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Alteration of functional brain architecture in 22q11.2 deletion syndrome – Insights into susceptibility for psychosis

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A B S T R A C T

The 22q11.2 deletion is one of the most common copy number variants in humans. Carriers of the deletion have a markedly increased risk for neurodevelopmental brain disorders, including schizophrenia, autism spectrum disorders, and attention deficit hyperactivity disorder. The high risk of psychiatric disorders associated with 22q11.2 deletion syndrome offers a unique possibility to identify the functional abnormalities that precede the emergence of psychosis. Carriers of a 22q11.2 deletion show a broad range of sensory processing and cognitive abnormalities similar as in schizophrenia, such as auditory and visual sensory processing, response inhibition, working memory, social cognition, reward processing and arithmetic processing. All these processes have a significant negative impact on daily life if impaired and have been studied extensively in schizophrenia using task-based functional neuroimaging. Here, we review task-related functional brain mapping studies that have used electroencephalography or functional magnetic resonance imaging to identify functional alterations in carriers with 22q11.2 deletion syndrome within the above mentioned cognitive and sensory domains. We discuss how the identification of functional changes at the brain system level can advance the general understanding of which neurobiological alterations set the frame for the emergence of neurodevelopmental disorders in the human brain. The task-based functional neuroimaging literature shows conflicting results in many domains. Nevertheless, consistent similarities between 22q11.2 deletion syndrome and schizophrenia have been found for sensory processing, social cognition and working memory. We discuss these functional brain alterations in terms of potential biomarkers of increased risk for psychosis in the general population.

1. Introduction

The 22q11.2 deletion syndrome (22q11.2DS) is the most common copy number variant (CNV) in humans, with a prevalence of 1:2000 to 1:4000 (Goodship et al., 1998; Olsen et al., 2018; Oskarsdóttir et al., 2004; Shprintzen, 2005). The syndrome presents with many clinical signs and symptoms which can affect almost any part of the body. The presence of a 22q11.2 deletion confers a markedly increased risk for a range of neurodevelopmental brain disorders, including, schizophrenia, autism spectrum disorders and attention deficit hyperactivity disorder (Bassett et al., 2008; Purcell et al., 2009; Schneider et al., 2014). The international Consortium on Brain and Behaviour has estimated the prevalence of schizophrenia-spectrum disorders to be 41% in adult 22q11.2 deletion carriers (Schneider et al., 2014). At the population level, the risk of developing a schizophrenia-spectrum disorder was recently estimated in a Danish Nationwide registry study to be approximately 6–8 times higher for people carrying the 22q11.2 deletion as compared to the general population (Hoeffding et al., 2017; Vangkilde et al., 2016b).

Neurogenetically informed brain imaging has been successfully used to link brain structure and function with variations in the human genome. In particular, neuroimaging of people with 22q11.2DS has become a showcase for neuroimaging genetics, providing opportunities to study neurobiological correlates of a specific disease state or its absence in a group sharing the same genetic risk for neurodevelopmental disorders. Hence, neurogenetically informed brain imaging offers the possibility of linking individual variations in the genome to specific functional or structural alterations in the brain, thereby linking the genotype with human brain function, see (Siebner et al., 2009) for a review. The high risk of psychiatric disorders associated with 22q11.2DS offers a unique possibility to identify the functional abnormalities that precede the possible emergence of psychosis. The deletion at 22q11.2 includes deletion of multiple genes (Gothelf et al., 2008; McDonald-McGinn et al.,

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2015), where several of these have shown to be candidate genes for the susceptibility of schizophrenia (Karayiorgou et al., 2010). The catechol-O-methyltransferase (COMT) and proline dehydrogenase (PRODH) genes have shown to be one of the major candidate genes for the susceptibility for schizophrenia, amongst the ones located in the deleted 22q11.2 region (Gothelf et al., 2008). The COMT gene encodes for the COMT enzyme that plays a role in degradation of dopamine, particularly in the prefrontal cortex (Tunbridge et al., 2004). The PRODH gene encodes for the PRODH enzyme, playing a role in glutamatergic and dopaminergic transmission (Paterlini et al., 2005). While COMT and PRODH are only two of the many genes located within the deleted region in 22q11.2DS, these are the main two genes that have been studied in task-based functional neuroimaging research, given the known high risk for schizophrenia associated with these genes. In line with this, the majority of the neuroimaging research on 22q11.2 deletion carriers have focused on the susceptibility of psychosis, given its high associated risk. Yet it should be noted that the deletion includes multiple genes and the increased risk is not limited to psychosis, but to a broader range of psychiatric and neurodevelopmental disorders (Bassett et al., 2008; Olsen et al., 2018; Purcell et al., 2009; Schneider et al., 2014).

The 22q11.2DS, like other neurodevelopmental disorders, is associated with macrostructural as well as microstructural brain alterations. This has been thoroughly reviewed elsewhere (Boot and van Amelsvoort, 2012; Dennis and Thompson, 2013; Karayiorgou et al., 2010; Scariati et al., 2016; Sun et al., 2018; Tan et al., 2009; Walter et al., 2009a). In addition, resting-state functional brain mapping, which involves a task-free resting state approach, has shown that 22q11.2DS is associated with functional brain connectivity alterations at baseline, both using EEG and fMRI (Scariati et al., 2016; Tomescu et al., 2014).

Existing neuroimaging studies have provided convincing evidence that structural and functional resting-state connectivity is altered in 22q11.2 deletion carriers. Yet these studies do not provide clues on how the 22q11.2DS alters state-dependent dynamics in regional activity and inter-regional connectivity associated with specific cognitive processes, as well as how this can be linked to the psychotic symptoms observed in 22q11.2DS i.e. positive, negative, generalized and disorganised (Debbané et al., 2006; Miller et al., 2003; Vangkilde et al., 2016a). Studies on task based functional brain activity in 22q11.2DS have concentrated on cognitive abilities, previously known to be impaired in schizophrenia. Here, we review the existing functional neuroimaging literature in 22q11.2DS carriers focusing on the changes in functional activity using EEG or fMRI which includes auditory and visual sensory processing, reward processing, working memory, response inhibition, social cognition and arithmetic processing. These processes are known to be impaired in schizophrenia and significantly contribute to poor functional outcome, see Fig. 1 for an overview of the coverage of this review. While the presence of a 22q11.2 deletion is associated with a broad range of neurodevelopmental disorders, this review focuses on the relationship between changes in experimentally evoked brain activity that tap into the cognitive processes mentioned above and the emergence of psychosis. Psychosis is one of the most disabling mental health conditions; it is associated with significant distress, unemployment, impaired social functioning and suicidal ideation. We discuss the relevance of current neuroimaging findings with respect to individual susceptibility for psychosis.

2. Auditory sensory processing

Auditory sensory processing has been extensively studied in schizophrenia, especially with EEG, providing important insights into the underlying pathological mechanisms of the disorder (Javitt and Sweet, 2015). Although the literature on auditory processing in 22q11.2DS is growing, only eight studies so far have investigated this using EEG. These studies involve mismatch negativity, P300, sensory gating, and auditory steady state responses, see Fig. 2 for an overview of the findings.

2.1. Mismatch negativity

Mismatch negativity (MMN) is a functional brain marker of change

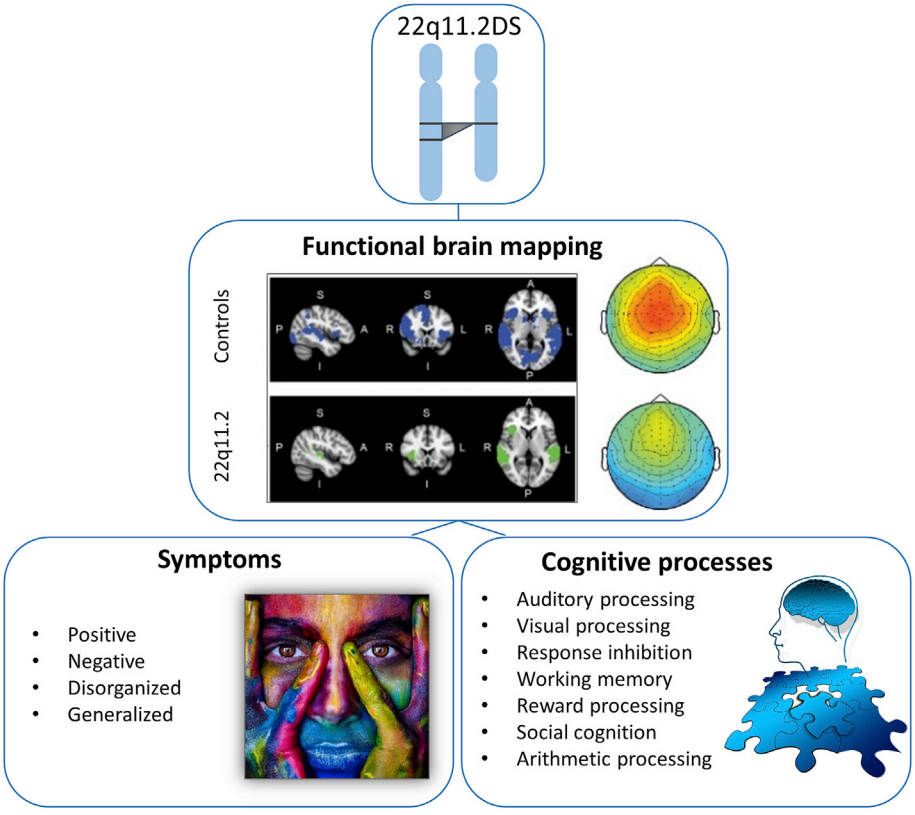

Fig. 1. Overview of review. Linking the 22q11.2DS genotype with sensory and cognitive function, and the presence of psychotic symptoms. Alterations in sensory evoked or task associated brain activity and connectivity provide an intermediate neurobiological readout at the brain circuit level, linking the 22q11.2DS genotype with its behavioural and clinical phenotype. This review will cover findings on the task-based functional neuroimaging research within the different cognitive processes listed here. The fMRI image is adapted with permission from (Montojo et al., 2014). The EEG image is adapted with permission from (Larsen et al., 2017).

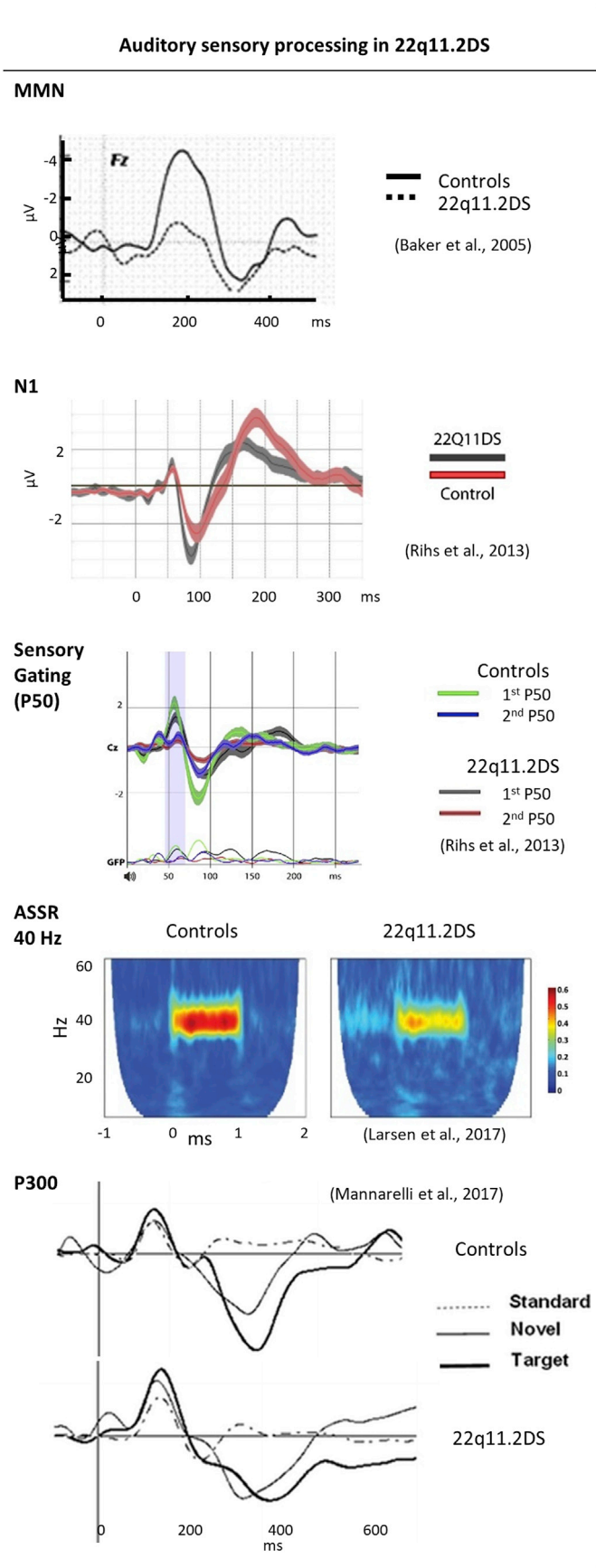

Fig. 2. Summary of EEG studies on auditory processing in 22q11.2DS. Deficits in MMN, P50 paired-pulse suppression, P300, and ASSR has been observed, whereas early auditory evoked potential (N1) is increased. However, results have not always been consistent across studies. The figure is adapted with permission from (Baker et al., 2005; Larsen et al., 2018, 2017; Mannarelli et al., 2018; Rihs et al., 2013).

detection typically evoked in oddball paradigms (Garrido et al., 2009; Näätänen, 1995). When measured with EEG, MMN is obtained by subtracting the responses to standard tones from responses to oddball tones and is considered to be a reliable pre-attentive index of information processing at the level of primary auditory cortex. It is well established that people with schizophrenia show reduced MMN (Catts et al., 1995; Michie, 2001; Näätänen and Kähkönen, 2009; Umbricht and Krljes, 2005). Interestingly, MMN is also reduced in first episode psychosis, (Atkinson et al., 2012; Hsieh et al., 2012; Nagai et al., 2013), first degree relatives (Jessen et al., 2001; Michie et al., 2002), as well as a promising marker for psychosis prediction (Bodatsch et al., 2015, 2011; Lavoie et al., 2018; Perez et al., 2014). Hence, mounting evidence suggests that MMN is reduced throughout the entire continuum of psychosis, being already expressed in individuals with increased risks but no clinical manifestation, see (Randeniya et al., 2017) for a review.

The very first neuropsychological evidence for reduced MMN in 22q11.2DS carriers was provided by Cheour et al. (1998, 1997), who showed reduction of responses to frequency deviants in a small group of children and infants (<1 years) with 22q11.2DS. Following up on this observation, Baker et al. (2005) employed a classic oddball paradigm in 22q11.2DS (N = 25) which used three types of deviants, a change in duration, pitch, and both. For all three deviants, MMN amplitudes were found to be reduced at frontal electrodes but intact at temporal sites, echoing a topographic expression found in patients with schizophrenia (Baldeweg et al., 2002). Post hoc analysis revealed that the reduction in MMN amplitude were driven by duration deviants in 22q11.2DS carriers compared to the control group. These initial findings could not be replicated in a later larger study including 41 carriers, (Zarchi et al., 2013). In that study, no difference in MMN amplitudes were found relative to controls without 22q11.2DS, in the deviants examined, namely frequency, duration, intensity, location, and a silent gap (Näätänen et al., 2004). Zarchi et al. (2013) used the PANSS (Positive and Negative Syndrome Scale) to assess the presence of schizophrenia-like symptoms in 22q11.2DS carriers. They found that the gap-evoked MMN amplitude explained 12% of the PANSS negative scale scores. However, no association between the PANSS positive scale score and the gap-evoked MMN amplitudes was found. Further, individual MMN amplitudes evoked by the other deviant types (i.e., intensity, directionality, frequency, and duration) were not significantly associated with the clinical scores. In line with Zarchi et al., (2013), a recent study also did not replicate such reduction in frequency MMN (N = 19), in young (12–25 years) non-psychotic 22q11.2DS carriers (Larsen et al., 2018). However, the carriers showed an increased N1 response to both standards and deviants. This abnormality suggests either an increased sensitivity to tones or a reduced adaptation to repeated tone exposure (Larsen et al., 2018). Further, the authors found that, compared to controls, the 22q11.2 deletion carriers had reduced connectivity between the right inferior frontal gyrus and the right superior temporal gyrus, as well as within the right primary auditory cortex, although the significance of these connectivity results did not survive correction for multiple comparison.

It is important to consider the disease states as well as the age range of the 22q11.2 deletion carriers when interpreting these MMN findings. In the study by Baker et al. (2005), the 25 carriers were 12–21 years of age and none of the carriers met criteria for a diagnosis of psychotic disorder. The sample size in the study by Zarchi et al. (2013) was larger, but the age range of the 41 participants was also larger (mean = 20.6, std = 9.6 years). Critically, 6 of the carriers met the DSM-IV-TR criteria for schizophrenia. The study by Larsen et al. (2018), which did not find MMN reductions, had a sample with a similar size (19 non-psychotic young carriers) and age range (aged 12–25 years), but used a frequency deviant instead of duration. Therefore, it also is conceivable that the sensitivity for detecting an abnormal MMN in 22q11.2DS might depend on the type of acoustic deviant. Given these differences among the studies, it is hard to disentangle whether the association of gap-MMN and psychotic scores found in Zarchi et al. (2013) is specific to 22q11.2DS or to schizophrenia.

Other genetic factors might influence the likelihood that 22q11.2 deletion carriers express an abnormal MMN. Both Baker et al. (2005) and Zarchi et al. (2013) evaluated the effect of a functional polymorphism (Val158Met) in the catechol-O-methyltransferase (COMT) gene on the MMN responses in the 22q11.2 deletion carriers. Baker et al. (2005) found that the presence of the COMT *Met* allele was associated with more marked MMN amplitude reduction in the 22q11.2DS group compared to healthy controls. In line with this, Zarchi et al. (2013) showed that overall MMN amplitudes were smaller for carriers of the COMT *Met* genotype than for *Val* carriers within the 22q11.2DS group.

2.2. Recordings of the P300 component

P300 is an extensively studied ERP component usually evoked in oddball paradigms where participants are actively discriminating rare stimuli against standard stimuli (Polich, 2007). The P300 can be divided into two subcomponents P3a and P3b, where P3a is associated with attentional switching towards salient stimuli and P3b is associated with memory storage and context updating. The amplitude of the P300 is reduced both in schizophrenia as well as first degree relatives, whereas the latency is increased (Jeon and Polich, 2003; Kidogami et al., 1991). The reduction in P300 in schizophrenia, is seen both for the P3a and the P3b component (Bachiller et al., 2015; Mathalon et al., 2000).

A single study has examined P300 responses in 22q11.2DS carriers (Mannarelli et al., 2018) using an oddball task where subjects had to count target tones and state how many they had counted at the end of the task. The study included 10 22q11.2 deletion carriers with no psychiatric disorder and a mean age of 25.2 years (SD = 3.25 years) and 10 healthy age-matched controls. The amplitude of the P3b to the target tones was significantly decreased for the 22q11.2 deletion carriers compared to controls, whereas the P3a amplitude was similar across the two groups. This might suggest that memory storage as well as context updating is decreased in 22q11.2DS carriers whereas the attentional switching towards salient stimuli is intact. However, given the small sample size, replication studies are needed to corroborate this finding.

2.3. Sensory gating

Sensory gating can be evoked using a paired-click paradigm where a pair of clicks is presented after each other at a short and constant inter-click time interval. It is a measure of the ability to suppress redundant information, which has been put forward as a way of explaining the positive symptoms in schizophrenia (Fletcher and Frith, 2009). Typically, individuals show a 80–90% reduction of the P50 amplitude evoked by the second click relative to the P50 amplitude evoked by the first click (Freedman et al., 1983; Wan et al., 2008). Sensory gating as reflected by the P50 suppression has shown to be reduced in patients suffering from schizophrenia as well as in fist-degree relatives, see (de Wilde et al., 2007; Earls et al., 2016), for meta-analyses. If sensory gating is abnormal, an intriguing question is how abnormal sensory gating in 22q11.2DS relates to the behavioural abnormalities seen in schizophrenia.

Three studies have investigated P50 sensory gating in 22q11.2 deletion carriers. While Vorstman et al. (2009) (N = 56) and Rihs et al. (2013) (N = 21) did not find altered P50 suppression, Zarchi et al. (2013) (N = 41) showed poorer sensory gating in 22q11.2 deletion carriers relative to controls. Again, methodological differences between the studies may account for the observed differences in results. Sensory gating is believed to have a late maturation and increase with age (Freedman et al., 1987; Marshall et al., 2004). Therefore, the different age ranges used in the three studies (Zarchi et al., 2013): mean 20.6 years, std 9.6; (Vorstman et al., 2009) age range 12–18 years; (Rihs et al., 2013): mean 17.4 years, std 4.7 may explain part of the differences in the results. In both Vorstman et al. (2009) and Rihs et al. (2013) none of the carriers met criteria for schizophrenia, whereas 14% of the participants included in Zarchi et al. (2013) were diagnosed with schizophrenia. In

idiopathic schizophrenia, the P50 sensory gating ratio is typically 10–20%, compared to 80–90% for healthy participants (Freedman et al., 1983). Since six of the participants in Zarchi et al. (2013), met criteria for schizophrenia, it is likely that the impairment of sensory gating is related to schizophrenia rather than to 22q11.2DS. However, further studies are needed in order to confirm this.

Although the study by Rihs et al. (2013) did not reveal a suppression of P50 in 22q11.2DS, the N1 component was enhanced at the central electrodes for the first tone. This was attributed to increased activation in dorsal anterior cingulate and medial frontal cortex. Hence, 22q11.2DS carriers showed higher sensitivity to the presented tones, while sensory gating itself being normal. This finding is in agreement with the MMN study by Larsen et al. (2018), in which 22q11.2DS showed a generally enhanced response to tones in a roving oddball paradigm. Since none of the carriers in Rihs et al. (2013) and Larsen et al. (2018) met criteria for schizophrenia (although six out of 21 22q11.2 deletion carriers experienced frequent psychotic symptoms in Rihs et al. (2013)), this might indicate that the increased N1 response is specific to the 22q11.2 deletion rather than the schizophrenia phenotype.

2.4. Auditory steady state responses

Auditory steady state responses (ASSRs) are evoked by trains of brief tones or clicks presented at a repetition rate of 40 Hz and provide a readily available, non-invasive means of probing neural gamma synchrony in the auditory system (Plourde et al., 1991). The ASSR to 40 Hz stimulation is attenuated in schizophrenia (Thuné et al., 2016), first episode psychosis (Spencer et al., 2008) as well as in non-affected first degree relatives (Rass et al., 2012). Since ASSR has been linked to cortical abnormalities in GABAergic and glutamatergic neurotransmission (Lewis et al., 2005; Uhlhaas and Singer, 2015), the ASSR is a promising electrophysiological index of cortical neurotransmission.

Only one study has examined the ASSR in 22q11.2 deletion carriers (Larsen et al., 2017). The ASSR of 18 non-psychotic 22q11.2 deletion carriers was compared to the ASSR of 27 controls with comparable age distribution and sex ratio (age range 12–25 years). Both, ASSR power as well as inter trial phase coherence were reduced in the 22q11.2 deletion carriers compared to controls. Critically, within the 22q11.2DS group, reduced phase-locking to the 40 Hz clicks was associated with more negative symptoms. These results corroborate the notion that impaired synchronization of cortical gamma-band activity may play an important role in the generation of negative symptoms in 22q11.2DS. Whether reduced phase locking to 40 Hz ASSR in 22q11.2DS is associated with altered levels of GABA, remains to be clarified in future studies with GABA-edited proton magnetic resonance spectroscopy, for example.

Altogether, some aspects of auditory processing in 22q11.2DS as reflected in the EEG activity are altered i.e. ASSR, P300 and N1. Conflicting results were found for sensory gating and MMN in response to deviants of stimulus duration and frequency. However, these are also the most studied electrophysiological markers in 22q11.2DS compared to the other components which have only been studied in one or two studies. While the abnormal ASSR and P300 parallels abnormalities associated with schizophrenia, the increased N1 response seems to be more specific to the 22q11.2 deletion itself. More studies, especially studies with a longitudinal study design, are needed to elucidate in more detail abnormal auditory processing in 22q11.2DS and the significance of these abnormalities as marker for psychosis susceptibility. For a summary of the findings on auditory processing in 22q11.2DS, see Fig. 2.

3. Visual processing

Early visual processing has been extensively studied in schizophrenia (Butler et al., 2001; Silverstein and Keane, 2011), motivating the study of this in 22q11.2DS. Visual processing has been studied in 22q11.2DS using EEG during an illusory contour detection task (Biria et al., 2018) and a texture segregation task (Magnée et al., 2011).

3.1. Visual processing during illusory contour detection

When edges lead to a percept of a contour in the absence of physical borders, an illusory contour appears. This illusion is an active process where missing information is filled in. Illusory contour processing have both been found to be impaired in schizophrenia as well as preserved (Foxe et al., 2005; Silverstein and Keane, 2011).

(Biria et al., 2018) investigated the process underlying illusory contour detection in 25 22q11.2 deletion carriers and 26 healthy controls in the age range 14–28 years, where 1 of the deletion carriers had a diagnosis of schizophrenia and 3 were diagnosed with a psychotic disorder. Subjects had to respond when the illusion was present as well as absent. While there was no group difference in accuracy, indicating that the illusion is preserved, 22q11.2 deletion carriers showed significantly faster reaction times compared to controls. Although the illusion contour completion was preserved, 22q11.2 deletion carriers showed a reduced amplitude of for the P1 as well as the N1 component at occipital electrodes compared to controls. Source analysis localized the reduction at P1 to areas in the dorsal and ventral visual stream, in line with what has been shown in schizophrenia (Foxe et al., 2005). The reduced amplitude at N1, was accounted for by reduced activity in cuneus, precuneus, middle temporal lobes, occipital lobes and posterior cingulate, a finding that has not been observed in schizophrenia.

Further, an increased global field power for the closure negativity component was observed for the 22q11.2 deletion carriers compared to controls. This negative component is seen in tasks involving visual completion and believed to be related to the process of shape discrimination. The global field power of this component further showed to be inversely related to the positive symptoms of the 22q11.2 deletion carriers. The higher the field power of this component, the lower the positive symptoms. The authors interpreted this finding as higher compensatory responses for illusory contours in carriers with a low degree of symptoms.

3.2. Visual processing during a texture segregation task

In a texture segregation task, visual stimuli containing line segments either making up checkerboards or homogenous fields are presented. By comparing the ERPs evoked by these two stimuli it is possible to assess information from visual feedforward activity from the C1 component peaking early between 70 and 100 ms as well as visual feedback activity via the later texture negativity component peaking 100–250 ms (Lamme, 1995).

Using the texture segregation task, visual processing in 58 22q11.2 deletion carriers and 100 typically developing controls in the age range 9–18 years was studied by Magnée et al. (2011). 30 out of 58 deletion carriers were diagnosed with autism spectrum disorder and 7 were diagnosed with a psychotic disorder. 22q11.2 deletion carriers showed larger negative amplitudes as well as longer latency in the time window of the C1 component, compared to controls. There was no difference in the C1 component for the 22q11.2 deletion carriers with an autism spectrum disorder diagnosis compared to those without. Further, 22q11.2 deletion carriers showed reduced amplitudes for the texture negativity component.

The C1 component has previously also been found to be reduced in chronic schizophrenia (Butler et al., 2007; Schechter et al., 2005). The effect of proline as well as COMT levels, were investigated on the texture negativity/C1 component ratio which the authors argue represents an index of a ratio between feedforward and feedback activity. An interaction between COMT and proline levels were found, revealing that high proline levels were associated with a decreased feedforward/feedback ratio in the COMT met carriers compared to COMT Val carriers.

This indicates that both COMT and proline levels play a role in visual processing deficits in 22q11DS.

While illusory contour completion in 22q11.2DS seems to be intact, 22q11.2DS is associated with increased early visual processing

alterations. Illusory contour completion have both been found to be impaired in schizophrenia as well as preserved, see (Foxe et al., 2005; Silverstein and Keane, 2011). Given that the ratio between the texture negativity and C1 component is believed to be related to the ratio between feedforward and feed-backward visual processing, it suggests that the connectivity between the different visual hierarchical areas are impaired, which is indeed the case in schizophrenia (Ford et al., 2015; van de Ven et al., 2017). As with the auditory processing, it is clear that more studies are needed in the visual processing domain for 22q11.2DS. In particular, it would be interesting and very informative to investigate task based connectivity to disentangle at which hierarchical level the deficits take place. This would be helpful in understanding the similarities and dissimilarities between schizophrenia and 22q11.2DS. For a summary of the studies on visual sensory processing, see Fig. 3.

4. Response inhibition

Response inhibition refers to the ability to stop a pre-potent yet inappropriate response tendency, and is a hallmark of executive control (Mostofsky and Simmonds, 2008; Verbruggen and Logan, 2008). One way to measure response inhibition, is to use a stop-signal task in which a go signal is unpredictably followed by a stop-signal, demanding participants to inhibit their response. A similar task intersperses Go trials with NoGo trials (i.e., Go/NoGo task). Schizophrenia has been associated with impaired response inhibition (Enticott et al., 2008; Hughes et al., 2012; Kiehl et al., 2000), and this motivated investigation of response inhibition in 22q11.2DS.

Romanos et al. (2010) recorded EEG while 13 22q11.2 deletion carriers and age-, sex-, and handedness-matched controls performed a Go-NoGo-task. Of note, 11 out of the 13 22q11.2 deletion carriers had a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD). The 22q11.2DS group made more errors in the go condition (failing to respond when there was a Go signal) as well as more errors after a distractor letter compared to the control group. Analysis of the event related potential, P300, showed a general (across Go and NoGo trials) increase in amplitude for the 22q11.2 deletion carriers compared to controls. Topographical analysis revealed a more anterior location of the responses to the Go trials in 22q11.2DS but no topographical difference for the NoGo trials. This pattern is dissimilar to what has been observed in schizophrenia (Weisbrod et al., 2000), where topographical changes were observed to the NoGo trials and normal responses were observed for the Go trials. Further, the P300 in Go/NoGo paradigms is usually seen reduced in people with schizophrenia (Ford et al., 2004). In other words, the 22q11.2DS and control groups showed comparable responses to the NoGo condition but altered responses to the Go condition. Therefore, observed alterations cannot easily be attributed to inhibitory dysfunction, but perhaps to a general increased recruitment of cortical sources.

Response inhibition in 22q11.2DS has also been examined using fMRI (Gothelf et al., 2007; Montojo et al., 2015b, 2015a). Gothelf et al. (2007) studied 13 adolescent 22q11.2 deletion carriers of which 3 had a psychotic disorder, 14 typically developing controls and 9 controls with developmental disabilities using a Go-NoGo task. While there were no consistent differences in task performance, 22q11.2 deletion carriers showed greater activation in left parietal regions compared to both control groups. The authors argue that this greater activation suggests that the 22q11.2 deletion carriers recruit the parietal regions to compensate for executive dysfunction. Montojo et al. (2015b) investigated response inhibition in 15 22q11.2 deletion carriers and 30 healthy controls (18–38 years of age) using a stop-signal task. The number of 22q11.2 deletion carriers with a psychotic disorder was not reported, however, authors reported that 3 deletion carriers took psychotropic medication. In agreement with (Gothelf et al., 2007), between-group comparisons did not reveal any differences in stop-signal reaction time or percent correct for the stop trials, indicating comparable response inhibition in the two groups. Yet, there were significant between-group differences for Go-trials, with controls showing faster reaction times and higher accuracy than 22q11.2 deletion carriers which is in accordance with (Romanos et al., 2010). Further, significant group differences were found for cognitive impulsivity as measured with the Barratt impulsiveness scale, with 22q11.2 deletion carriers scoring higher than controls. For successful stop trials, controls showed greater activation in the frontal cortex, anterior and posterior cingulate gyrus, bilateral striatum and thalamus, left parietal cortex, bilateral inferior and middle temporal gyri, and occipital cortex compared to 22q11.2 deletion carriers. No regions showed greater activation for 22q11.2DS than controls. Go trials resulted in greater activation of left angular gyrus, bilateral middle temporal gyri, and bilateral occipital cortex in controls relative to 22q11.2 deletion carriers. Finally, in unsuccessful stop trials, in which participants failed to inhibit the response, 22q11.2 deletion carriers showed greater activation in bilateral inferior and middle frontal gyri, right striatum and thalamus. No regions were greater for controls relative to 22q11.2 deletion carriers in this condition. In addition to this, the authors report significant negative correlations between activity in left middle frontal gyrus, right striatum and left thalamus with cognitive impulsivity during response inhibition. Altogether, these findings suggest that engagement of response inhibition related regions are reduced in 22q11.2 deletion carriers and that this might be related to the behavioural manifestations of the syndrome.

In a follow-up study, the same group investigated response inhibition using the same stop-signal task in 15 individuals with 22q11.2DS, 23 individuals with a ADHD diagnosis without deletion, and 30 healthy individuals without the deletion (Montojo et al., 2015a). As in their first study (Montojo et al., 2015b), it was not reported how many 22q11.2 deletion carriers had a psychotic disorder, yet three deletion carriers took psychotropic medication. There was no difference between groups in the stop-signal reaction times. However, the accuracy of responses differed for the Go trials with 22q11.2 deletion carriers showing fewer correct answers as well as slower responses than both ADHD and controls. Compared to controls, 22q11.2DS had lower activation in the frontal cortex, posterior cingulate cortex and adjacent precuneus, bilateral caudate and thalamus, left parietal cortex, right middle temporal gyrus, bilateral occipital cortex and cerebellum in the successful stop vs. go contrast. Furthermore, ADHD had significantly greater activation in bilateral middle frontal gyrus relative to 22q11.2DS. Impulsivity was negatively correlated with activity in the successful stop trials in medial frontal cortex precuneus for 22q11.2DS, whereas ADHD showed a positive correlation for the same regions (though not surviving correction for multiple comparisons in the ADHD group).

In Gothelf et al. (2007), the 22q11.2 deletion carriers were also genotyped for the Val158Met polymorphism in the COMT gene. For the 22q11.2DS Met carriers, an increased activation was found in the anterior cingulate gyrus as compared to the Val carriers. This difference adds further evidence for a modulatory effect of the Val158Met COMT genotype on task-related brain activity in the 22q11.2DS. However, the sample size was very small with only 13 22q11.2 deletion carriers (seven COMT Met carriers, six COMT Val carriers). Therefore, one cannot draw any strong conclusions from this subgroup analysis.

While the ability to inhibit a response seems to be intact at the behavioural level in all four studies, task-related activation of response-inhibition areas was only found to be reduced in the studies by Montojo et al. (2015a, 2015b). Further, the behaviour showed longer reaction times and higher error rates for the go signal in all studies, suggesting that the ability to inhibit a response itself is intact in 22q11.2DS whereas the response initiation is impaired. This is dissimilar to what is observed in schizophrenia, where response inhibition is usually seen to be impaired (Enticott et al., 2008; Hughes et al., 2012; Kiehl et al., 2000). Go/NoGo and Stop-signal tasks are known to produce different neural responses in healthy people (Rubia et al., 2001). While both tasks engage the bilateral middle and inferior frontal gyri, pre-supplementary motor area (SMA), anterior cingulate cortex as well as inferior parietal cortex,

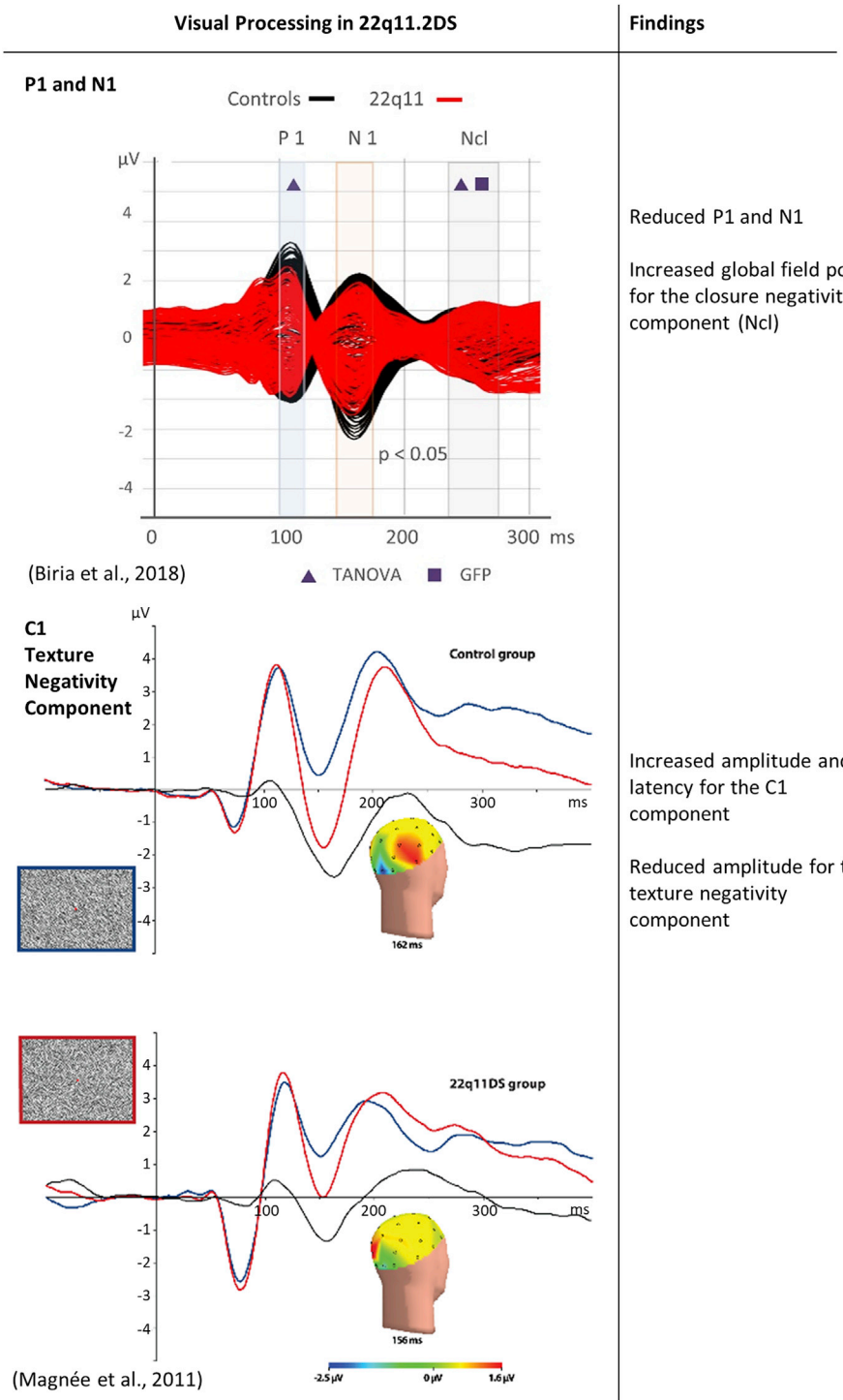

Fig. 3. Summary of EEG studies on visual processing in 22q11.2DS. Increased amplitudes in 22q11.2 deletion carriers have been observed for the C1 component and closure negativity component when comparing to controls. Decreased responses have been observed for P1 and N1 as well as texture negativity component. The figure is adapted with permission from (Biria et al., 2018; Magnée et al., 2011). The black line indicates the difference between checkerboards (red lines) and homogenous stimuli (blue lines).

the tasks differ in their engagement of left superior prefrontal, medial and parietal cortices. The difference has been attributed to additional activity subserving response selection in the Go/NoGo task. More studies are needed in order to delineate if task differences can explain the differences in the reported results. Despite of these differences, there is an overall agreement among existing studies that response inhibition is intact while the response initiation is impaired. It would be highly interesting to follow developmental trajectories of response inhibition in 22q11.2 deletion carriers (Maeder et al., 2016).

The brain mapping studies addressing response inhibition in 22q11.2 deletion carriers are summarized in Table 1 and Fig. 4. From Fig. 4 it is seen that there is a relatively big overlap between the areas where 22q11.2 deletion carriers show reduced activity compared to controls for response inhibition and response initiation (indicated in blue). 22q11.2DS show reduced activity for response inhibition mainly in the frontal areas (labelled in green). The left parietal cortex, shaded in dark green, had mixed findings where 22q11.2 deletion carriers either showed increased or decreased activity compared to healthy controls during response inhibition.

4.1. Sensorimotor integration

In a recent EEG study, Mannarelli et al. (2018) found reduced responses in the preparatory phase of a motor response using a double choice reaction task. The study included 10 22q11.2 deletion carriers with no psychiatric disorder and a mean age of 25.2 (SD = 3.25) and 10 healthy age-matched controls. Subjects had to respond with their right hand whenever they heard a target tone embedded in an oddball paradigm. Before each tone, a flash light was presented in order to make the participants prepare for their response. Hence, when subjects were presented with the tone they had to either inhibit or execute their prepared response. In the period between the flash light and the tone, the 22q11.2 deletion carriers showed significantly lower responses. Further 22q11.2 deletion carriers showed more errors as well as longer reaction times than the control group.

Together the results suggest that attentive discrimination and the preparatory processes of motor responses are reduced in 22q11.2DS, which is in line with the above studies on response inhibition showing that the initiation of a response is impaired. However, the small sample size is a limitation in the study and the results need to be replicated in larger samples in order to make strong conclusions.

5. Working memory

Working memory has been extensively studied in schizophrenia (Manoach, 2003; Manoach et al., 2000) and is one of the core cognitive deficits that consistently can be found throughout the course of the illness. There is evidence that schizophrenia is associated with task-related hypoactivation of the dorsolateral prefrontal cortex (DLPFC), see Glahn et al. (2005) for a meta-analysis. However, that meta-analysis also showed that alterations in working memory in schizophrenia are not only restricted to the DLPFC, but extend to the anterior cingulate cortex and left frontal pole regions with activity being greater for schizophrenia patients than controls.

Working memory is also typically impaired in 22q11.2DS (Bearden et al., 2001; Jalbrzikowski et al., 2012). Kates et al. (2007) investigated non spatial working memory using a 2-back task (in which participants had to report when they saw the same letter as two letters back) in 17 children with 22q11.2DS (psychotic status not reported), 10 siblings of 22q11.2DS participants and 10 age-matched controls. There was no difference in reaction time across groups, however, the 22q11.2 deletion carriers showed lower hit rates than the sibling group. Whole brain fMRI analysis revealed greater activation in controls relative to 22q11.2DS in the right middle and inferior frontal gyri, bilateral inferior parietal lobules, right superior parietal lobule, left middle occipital and right superior occipital cortex. Contrary to this, 22q11.2DS showed greater activations in left inferior frontal gyrus, right anterior cingulate, right medial and superior occipital gyri and cuneus relative to controls. Siblings displayed increased working memory related activity relative to 22q11.2 deletion carriers in the anterior cingulate cortex and angular gyri, as well as in left SMA, right superior occipital and left middle occipital cortex. 22q11.2DS did not show greater activation than siblings anywhere in the brain. In line with this finding, Harrell et al. (2017) found decreased activation in the right superior and middle frontal gyri, the frontal pole and the anterior cingulate cortex using a similar 2-back task in 11 children with 22q11.2DS and 8 controls. None of the participants had psychotic symptoms and thus this finding cannot be attributed to the presence of psychosis. The results of a decreased activation in the frontal areas might be due to reported reduced grey matter volumes in 22q11.2DS (Shashi et al., 2010). Azuma et al. (2009) used a spatial working memory task in eight 22q11.2 deletion carriers in the age range 9–16 years (psychotic status not reported) and 13 healthy controls with the age range 8–17 years. The overall performance accuracy was

Table 1
Response inhibition neural activity alterations in 22q11.2 deletion syndrome. Underlined text refers to the findings included in the corresponding figure. *uncorrected, indicates that the results of the given study did not survive correction for multiple comparison.

Response Inhibition			
Authors	Participants	Method/Analysis	fMRI findings for 22q11.2DS carriers
Gothelf et al., 2007	13 with 22q11.2DS (Mean age: 17.8; Males/Females: 8/5) 14 HCs (Mean age: 17.2; Males/Females: 7/7) 9 with DD (Mean age: 18.1; Males/Females: 4/5)	**Go-NoGo task.** Go/NoGo vs. Go condition.	Increased activity compared to HCs and DD in the left parietal cortex. Increased activity in *COMT* Met vs. *COMT* Val in the cingulate gyrus (7 COMT Met carriers, 6 COMT Val carriers).
Montojo et al., 2015a	15 with 22q11.2DS (Mean age: 22.73; Males/Females: 8/7) 30 HCs (Mean age: 23; Males/Females: 18/12) 23 with ADHD (Mean age: 24.28; Males/Females: 11/12)	**Stop-signal task.** Successful stop vs. Go condition.	Decreased activity compared to HCs in bilateral middle frontal gyri, right medial/superior frontal gyri, left inferior frontal gyrus, right posterior cingulate/precuneus, bilateral caudate/thalamus, right middle temporal gyrus, left parietal cortex, bilateral occipital cortex and bilateral cerebellum. Decreased activity compared to ADHD in bilateral middle frontal gyri.
Montojo et al., 2015b	15 with 22q11.2DS (Mean age: 22.5; Males/Females: 11/6) 30 healthy controls (Mean age: 23; Males/Females: 18/12)	**Stop-signal task.** 1 Successful stopping vs. Go condition. 2 Unsuccessful stopping vs. Successful stopping. 3 Go trials vs. Null.	1 Decreased activity in bilateral frontal pole, right inferior frontal gyrus, right anterior cingulate, right posterior cingulate, bilateral caudate/thalamus, bilateral putamen, bilateral inferior/middle temporal gyri, left parietal cortex and bilateral occipital cortex. 2 Increased activity in bilateral inferior/middle frontal gyri, right caudate/thalamus and right putamen. 3 Decreased activity in bilateral middle temporal gyri, left angular gyrus and bilateral occipital cortex.

Abbreviations: Healthy controls (HCs), Idiopathic developmental disabilities (DD), Attention deficit hyperactivity disorder (ADHD), Catechol-O-methyltransferase (COMT).

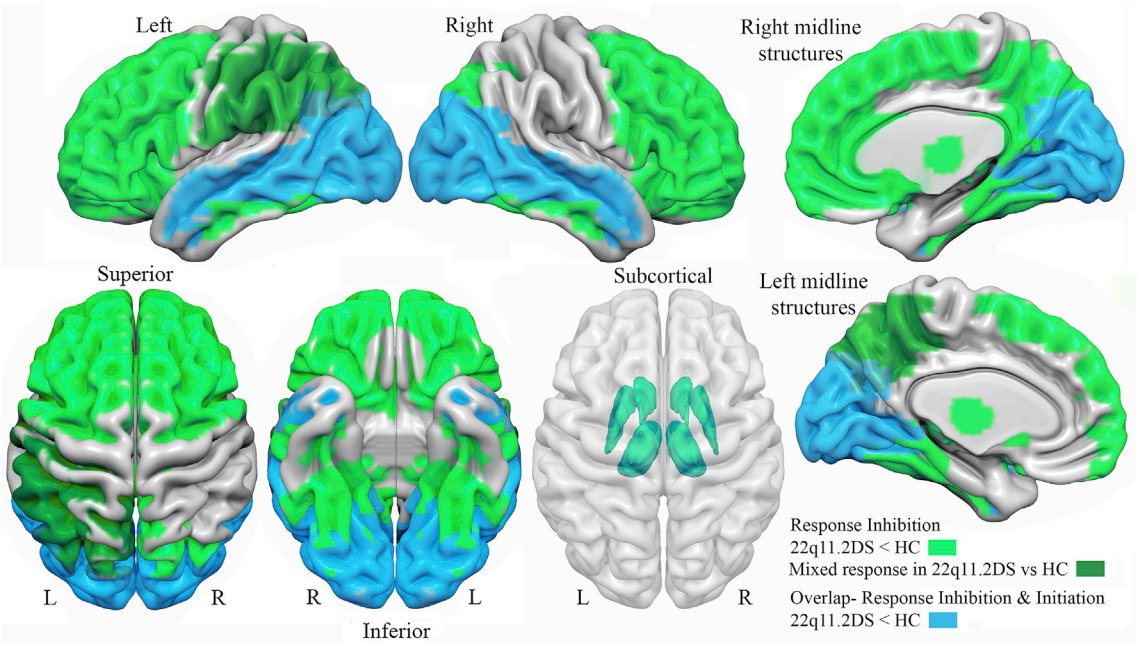

Fig. 4. Functional brain mapping of alterations in response inhibition in the 22q11.2 deletion syndrome. Areas in green indicate decreased activity in 22q11.2 deletion carriers compared with healthy controls during response inhibition and include the bilateral middle and inferior frontal gyri and frontal poles, right medial and superior frontal gyri, right anterior and posterior cingulate, right precuneus, bilateral caudate, thalamus and putamen, bilateral inferior temporal gyri. The left parietal cortex, shaded in dark green, had mixed findings (increased and decreased activity) in 22q11.2 deletion carries compared to healthy controls during response inhibition. Areas in blue indicate decreased activity in 22q11.2 deletion carriers compared with healthy controls during response inhibition and initiation and encompass bilateral middle temporal gyri, left angular gyrus and bilateral occipital cortex. The images were created using Surf Ice (https://www.nitrc.org/projects/surfice/) and Mango (http://ric.uthscsa.edu/mango/). The regions were defined using an online FSL atlas (Talairach atlas registered into MNI 152 space), and based on the findings from (Montojo et al., 2015b, 2015a), which were corrected for multiple comparisons at the cluster level.

significantly higher in the controls than in 22q11.2DS. Consistent with Kates et al. (2007) and Harrell et al. (2017), Azuma et al. (2009) found significant increased activation for controls in the right cingulate gyrus, bilateral precuneus, the right superior parietal lobule and the cuneus. However, they did not observe any significant between-group difference in prefrontal task-related activation. Montojo et al. (2014) investigated spatial working memory in 16 22q11.2 deletion carriers (2 reported to have psychotic disorder) and 25 healthy controls (18–43 years old) using a spatial capacity working memory task and found that controls showed significantly increased activation in the left intraparietal sulcus (IPS) relative to 22q11.2 deletion carriers. Interestingly, the authors report that the presence of unusual thought content or delusional ideas (one subscale derived from the structured interview for prodromal symptoms) was negatively correlated with activation in the left IPS. Further, the activation in left IPS was also negatively correlated with the positive symptoms scores, with greater activation being associated with lower symptoms. This activation in the left IPS during spatial working memory may play a role in the generation of psychotic symptoms in 22q11.2DS. However, no causal inference between psychotic symptoms and activation in left IPS can be drawn from these findings.

The studies on working memory in 22q11.2DS provide converging evidence that the working memory circuitry in 22q11.2DS is disrupted, in line with what is observed in schizophrenia (Glahn et al., 2005) as well as in first-episode schizophrenia (Schneider et al., 2007). For a summary of the findings on working memory, see Table 2 and Fig. 5. More specifically, activation in the right anterior cingulate is decreased in 22q11.2DS when participants are engaged in a non-spatial working memory task (such as the N-back) (Harrell et al., 2017; Kates et al., 2007) (green in Fig. 5), whereas activation in bilateral parietal, occipital and left frontal regions is decreased in 22q11.2DS when participants are engaged in a spatial working memory task (Azuma et al., 2009; Montojo et al., 2014) (purple in Fig. 5). The overlap between the two working memory tasks, where 22q11.2 deletion carriers show reduced activity, is found in right frontal regions and bilateral precuneus (blue in Fig. 5). Further, more studies are crucial in order to establish a clearer link between the activity in left IPS and the presence of psychotic symptoms in 22q11.2DS. A limitation common to all four studies on working memory in 22q11.2DS is the reported group differences for IQ, in line with previous literature. However, since none of the studies, to our knowledge, included IQ as a covariate in their analysis, it is hard to delineate whether the differences in IQ could explain some of the observed brain differences.

6. Arithmetic processing

Arithmetic processing was investigated with fMRI by Eliez et al. (2000) in eight young 22q11.2 deletion carriers and eight healthy controls. Participants had to solve either an easy math (2-operand) question or a hard math question (3-operand) by responding whether the shown math result was correct or not. 22q11.2 deletion carriers (psychotic status not reported) showed similar performance on the easy math task, but reduced performance for the hard math task. Reaction times were not different between groups. Regions of interest analysis showed that 22q11.2 had significantly increased activation in the left supramarginal gyrus during the difficult math task, but not for the easy task compared to controls. Voxel based analysis showed that 22q11.2 deletion carriers further had increased activation in left precentral gyrus as well as in the right supramarginal gyrus, insula and intraparietal sulcus. This study pioneered the fMRI research in 22q11.2DS, however, the results were preliminary given the relative small sample size. See the results summarized in Table 3.

7. Reward processing

Reward is a key driver of behaviour. Reward processing is typically associated with activation in the ventral striatum and the ventral

Table 2
Working memory neural activity alterations in 22q11.2 deletion syndrome. Underlined text refers to the findings included in the corresponding figure. *uncorrected, indicates that the results of the given study did not survive correction for multiple comparison.

Working memory			
Authors	Participants	Method/Analysis	fMRI findings for 22q11.2DS carriers
Kates et al., 2007 *uncorrected	17 with 22q11.2DS (Ages: 8–15; Males/Females: 10/7) 10 siblings of 22q11.2DS (Ages: 8–15; Males/Females: 5/5) 10 HCs (Ages: 8–15; Males/Females: 6/4)	**Two-back task.** Two-back vs. 0-back.	Decreased activity compared to HCs in the right middle/inferior frontal gyri, bilateral inferior parietal lobules, right superior parietal lobule, right superior occipital gyrus and left middle occipital gyrus. Decreased activity compared to siblings in the bilateral anterior cingulate cortex, bilateral angular gyri, left supplementary motor area and right superior/middle occipital gyri. Increased activity compared to HCs in left inferior frontal gyrus, right anterior cingulate cortex, right medial/superior occipital gyri and right cuneus.
Harrell et al., 2017	11 with 22q11.2DS (Mean age: 14.5; Males/Females: 4/7) 8 HCs (Mean age: 14; Males/Females: 3/5)	**One-back and Two-back task** 1 Two-back vs. 0-back. 2 Two-back vs. One-back.	1 Decreased activity in right superior/middle/frontal pole and right anterior cingulate cortex. 2 Decreased activity in right superior/middle/frontal pole and bilateral precuneus.
Azuma et al., 2009	8 with 22q11.2 (Ages: 9–16; Males/Females: 4/4) 13 HCs (Ages: 8–17; Males/Females: 8/5)	**Spatial working memory task.** Spatial working memory vs. baseline detection condition.	Decreased activity in bilateral precuneus, right superior parietal lobule, right cuneus and right cingulate gyrus.
Montojo et al., 2014	16 with 22q11.2 (Mean age: 23.88; Males/Females: 6/10) 25 HCs (Mean age: 24.36; Males/Females: 10/15)	**Spatial capacity working memory.** 1 All conditions. 2 Load 7, 5 & 3 vs. Load 1. 3 Structured interview for prodromal symptoms.	1 Decreased activity in the left superior/inferior parietal lobule and left IPS. 2 Decreased activity in bilateral SFS, bilateral middle frontal gyri, bilateral precentral gyri, right postcentral gyrus, bilateral IPS, bilateral superior/inferior parietal lobules, bilateral fusiform gyri and bilateral occipital cortex. 3 Positive symptoms scores and unusual thought content/delusional ideas: Negative correlation with activity in the left IPS.

Abbreviations: Healthy controls (HCs), intraparietal sulcus (IPS), superior frontal sulci (SFS).

tegmental area and is tightly related to dopaminergic neurotransmission (Haber and Knutson, 2010). Current theories of psychosis have suggested that aberrant reward processing might contribute to the clinical symptoms of the disorder (Kapur, 2003). Indeed, people with schizophrenia exhibit alterations in the reward network, particularly in the striatal system (Jensen et al., 2008; Juckel et al., 2006; Walter et al., 2009b). In addition, activation in the reward system is reduced in individuals at ultra-high risk for psychosis (Roiser et al., 2013). This motivated van

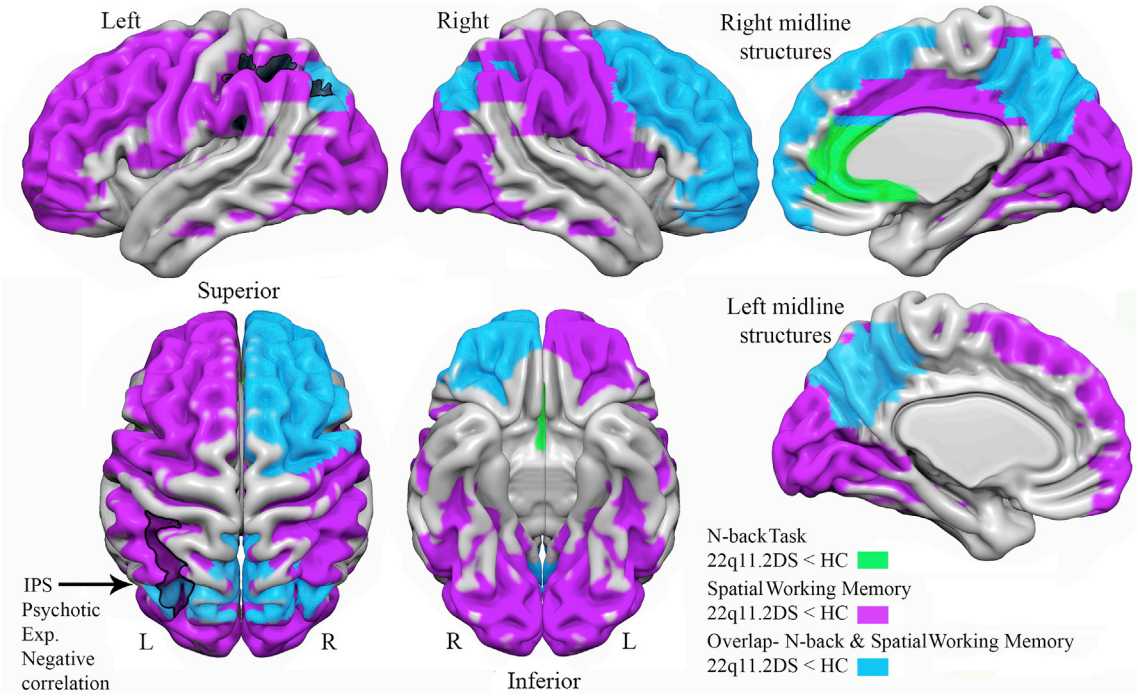

Fig. 5. Functional brain mapping of alterations in working memory in the 22q11.2 deletion syndrome. Areas in purple indicate decreased activity in 22q11.2 deletion carriers compared with healthy controls during spatial working memory. Brain regions include bilateral precentral gyri, right postcentral gyrus, bilateral Intraparietal sulci (IPS), bilateral superior and inferior parietal lobules, bilateral fusiform gyri, bilateral occipital cortex, right cuneus and right cingulate gyrus. Areas in blue indicate decreased activity in 22q11.2 deletion carriers compared with healthy controls during spatial working memory and the N-back task in the right superior and middle frontal gyri and frontal pole, and bilateral precuneus. The right anterior cingulate cortex, shaded in green, had decreased activity in 22q11.2 deletion carries compared to healthy controls during the N-back task (two-back vs 0-back/one-back). Activity in the IPS, shaded in black, was negatively correlated with psychotic scores. The images were created using Surf Ice (https://www.nitrc.org/projects/surfice/) and Mango (http://ric.uthscsa.edu/mango/). The regions were defined using an online FSL atlas (Talairach atlas registered into MNI 152 space), and based on the findings from (Harrell et al., 2017)(Azuma et al., 2009)(Montojo et al., 2014), which were corrected for multiple comparisons at the cluster level.

Table 3
Arithmetic neural activity alterations in 22q11.2 deletion syndrome. *uncorrected, indicates that the results of the given study did not survive correction for multiple comparison.

Arithmetic			
Authors	Participants	Method/Analysis	fMRI findings for 22q11.2DS carriers
Eliez et al., 2000 *uncorrected	8 with 22q11.2 (Mean age: 15.5; Males/Females: 5/3) 8 HCs (Mean age: 15.8; Males/Females: 5/3)	**Arithmetic computation.** Difficult arithmetic vs. Control (detect a 0)	Increased activity in left precentral gyrus, bilateral supramarginal gyrus, right insula and right intraparietal sulcus.

Abbreviations: Healthy controls (HCs).

Duin et al. (2016) to study reward processing in 16 22q11.2 deletion carriers (mean age = 28.2, std = 6) and 12 healthy controls while they engaged in a monetary incentive delay task. Five of the 22q11.2 deletion carriers had a psychotic disorder. During anticipation of reward, the 22q11.2DS group showed less activation compared to controls in the right medial frontal gyrus, bilateral cingulate gyri, the paracentral lobules and the right postcentral gyrus, indicated in green in Fig. 6. In contrast, during anticipation of loss the 22q11.2DS group showed less activation in the left posterior cingulate cortex, bilateral cuneus and the right precuneus (purple in Fig. 6). The 22q11.2DS group had decreased activity during both anticipation of loss and reward in the left precuneus (blue in Fig. 6). Hence, disruptions in the brain networks underlying reward processing and its consequences on behavioural impairments in 22q11.2DS are akin to those seen in schizophrenia. This suggests that behavioural impairments common to schizophrenia such as decreased motivation and anhedonia are seen in 22q11.2DS as well. However, it is important to note here, that 5 of the 16 deletion carriers met criteria for a psychotic disorder, which makes it hard to delineate if the observed effect is due to the presence of psychosis or the 22q11.2 deletion. In that study, there was no relation between the symptoms present in 22q11.2 deletion carriers and the reward or loss related activity. However, it would be interesting to investigate this in a larger cohort, since this link is established in schizophrenia, especially with negative symptoms such as anhedonia, avolition, and reward processing (Galderisi et al., 2015). Please see Table 4 for a summary of the findings.

During anticipation of reward, the Val carriers (N = 6) showed higher activation compared to Met carriers (N = 10) in the right middle frontal gyrus, bilateral cingulate gyri, right posterior cingulate cortex and bilateral precuneus (van Duin et al., 2016). Contrary to this, during anticipation of loss, the Met carriers showed greater activation than the Val carriers in the anterior/posterior cingulate cortex, the insula and the striatum, suggesting that the Met genotype is associated with greater loss aversion. As pointed out previously, genotype-phenotype associations usually require large samples for single nucleotide polymorphisms. Therefore, the reported effects of the Val158Met COMT polymorphism are preliminary and need to be replicated in a larger sample.

8. Social cognition

Emotion processing, in particular processing of facial emotions, has been extensively studied in schizophrenia (Kring and Elis, 2013). In healthy people, viewing faces with a range of emotional expressions consistently engage a set of brain areas, including the amygdala, the superior temporal sulcus, the dorsomedial prefrontal cortex, the anterior cingulate cortex, the supramarginal gyrus, the orbitofrontal cortex, the insula and other subcortical areas (Haxby et al., 2000; Kober et al., 2008). People with schizophrenia typically show reduced activation in the amygdala, the anterior cingulate cortex, the dorsolateral prefrontal

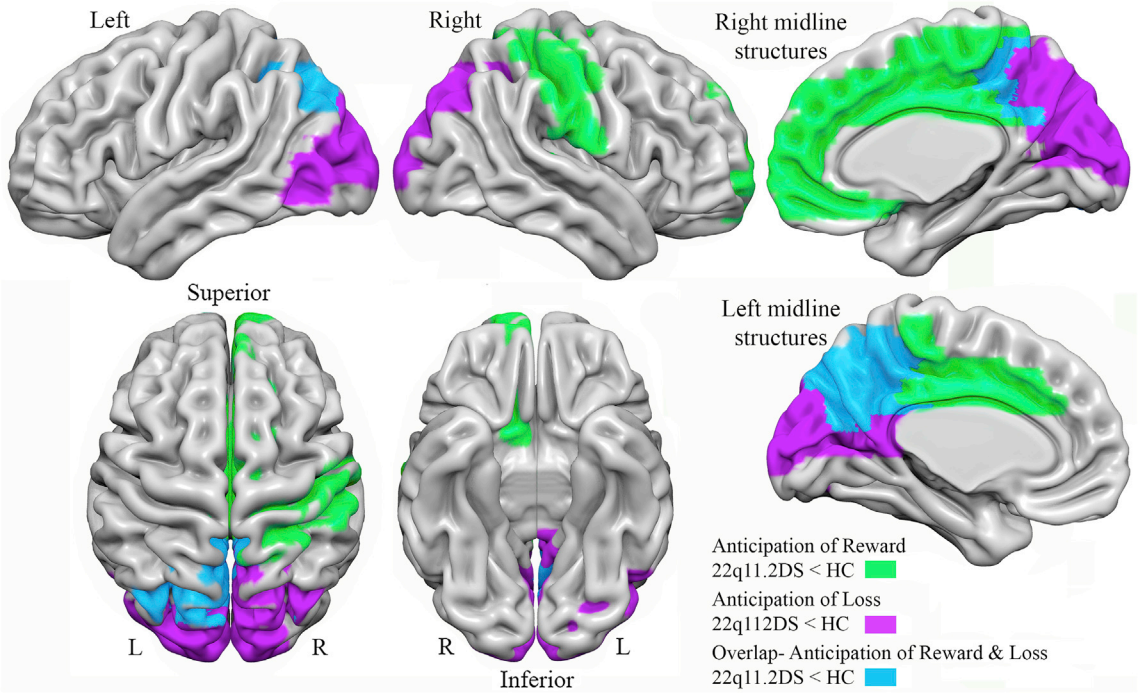

Fig. 6. Functional brain mapping of alterations in reward processing in the 22q11.2 deletion syndrome. Areas in green indicate decreased activity in 22q11.2 deletion carriers compared with healthy controls during anticipation of reward in the right medial frontal gyrus, bilateral paracentral lobules, bilateral cingulate gyri and right postcentral gyrus. Areas in purple indicate decreased activity in 22q11.2 deletion carriers compared with healthy controls during anticipation of loss in the bilateral cuneus, right precuneus, left posterior cingulate and left middle occipital gyrus. The right precuneus, shaded in blue, had decreased activity in 22q11.2 deletion carries compared to healthy controls during anticipation of reward and loss. The images were created using Surf Ice (https://www.nitrc.org/projects/surfice/) and Mango (http://ric.uthscsa.edu/mango/). The regions were defined using an online FSL atlas (Talairach atlas registered into MNI 152 space), and based on the findings from van Duin et al., 2016, which were corrected for multiple comparisons at the cluster level.

Table 4
Reward processing neural activity alterations in 22q11.2 deletion syndrome. Underlined text refers to the findings included in the corresponding figure. *uncorrected, indicates that the results of the given study did not survive correction for multiple comparison.

Reward processing			
Authors	Participants	Method/Analysis	fMRI findings for 22q11.2DS carriers
van Duin et al., 2016	16 with 22q11.2 (Mean age: 28.2; Males/Females: 8/8) *5 with a psychotic disorder 12 HCs (Mean age: 29; Males/Females: 8/4)	**Monetary incentive delay task.** 1 Anticipation of reward vs. Anticipation of no monetary outcome. 2 Anticipation of loss vs. Anticipation of no monetary outcome.	1. Decreased activity in right medial frontal gyrus, bilateral paracentral lobules, bilateral cingulate gyri, right postcentral gyrus and left precuneus. Increased activity in *COMT* Val vs. *COMT* Met in the right middle frontal gyrus, right precentral gyrus, right paracentral lobule, bilateral postcentral gyri, bilateral posterior cingulate cortex and bilateral precuneus. 2. Decreased activity in bilateral cuneus, bilateral precuneus, left posterior cingulate and left middle occipital gyrus. Increased activity in *COMT* Met vs. *COMT* Val in the left anterior cingulate cortex, left insula, left posterior cingulate cortex, left putamen, left superior temporal gyrus, left thalamus and bilateral caudate (six COMT Met carriers, 10 COMT Val carriers).

Abbreviations: Healthy controls (HCs), Catechol-O-methyltransferase (COMT).

cortex, the medial frontal cortex, and visual areas, see Taylor et al. (2012) for a meta-analysis.

The first study investigating responses to emotional faces in 22q11.2DS was a preliminary one, including eight 22q11.2 deletion carriers, three of which had a diagnosis of schizophrenia and 9 healthy controls (Van Amelsvoort et al., 2006). Participants viewed a series of angry and happy faces as well as neutral facial expressions. Across conditions the 22q11.2 deletion carriers showed reduced activity in the right insula and premotor cortex and increased activity in bilateral occipital regions compared to controls. None of the results survived correction for multiple comparison and the study does not report on any psychotic symptoms in the group. Therefore, no strong conclusions can be drawn from this study.

A group of 15 22q11.2 deletion carriers of which five were reported to have psychotic symptoms did not recruit the face processing network typically engaged in 16 age and sex matched controls (Andersson et al., 2008). More specifically, when comparing responses to neutral faces and houses, decreased activation was found in the fusiform face area in the deletion carriers relative to controls. Further, controls showed a clear category-specificity (faces > houses) for faces relative to houses, which was lacking in the 22q11.2 deletion carriers. Repetition suppression (to the second presentation of the same picture) was found for fearful faces in the left middle and inferior temporal gyrus and right ventro-lateral amygdala in controls. 22q11.2 deletion carriers only showed repetition suppression in prefrontal regions, with an apparent lack of modulation by fear expression for the 22q11.2 deletion carriers in the amygdala. Further, a difference between 22q11.2 deletion carriers with and without psychotic symptoms were found in left fusiform gyrus, where carriers with psychotic symptoms showed decreased activation. In Azuma et al. (2015) children with 22q11.2DS (N = 14, none reported to have psychotic symptoms) showed reduced activity in the right superior frontal gyrus, the left postcentral/precentral gyrus, the insula, the right cingulate gyrus, bilateral fusiform gyrus, the inferior occipital gyrus and the cerebellum for fearful and disgusted faces (see areas in green in Fig. 7). Further, decreased activation in the left precentral and fusiform gyri, the right lingual gyrus and bilateral cerebellum was negatively correlated with social difficulties as indexed by the Total Difficulties Score from the Strengths and Difficulties Questionnaires. This correlation suggests that hypoactivation might be associated with social impairments in 22q11.2DS.

Coman et al. (2010) studied 43 individuals with 22q11.2DS from whom nine had psychotic symptoms. They found that young females activated the left anterior mid-cingulate gyrus more than young males when processing positive emotions. Investigating the effect of Val158Met COMT polymorphism on emotion processing revealed a gender-allele interaction effect in the frontal lobe during pleasant stimuli, with female Val and male Met allele carriers showing significantly greater activation compared to the male Val and female Met carriers. Further, a gender-allele interaction effect was observed for the limbic regions when processing unpleasant stimuli. Here, Val male and Met female participants showed greater activation than female Val and male Met allele carriers. Results therefore pointed to COMT polymorphism being moderated by gender in 22q11.2DS during processing of emotional stimuli.

A recent study investigated social perception in 22 young non psychotic 22q11.2 deletion carriers and 22 healthy controls (Dubourg et al., 2018). Participants were watching a stream of images varying in emotional valence and social content, they were instructed to indicate if an image was intact or scrambled. Comparing the neural responses to social vs. non-social images revealed that 22q11.2 deletion carriers had reduced activity in bilateral middle frontal gyrus, left anterior cingulate, medial/superior frontal gyrus, as well as in the right supramarginal gyrus, inferior parietal lobule, precuneus, and posterior cingulate (orange in Fig. 7). There were no group differences observed in the responses to positive vs. negative emotions, indicating that the alterations observed in the social perception network are present irrespective of valence.

The concept of self-referential processing concerns how strongly a stimulus is experienced to be related to oneself compared to others. In the healthy brain, self-referential processing is mediated by cortical midline structures (Northoff et al., 2006; Northoff and Bermpohl, 2004). In schizophrenia, the activation of the self-referential network is typically altered. More specifically, it has been shown that schizophrenia patients compared to controls have smaller activation in posterior midline structures, whereas activation of anterior midline structures is sometimes greater, see Shad et al. (2011) and van der Meer et al. (2010) for a review. Self-referential processing has further been investigated in first episode psychosis, where reduced activation in the right middle temporal gyrus and left precuneus was found for patients compared with healthy controls (Kambeitz-Ilankovic et al., 2013). In addition, activation in the right middle temporal gyrus correlated negatively with positive psychotic symptoms. Whole-brain fMRI was used to evaluate self- and other-related processing in 14 22q11.2 deletion carriers, aged 12–20 years and 17 controls (Schneider et al., 2012). None of the 22q11.2DS carriers met criteria for psychosis. Participants had to judge if a series of adjectives applied to a fictional character, to their best friend or to themselves. Compared to controls, 22q11.2 deletion carriers showed decreased activation in the cortical midline structures as well as in the striatum in the self-relating condition. Specifically, the activation in the anterior cingulate cortex was negatively associated with the severity of prodromal positive symptoms from the PANSS score, in line with the findings in first episode psychosis (Kambeitz-Ilankovic et al., 2013). This correlation between psychotic symptoms in 22q11.2DS and activation in the anterior cingulate cortex is suggestive of the anterior cingulate cortex playing a role in the generation of psychotic symptoms in 22q11.2DS, however, no causal role can be established from this finding. In a similar study, (Dahoun et al., 2013) investigated self-other discrimination processes in 12 people with auditory hallucinations, 13 22q11.2 deletion carriers and 22 controls. Participants had to either imagine doing a task (for example

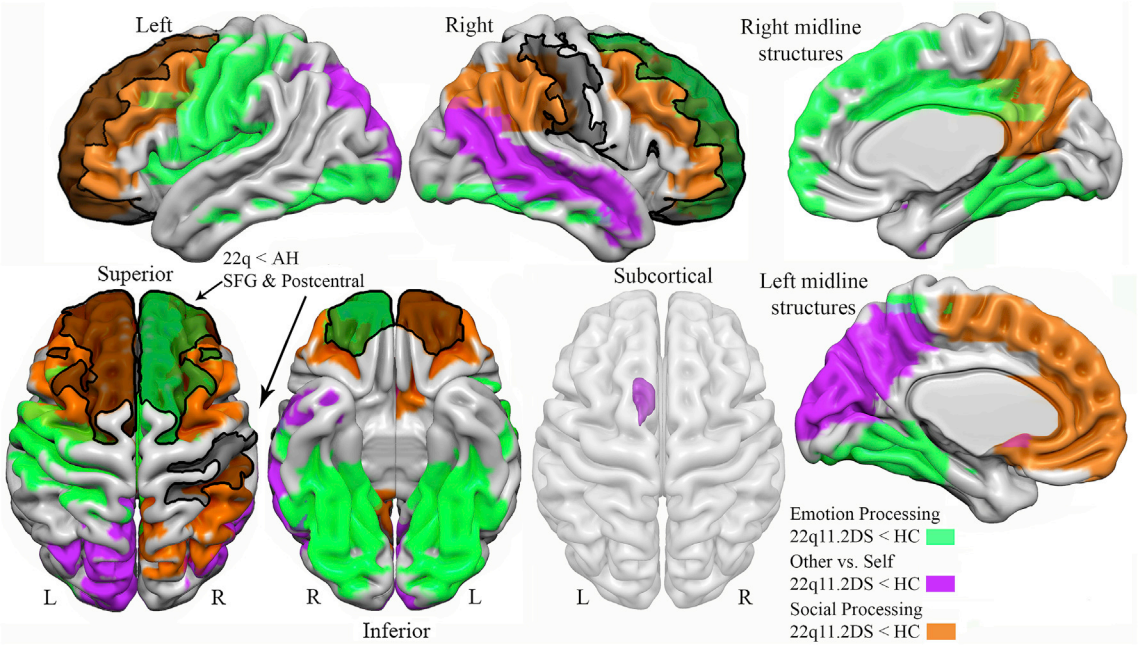

Fig. 7. Functional brain mapping of alterations in social cognition in 22q11.2 deletion syndrome. Areas in green indicate regions of decreased activity in 22q11.2 deletion carriers compared with healthy controls during facial emotion processing. Brain regions include right superior frontal gyrus, left postcentral gyrus, left precentral gyrus, right cingulate gyrus, left inferior occipital gyrus, left insula, left transverse temporal gyrus and bilateral fusiform gyri. Areas in purple indicate decreased activity in 22q11.2 deletion carriers compared with healthy controls during other versus self processing in the right middle temporal gyrus, left cuneus, left precuneus, left caudate and right superior occipital gyrus. The bilateral superior frontal gyri and right precentral, shaded in black, had decreased activity in 22q11.2 deletion carriers compared to participants with auditory hallucinations. Areas in orange indicate decreased activity in 22q11.2 deletion carriers compared with healthy controls during social processing in left medial and superior frontal gyri, bilateral middle frontal gyrus, left anterior cingulate, right inferior parietal lobule, right supramarginal gyrus, right posterior cingulate and right precuneus. The images were created using Surf Ice (https://www.nitrc.org/projects/surfice/) and Mango (http://ric.uthscsa.edu/mango/). The regions were defined using an online FSL atlas (Talairach atlas registered into MNI 152 space), and based on the findings from Andersson et al. (2008); Azuma et al., 2015; Coman et al., 2010 and Schneider et al., 2012.

"open a bottle") themselves or imagine their best friend doing it. The group with auditory hallucinations showed decreased activity during the action simulation period in the left middle occipital gyrus, left cingulate gyrus and in the right precuneus for the contrast "best friend" vs "self". For the same contrast, 22q11.2 deletion carriers showed reduced activation in the right superior occipital gyrus, left caudate tail and left precuneus (purple in Fig. 7). The task included a prime period during which subjects got the prime cue to imagine either yourself or your best friend performing the following task. When contrasting brain responses to primes referring to one's friend versus oneself, 22q11.2 deletion carriers showed reduced activity in the left cuneus, precuneus and right middle temporal gyrus (purple in Fig. 7). Further, a difference was observed between the group with auditory hallucinations and 22q11.2 deletion carriers in the prime period where 22q11.2 deletion carriers showed reduced activity in the left caudate, right anterior cingulate cortex and right superior frontal gyrus for "prime self" trials versus "prime other" and in right postcentral gyrus and bilateral superior frontal gyrus for "prime other" versus "prime self" (black shaded area in Fig. 7).

For a summary of the studies on social cognition please see Fig. 7 and Table 5. Only the studies surviving correction for multiple comparison have been included in the figure and this has been indicated in the table. The findings on social cognition in 22q11.2DS provides converging evidence that emotion cognition as well as self-referential processing in 22q11.2DS is altered in similar ways as in schizophrenia (Shad et al., 2011; Taylor et al., 2012; van der Meer et al., 2010). Interestingly, only one study on social cognition found correlation between brain activity and psychotic symptoms (Schneider et al., 2012), where a negative correlation between activation in the left anterior cingulate cortex with psychotic symptoms was found. Andersson et al. (2008) reported decreased activation in psychotic compared to non-psychotic 22q11.2 deletion carriers the in left fusiform gyrus. However, none of these results survived correction for multiple comparison. Dahoun et al. (2013) though found that 22q11.2DS had decreased activity compared to people with auditory hallucinations in bilateral superior frontal gyri and right postcentral, see the black shaded area in Fig. 7. These associations between altered brain activity and symptoms would be a really interesting topic on which to follow up on and may yield insights into altered social cognition that may contribute to the generation of psychotic symptoms in 22q11.2DS. For a summary of the findings on social cognition, see Fig. 7 and Table 5.

9. Discussion and future directions

The neuroimaging literature in 22q11.2DS is rapidly growing. Being able to map brain alterations with variations in the human genome can give important insights into the pathophysiology of the specific deletion. Further, it can help in advancing the general understanding of which neurobiological alterations set the frame for the emergence of neurodevelopmental disorders in the human brain. In this review, we have focused on task-based functional brain alterations with a specific emphasis on the susceptibility to psychosis, given the significant higher risk for psychosis associated with the deletion. However, it is important to note that the deletion involves multiple genes and, as a consequence, it is not only associated with a high risk of psychosis but with a broader range of psychiatric and neurodevelopmental disorders.

Even though 22q11.2DS is one of the most common copy number variants, the prevalence, 1:2000-1:4000, is still relative small (Goodship et al., 1998; Olsen et al., 2018; Oskarsdóttir et al., 2004; Robin and Shprintzen, 2005). A natural consequence of such low prevalence is that studies on 22q11.2DS suffer from relatively small sample sizes. A small sample size is characteristic for the majority of the studies reviewed here, which makes it hard at times to disentangle whether a lack of association

Table 5
Social cognition neural activity alterations in 22q11.2 deletion syndrome. Underlined text refers to the findings included in the corresponding figure. *uncorrected, indicates that the results of the given study did not survive correction for multiple comparison.

Social cognition			
Authors	Participants	Method/Analysis	fMRI findings for 22q11.2DS carriers
Andersson et al., 2008 *uncorrected	15 with 22q11.2 (Mean age: 15.27; Males/Females: 5/10) *5 with a psychotic disorder 16 HCs (Mean age: 15.03; Males/Females: 7/9)	**Visual categorization task.** 1 Neutral faces vs. Houses. 2 Fearful faces vs. Neutral faces. 3 Fearful face adaptation. 4 Psychotic symptoms and Faces vs. houses	1 Decreased activity in the left fusiform gyrus. 2 Decreased activity in the right anterior cingulate cortex. 3 Failed to decrease activity in the left middle frontal gyrus, left inferior temporal gyrus and right ventro-lateral amygdala. 4 Decreased activity in psychotic compared to non-psychotic patients in left fusiform gyrus.
Azuma et al., 2015	14 with 22q11.2DS (Ages: 9–17; Males/Females: 7/7) 14 HCs (Ages: 8–17; Males/Females: 9/5)	**Emotion task.** 1 Fear condition vs. fixation cross. 2 Disgust condition vs. fixation cross.	1 Decreased activity in right superior frontal gyrus, left postcentral gyrus, left precentral gyrus, right cingulate gyrus, left fusiform gyrus, left inferior occipital gyrus and left cerebellum. 2 Decreased activity in left postcentral gyrus, left precentral gyrus, left insula, left transverse temporal gyrus, bilateral fusiform gyri and bilateral cerebellum.
Coman et al., 2010	43 with 22q.11.2DS Met allele (Mean ages: 14.3/15.9; Males/Females: 9/8) Val allele (Mean ages: 15.4/15.2; Males/Females: 9/17)	**Emotion induction.** Unpleasant vs. Neutral pictures.	Increased activity in *COMT* Met vs. *COMT* Val in left cingulate gyrus.
Schneider et al., 2012 *uncorrected	14 with 22q11.2DS (Mean age: 16.13; Males/Females: 7/7) 17 HCs (Mean age: 15.79; Males/Females: 12/5)	**Self-referential processing.** 1 Self vs. Rest. 2 Self vs. Semantic. 3 Self vs. Other. 4 PANSS positive scores.	1 Decreased activity in left caudate, left anterior cingulate and left frontal gyrus. 2 Decreased activity in left caudate and bilateral anterior cingulate cortex. 3 Decreased activity in left anterior cingulate and left medial frontal gyrus and right caudate. 4 Negative correlation with activation in the left anterior cingulate cortex.
Van Amelsvoort et al., 2006 *uncorrected	8 with 22q11.2DS (Mean age: 34; Males/Females: 1/7 *3 with schizophrenia 9 HCs (Mean age: 37; Males/Females: 4/5)	**Facial emotion processing.** Happy or angry facial expressions vs. neutral facial expression.	Decreased activity in right precentral, right insula and right postcentral gyrus. Increased activity in left fusiform, left middle temporal gyrus, right lingual and right cuneus.
Dahoun et al., 2013	13 with 22q11.2DS (Mean age: 16.14; Males/Female: 9/4) 12 with subclinical AH (Mean age: 15.97; Males/Female: 5/7) 22 HCs (Mean age: 16; Males/Female: 16/6)	**Action simulation task. Self-referential and other processing.** 1 Other vs. Self 2 Self vs. Other 3 3rd person perspective vs. 1st person perspective	1 Decreased activity in 22q vs. HCs in right middle temporal gyrus, left cuneus and left precuneus. 3 Decreased activity in 22q vs. HCs in left caudate, right superior occipital gyrus and left precuneus. 1 Decreased activity in 22q vs. AH in bilateral superior frontal gyri and right postcentral. 2 Decreased activity in 22q vs. AH in right superior frontal gyrus, right anterior cingulate and left caudate.
Dubourg et al., 2018	22 with 22q11.2DS (Mean age: 20.3; Males/Female: 5/17) 22 HCs (Mean age: 19.7; Males/Female: 7/15)	**Socio-emotional perception.** Social vs. Non-social	Decreased activity in left medial/superior frontal gyri, bilateral middle frontal gyrus, left anterior cingulate, right inferior parietal lobule, right supramarginal gyrus, right posterior cingulate and right precuneus.

Abbreviations: Healthy controls (HCs), Catechol-O-methyltransferase (COMT), Positive and Negative Symptom Scale (PANSS), Auditory Hallucinations (AH).

between the neuroimaging findings and the presence of a deletion vs. no presence of deletion is non-existent, or simply due to insufficient power. Future trans-national large-scale studies are needed as well as meta-analysis of existing studies on 22q11.2DS. Another limitation is that very few studies have looked at the relationship between symptoms and the found brain alterations. It has therefore been very hard to make any general conclusions on the links between brain alterations in 22q11.2DS and symptoms. Future studies should aim for larger sample sizes that enable the investigation of the links between the brain alterations and psychotic symptoms. This will be crucial to advance our understanding of the link between psychiatric symptoms and brain alterations in general, but also to establish links between individual brain abnormalities and the individual symptoms in people with 22q11.2DS.

The disease state of the 22q11.2 deletion carriers varied considerably across the different studies reviewed here. Inconsistencies across studies may, at least in part, be explained by the heterogeneity of the clinical phenotypical spectrum across studies. For example, reduced sensory gating was found by Zarchi et al. (2013) including 22q11.2DS carriers with psychosis (14%), but not in studies where carriers did not have schizophrenia (Rihs et al., 2013; Vorstman et al., 2009). However, it should be noted that six out of 21 carriers in Rihs et al. (2013) experienced psychotic symptoms. It is unclear whether the effect reported by Zarchi et al. (2013) would persist when controlling for psychosis. Hence, the question remains as to whether reduced sensory gating is caused by the deletion itself, or a consequence of psychosis. To answer this question, future studies should aim at comparing 22q11.2 deletion carriers with and without psychosis. Another possibility, which has recently gained some traction, would be to take a continuum of psychosis approach (van Os et al., 2009). In this way, the amount of symptoms could be mapped in a continuous fashion to functional neuroimaging deficits. This has been well studied using MMN, see (Randeniya et al., 2017) for a recent review. In this way, the attenuation of MMN responses is accentuated throughout the spectrum of psychosis, from healthy people with a small degree of psychotic tendency to chronic patients with a high degree of psychotic symptoms. However, while this approach would be very helpful in the delineation of the processes involved in the generation of psychotic symptoms, it would be hard to distinguish which functional neuroimaging alterations would be specifically related to the deletion itself and those generally caused by the symptoms. Longitudinal studies would be critically informative, but are logistically extremely demanding.

Age range is another important methodological difference amongst the studies reviewed here. The difference in age range of the deletion carriers becomes particularly important when comparing effects across studies, since studying children versus adults naturally introduces neurodevelopmental differences that might contribute to divergent findings across studies (Moberg et al., 2018).

As mentioned, the 22q11.2 deletion involves deletion of multiple

genes with the COMT and PRODH being one of the major genes involved in the genetic susceptibility to schizophrenia (Gothelf et al., 2008). Despite small sample sizes, all studies that investigated the Val/Met status of the Val158Met COMT polymorphism in the remaining allele, showed that the residual COMT allele had a modulating effect on cognitive functioning and its brain correlates, namely MMN (Baker et al., 2005; Zarchi et al., 2013), reward (van Duin et al., 2016) and emotion processing (Coman et al., 2010), as well as response inhibition (Gothelf et al., 2007). The effect of COMT is very appealing to study due to its involvement in dopamine, as well as the associated susceptibly to schizophrenia. However, it includes subgrouping of the 22q11.2DS group and thereby requires a relatively large sample size. Given that the results looking both at COMT and PRODH in this review are very promising, future large-scale studies including larger cohorts as well as longitudinal studies following the life-span of 22q11.2DS are needed to corroborate the above mentioned findings on COMT.

The emergence of psychosis in 22q11.2DS has been associated with abnormal resting-state connectivity in frontal and midline structures, see (Scariati et al., 2016) for a review. While these findings on connectivity at "rest" can give us insights into how different brain regions interact in a task-free context, they cannot tell us about the (altered) brain mechanisms underpinning sensory processes and behaviour. In light of this, future studies should further delineate whether this dysconnectivity is also present in task-based functional neuroimaging. In this way, altered connectivity could be related to a specific cognitive function and/or behaviour, thereby providing important insights into their underlying brain mechanisms, see (Larsen et al., 2018). As an additional note, more computational approaches are needed to derive causal models of the underlying brain mechanisms associated with alterations in sensory and cognitive processes in 22q11.2DS.

In sum, we have reviewed existing task-based functional neuroimaging in 22q11.2DS with a focus on the susceptibility to psychosis. The working memory and social cognition findings in 22q11.2DS seem to be in line with the schizophrenia literature. Response inhibition, on the other hand is intact at the behavioural level in 22q11.2DS, but not in schizophrenia. The brain regions engaged in reward and visual processing in 22q11.2DS were in line with the schizophrenia literature. However, caution is needed as these conclusions were drawn by one study for each domain. Given that the tasks reviewed here are very different in their nature, it is hard to make an overall conclusion of the affected regions. However, when comparing Figs. 4–7, it is clear that especially the frontal areas show reduced activity in 22q11.2DS compared to healthy controls across the different tasks. Recent results from the ENIGMA 22q11.2DS working group showed that the frontal gyrus were among the regions showing significantly smaller surface area in 22q11.2DS compared to controls (Sun et al., 2018). Future studies are still needed in order to elucidate if this reduced surface area is associated with the observed reduced frontal activation across the tasks presented here.

Results on auditory processing in 22q11.2DS showed controversial findings for mismatch negativity and sensory gating. However, the amplitude of the N1 peak and the auditory steady state responses seem to be altered. In order to provide a stronger link between schizophrenia and 22q11.2DS in terms of functional alterations, more studies and greater samples are needed.

Human behaviour and brain function arise from a complex interplay between genes and environment. 22q11.2DS offers a unique possibility to link a specific genetic alteration to cognitive dysfunction and aberrant neural development and thereby a more thorough understanding of the effects of genes in the human brain. Studying variations in the genome known to have a direct link to psychosis can help the neuroimaging field in the search for functional abnormalities anchored in the brain. This would ideally result in a more clear direction towards an objective functional biomarker for psychosis integrating features from different domains i.e. genetics, cognition and neuroimaging (Van et al., 2017). Such functional biomarkers will be critical in informing diagnosis and targeting new treatment strategies in the future.

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Conflicts of interest

These disclosures are UNRELATED to the present work:

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