$) to obtain stringent results (Genovese et al., 2002). Deleting scans with structural and functional issues allowed us to

complete a classical RFX GLM analysis of the groups. After converting volumes of interest (VOIs) to voxels at a 300-voxel threshold, average signal change, cluster count, peak voxels, and values were calculated using BVQX. Coordinates of activation were then entered into Talairach Daemon to identify activation by hemisphere, lobule, structure, and cortices (Lancaster et al., 2000).

Results

FSIQ

Overall, TD children have higher composite FSIQ than children with 22q11.2DS: TD= 109.33 (3.54); 22q= 65.47 (2.45). TD children in our sample have also displayed greater aptitude in verbal comprehension, working memory, processing speed, and perceptual reasoning than children with 22q11.2DS. See Tables 2 and 3. Children with 22q11.2DS tend to perform better in verbal comprehension than the other subscale domains; however, it is still much lower than their TD peers: verbal comprehension: TD= 110.47 (3.42); 22q= 65.47 (2.45). See Figures 3 and 4; Tables 2 and 3. FSIQ scores were not added as covariates of this study as scores are not an accurate indicator of intelligence, particularly in 22q11.2DS. Subscales of the WISC-IV were not added as covariates of fMRI activation as a previous experiments using multiple eye tracking (Cabaral et al., 2012) established the inability of intelligence scores to properly link both cognitive and neural substrates such as processing visual stimuli (Simon, 2007).

Analysis 1

Fixed Effects GLM

Results revealed significant activation for FFX GLM revealed peak differences between groups in the inferior frontal gyrus, $t(36) = 4.21$, parahippocampal gyrus, $t(36) = 4.80$, thalamus, $t(36) = 5.82$, precuneus, $t(36) = 506$, and temporal lobes (See Table 4). Differences appear to favor the right hemisphere (see Figure 5). FFX also revealed within group differences in TD where three major clusters with peaks in the middle occipital gyrus β=33.86, inferior temporal gyrus β=32.94, and the inferior parietal lobule β=28.75. See Table 5a and Figure 6a. FFX GLM also revealed within the 22q11.2DS group three major clusters with peaks in the middle temporal gyrus β=22.32 and the middle occipital gyri, β=23.13, β=22.62 respectively. See Table 5b and Figure 6b.

Random Effects GLM[1]

Significant activation was found in both groups for all major regions associated with the mirror neuron network. Results revealed peak differences between groups in the inferior frontal gyrus $t(36)= 4.40$, $p<.001$, parahippocampal gyrus $t(36)= 4.60$, $p<.001$, and fusiform gyrus $t(36)= 4.30$, $p<.001$, where t-values represent statistical differences between group during the active condition (video). See Table 6 and Figure 7. Within group differences revealed TD having peak activation in the fusiform gyrus $t(20)= 100$, postcentral gyrus $t(20)= 81.86$, MFG $t(20)= 76.89$, and cingulate gyri $t(20)= 87.19$ (See Table 7a and Figure 8a). Within group differences

[1] Classical RFX analysis could not be conducted during Analysis 1 due to the lack of signal change and activation in the 22q11.2DS group, even when lowering the threshold of shared activation to 10%. While half the group had activation, four participants had little to no activation and another four participants with very robust activation.

for 22q11.2DS (22q) showed peak activation in the middle occipital gyrus $t(16)= 99.99$ and medial frontal gyrus $t(16)= 92.19$. See Tables 7b and 8; Figures 8b. Most activation in 22q11.2DS appears to overlap with TD activation.

Signal change between groups were not significantly different using FCA, 22q: $\beta= 74.68$; TD: $\beta= 73.89$. See Figure 9. Region of interest (ROI) time course averages resulted in 22q11.2DS having a lower average during mirror neuron task in the following regions: inferior frontal gyrus (TD= 809, 22q= 700), postcentral gyrus (TD= 980, 22q= 980), precentral gyrus (TD= 915, 22q= 804), superior temporal gyrus (TD= 1094, 22q= 1025), and globus pallidus (TD= 780, 22q= 729). See Figures 10 and 11a-11e.

Because signal changes are not significantly different, voxel count was documented using fuzzy clustering analysis (FCA) from the statistical parametric maps generated from the RFX GLM. The sensorimotor, motor, and premotor cortices (BA 3, BA 7, BA 9, BA 13, BA 40, BA 44, BA 45) showed differences in activation by voxel count (VC). TD had robust activation in the postcentral gyrus (VC= 32,899), superior parietal lobule (VC= 9,700), precentral gyrus (VC= 54,003), inferior frontal gyrus (VC= 77,898), superior frontal gyrus (VC= 64,764), insula (VC= 30,017), middle frontal gyrus (VC= 99,711), precuneus (VC= 49,299) and supramarginal gyrus (VC= 8970). See Table 8. In 22q11.2DS, activation did occur in all motor areas, but to a lesser extent: postcentral gyrus (VC= 3,885), superior parietal lobule (VC= 626), precentral gyrus (VC= 3,847), inferior frontal gyrus (VC= 1,852), superior frontal gyrus (VC= 2,391), insula (VC= 1,651), middle frontal gyrus (VC= 7,296), precuneus (VC= 1,967) and supramarginal gyrus (VC= 1,564). See Table 9.

In the TD group, clusters of activation were found in the opercular region (BA 22, BA 41, BA 42), mainly the superior temporal gyrus (VC= 54,623), middle temporal gyrus (VC=

66,575), inferior frontal gyrus (VC= 77,898), and transverse gyrus (VC= 2,329). As a group, children with 22q11.2DS clusters of activation in reponse to watching the video segments of motor activity were found in the superior temporal gyrus (VC= 3,978), middle temporal gyrus (VC= 6,813), inferior frontal gyrus (VC= 1,852), but not the transverse gyrus.

The basal ganglia, involved in attentional and motor processes as well as the sensory integration, was also active in TD in the caudate (VC= 10,541), globus pallidus (VC= 10,754), and substantia nigra (VC= 4,022). Activation occurred in the whole caudate (head, body, tail) for TD, but only the caudate body for 22q11.2DS (VC= 133). While both medial and lateral globus pallidus was active in TD, only the lateral GP was active in 22q11.2DS (VC=106). Activation in the substantia nigra was not found in 22q11.2DS. See Figure 12 and 13.

Analysis 2

Classical Random Effects GLM

Significant activation was found in both groups for all major regions associated with the mirror neuron network. Results revealed peak differences between groups in the middle temporal gyri $t(30)= 5.46$ and 5.97, $p<.001$, inferior frontal gyri $t(30)= 5.59$ and 5.85, $p<.001$, and middle temporal gyrus $t(30)= 5.97$, $p<.001$, where t-values represent statistical differences between group during the active condition (See Table 10 and Figure 14). Within group differences revealed TD having peak activation in the culmen of the cerebellum $t(16)= 100$ and middle frontal gyrus $t(16)= 92.19$ (See Table 10 and Figure 15a). Within group differences for 22q11.2DS showed peak activation in the middle occipital gyrus $t(15)= 99.99$ and 98.3, the inferior frontal gyrus $t(15)= 75.59$, and the insula $t(15)= 74.79$ (See Tables 11a and 11b; Figure 15b).

Signal change between groups varied slightly, with 22q11.2DS being lower, 22q: β= 75.01; TD: β= 82.84. The average rate of change noted activation agreement within groups between 70% to 100% of the time with TD showing greater rate of change, 22q11.2DS: low: 70, high 87.19; TD: low: 70, high: 96.1. See Figure 16. Region of interest (ROI) time course averages resulted in 22q11.2DS having a lower average during mirror neuron task in the following regions: inferior frontal gyrus (TD= 809, 22q= 700), parahippocampal gyrus (TD= 949, 22q= 939), precentral gyrus (TD= 919, 22q= 920), superior temporal gyrus (TD= 1014, 22q= 1004), and putman (TD= 889, 22q= 649). See Figures 17 and 18a -18e.

Because signal changes were not significantly different, voxel count was documented from the statistical parametric maps generated from the classical RFX GLM. The premotor cortex appeared to be more active than motor and sensorimotor cortex noted by voxel count (VC) in the following Brodmann areas (BA 9, BA 13, BA 40, BA 44, BA 45). TD had the most robus activation in the inferior parietal lobule (VC= 37), middle frontal gyrus (VC= 8,549), precentral gyrus (VC= 2,493), inferior frontal gyrus (VC= 41,494), and insula (VC= 11,697). In 22q11.2DS, activation occurred in the same regions as TD, but to a lesser extent: inferior parietal lobule (VC= 39), middle frontal gyrus (VC= 1,051), precentral gyrus (VC= 275), inferior frontal gyrus (VC= 3,588), and insula (VC= 1,424).

In the TD group, clusters of activation were found in the opercular region (BA 22, BA 41, BA 42), mainly the superior temporal gyrus (VC= 8,576), middle temporal gyrus (VC= 12,835), inferior frontal gyrus (VC= 21,494), and transverse gyrus (VC= 49). As a group, children with 22q11.2DS clusters of activation in reponse to watching the video segments of motor activity were found in the superior temporal gyrus (VC= 3,689), middle temporal gyrus (VC= 6,807), inferior frontal gyrus (VC= 3,588), and the transverse gyrus (VC= 364).

The basal ganglia, involved in attentional and motor processes as well as the sensory integration, was also active in TD in the putamen (VC= 5,645), globus pallidus (VC= 2,288), caudate (VC= 2,122), red nucleus (VC= 469) and substantia nigra (VC= 333). Activation occurred in the whole caudate (head, body, tail) for TD, but only the caudate body for 22q11.2DS (VC= 135). While both medial and lateral globus pallidus was active in TD, only the lateral GP was active in 22q11.2DS (VC= 138). Activation was found in the putamen (VC= 611), but not the substantia nigra in 22q11.2DS. See Tables 12 and 13 and Figures 19 and 20.

Discussion

Children with 22q11.2DS

The aim of this study was to measure brain activity in regions that make up the mirror neuron system in children with 22q11.2DS in comparison to TD children. Children with 22q11.2DS demonstrated less activation overall than their TD peers with little differences in signal change in both analyses. Overall, the groups did not differ in the locations of shared activation across individuals within each group. Though not wholly in agreement of specific regions of activation, FCA and classical RFX-GLM analyses both demonstrate that children with 22q11.2DS have greater variability as evidenced by less overlap in activation within group, whereas typically developing children did not. We concur that MNS was functioning successfully in 22q11.2DS despite the differences in voxel count between groups.

Children with 22q11.2DS exhibit difficulties in other cognitive domains that are not necessarily shared by children with ASD such as poorer visuospatial and temporal acuity (Simon, 2007, 2008; Swillen et al., 1999; Villalon-Reina et al., 2013). Children with 22q11.2DS

often have delayed motor development and structural differences in brain regions involved in associating visual, motor, and spatial sensory information (Simon, 2007, 2008; Simon et al., 2005; Swillen et al., 1999; Tang et al., 2014; Villalon-Reina et al., 2013). Thus, examining the motor neuron system in these children provides insight into the junction of visual and motor perception of others' actions and serves as a foundational element to developing an 'accurate' theory of mind.

Findings in this study were fairly congruent with previous studies with control groups. Consistent with hypotheses, TD children did have larger regions of interest in clusters with high voxel counts (VC) in the sensorimotor areas than children with 22q11.2DS during using FCA. TD children also had greater activation in the operculum region and in the basal ganglia, areas that are thought to be involved in ToM, executive, memory, and attentional processes that are considered to be canonical activation involved in MNS as well as the visual processes.

By using classical random effects analysis, we found the operculum and basal ganglia regions also showed higher VC in TD than 22q11.2DS, but that parietal activation (sensorimotor) was limited in both groups, challenging our expectation of mirror neuron theory. Evidence of high activation levels in the basal ganglia, thalami, brainstem, and cerebellum demonstrates that children in both groups are using motor mechansims and higher order thinking, just not through conventional channels.

Keeping in mind that 70% to 100% of activation was shared within groups, robust activation was noted in sensorimotor areas in both groups using FCA. FCA showed TD children had higher voxel counts in visuospatial (BA 45) and visuomotor attention (BA 7) areas that are necessary to activate MNS in basic sensorimotor areas; classical RFX analysis demonstrated less activation in sensorimotor areas (particularly most of the parietal region) for both groups but

noted higher VC in the thalamic, midbrain, and brainstem regions. Use of the sensory relay station and older evolutionary structures, such as the brainstem and cerebellum, may demonstrate understanding of motor movements outside the parietal regions typically thought to be involved in motor movement and understanding. Where FCA showed increased VC in areas for motor learning (BA 1-3, BA 13), motor imagery (BA 5, BA 7), saccadic movements (BA 5, BA 7), and somatosensory detection and integration (BA 13, BA 40), classical RFX appeared void of saccadic movement and somatosensory detection and integration; motor imagery appeared active only though the insula region. Memory retrieval (BA 9) was more notable in TD than in 22q11.2DS in both analyses as was WM and behavioral inhibition (BA 9, BA 13, BA 40) which are necessary in recognizing movement.

Activation in the opercular region also yielded differences between groups. Involving areas of the frontal and temporal lobes, this region is thought to integrate higher order processes in executive function. Working (BA 7, BA 41, BA 44, BA 45) and episodic memory (BA 44, BA 45) are necessary in recognizing movement. During FCA and classical RFX analysis, VC in executive functions such as motor and behavioral inhibition (BA 44, BA 45) and ToM (BA 22) were higher in TD. This is striking, as the deficits in attention for 22q11.2DS should have required greater efforts in attentional processes. Retrieval and topokinetic memory (BA 31) were found in the posterior cingulate in TD, but not in 22q11.2DS. This finding is consistent with previous research which has found evidence of reduced volume in posterior regions of the brain in 22q11.2DS (Simon et al., 2005; Van Amelsvoort et al., 2001).

Activation in the basal ganglia is another necessary region in MNS involving motor movement and sensory processing. As hypothesized, activation of the caudate, globus pallidus, substantia nigra, and putamen were present in both groups. However, where TD children had

activation in the red nucleus, children with 22q11.2Ds did not. Less activation in the basal ganglia was expected than in the sensorimotor and operculum regions. Basal ganglia activation in MNS tasks are necessary, given its role in attention and motor processes like detecting change, responding to movement, and working memory integration (Bonini, 2017). As predicted, TD children had greater cluster sizes in the basal ganglia.

The classical RFX analysis revealed other notable activation. For example, activation of the cuneus of occipital lobe gives us evidence that participants in both groups are receiving and processing visual information. Oddly, we found no precuneus activation in 22q11.2DS nor enough in TD to make the statistical threshold cutoff. Superior frontal gyrus activation appeared to be greatly overestimated in FCA, as TD barely made the cutoff where 22q11.2DS could not. We also found the inferior temporal gyrus, active in processing visual information in the ventral "what" stream, appeared comparable in both groups affirming that children with 22q11.2DS deficits in visual processing noted in IQ subscales may not always translate into real world problems.

Also of note, the classical analysis showed parahippocampal gyrus to be a peak area of activation in 22q11.2DS as well as the second greatest area of activation in TD by voxel count. The analysis also showed greater activation in both groups in the hippocampus (over 10 times more in TD than 22q11.2DS), amygdala, and uncus. Though TD has a greater VC than 22q11.2DS in all cases, it may be possible that memory retrieval in mirror neuron tasks play a greater role than the motor cortex as previously thought. Like the thalamus and brainstem activation playing a role in motor movement and understanding, high cerebellar activation was also found in both groups with the declive of the cerebellum being a peak activation point in TD children.

Implications for ToM in 22q11.2DS

ToM is noted to demonstrate activation in the inferior frontal gyrus and inferior parietal lobule, and it is a complicated concept (Schulte-Rüther et al., 2007). While ToM is implicated in inferring intention, however, it is unclear if it is also involved in inferring the feelings of others (i.e., empathy). Do we merely witness an action and make our own inferences about the action, or do we infer the intended behavior of others solely as to how it relates to our own self-preservation (Rizzolatti et al., 2001; Schulte-Rüther et al., 2007)? Sensorimotor areas (e.g., parietal and frontal motor areas) are active when observing movement with a specific goal rather than random movement of body parts. In fact, the primary motor cortex has been found to encode nearly 40% of neurons for motor acts (Rizzolatti et al., 2009). Activation of the opercular and sensorimotor regions are noted to occur in response to salient stimuli. It could be complicit in ToM, but it may also be evidence of canonical MNS and nothing more (Debbané et al., 2012; Downar, Crawley, Mikulis, & Davis, 2002). Spatial memory and visual feedback involving movement stimulates topokinetic memory which explains the activation in limbic regions, such as the cingulate gyrus and hippocampus (Berthoz, 1997; Cole & Paillard, 1995; Kamphaus & Reynolds, 2007).

The basal ganglia is implicated in noticing sudden changes, particularly when the change is unexpected (Casey et al., 2000). It is possible that paying attention to the task may have reduced activation in these areas for children with 22q11.2DS. Witnessing goal-directed behavior (which activates the production of dopamine) may account for activation in the basal ganglia, particularly in the substantia nigra (Seitz et al., 2011; Wittmann et al., 2005). Procedural learning and memory are activated in the bilateral globus pallidus (Millan et al., 2012), but it is unclear as to why activation was limited to the lateral GP in 22q11.2Ds but encompassed both

medial and lateral GP in TD children during basic motor movements (Howley et al., 2012; Rizzolatti et al., 2009; Rizzolatti et al., 2001). It is unclear if having less agreement in activation in 22q11.2DS is due to impairments with basic cognitive or attentional processes.

Results suggest TD children may utilize higher cognitive mediation like ToM outside of basic observation of motor tasks. Activation of the inferior frontal gyrus in 22q11.2DS may be more indicative of inhibition and higher-level social cognitive processing, even if the results are obtained by different neural mechanisms (shown in BOLD activation and signal change) (Spengler, 2010). Noted from previous studies, damaged and under-developed areas in the operculum and somatosensory regions can lead to difficulty in processing the actions of other people (Rolland et al., 1995; Spengler et al., 2010). In children, dorsal and ventral streams involved in visual processes are not as well developed as in adults, and impairments in these regions may have affected the task for children with 22q11.2DS (Villalon-Reina et al., 2013). With age, however, MNS can change by sensorimotor learning stemming from multitudes of sensorimotor experiences obtained through interactions with others (Heyes, 2010). Clearly, children with 22q11.2DS do have an understanding of motor movement and intentionality in others as well as the executive ability to inhibit mimicry of the behavior. However, they may not fully grasp the intention of the movement outside of movement's sake, a requirement implicated in ToM.

Observing motor manipulation of objects demonstrated the working conditions within components of motor, executive, attentional, and memory function in 22q11.2DS (Azuma et al., 2015; Inan, Petros, & Anderson, 2013). As children with 22q11.2DS have shown less overall activation in valenced and non-valenced tasks in previous studies (Azuma et al., 2015), they also showed lower signal change when compared to TD peers. Even though somatosensory and motor

abilities eventually develop, early delays in gross motor skills like coordination and balance may inhibit speed abilities later in life, especially in the somatosensory and motor cortex during MNS tasks (Swillen et al., 1999). While visuospatial and visuomotor impairments in 22q11.2DS are the result of parietal lobe dysfunction (Simon et al., 2005), classical RFX analysis showed less parietal activation in both 22q11.2DS and TD children. This is particularly striking as TD individuals in previous studies usually showed robust activation during mirror neuron tasks. As visual and motor activation is not always indicative of higher order processes, there is no explanation for any participant having less activation in the absence of a cognitive, social, or motor impairments (Rizzolatti et al., 2009) despite their performance demonstrating neural competence during MNS tasks. The brainstem is implicit in basic motor movement occurring in non-human mammals that is necessary for social interactions and survival (Smith et al., 2008), while the thalamus is the relay station for most sensory input. No activation was found in the brainstem or thalamic nuclei in 22q11.2DS during FCA but was found in classical RFX analysis. This cites evidence that cutting out temporal features also removes evidence of motor movement understanding.

Increased cognition demonstrated by executive functions is more pertinent in theory of mind, but it is not needed to stimulate visuospatial and visuomotor areas if observers are aware of the outcome of the motor act and understand what other individual is doing. The higher-order perception of emotional states and intentions that encompass ToM are underpinned by middle-level processes that simulate observed behavior in the brain of the participant (Rizzolatti et al., 2009; Spengler et al., 2010). Previous studies suggest that basic somatosensory, motor, and basic visual input are necessary while processing a mirror task. Even a subtle impairment could reverberate through development as brain systems interdependently rely on one another not just

in function, but also in a foundational way. For example, normal development and function of associative regions such as the superior parietal cortex depends on the normal development and function of the systems that send neural signals to it (Bressler & Menon, 2010).

Limitations and Future Directions

Results of this study should be interpreted within the context of known limitations. Small sample size with unequal grouping of participants may have an effect on the ability to detect differences between and within the groups. In addition, given the relative rarity of people with 22q11.2DS, recruiting large samples of participants in a narrower age range (children 6-10, adolescents 11-16) is often problematic. Taking into consideration the array of developmental changes that occur during this time, the current study is likely affected by different stages in brain development in addition to varying abilities in attention, social interactions, intelligence, and maturity given the age range of the samples. Due to this heterogeneity in 22q11.2DS, our results may not truly be representative of the population as a whole. For example, differences in medical issues, and psychological and cognitive abilities underpin different types and levels of impairments that are difficult to establish phenotypes (Kates et al., 2007; Swillen et al., 1999; Tang et al., 2014; Vorstman et al., 2006; Wenger et al., 2016).

Furthermore, despite being stabilized with a head restraining system of padding specifically designed for MRI head coils, movement inside the MRI machine still occurs. Even with offline image processing tools like motion correction, extreme movement mars the ability to create brain masks and accurately map activation. As a consequence, we had to remove two participants from the study. Because eye-tracking confirmation was not available, it was difficult to establish how much participants were paying attention to the task. We had to remove 7

participants in Analysis 2 due to lack of activation and signal change to get a better picture of the overall motor, sensory, and cognitive processing abilities.

Perhaps the largest limitation in this study is heterogeneity, the same issue that makes it difficult to establish behavioral and psychological phenotypes for 22q11.2DS. While heterogeneity is expected in special populations, it results in probability maps that show activation shared by 70 to 100 percent of the population and may overlook other modes of neurocorrelates in the MNS. While not a common method in multigroup analysis, fuzzy clustering analysis (FCA) allowed us to take a glimpse at the amount of activation shared in most participants within a heterogeneous group. However, when compared to classical RFX analysis, we found that the temporal cutoffs in FCA actually overestimated activation in sensorimotor areas and underestimated activation in basic structures implicit in motor movement and motor observation. Eye-tracking confirmation was not available, so it is possible that children varied in their gaze time. However, since we saw activation as predicted in appropriate areas, it was highly likely that all participants were watching the video. Furthermore, the use of anti-depressants, including norepinephrine-dopamine reuptake inhibitors (NDRI), may influence all group participants regarding activation in the substantia nigra.

Future studies may be helpful in investigating activation differences between TD and 22q11.2DS. For example, explaining the role the caudate plays in a mirror task that would result in activation in the body of the caudate only in 22q11.2DS but the head, body, and tail of the caudate in TD. Explaining the role in MNS may help understand the activation presence of the anterior cingulate cortex and posterior cingulate cortex in TD; in 22q11.2DS, however, the absence of activation would warrant further study. The function of the thalamus in the MNS, including specific thalamic nuclei, could help explain the why the TD group had nearly 20 times

more voxels than 22q11.2DS and why having a lower voxel count was not solely the response of an impairment. Other considerations would include the role of fusiform gyrus and insula in mirror neuron tasks as VC is comparable in both groups. Future studies should also include other behavioral measures such as the Behavioral Assessment System for Children (BASC-2) (Kamphaus & Reynolds, 2007) to be used examine associations with functional activation.

Implications

While 22q11.2DS participants did have less activation overall when compared to TD children, the difference in signal change did not vary too greatly, and activation in regions central to MNS was present, even if it was not as robust as TD. These results may be a limitation of the sample and differences in cognition by age, or it may be an indicator that children with 22q11.2DS may not be as compromised in basic visual and cognitive processes as previously thought. While their visuospatial impairments still suggest they have more fundamental issues with certain components of their visuoperceptual systems, differences may also be attributed to deficits in attention, particularly attention shifting or sharing attention for multiple stimuli, such as noise from the MRI machine or temperature of testing room.

Given the high rate of comorbidity and symptomology with ASD, investigating differences in activation with 22q11.2DS may shed light on cognitive processes that are not well understood. While most of the activation for 22q11.2DS does not appear to be impaired while observing basic motor tasks, it still shares similarities with ASD during neuroimaging studies (like reduced activation) and warrants further investigation.

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Vita

Ade Marais received her B.A. in Secondary English Education from Nicholls State University. She also received her M.Ed. in Curriculum and Instruction with a concentration in curriculum planning and evaluation of adult programs as well as her M.A. in Linguistics and Rhetoric & Comp from the University of New Orleans. Ade was also knighted (MBE) for her work in English public schools for advocating correct placement for special population students. Ade joined the SCAN Lab in Fall 2014 under the supervision of Dr. Elliott Beaton. Using functional MRI, Ade is studying the neurocorrelates of theory of mind in children diagnosed with chromosome 22q11.2DS. Her interests lean toward identifying an emergence of physiological and psychophysiological patterns that may result in schizophrenia.

Figure 1 – Example action sequences from the task demonstrating object manipulation.

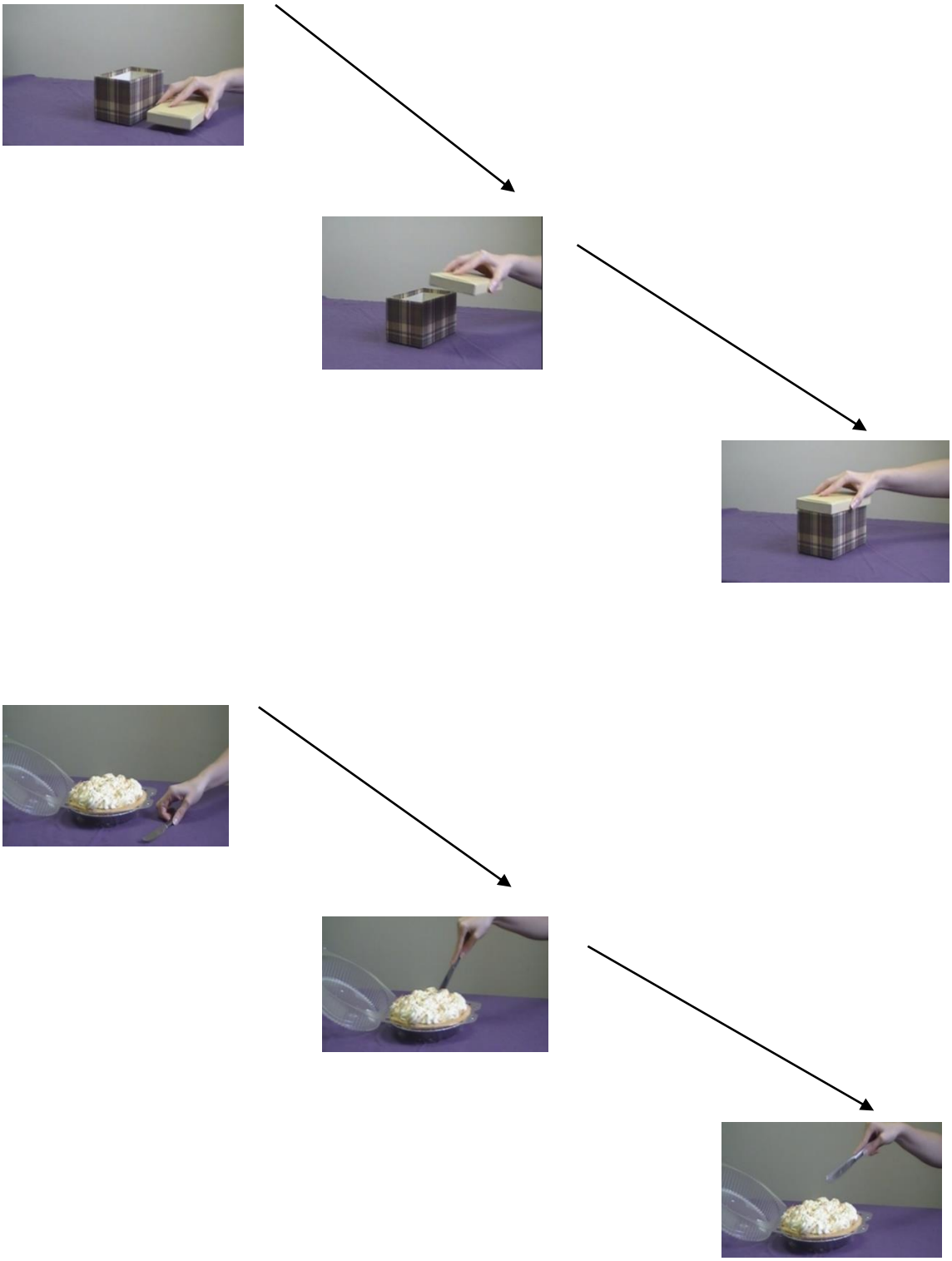


Figure 2: Age differences in groups

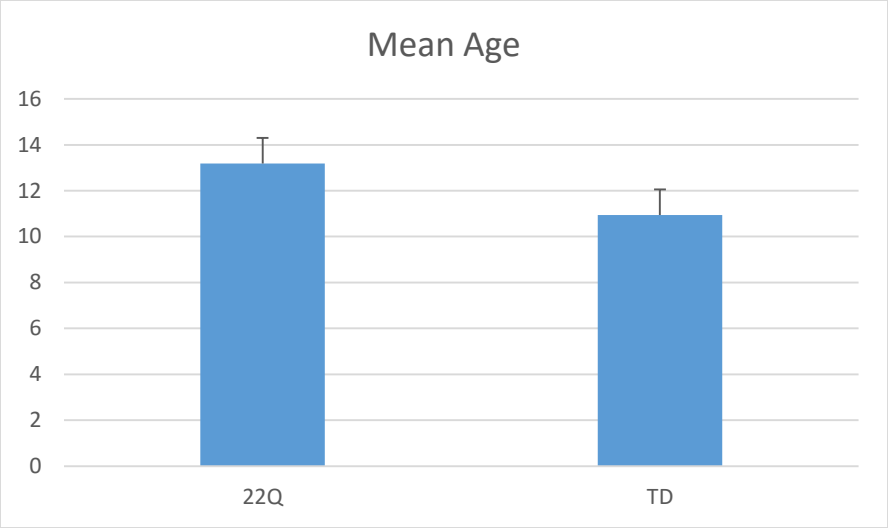


Figure 2: Mean Age for TD: 10.94; 22q11.2DS: 13.18

Figure 3: FSIQ subscale composite scores

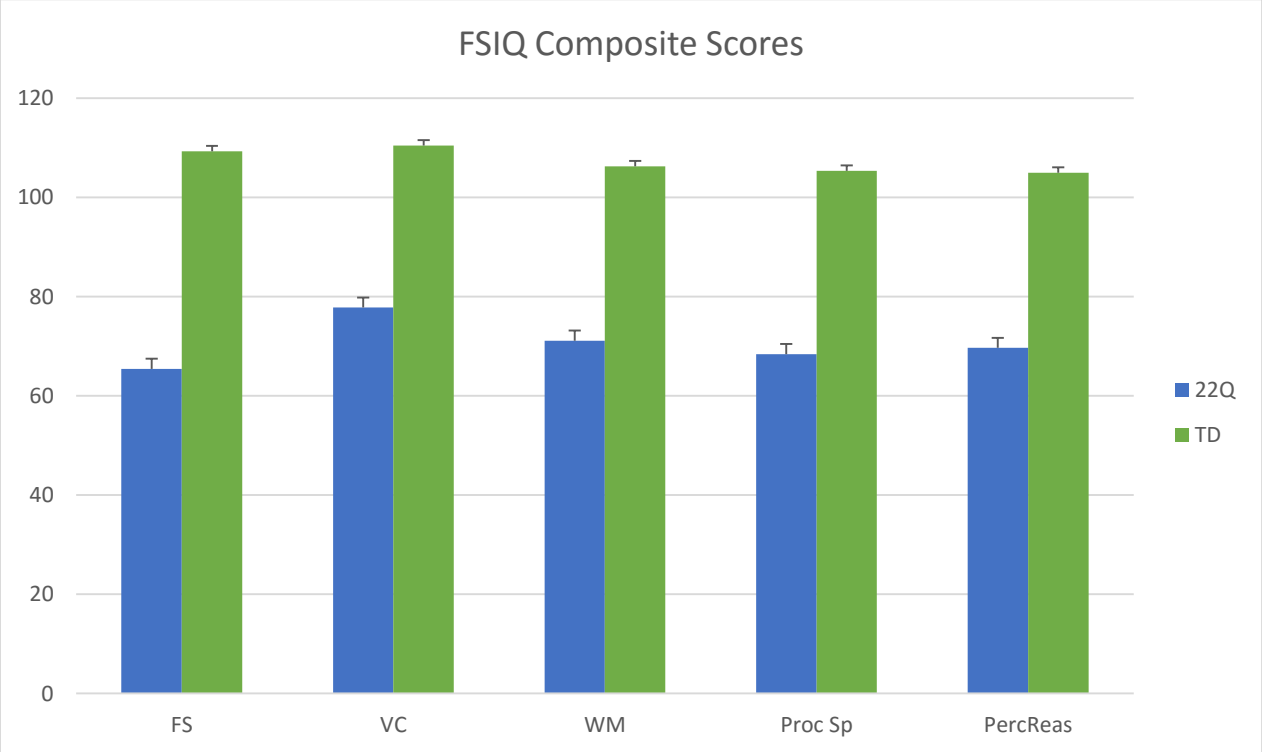


Figure 3: FS: Full Scale IQ; VC: Verbal Comprehension; WM: Working Memory; Proc Sp: Processing Speed; PerReas: Perceptual Reasoning. Although TD children tend to score higher on FSIQ subscales, children with 22q11.2DS tend to do better in verbal comprehension over other domains.

Figure 4: FSIQ subscales by percentile rank

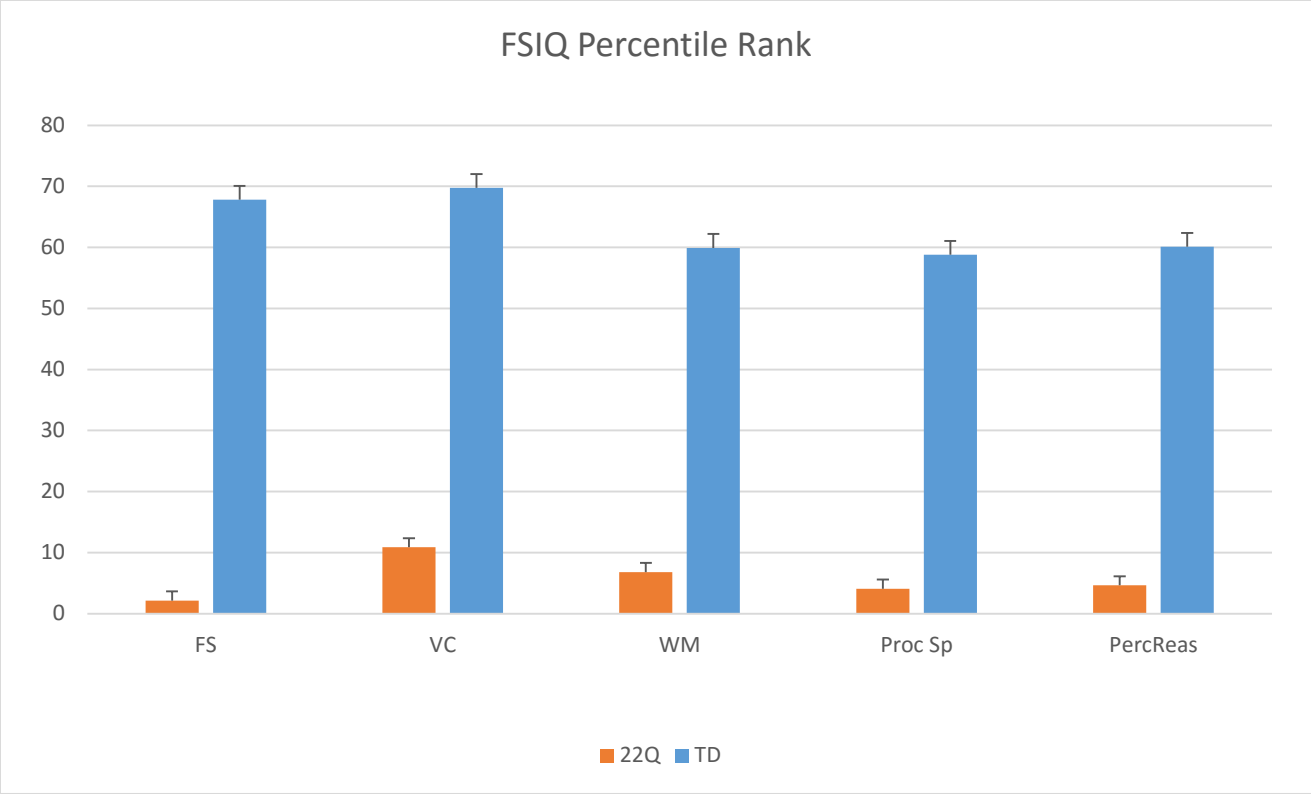


Figure 4: TD tend to perform better overall on FSIQ testing than children with 22q11.2DS.

Figure 5: Between group analysis for FFX GLM in both TD and 22q.

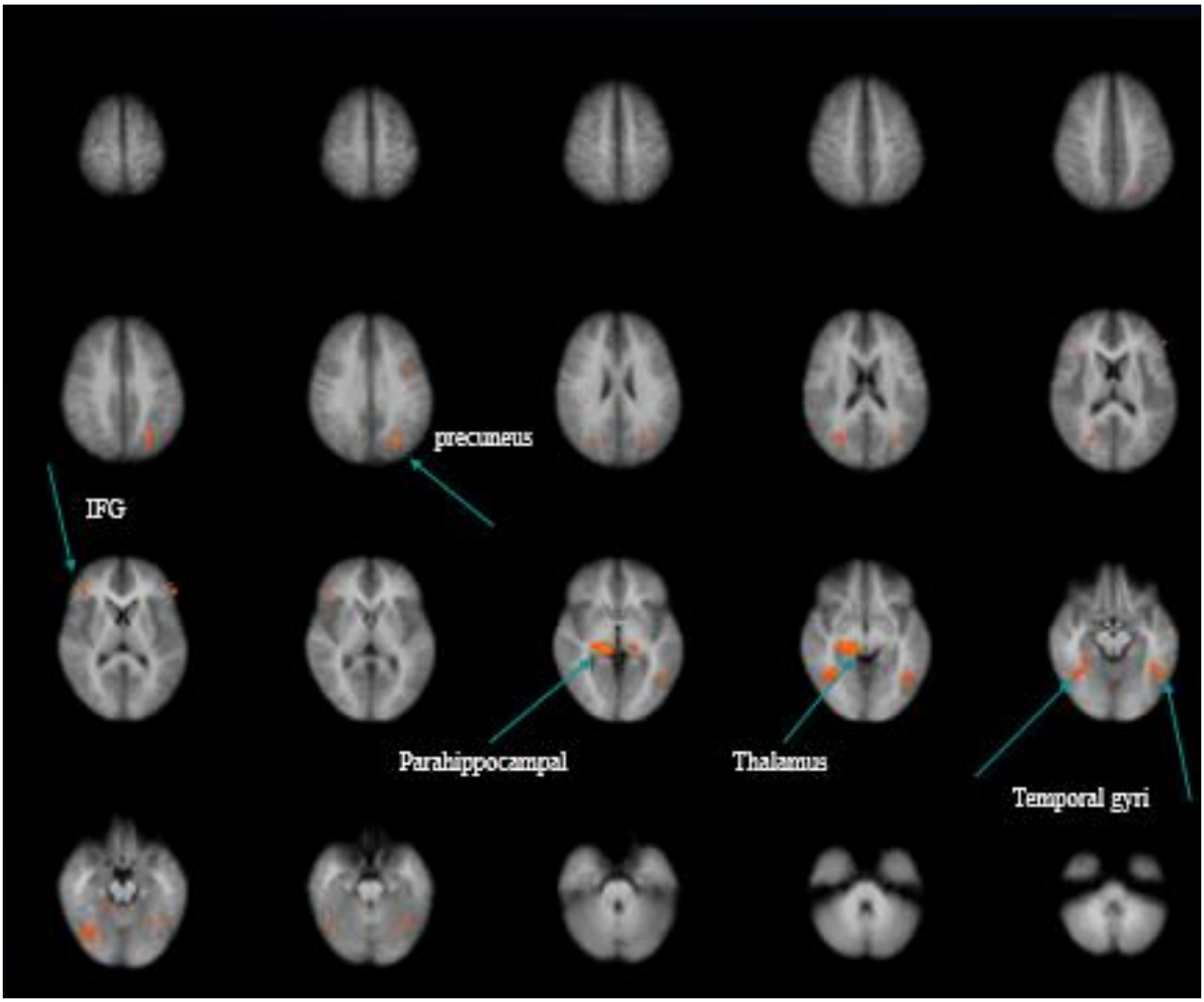
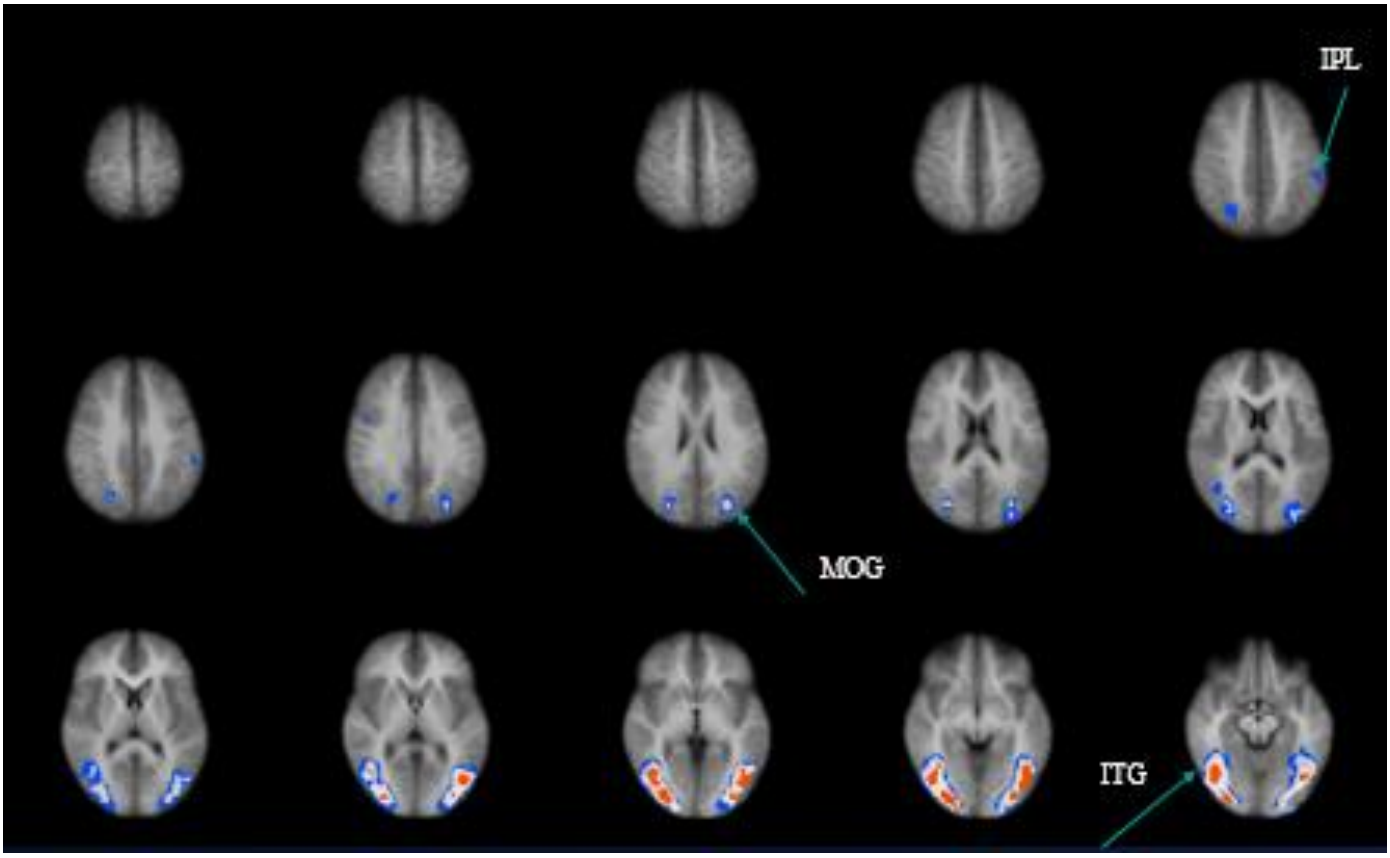


Figure 5: Peak differences between group show greatest activation in the inferior frontal gyrus $t(36) = 4.21$, parahippocampal gyrus $t(36) = 4.80$, thalamus $t(36) = 5.82$, precuneus $t(36) = 5.06$, and bilateral temporal lobes $t(36) = 4.37$ and $t(36) = 4.77$, respectively. TD had greater activation overall than 22q11.2DS.

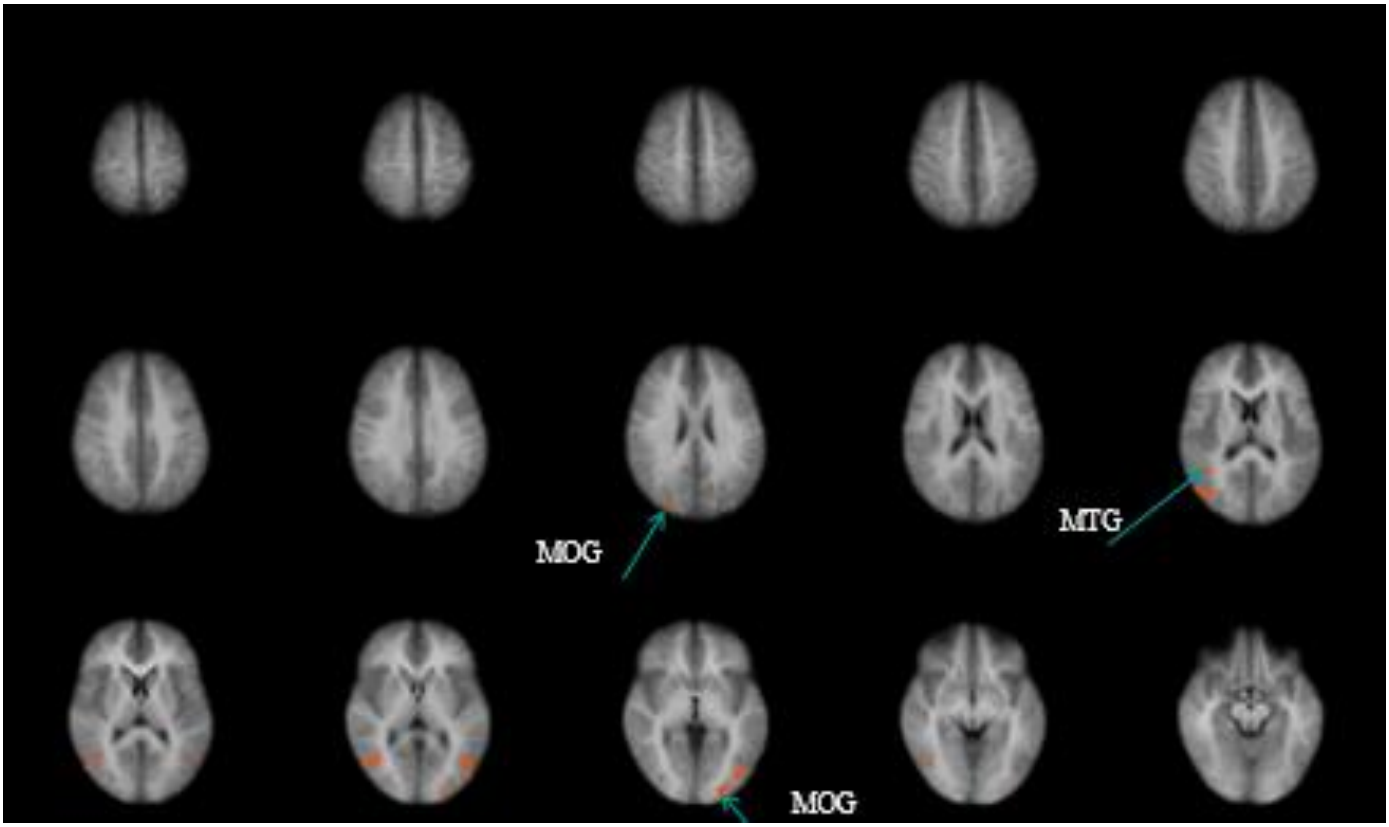
Figure 6a and 6b: FFX for TD Fixed effects for TD mostly shows activation in the visual areas whereas 22q11.2DS show less in the same area. FFX removes the variable bias and is not helpful for between group comparisons

6a. Typically developing FFX GLM



6a. TD children showed peak activation in the middle occipital gyrus β=33.86, inferior temporal gyrus β=32.94, and inferior parietal lobule β=28.75.

6b: 22q11.2DS FFX GLM



6b. Children with 22q11.2DS showed peak activation in the middle temporal gyrus β=22.32, and the bilateral middle occipital gyrus β=23.13, β=22.62, respectively.

Figure 7: Between group RFX GLM analysis with FCA

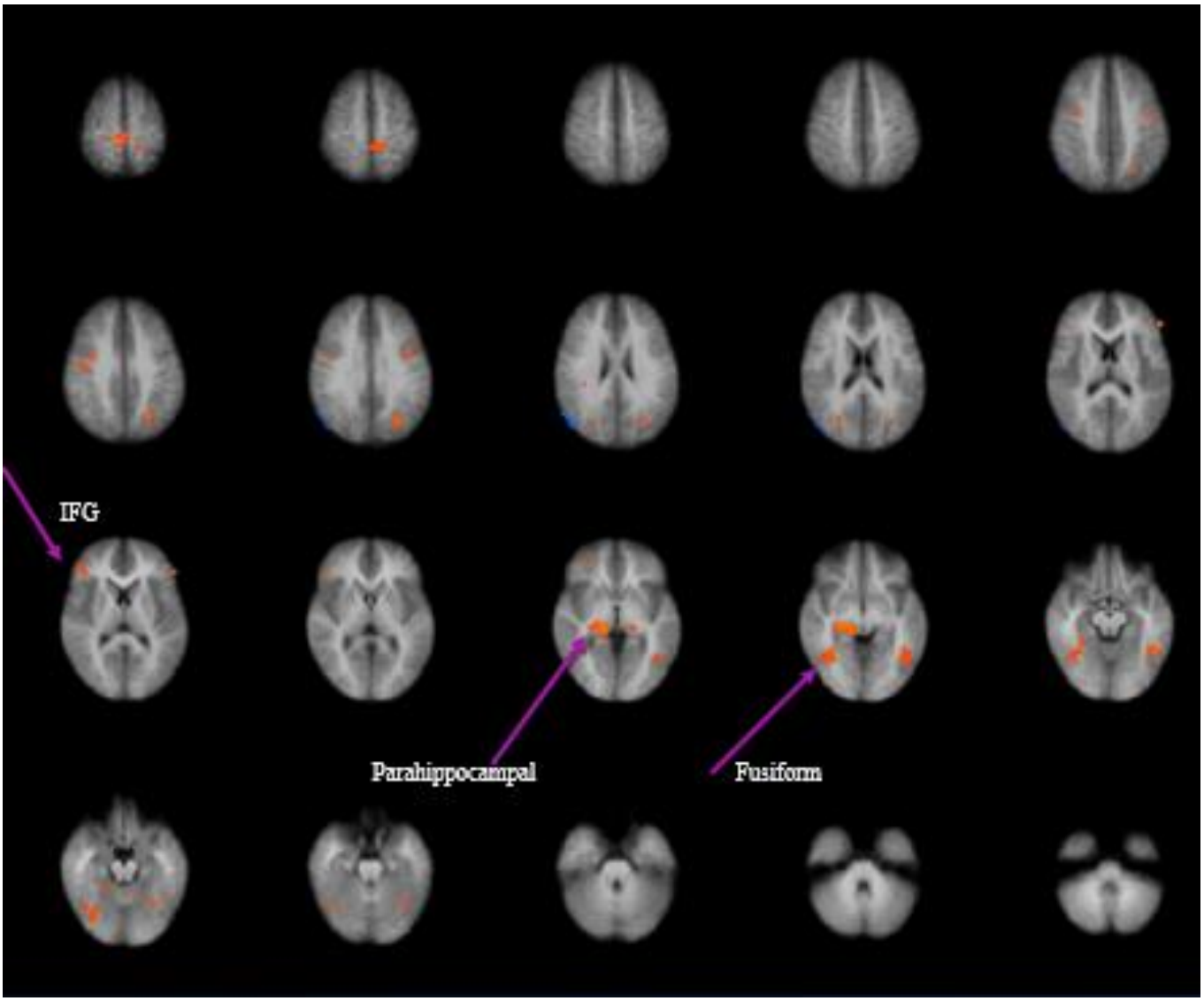
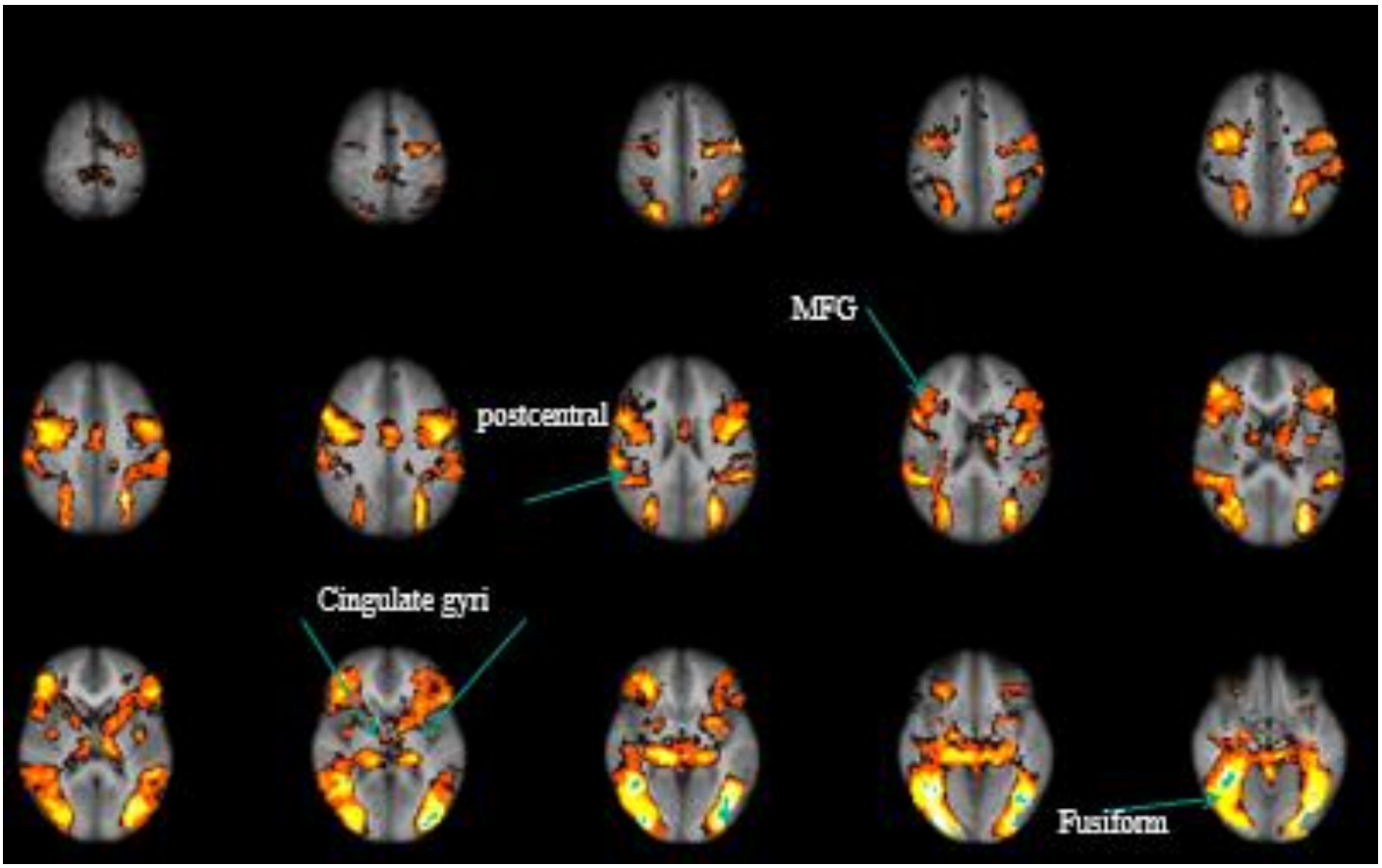
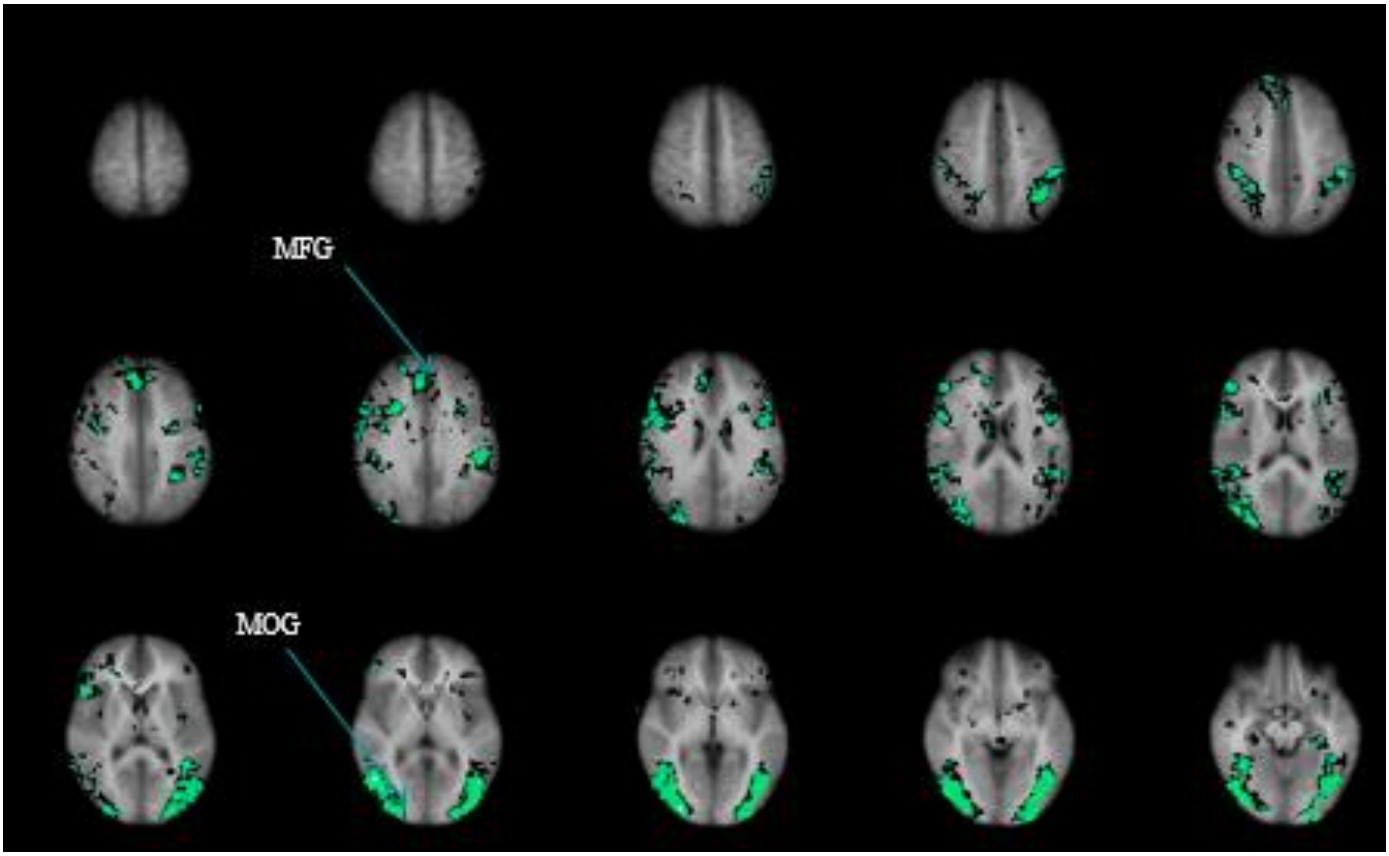


Figure 7: Peak differences between groups showed activation in the inferior frontal gyrus $t(36)= 4.40$, $p<.001$, parahippocampal gyrus $t(36)= 4.60$, $p<.001$, and fusiform gyrus $t(36)= 4.30$, $p<.001$, with TD having greater activation than 22q11.2DS.

Figure 8a and 8b: Within group RFX using fuzzy clustering analysis (FCA). FCA allowed overlapping in activation by separate artifacts within the task. FCA allowed activated voxels to belong to two or more clusters by group by manipulating activation around the centroid to merge clusters by temporal features (e.g. eliminating physiological data like cardiac action and breathing). TD shows significant activation in visual, motor, and executive processes (3a) where 22q11.2DS shows similar activation, but to a lesser degree noted by a lower VC (3b).



8a. TD RFX with FCA showed peak activation in the fusiform gyrus $t(20)=100$, postcentral gyrus $t(20)=81.86$, cingulate gyri $t(20)=87.19$, and middle frontal gyrus $t(20)=76.89$.



8b. 22q11.2DS RFX with FCA showed peak activation in the middle occipital gyrus $t(16)=99.9$, and the middle frontal gyrus $t(16)=92.19$.

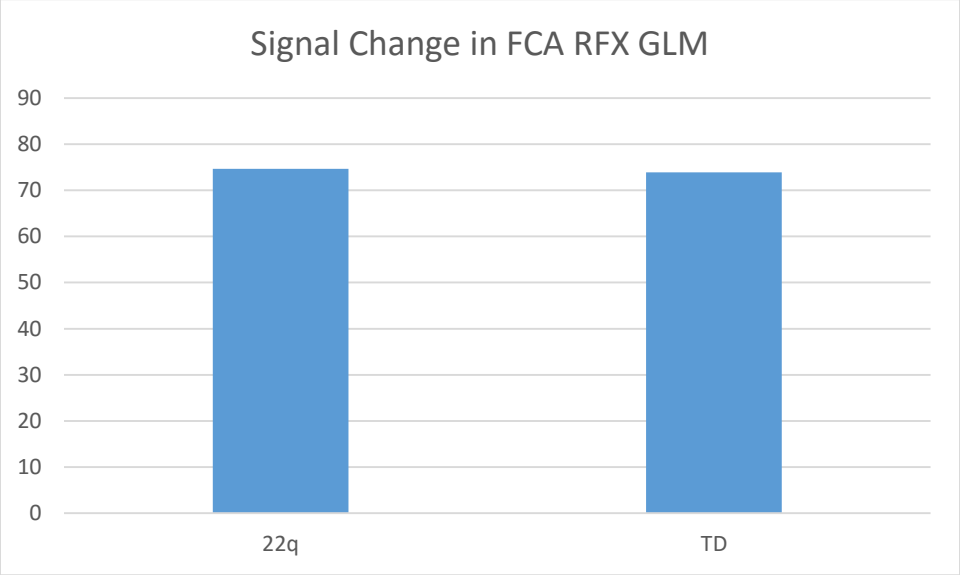


Figure 9: Average signal change in groups: 22q: 74.68; TD: 73.89. Because of the signal change is similar, voxel count was studied. The average rate of change within groups is also comparible: 22q: low: 70, high 78.66; TD: low: 70, high: 76.59.

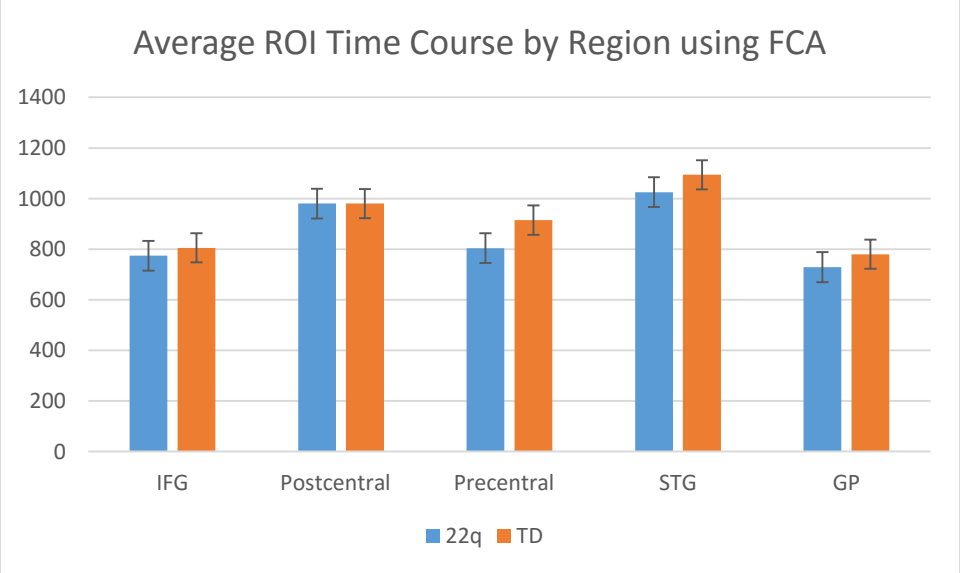
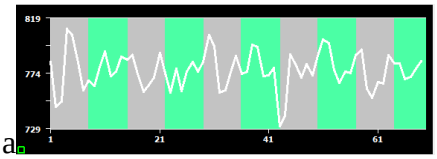
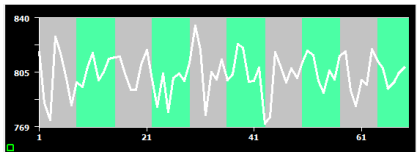


Figure 10: Region of interest (ROI) time course averages resulted in 22q having a lower average during mirror neuron task in the following regions: inferior frontal gyrus (TD=805, 22q=774), postcentral gyrus (TD=980, 22q=980), precentral gyrus (TD=915, 22q=804), superior temporal gyrus (TD=1094, 22q=1025), and globus pallidus (TD=780, 22q=729).

Figure 11: ROI time course by region. Time courses are indicated by activation within a set of coordinates in both groups. Activity looks consistent across TD and 22q11.2DS groups.

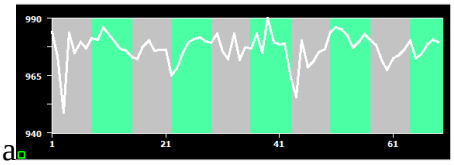


a

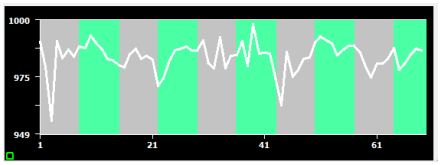


b

11a. ROI in the inferior frontal gyrus for TD (a) and 22q (b). Coordinates x= -50, y= 30, z= 32.

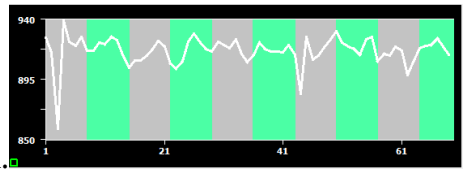


a

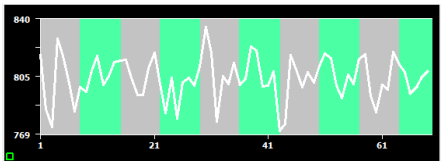


b

11b. ROI in the postcentral gyrus for TD (a) and 22q (b). Coordinates x= -53, y= -24, z= 37.

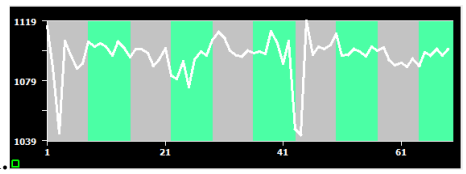


a.



b

11c. ROI in the precentral gyrus for TD (a) and 22q (b). Coordinates x= 16, y= -19, z= 38.



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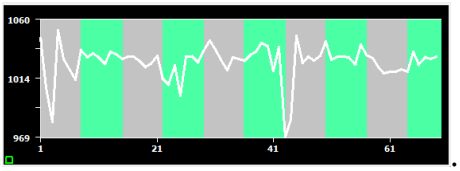
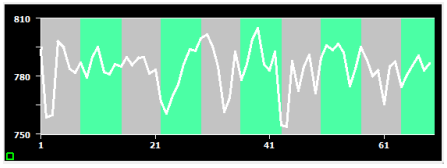
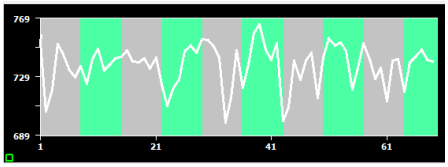


b.

11d. ROI in the superior temporal gyrus for TD (a) and 22q (b). Coordinates x= 53, y= -16, z= 2.



a.



b.

11e. ROI in the globus pallidus for TD (a) and 22q (b). Coordinates x= -19, y= -1, z= -2.

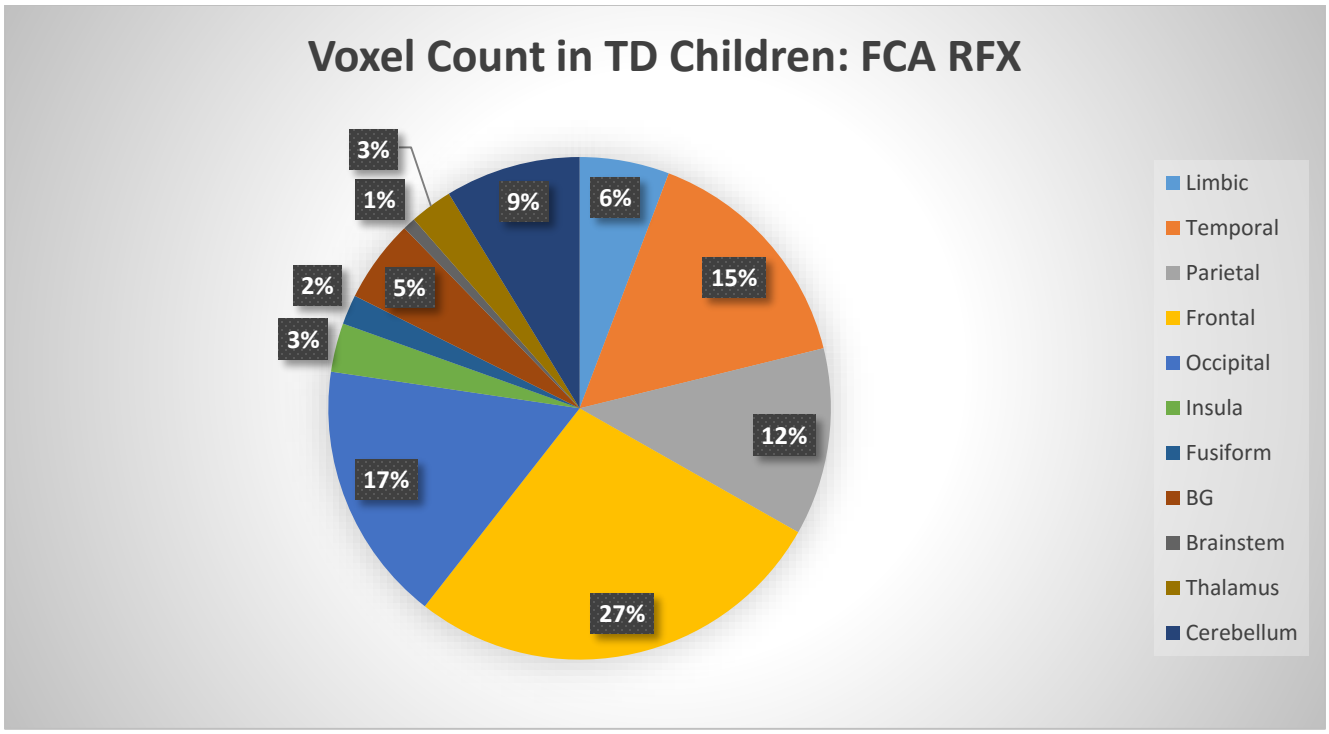


Figure 12: VC by region in TD childrens using FCA in RFX. Aside from a larger overall VC, TD children show greater activation in the frontal (27%), occipital (17%), temporal (15%), and parietal (12%) lobes.

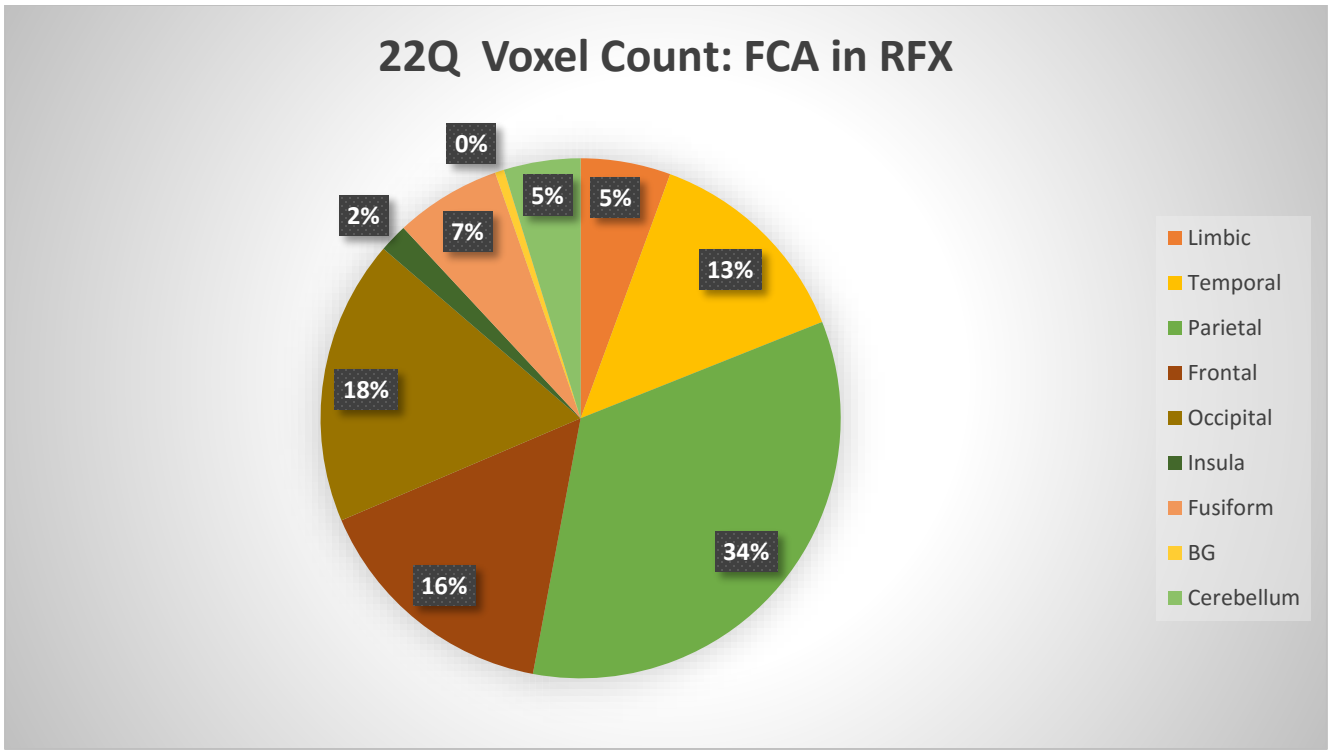


Figure 13: VC in FCA RFX by region in children with22q11.2DS noted by lower overall VC. Children with 22q11.2DS show greater activation in the parietal (24%), occipital (18%) frontal (16%), and temporal (13%) lobes.

Figure 14: Classical RFX between group differences

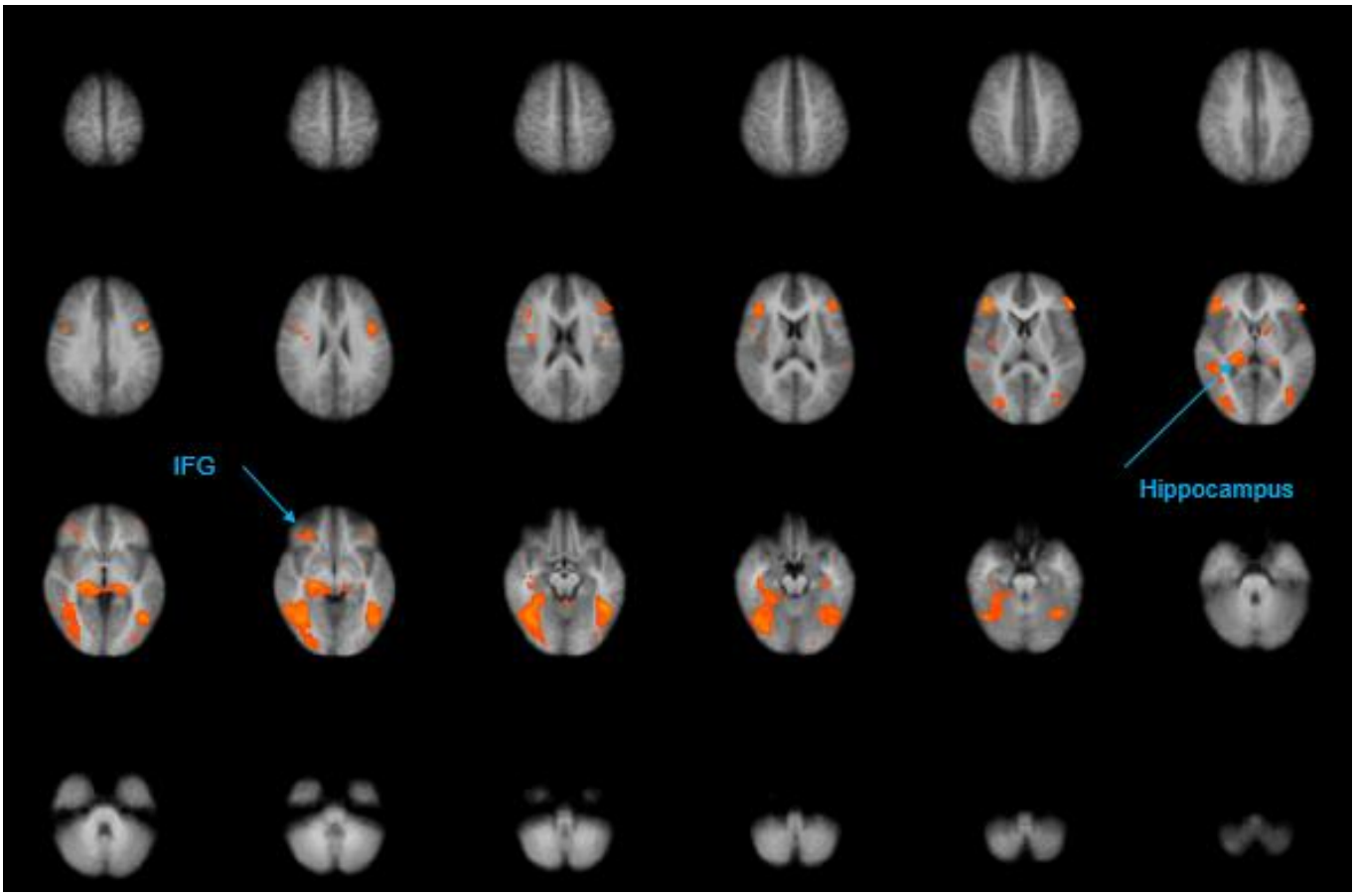


Figure 14: Peak differences between groups showed activation in the hippocampus β(30)=3.21, inferior frontal gyri β(30)=3.82. Total VC between groups is 50,058 voxels.

Figures 15a and 15b: Classical RFX GLM for TD (15a) and 22q11.2DS (15b).

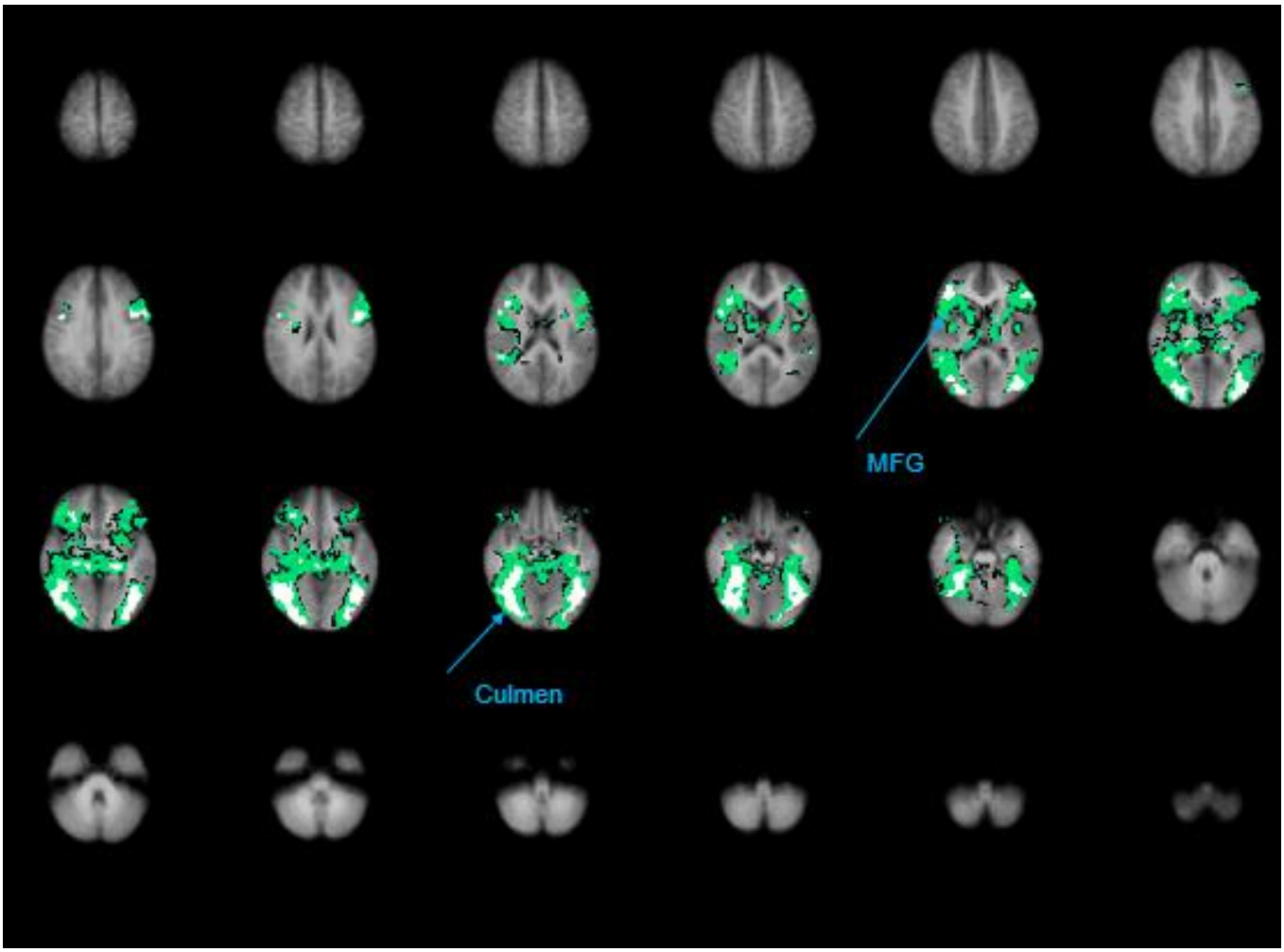


Figure 15a: Peak differences within the TD group showed greatest activation in the culmen of the cerebellum t(16)=100, and the middle frontal gyrus t(16)=92.19. Total VC within the TD group in 240,742 voxels.

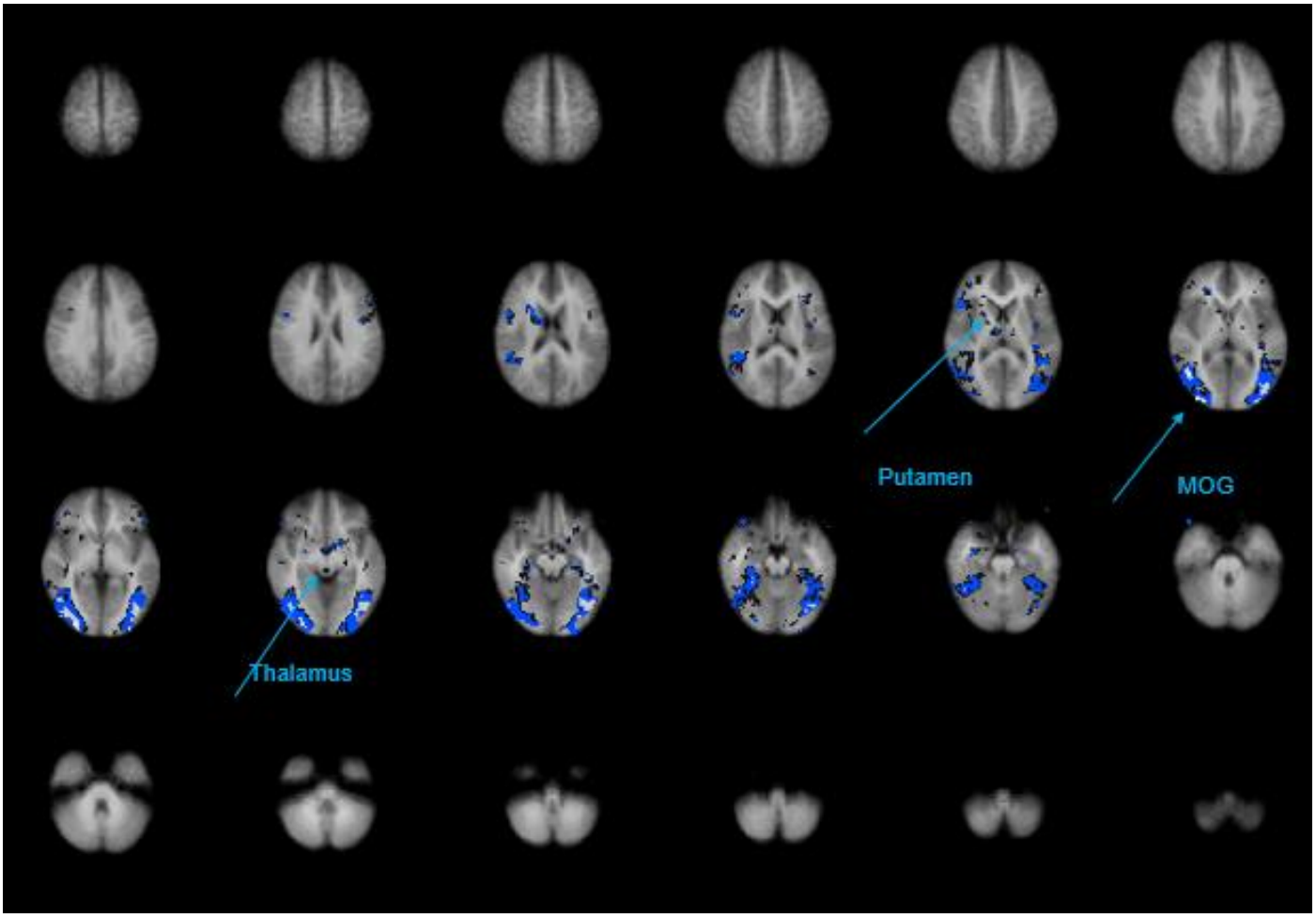


Figure 15b: Peak differences within the 22q11.2DS group showed greatest activation in the thalamus t(15)=82.81, putamen t(15)=78.33, and middle occipital gyrus t(15)=99.99. Total VC within the 22q11.2DS group is 74,722 voxels.

Figure 16: Overall signal change between groups

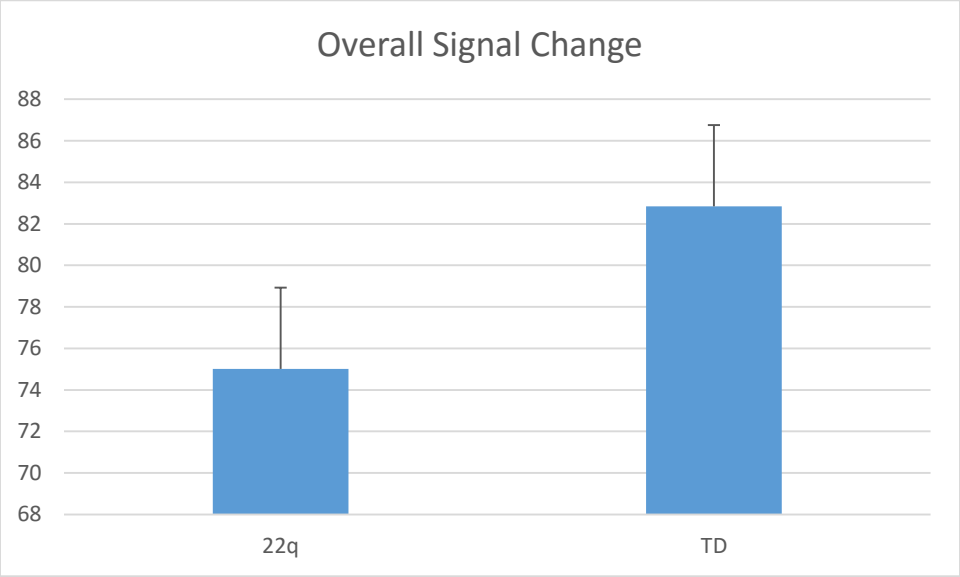


Figure 16: In Analysis 2, average overall signal change in the mirror task was lower in 22q11.2DS (75.01) than TD (82.84).

Figure 17: Signal change in classical RFX GLM by region

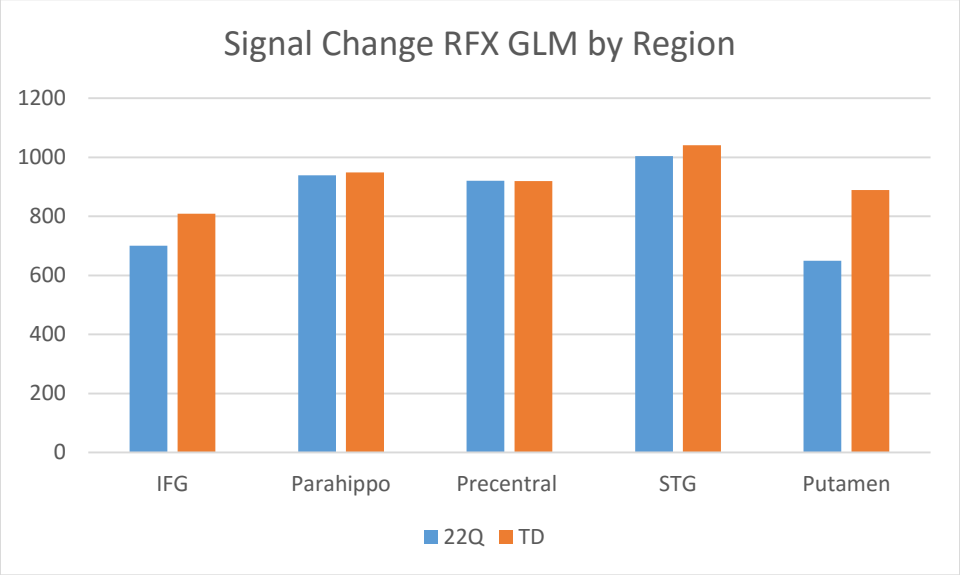
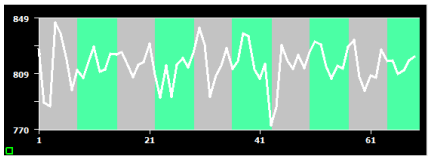
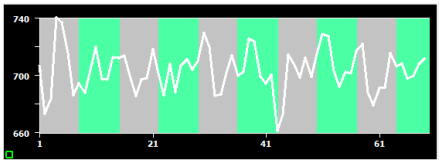


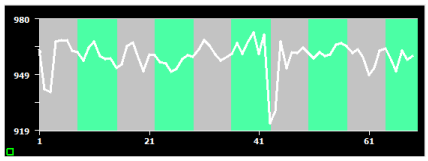
Figure 17: Average signal change β=75.01; TD: β=82.84. 22q: low: 70, high 87.19; TD: low: 70, high: 96.1.

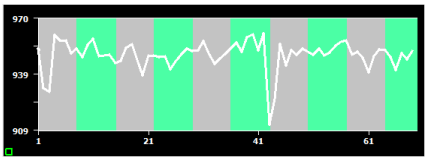
Figure 18: ROI time course by region in classical RFX GLM analysis. Time courses are indicated by activation within a set of coordinates in both groups. Activity looks consistent across TD and 22q11.2DS groups.

a 

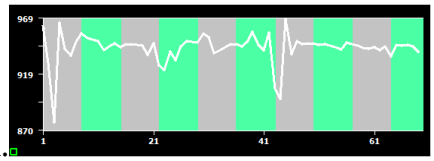
b 

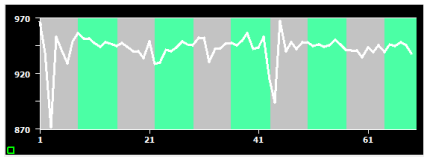
18a. ROI in the inferior frontal gyrus for TD (a) and 22q (b). Coordinates x= -50, y= 28, z= 0.

a 

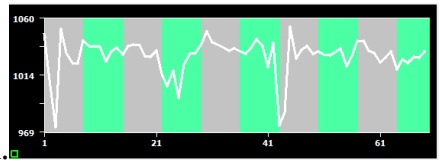
b 

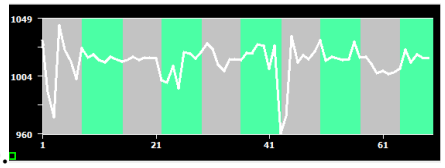
18b. ROI in the parahippocampal gyrus for TD (a) and 22q (b). Coordinates x= -26, y= -25, z= -12.

a. 

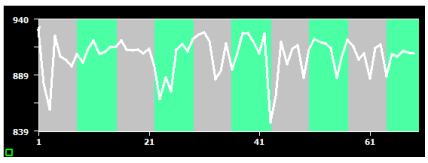
b 

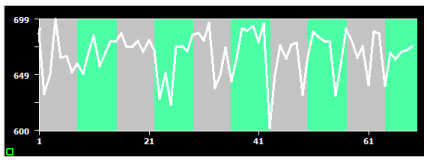
18c. ROI in the precentral gyrus for TD (a) and 22q (b). Coordinates x= 46, y= 12, z= 9.

a. 

b. 

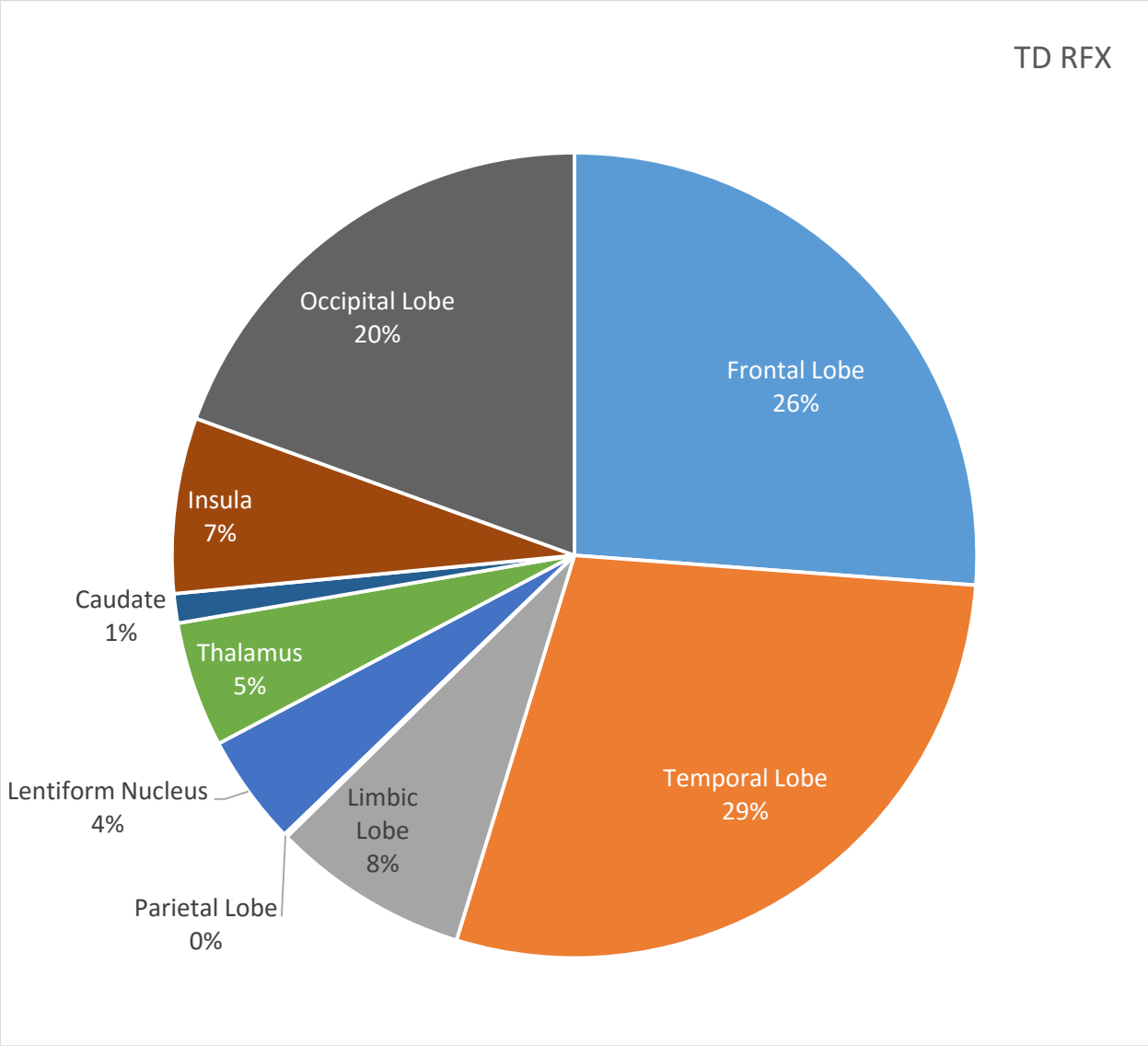
18d. ROI in the superior temporal gyrus for TD (a) and 22q (b). Coordinates x= 53, y= -16, z= 2.

a. 

b. 

18e. ROI in the putamen for TD (a) and 22q (b). Coordinates x= -18, y= 7, z= -2.

Figure 19: Classical RFX GLM voxel count by region in TD children



Figures 20: Classical RFX GLM voxel count by region in children with 22q11.2DS

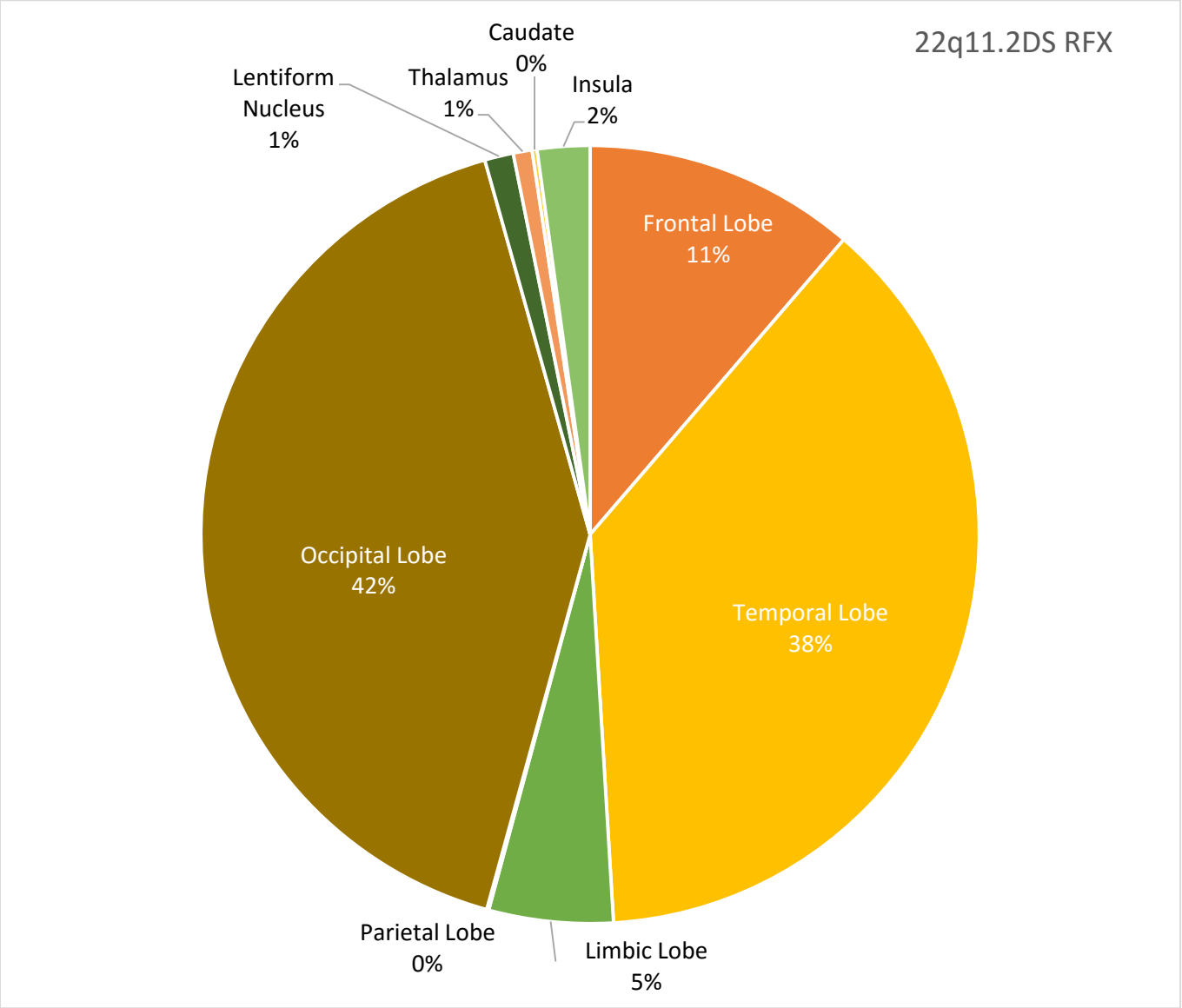


Table 2: Subscales by composite scores

	TD (n=16)	**22q11.2DS** (n=15)
Age	10.94 (.67)	13.18 (.73)
Full Scale	109.33 (3.54)	65.47 (2.45)
Verbal Comprehension	110.47 (3.42)	77.8 (2.72)
Working Memory	106.27 (4.08)	71.13 (3.32)
Processing Speed	105.40 (4.29)	68.4 (2.63)
Perceptual Reasoning	105.00 (3.24)	69.67 (2.58)

Table 3: Subscales by percentile rank

	TD (n=16)	**22q11.2DS** (n=15)
Full Scale	67.80 (6.54)	2.14 (.58)
Verbal Comprehension	69.73 (6.22)	10.87 (3.27)
Working Memory	59.91 (7.23)	6.80 (2.02)
Processing Speed	58.80 (8.39)	4.07 (1.73)
Perceptual Reasoning	60.10 (6.46)	4.63 (2.48)

Table 4: Between group FFX

Cluster	x	y	z	t	p	VC	Lobe	Structure	BA
1	44	39	11	4.210046	0.000177	464	Frontal Lobe	Inferior Frontal Gyrus	45
2	33	-51	-4	4.798808	0.000031	2526	Limbic Lobe	Parahippocampal Gyrus	
3	21	-23	-4	5.821696	0.000001	2032	Sub-Lobar	Thalamus	
4	26	-62	18	4.370368	0.000111	661	Temporal Lobe	Sub-Gyral	
5	-25	-61	34	5.058458	0.000014	1340	Parietal Lobe	Precuneus	18
6	-46	-48	-9	4.772732	0.000034	1833	Temporal Lobe	Sub-Gyral	

Table 4: Between group activation in fixed effects GLM is noted by peak voxel areas.

Table 5a: FFX GLM for TD activation

Structure	Lobes	Voxel Count	Brodmann areas
Declive	Cerebellum	6252	
Culmen	Cerebellum	2966	
Inferior Occipital Gyrus	Occipital	4811	17, 18, 19
Middle Occipital Gyrus	Occipital	15622	17, 18, 19, 37, 39
Superior Occipital Gyrus	Occipital	606	19
Cuneus	Occipital	2910	17, 18, 19
Precuneus	Occipital, Parietal	1264	18, 19, 39
Lingual Gyrus	Occipital	6534	17, 18, 19
Fusiform Gyrus	Occipital, Temporal	11152	19, 20, 37
Inferior Temporal Gyrus	Temporal	4903	19, 20, 21, 37
Middle Temporal Gyrus	Temporal, Occipital	2665	19, 20, 37
Parahippocampal Gyrus	Limbic	2069	30, 36, 37
Postcentral Gyrus	Parietal	2560	1, 2, 3, 40
Inferior Parietal Lobule	Parietal	1716	40
Cingulate Gyrus	Limbic	889	24, 31, 32
Posterior Cingulate	Limbic	224	30, 31

Table 5a: Activation within TD children notes greater activation in the middle occipital gyrus (VC=15,622) and fusiform gyrus (VC=11,152). Brodmann areas in both the occipital and fusiform gyrus are active during saccadic eye movement and recognizing visual patterns. The middle occipital gyrus is further distinguished for visual motion detection and encoding (memory).

Table 5b: FFX GLM for 22q11.2DS Activation

Structure	Lobes	Voxel Count	Brodmann areas
Inferior Occipital Gyrus	Occipital	94	17, 18, 19
Middle Occipital Gyrus	Occipital	1262	17, 18, 19
Cuneus	Occipital	94	18, 19
Lingual Gyrus	Occipital	72	17, 18, 19
Inferior Temporal Gyrus	Temporal	293	20, 21, 37
Middle Temporal Gyrus	Temporal, Occipital	1336	19, 20, 37
Superior Temporal Gyrus	Temporal	176	21, 22, 41, 42

Table 5b: Activation within TD children notes greater activation in the middle temporal gyrus (VC=1,136) and middle occipital gyrus (VC=1,262). Brodmann areas in both middle temporal and middle occipital gyri are active during saccadic eye movement and recognizing visual patterns. The middle temporal gyrus is further distinguished for visual motion detection, visual integration, comprehension, and WM and encoding.

Table 6: Between-group differences RFX with FCA

Cluster	Coordinates	Structure	Voxels	t	p
1	x=40 y=-31 z=-12	Inferior Frontal Gyrus	915	4.40	*
2	x=33 y=-51 z=-4	Parahippocampal Gyrus	2097	4.60	*
3	x=29 y=-38 z=-11	Fusiform Gyrus	460	4.60	*
4	x=-25 y=-61 z=33	Sub-gyral (parietal lobe)	1113	4.82	*
5	x=-45 y=-46 z=-9	Sub-gyral (temporal lobe)	2189	4.93	*
6	x=-53 y=34 z=10	Inferior Frontal Gyrus	1850	5.13	*

*=<.001

Table 6: Between group activation in random effects GLM is noted by peak voxel areas prominent in the parahippocampal gyrus, inferior frontal gyrus, and sub-gyral areas within the temporal and parietal lobes.

Table 7a: Typically developing Within Group RFX_FCA

Cluster	Coordinates	Structure	BA	VC	Beta	t	p	Avg Mass
1	x=34 y=-36 z=-13	Fusiform Gyrus	37	1683919	76.59	100	*	4767309.61
2	x=10 y=-31 z=63	Postcentral Gyrus	3	5098	73.69	81.88	*	375662.31
3	x=9 y=43 z=42	Medial Frontal Gyrus	6	1065	72.18	76.88	*	76872.66
4	x=-9 y=20 z=42	Cingulate Gyrus	32	401	72.35	77.65	*	29013.52
5	x=-18 y=-28 z=32	Cingulate Gyrus	32	684	74.65	87.19	*	51065.63

**=<.001*

Table 7a: Activation within TD children notes greater activation in the fusiform and postcentral gyri when fuzzy clustering analysis (FCA) is used. Brodmann areas in the fusiform gyrus are active during visual attention and motion processing, as well as encoding (memory) and ToM. The postcentral gyrus is active during primary motor movement and motor learning, visual motion processing, encoding, comprehension and ToM.

Table 7b: 22q11.2DS Within Group RFX

Cluster	Coordinates	Structure	BA	Voxels	Beta	t	p	Avg Mass
1	x=29 y=-85 z=1	Middle Occipital Gyrus	18	67449	77.1	99.90	*	5200000.5
2	x=31 y=35 z=-5	Middle Frontal Gyrus	6	309	72.42	79.30	*	22378.89
3	x=10 y=35 z=33	Medial Frontal Gyrus		8767	72.42	92.19	*	662860.88
4	x=17 y=3 z=28	Cingulate Gyrus		901	75.61	82.62	*	66522.67
5	x=10 y=-35 z=33	Medial Frontal Gyrus	8	11431	73.94	85.84	*	845143.19
6	x=-32 y=-92 z=5	Middle Occipital Gyrus	18	47412	78.66	98.43	*	3729215.5
7	x=-18 y=0 z=-4	Lateral Globus Pallidus		598	72.52	82.85	*	43364.27

**=<.001*

Table 7b: Activation within children with 22q11.2DS notes greater activation in the middle occipital gyrus and medial frontal gyrus when fuzzy clustering analysis (FCA) is used. Brodmann areas in the middle occipital gyrus is active during saccadic eye movement, visual attention, and pattern detection. The medial frontal gyrus is active during sensorimotor (secondary) motor processes, proprioception, WM and memory retrieval, visuomotor attention, planning, and behavioral inhibition.

Table 8: Activation by voxel count in TD group.

Cingulate Gyrus	Limbic	24108	23, 24, 31, 32
Anterior Cingulate	Limbic	18840	24, 25, 32, 33
Posterior Cingulate	Limbic	12198	23, 29, 30, 31
Amygdala/Uncus	Limbic	5273	20, 28, 34, 36, 38
Parahippocampal Gyrus	Limbic	18415	27, 28, 29, 30,35, 36
Hippocampus	Limbic	1824	
Superior Temporal Gyrus	Temporal	54623	21, 22, 28, 41, 42
Middle Temporal Gyrus	Temporal	66575	21, 22, 37, 38, 39
Inferior Temporal Gyrus	Temporal	29072	20, 21, 22, 37
Transverse Temporal Gyrus	Temporal	2329	41, 42
Supramarginal Gyrus	Temporal, Parietal	8970	40
Angular Gyrus	Temporal, Parietal, Occipital	6087	39
Superior Parietal Lobule	Parietal	9700	7
Inferior Parietal Lobule	Parietal	32420	2, 39, 40
Postcentral Gyrus	Parietal	32899	1, 2, 3, 5, 7, 40, 43
Precentral Gyrus	Frontal	54003	4, 6, 9, 43, 44
Superior Frontal Gyrus	Frontal	64764	6, 8, 9, 10
Middle Frontal Gyrus	Frontal	99711	6, 8, 9, 10, 46, 47
Medial Frontal Gyrus	Frontal	39342	6, 8, 9, 10, 11, 32
Inferior Frontal Gyrus	Frontal	77898	9, 10, 11, 44, 45, 46, 47
Orbital Gyrus	Frontal	686	47
Rectal Gyrus	Frontal	1902	11
Subcallosal Gyrus	Frontal	1387	25
Paracentral Lobule	Frontal	8286	3, 4, 5, 6
Superior Occipital Gyrus	Occipital	2083	19
Middle Occipital Gyrus	Occipital	40567	17, 18, 19, 37, 39
Inferior Occipital Gyrus	Occipital	14403	17, 18, 19
Insula	Sub-lobar	30017	13, 47
Claustrum	Sub-lobar	3574	13, 47
Cuneus	Occipital	30832	17, 18, 19, 30
Precuneus	Occipital, Parietal	49299	7, 18, 19, 31, 39
Lingual Gyrus	Occipital	42315	17, 18, 19
Fusiform Gyrus	Occipital, Temporal	20464	19, 20, 37
Globus Pallidus	Basal Ganglia	10754	Lateral and Medial
Caudate	Basal Ganglia	10541	Head, Body, Tail
Putamen	Basal Ganglia	25081	
Red Nucleus	Lentiform Nucleus	6723	
Substantia Nigra	Lentiform Nucleus	4022	
Pons	Midbrain	8768	
Thalamic Nuclei	Thalamus	29464	
Hypothalamus		116	

Declive	Cerebellum	21097	
Culmen	Cerebellum	37436	
Cerebellar Lingual	Cerebellum	1278	
Pyramis	Cerebellum	6662	
Dentate of Cerebellum	Cerebellum	4394	
Tuber	Cerebellum	14748	
Nodule	Cerebellum	2232	
Uvula	Cerebellum	5065	
Fastigium	Cerebellum	321	
Corpus Callosum		18876	
Anterior Commissure		6746	
Optic Tract		3598	

Table 8: Gross voxel count for TD children when using FCA. Please see Figure 8 for corresponding information.

Table 9: Activation by voxel count in 22q11.2DS

Structure	Lobes	Voxel Count	Brodmann area
Cingulate Gyrus	Limbic	1078	24, 32
Anterior Cingulate	Limbic	764	24, 32, 33
Amygdala/Uncus	Limbic	296	
Parahippocampal Gyrus	Limbic	2759	35, 36, 37
Hippocampus	Limbic	677	
Superior Temporal Gyrus	Temporal	3978	13, 22, 39, 41
Middle Temporal Gyrus	Temporal	6813	19, 20, 21, 37, 39
Inferior Temporal Gyrus	Temporal	853	19, 20, 37
Supramarginal Gyrus	Parietal, Occipital	1564	40
Angular Gyrus	Temporal; Parietal	95	39
Superior Parietal Lobule	Parietal	626	7
Inferior Parietal Lobule	Parietal	10764	2, 40
Postcentral Gyrus	Parietal	3885	1, 2, 3, 40
Precentral Gyrus	Frontal	3847	4, 6, 9, 44
Superior Frontal Gyrus	Frontal	2391	8, 9, 10
Middle Frontal Gyrus	Frontal	7296	6, 8 ,9 ,10 ,46
Medial Frontal Gyrus	Frontal	4036	6, 8, 9
Inferior Frontal Gyrus	Frontal	1852	17, 18, 19, 39
Paracentral Lobule	Frontal	1375	31
Superior Occipital Gyrus	Occipital	197	19
Middle Occipital Gyrus	Occipital	10016	17, 18, 19, 37, 39
Inferior Occipital Gyrus	Occipital	1852	17, 18, 19
Insula	Sub-lobar	1651	13, 47
Claustrum	Sub-lobar	108	13, 47
Cuneus	Occipital	1614	17, 18, 19
Precuneus	Occipital, Parietal	1967	7, 19, 37

Lingual Gyrus	Occipital	1999	17, 18, 19
Fusiform Gyrus	Occipital, Parietal	6570	18, 19, 20, 36, 37
Globus Pallidus	Basal Ganglia	106	Lateral
Caudate	Basal Ganglia	133	Body
Putamen	Basal Ganglia	326	
Declive	Cerebellum	2163	
Culmen	Cerebellum	2579	
Corpus Callosum		304	

Table 9: Gross voxel count for children with 22q11.2DS when using FCA. Please see Figure 9 for corresponding information.

Table 10: Classical RFX GLM between group differences

Cluster	Coordinates	Structure	VC	Beta	p
1	x=22, y=-22, z=-3	Middle Temporal Gyrus	30,245	3.68	*
2	x=44, y=35, z=12	Inferior Frontal Gyrus	4,266	3.82	*
3	x=36, y=-4 z=24	Middle Frontal Gyrus	1,280	3.64	*
4	x=-44, y=-46, z=-9	Middle Temporal Gyrus	10,361	3.72	*
5	x=-33, y=-22, z=-14	Hippocampus	302	3.21	*
6	x=-42, y=6, z=32	Inferior Frontal Gyrus	1,457	3.78	*
7	x=-54, y=33, z=10	Inferior Frontal Gyrus	2,147	3.58	*

*=<.001

Table 11a: Classical RFX GLM within group TD

Cluster	Coordinates	Structure	BA	VC	Beta	t	p	Avg Mass
1	x=23, y=-40, z=-17	Culmen of Cerebellum		240246	85.87	100	*	20630222
2	x=33, y=12, z=32	Middle Frontal Gyrus	9	496	79.82	92.19	*	39593.13

*=<.001

Table 11b: Classical RFX GLM within group 22q11.2DS

Cluster	Coordinates	Structure	BA	VC	Beta	t	p	Avg Mass
1	x=31, y=-90, z=0	Middle Occipital Gyrus	18	33657	79.18	99.99	*	2664834.50
2	x=50, y=9, z=16	Inferior Frontal Gyrus		2651	75.59	90.62	*	200380.92
3	x=34, y=42, z=11	Middle Frontal Gyrus		646	74.70	85.77	*	48257.41
4	x=35, y=-6, z=-20	Parahippocampal Gyrus		895	75.56	91.67	*	67619.94
5	x=21, y=35, z=4	Sub-Gyral		389	75.95	83.93	*	29156.04
6	x=18, y=9, z=-9	Putamen		420	73.02	78.33	*	30666.60

7	x=5, y=-15, z=12	Thalamus: Medial Dorsal Nucleus		554	75.18	82.81	*	41651.34
8	x=-8, y=1, z=-8	Insula	13	2006	74.27	89.50	*	148978.50
9	x=-32, y=-92, z=5	Middle Occipital Gyrus	18	30068	80.21	98.33	*	2411653.50
10	x=-48, y=31, z=0	Inferior Frontal Gyrus		1400	73.94	85.17	*	103210.53
11	x=-34, y=-4, z=14	Insula	13	696	74.79	83.44	*	52054.64
12	x=-39, y=-2, z=25	Sub-Gyral		819	72.95	80.00	*	59749.03
13	x=-49, y=20, z=25	Middle Frontal Gyrus		521	73.44	79.90	*	38261.01

*=<.001

Table 12: TD activation by VC using classical RFX GLM analysis

Structure	Lobe	VC	BA
Inferior Frontal Gyrus	Frontal Lobe	21494	9, 10, 13, 44, 45, 46, 47
Middle Frontal Gyrus	Frontal Lobe	8549	9, 10, 11, 46, 47
Precentral Gyrus	Frontal Lobe	2493	6, 9, 44
Superior Frontal Gyrus	Frontal Lobe	37	6, 8, 9, 10
Sub-Gyral	Frontal Lobe	14875	
Inferior Temporal Gyrus	Temporal Lobe	2010	19, 37
Middle Temporal Gyrus	Temporal Lobe	12835	19, 21, 22, 37, 39
Superior Temporal Gyrus	Temporal Lobe	8576	13, 22, 38, 39, 41
Transverse Temporal Gyrus	Temporal Lobe	49	41
Sub-Gyral	Temporal Lobe	19671	
Amygdala	Limbic Lobe	805	
Anterior Cingulate	Limbic Lobe	42	25
Hippocampus	Limbic Lobe	1262	
Parahippocampal Gyrus	Limbic Lobe	13317	19, 27, 28, 34, 35, 36, 37
Posterior Cingulate	Limbic Lobe	159	30
Sub-Gyral	Limbic Lobe	323	
Uncus	Limbic Lobe	250	28, 34, Amygdala
Inferior Parietal Lobule	Parietal Lobe	37	2, 39, 40
Sub-Gyral	Parietal Lobe	178	
Cuneus	Occipital Lobe	1328	17, 18, 30
Fusiform Gyrus	Occipital Lobe	13344	18, 19, 20, 36, 37
Inferior Occipital Gyrus	Occipital Lobe	2976	17, 18, 19
Lingual Gyrus	Occipital Lobe	6612	17, 18, 19
Middle Occipital Gyrus	Occipital Lobe	11376	18, 19, 37
Sub-Gyral	Occipital Lobe	7181	
Lateral Globus Pallidus	Lentiform Nucleus	1730	
Medial Globus Pallidus	Lentiform Nucleus	558	
Putamen	Lentiform Nucleus	5645	
Anterior Nucleus	Thalamus	645	
Lateral Posterior Nucleus	Thalamus	80	
Medial Dorsal Nucleus	Thalamus	1402	

Pulvinar	Thalamus	2099	
Ventral Anterior Nucleus	Thalamus	376	
Ventral Lateral Nucleus	Thalamus	876	
Ventral Posterior Lateral Nucleus	Thalamus	388	
Ventral Posterior Medial Nucleus	Thalamus	265	
Mammillary Body	Brainstem	298	
Medial Geniculum Body	Brainstem	82	
Caudate Head	Caudate	521	
Caudate Body	Caudate	1403	
Caudate Tail	Caudate	198	
Insula	Insula	10900	13
Claustrum	Insula	1797	13
Pons	Brainstem	416	
Midbrain	Brainstem	10152	
Lateral Geniculum Body	Brainstem	54	
Red Nucleus	Brainstem	469	
Substantia Nigra	Brainstem	333	
Subthalamic Nucleus	Brainstem	209	
Cerebellar Lingual	Anterior Lobe of Cerebellum	861	
Culmen	Anterior Lobe of Cerebellum	8650	
Declive	Posterior Lobe of Cerebellum	9107	

Figure 12: As 37 voxels was the cutoff point in STE, regions containing less than 37 voxels are not shown.

Table 13: 22q11.2DS activation by VC using classical RFX GLM analysis

Structure	Lobe	VC	BA
Inferior Frontal Gyrus	Frontal Lobe	3588	9, 10, 13, 44, 45, 46, 47
Middle Frontal Gyrus	Frontal Lobe	1051	9, 10, 11, 46, 47
Precentral Gyrus	Frontal Lobe	275	6, 9, 44
Sub-Gyral	Frontal Lobe	1788	
Hippocampus	Temporal Lobe	106	
Inferior Temporal Gyrus	Temporal Lobe	1279	19, 37
Middle Temporal Gyrus	Temporal Lobe	6807	19, 21, 22, 37, 39
Superior Temporal Gyrus	Temporal Lobe	3689	13, 22, 38, 39, 41
Transverse Temporal Gyrus	Temporal Lobe	364	41
Sub-Gyral	Temporal Lobe	6633	
Amygdala	Limbic Lobe	182	
Hippocampus	Limbic Lobe	174	
Parahippocampal Gyrus	Limbic Lobe	3138	9, 27, 28, 34, 35, 36, 37
Uncus	Limbic Lobe	186	28, 34, Amygdala
Inferior Parietal Lobule	Parietal Lobe	39	2, 39, 40
Cuneus	Occipital Lobe	585	17, 18, 30
Fusiform Gyrus	Occipital Lobe	9426	18, 19, 20, 36, 37
Inferior Occipital Gyrus	Occipital Lobe	2946	17, 18, 19
Lingual Gyrus	Occipital Lobe	3616	17, 18, 19
Middle Occipital Gyrus	Occipital Lobe	9915	18, 19, 37
Sub-Gyral	Occipital Lobe	5958	
Lateral Globus Pallidus	Lentiform Nucleus	138	

Putamen	Lentiform Nucleus	611	
Anterior Nucleus	Thalamus	55	
Medial Dorsal Nucleus	Thalamus	217	
Ventral Lateral Nucleus	Thalamus	100	
Caudate Body	Caudate	135	
Insula	Insula	1314	13
Claustrum	Insula	110	13
Culmen	Anterior Lobe of Cerebellum	2955	
Declive	Posterior Lobe of Cerebellum	3854	

Figure 13: As 37 voxels was the cutoff point in STE, regions containing less than 37 voxels are not shown.