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Reduced brain activation during spoken language processing in children with developmental language disorder and children with 22q11.2 deletion syndrome

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ABSTRACT

Language difficulties of children with Developmental Language Disorder (DLD) have been associated with multiple underlying factors and are still poorly understood. One way of investigating the mechanisms of DLD language problems is to compare language-related brain activation patterns of children with DLD to those of a population with similar language difficulties and a uniform etiology. Children with 22q11.2 deletion syndrome (22q11DS) constitute such a population. Here, we conducted an fMRI study, in which children (6-10yo) with DLD and 22q11DS listened to speech alternated with reversed speech. We compared language laterality and language-related brain activation levels with those of typically developing (TD) children who performed the same task. The data revealed no significant differences between groups in language lateralization, but task-related activation levels were lower in children with language impairment than in TD children in several nodes of the language network. We conclude that language impairment in children with DLD and in children with 22q11DS may involve (partially) overlapping cortical areas.

1. Introduction

Five to seven percent of children receive a diagnosis of Developmental Language Disorder (DLD), indicating they experience severe problems in language development that cannot be attributed to an obvious cause, such as known genetic or physical abnormalities, lack of exposure, hearing loss or low intellectual functioning (Bishop et al., 2017; Norbury et al., 2016; Tomblin et al., 1997). A large variety of genetic and environmental risk factors, such as being male, a low 5-min Apgar score, low maternal education level and a younger position in the birth order, have been associated with DLD (Ganga et al., In preparation; Harrison and McLeod, 2010; Rudolph, 2017; Whitehouse et al., 2014), making it difficult to identify the underlying neurocognitive mechanisms that result in the language difficulties of DLD (Bishop, 2006; Tomas and Vissers, 2018). However, to effectively tailor prevention and intervention strategies for DLD, we need to better understand these neurocognitive mechanisms and increase our insight in the pathways through which such risk factors cause alterations in the neural networks involved in language processing that, in turn, lead to impaired language development. A first step to address this aim is to carefully describe any alterations in the language-related brain activity patterns in DLD. A second step is a comparison of these brain activity patterns to those of a genetically uniform population that has a similar behavioral language phenotype as DLD. The rationale behind this comparison is that, if DLD and the genetically uniform population also share alterations at the level of neural activity, it can be surmised that the risk factors that are associated with DLD affect similar target points within the neural language processing network as the mutation in the genetically uniform population. A careful characterization of the genetically uniform population may then contribute to elucidating these target points for DLD and thereby increase our understanding of DLD (c.f. (Bathelt et al., 2016)). In the current study, we focus on children with 22q11.2 deletion syndrome as the genetically uniform population for comparison with children with DLD.

The 22q11.2 deletion syndrome (22q11DS) is caused by a microdeletion on the long arm of chromosome 22 and is identified in an

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estimated one out of every 3000–6000 live births (McDonald-McGinn et al., 2015). Children with 22q11DS may have various physical symptoms involving multiple organ systems. The most frequently occurring physical symptoms are congenital heart defects and palate abnormalities. Common developmental symptoms include delays in language and motor milestones, and low to borderline intellectual functioning. In addition, the deletion is associated with elevated levels of psychopathology, in particular schizophrenia (Fiksinski et al., 2018; McDonald-McGinn et al., 2015; Vorstman et al., 2015).

Many children with 22q11DS present with severe difficulties in language development, which overlap with those presented by children with DLD. Both children with 22q11DS and children with DLD show a delayed achievement of language milestones. Consequently, speech and language therapy is often indicated (Solot et al., 2019; Bishop et al., 2017). Even though language abilities of children with 22q11DS and children with DLD progress with increasing age, affected children do not seem to catch up with their typically developing peers and language difficulties therefore dominate concerns of parents of both groups (Conti-Ramsden et al., 2012; Norbury et al., 2016; Rice and Hoffman, 2015; Solot et al., 2000; Van den Heuvel et al., 2018). In addition, for both populations, language difficulties may be present in all language domains, such as expressive and receptive grammar and vocabulary, as well as social communication, with wide inter-individual variability of affected language domains seen among both children with 22q11DS and children with DLD (Conti-Ramsden et al., 2012; Van den Heuvel et al., 2017). Finally, it has been suggested that, similar to children with DLD, some children with 22q11DS have weaker language skills than expected for their level of intellectual functioning (Goorhuis-Brouwer et al., 2003; Norbury et al., 2016; Persson et al., 2006; Van den Heuvel et al., 2018). Although there are phenotypical differences between 22q11DS and DLD (e.g. heart defects, palate abnormalities and the occurrence of mental disorders such as schizophrenia (McDonald-McGinn et al., 2015)), the similarities in developmental language profiles are quite striking. Given these similarities, it is possible that the language difficulties in children with 22q11DS and children with DLD share a common underlying mechanism in that the genetic alterations of 22q11DS and the risk factors for DLD induce comparable changes in the neural networks involved in language processing that, in turn, lead to similar language problems. If that is the case, we would expect the language activation patterns in the brains of these groups of language-impaired children to be altered in a similar fashion, compared to those of their typically developing peers.

Language processing in the brain has historically been associated with two canonical language regions, Broca's area in the inferior frontal cortex and Wernicke's area in posterior temporal region (Broca, 1861; Wernicke, 1874), with a clear left hemispheric dominance in most people (Knecht et al., 2000). Over the past decades, however, advances in brain imaging technology, including functional magnetic resonance imaging (fMRI), and in the conceptual understanding of language, have led to new insights in the neural substrate of language perception and production (Poeppel et al., 2012; Price, 2012). It is now widely accepted that language processing involves an extended network of peri-Sylvian brain areas and their connecting pathways (Poeppel et al., 2012; Price, 2012). Functional MRI studies in healthy children have revealed that brain areas activated during the performance of language tasks largely correspond with those observed in adults (Moore-Parks et al., 2010; Wood et al., 2004) and that the left-hemispheric specialization for speech processing emerges very early in life (Dehaene-Lambertz et al., 2002).

Importantly, current evidence on the language representation in DLD is scarce and results on whether or not this condition is associated with changes in language laterality and language-related activation levels in the brain have been inconsistent (Badcock et al., 2012; de Guibert et al., 2011; Ellis Weismer et al., 2005; Hugdahl et al., 2004; Pigdon et al., 2020). In addition, as far as we are aware, there are no published fMRI studies on language-related brain activity patterns in children with 22q11DS. Therefore, we here conducted an exploratory study to investigate language activation patterns in the brains of children with DLD and children with 22q11DS. We acquired 3T fMRI data from children of both groups while they performed a spoken language processing (story listening) task and compared language laterality and amplitude of fMRI activity with those of a group of typically developing (TD) children who performed the same task.

2. Methods

2.1. Participants

Children of 6–10 years old with a diagnosis of DLD were recruited via schools in the Utrecht area specialized in the education of children with language impairment. In the Netherlands, children with DLD enrolled in these schools have met one of the following criteria: 1) one score of at least 2 standard deviations below the mean on a comprehensive standardized language test, or 2) a score of at least 2 standard deviations below the norm on at least 2 subtests of a standardized language test addressing the language domains speech, pragmatics, grammar, semantics, respectively, or 3) a score of 1.5 standard deviations below the norm on at least two subtests of a standardized language test in at least two language areas, or 4) a score of 1.3 standard deviations below the norm on at least two subtests of a standardized language test in at least three language areas (Simea, 2017).

Children (6–10 years old) with a genetically confirmed diagnosis of 22q11DS were recruited via the 22q11DS childhood outpatient clinic at the Wilhelmina Children's Hospital (part of the University Medical Center Utrecht).

Exclusion criteria for both groups were low IQ (verbal and non-verbal IQ < 70), moderate hearing impairment or worse (>35 dB), MRI-incompatible metal objects on or inside the body, anxiety in the scanner, and relevant comorbidities (e.g. severe autism). In total, 16 children with DLD and 14 children with 22q11DS were included. For the DLD group, two children were not included in the analyses below, because of various reasons (left-handedness, diagnosis no longer valid). Here, we report on the remaining 14 right-handed children with DLD (7 male, 7 female) and 14 right-handed children with 22q11DS (8 male, 6 female). The fMRI data of these children were compared with those of a group of typically developing (TD) children of the same age range (control group, $n = 25$, 11 male, 14 female, all right-handed, native Dutch speakers, one bilingual, one dyslexic), who were included in another fMRI study in which the same tasks were used (Charbonnier et al., 2020). All TD children attended regular schools and were not reported to have any relevant medical issues.

Parents of all participants gave written informed consent for their child to participate in the study. The studies were approved by the Medical Ethical Committee of the UMC Utrecht and performed in accordance with the Declaration of Helsinki (2013).

2.2. Hearing, IQ and language performance

A trained member of the research team evaluated hearing in each child with 22q11DS or DLD. Pure tone audiometry was performed measuring the unmasked air conduction. Hearing loss was defined as an average hearing loss (average of 250, 1000 and 4000 Hz) of more than 35 dB. Children who had >35 dB hearing loss in both ears were excluded from the study. In addition, a shortened version of the Dutch version of the Wechsler Non Verbal intelligence scale of ability (WNV-NL (Wechsler and Naglieri, 2008)) was used to examine intellectual function of children with DLD and children with 22q11DS. We report a composite IQ score, which was calculated based on performance on the subtasks Matrix Reasoning and Picture Recall or Spatial Orientation, dependent on a child's age.

As a measure of grammatical competence, the sentence repetition task of the Dutch adaptation of the Clinical Evaluation of Language Fundamentals (CELF 4-NL (Kort et al., 2010)) was used. Below-average

performance on sentence repetition tasks is an important characteristic of language impairment, and such tasks are widely used in clinical settings (Klem et al., 2015). In this task, children were requested to exactly repeat sentences with increasing difficulty that were read by the experimenter. A higher score indicates a larger number of correctly repeated sentences. Raw scores were converted into standardized scores (M = 10; SD = 3).

To obtain a measure of receptive vocabulary, we used the Dutch version of the Peabody Picture Vocabulary Test (PPVT III-NL (Schlichting, 2005)). The PPVT is a standardized vocabulary test that consists of 204 items that are divided over 17 sets. Children were visually presented with four pictures and were requested to point at the drawing that matched the target word that had been read out loud by the experimenter. Raw scores, which represent the number of correct responses, were converted to standardized scores (M = 100; SD = 15).

For some participants, a recent audiogram, IQ test result and/or language test result was already available. In these cases, the respective tests were not repeated to avoid imposing unnecessary burden to the participants and potential confounds due to retesting. Notably, the TD children did not take part in the hearing, IQ or language tests, since their data was acquired within another study.

2.3. Participant preparation

All children were prepared for the fMRI scan in a dedicated room of the UMC Utrecht, which was equipped with a full-scale mock scanner. First, the Edinburgh Handedness Inventory (Oldfield, 1971) and an fMRI safety screening form were filled out by the participants or their parents on their behalf. Subsequently, participants practiced the fMRI tasks using a laptop computer. Finally, participants were acquainted with the MRI environment using the mock-scanner. Before and after the mock-scanner preparation, participants, their parents and the researcher filled out two Visual Analogue Scales (VAS), to indicate how much anxiety the participant felt about the fMRI experiment, and how enjoyable the participant considered participation. The VAS scales ran from 1 (not anxious, very enjoyable) to 10 (very anxious, not at all enjoyable). Three TD participants had had a prior fMRI scan. For them, mock-scanner preparation was not performed, but tasks were practiced before entering the real MRI scanner. Note that the VAS data of the TD children were included in a previous report of our group (Charbonnier et al., 2020).

2.4. Functional MRI data acquisition

Functional MRI data were acquired on a Philips Achieva (Best, the Netherlands) 3T scanner. To minimize the confounding effect of large blood vessels, we used a PRESTO pulse sequence, which involves a multi-shot 3D acquisition scheme (Neggers et al., 2008; Rutten et al., 1999; Van Gelderen et al., 2012), and is routinely used in our institute for clinical, presurgical function mapping (Jansma et al, 2015, 2020). FMRI acquisition parameters were: TR = 22.5 ms, TE = 31.22 ms, flip angle 10°, voxel size 4 mm isotropic, 40 slices, FOV 224 × 256 × 160 mm, prescribed sagittal, ear to ear, volume acquisition time 608 ms. For each participant, a T1-weighted anatomical scan was acquired (1 mm isotropic), while participants watched a video of their choice.

2.5. Tasks

While in the MRI scanner, participants performed a language task (Story task, SR) and/or a Hand-Movement task (HM).

2.5.1. Story task (SR)

The SR task (SR, duration 9.3 min, 921 vol (Charbonnier et al., 2020)) had a block design in which periods of spoken language processing (story listening, comprising speech comprehension and speech recognition) alternated with periods of rest. During the story listening blocks, participants listened to the voice of a female speech and language therapist who read a shortened version of a children's story (target age 5–8 years). To maximally attract the attention of the participants to the content of the story, children watched a colorful illustration that supported the narrative during each speech block (n = 14 blocks, 8.7–38.6s in duration). During the rest conditions (reversed speech, n = 14 blocks, 16.6–19.1s in duration), the illustration slowly turned to the next illustration (like turning a book page), which supported the narrative of the next story listening block, in which the story continued where it ended during the previous story listening block. Sound was delivered through an MRI-compatible audio system with in-ear plugs (MR Confon, Magdeburg, Germany). Children could press the alarm button if they needed adjustment of the audio volume. Note that the SR task data of the TD children have been reported on earlier (Charbonnier et al., 2020).

2.5.2. Hand-movement task (HM)

A Hand-Movement (HM, duration ~4.5 min, 442 vol) task was used in this study to assess the presence of any non-language related differences in brain-activation between TD and language-impaired children. During the task, a red or green colored circle was visually presented (3s for first trial of a block, 0.5s for the remaining trials), which alternated with an illustration of a cartoon character (0.5–3s, 11 trials per block). During rest blocks, the circle was red, instructing the participants to relax and just watch the illustrations. During active blocks, the circle was green, instructing the participants to squeeze a response-balloon with their right hand every time they saw an illustration (i.e. a target). Each squeeze was rewarded with a colored line around the image. Response accuracy during this task was computed as the percentage of targets that was responded to with a balloon squeeze (true positives). Reaction time was defined as the time between the onset of target presentation and the balloon squeeze.

2.6. Functional MRI data analysis

FMRI data analysis was performed offline with SPM12 (http://www.fil.ion.ucl.ac.uk/). Preprocessing involved realignment to the first functional scan, co-registration to the individual T1-weighted anatomical scan, normalization to standard, Montreal Neurological Institute (MNI), space and smoothing (Gaussian kernel, 8 mm full width half max). Statistical analysis was performed by fitting a General Linear Model (GLM) to the data and the generation of contrast maps for each participant.

Motion correction was performed by inclusion of two confound factors in the GLM, being 1) the six realignment parameters produced by SPM12 in the realignment preprocessing step and 2) a motion filter, as described before (Charbonnier et al., 2020). In short, the motion filter included a set of Finite Impulse Response Functions, which effectively remove images with excessive head motion from the analysis. To make sure that the motion filter did not result in an unacceptable decrease in statistical power (due to removal of large numbers of images), we computed the proportion of statistical power (PSP) remaining after the addition of the motion filter, and excluded datasets with PSP values of 0.4 or lower from further analyses. For the computation of the PSP, the following formula was used:

$$PSP = \frac{R_m^2 \times \sqrt{df_m}}{R^2 \times \sqrt{df}}$$

where R_m^2 and R^2 are the multiple correlation coefficients between the task and the remaining factors of the design matrix with the motion filter and the design matrix without the motion-filter, respectively; df_m and df are the degrees of freedom of the design with and without motion filter.

Groupwise activity maps were obtained by entering the single subject contrast maps into a second level analysis (one sample *t*-test). We used the 3dClustSim tool in AFNI (version 16.2.07) to derive a cluster

level threshold of $p < 0.05$ (corrected for multiple comparisons) using Monte Carlo simulations (10.000 iterations) of random noise distribution (Cox, 1996; Forman et al., 1995). This approach combines an individual voxel probability threshold with a minimum cluster size to estimate the probability of a false positive, effectively taking into account both effect size and the spatial extent of the activity. We used the 3DFWHMx tool in AFNI (Auto-Correlation Function; ACF) to estimate noise smoothness values of the data. The resulting 2-sided threshold was obtained for an individual voxel threshold of $p < 0.001$ (uncorrected) with a cluster extent and t-threshold varying with group and task. The existence of any differences between the activation patterns of the SR and the HM tasks of the three groups was investigated using second-level analyses according to the same procedures.

2.7. Regions of interest

To specifically focus on the most relevant brain areas, most analyses were conducted on anatomically defined Regions of Interest (ROIs). Using the Brainnetome atlas (Fan et al., 2016), we generated a language-ROI that contained the peri-Sylvian language areas (i.e. Broca, Wernicke, Anterior Temporal and Auditory; Supplementary Table 1; Supplementary Fig. 1A–D). For more detailed analyses of the language activation patterns, we also analyzed the language-sub-ROIs. In these analyses, we included, besides the peri-Sylvian language areas, also the caudate nucleus as an ROI (Supplementary Table 1; Supplementary Fig. 1E), since that area has been indicated to show atypical structure and function in children with DLD (de Guibert et al., 2011; Dibbets et al., 2006) and in another speech disorder (orofacial verbal dyspraxia (Vargha-Khadem et al., 1998)). In addition, we investigated a motor-ROI. The motor-ROI was generated using the automated anatomical labeling atlas (AAL (Tzourio-Mazoyer et al., 2002)) and included the precentral and postcentral gyri (Precentral, Postcentral; Supplementary Fig. 1F).

2.8. Lateralization index

We used a threshold-independent method to compute the Lateralization Index (LI (Branco et al., 2006)). For each (sub-)ROI of both the left and right hemisphere, the product between the height of the bins of the histogram of voxel's t-values (t-value range $0 - \infty$, bin size 0.25) and the square of the index of the bins was computed. As such, voxels with higher t-values were assigned a heavier weight. The areas under the curve for the left and right hemisphere were subsequently used in the computation of the LI. LI differences between groups were tested for statistical significance using independent one-way ANOVAs and we used the Bonferroni method to correct for multiple comparisons.

2.9. Activation levels: mean betas from GLM fit on fMRI data

Using the results of the GLM fit on the fMRI data, we computed, per participant and per task, the mean beta value (a measure of the size of the BOLD signal change induced by performing a task) for each of the language sub-ROIs and the motor-ROI. To match the dimensions, resolution and orientation of the fMRI data, the volume including the relevant regions of interest in MNI-space was resliced to the volumes containing the beta-coefficients, using nearest neighbor interpolation. Subsequently, a particular fixed percentage of voxels was selected, for each participant and task and within each ROI (i.e. 10% with the highest beta coefficients [i.e. strongest activation, top 10%], and 10% with the lowest beta coefficients [strongest de-activation, bottom 10%]), to avoid loss of power due to the inclusion of a large proportion of non-task-related voxels. By providing information about both the strongest activating and the strongest de-activating voxels, we aimed to offer a representation of the full range of beta values for each group, task and ROI. In earlier studies, the selection of a subset of voxels, based on their level of activity, as a basis for a single measure of task-related signal changes within an anatomically defined ROI, has been found to be a useable and valid approach (Buck et al., 2008; Buma et al., 2016; Mitsis et al., 2008; Tong et al., 2016). Using each of these two voxel selections, we subsequently calculated the mean (de-)activation per ROI. This resulted in a single (de-)activation estimate for each voxel selection, ROI, task, and participant. Differences between groups were tested for significance with independent one-way ANOVAs (Bonferroni correction for multiple comparisons).

2.10. Relation between beta values and IQ and language scores

As a post-hoc analysis, we used ANCOVA to investigate the relationship between the beta values and the groups of participants by controlling for additional behavioral measures, such as IQ and language performance scores (sentence repetition and PPVT). A pairwise-interaction model was specified per analysis, thus including modeling of the main effects per variable (group, IQ, sentence repetition and PPVT) and all their pair-wise interactions. We used the MATLAB implementation of ANCOVA (*anovan* with a combination of continuous and categorical variables) and used the type III sum of squares in estimating the main effects of the model given the previously observed interaction effects between the groups and the behavioral measures (IQ and PPVT in particular). The ANCOVA analyses were performed only for the ROIs with a significant group effect for the beta values from the previous analysis: left Anterior Temporal, Broca and Wernicke regions and using only the top 10% of beta values of the SR task. The results were corrected for multiple comparisons using a Bonferroni correction for the number of ROIs.

3. Results

3.1. VAS scores

Children of the three groups reported comparable Visual Analogue Scale (VAS) scores for anxiety and enjoyment before and after the practice scan (Supplementary Table 2), and there were no significant differences between groups (anxiety: multivariate GLM, $F(6,92) = 1.15$, $p = 0.34$; enjoyment: multivariate GLM, $F(6,92) = 2.0$, $p = 0.10$). The practice scan itself mostly resulted in a decrease in the VAS scores for anxiety and enjoyment (i.e. a more positive perception), as reported by the participant, parent and researcher. For anxiety, this effect was significant for the DLD and the TD group, but not for the 22q11DS group (repeated measures GLM; DLD: $F(1,10) = 10.75$, $p = 0.01$; 22q11DS: $F(1,13) = 1.78$, $p = 0.21$; TD: $F(1,20) = 18.57$, $p < 0.001$). Also for the levels of enjoyment, there was a significant effect of practice in the DLD and TD group, but not in the 22q11DS group (repeated measures GLM; DLD: $F(1,11) = 13.55$, $p = 0.004$); 22q11DS: $F(1,13) = 0.17$, $p = 0.69$; TD: $F(1,20) = 11.39$, $p = 0.003$). Two 22q11DS participants had high levels of anxiety after mock-scanner preparation and were excluded from further participation. No fMRI data were acquired for these participants and their results are not included in the analyses below. Also after the fMRI scan, there were no significant differences between groups for anxiety (one-way ANOVA, $F(2,44) = 0.03$, $p = 0.97$) and enjoyment (one-way ANOVA, $F(2,44) = 0.72$, $p = 0.49$).

3.2. Hearing, IQ and language performance

Participants with DLD and participants with 22q11DS had no hearing impairment (i.e. impairment levels of <25 dB in at least one ear; grade 0 (WHO, 1991)), except one 22q11DS participant, who had a slight hearing impairment in both ears (grade 1 (WHO, 1991)). Notably, this child had a cold on the day of the hearing assessment. Both IQ and language were deviant for this participant compared to typically developing peers, but not compared to other children with 22q11DS. Demographic information of the participants and the results of the IQ and language tests are given in Supplementary Table 3. The three groups

did not differ significantly in age (one-way ANOVA, F (2,48) = 0.76, p = 0.48). On average, the IQ of children with 22q11DS was 73 (SD = 9; n = 12), which is in the borderline impaired range and significantly lower than that of children with DLD, who had a mean IQ of 107 (SD = 15; n = 13; IQ data of one participant was missing), which is in the average range (Students t-test, $p < 0.001$). Scores on the sentence repetition task were below the norm for their age for both children with DLD (M = 4; SD = 2; n = 14) and 22q11DS (M = 5; SD = 2; n = 12) and did not differ significantly between these two groups (Students t-test, p = 0.19). Peabody Picture Vocabulary Test (PPVT) scores of children with 22q11DS (M = 81; SD = 13; n = 12) were more than one standard deviation below the mean for their age and were significantly lower than for children with DLD, who reached scores that fell in the average range (M = 95; SD = 13; n = 14; Students t-test, p = 0.01). As noted in the Methods section, no hearing, IQ or language performance tests were performed by the TD children, as their data were acquired in a different study. All TD children attended regular schools.

3.3. Task performance

Due to time constraints, the number of fMRI tasks performed varied across participants (Supplementary Table 3). Hand-Movement (HM) task performance was adequate in general. Mean response accuracies per group were 81% (SD = 11; n = 14; DLD), 81% (SD = 17; n = 12; 22q11DS) and 84% (SD = 9; n = 15; TD) correct, respectively. The corresponding mean reaction times were 618 ms (SD = 150; DLD), 576 ms (SD = 95; 22q11DS) and 578 ms (SD = 92; TD), respectively. There was no significant difference in accuracy (one-way ANOVA, F (2,38) = 0.30, p = 0.74), or in reaction time (one-way ANOVA, F (2,38) = 0.57, p = 0.57) between groups. Due to the nature of the SR task, quantification of performance during the scan was not possible.

3.4. Head motion

The motion filter effectively removed 21% (SD = 22; DLD), 30% (SD = 28; 22q11DS), and 13% (SD = 14; TD) of scans of the SR task, respectively, and 20% (SD = 15; DLD), 23% (SD = 24; 22q11DS) and 14% (SD = 12; TD) of scans of the HM task (Fig. 1A and B). There was no significant difference between groups in the percentage of scans removed by the motion filter for either task (one-way ANOVAs; F (2,43) = 2.65, p = 0.08 and F (2,38) = 0.88, p = 0.42, respectively).

For the SR-task dataset of one DLD participant, the Proportion of Statistical Power (PSP) value was lower than 0.4, indicating that removal of the scans with excessive head motion resulted in an unacceptable loss of power, and this dataset was therefore excluded from further analysis (Supplementary Table 3). For the 22q11DS group, three datasets of the SR task, and one dataset of the HM task were excluded because the PSP value was lower than 0.4. For the control group, no dataset was excluded. The mean PSP values of the remaining datasets did not differ significantly between groups for both the SR and the HM task (Fig. 1C and D; one-way ANOVAs; F (2,39) = 0.48, p = 0.62 and F (2,37) = 0.59, p = 0.56, respectively).

3.5. Group maps

Visual inspection of the SR group activity pattern of TD participants showed strongly left-lateralized activation in the inferior frontal gyrus, middle temporal gyrus and posterior temporal gyrus/angular gyrus (Fig. 2). Anterior temporal cortex activation was largely bilateral, but somewhat stronger in the left hemisphere. Activity was also found in the superior frontal gyrus (more left than right) and in the bilateral posterior cingulate cortex. The group activation patterns of the children with DLD and children with 22q11DS showed activation in the left anterior temporal cortex, in a similar location as TD children (Fig. 2). Notably, lowering the threshold in the group-map visualization revealed that both groups of language-impaired children showed an activation pattern

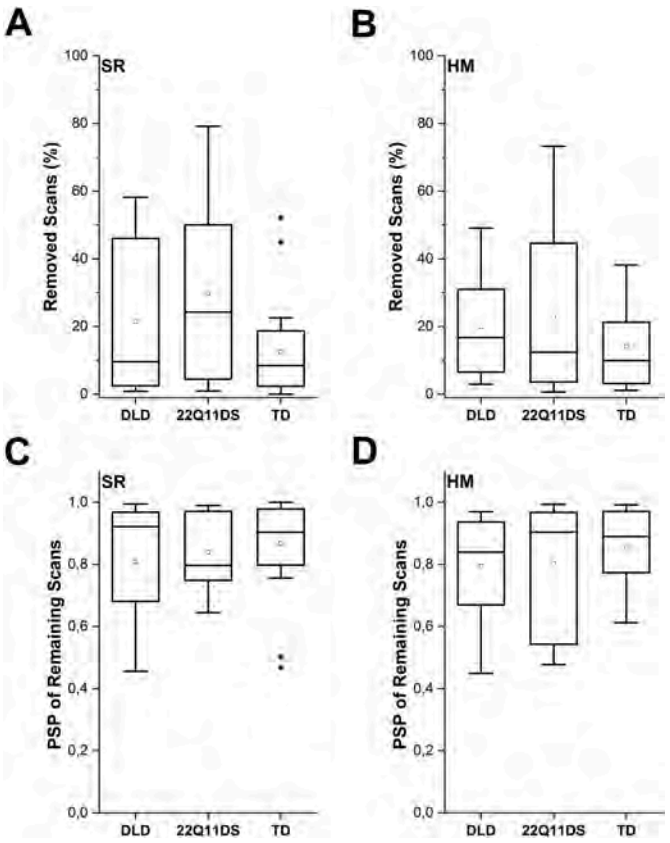

Fig. 1. Motion. Top panels: Boxplots indicating the percentage of removed scans of the SR task (A) and the HM task (B) for the three groups. Bottom panels: Boxplots for the proportion of statistical power (PSP) remaining after motion correction of the SR task (C) and the HM task (D). Note that only participants for whom the PSP value was larger than 0.4 (i.e. the participants used in further analysis) were included in these PSP plots.

that was highly similar to that of TD children (Supplementary Fig. 2). Whole brain comparison of the group activation patterns did not reveal any significant differences between groups.

The HM activation pattern of TD children showed activation in the contralateral (left) precentral and postcentral sensorimotor hand area (Fig. 3). In addition, hotspots of activated voxels were observed in the cerebellum (right more than left), the occipital lobe (visual cortex, mostly right), the temporo-occipital area (~brodmann area 37; more left than right), the left thalamus, two areas around the inferior part of the sensorimotor cortex bilaterally and in the supplementary motor area of the left hemisphere. In the group maps of the children with DLD and children with 22q11DS, clusters of activity were found in the right cerebellum and the left sensorimotor hand area, largely corresponding to the respective regions that showed activity in the TD children (Fig. 3). Whole brain comparison of the group activation patterns revealed a cluster of voxels in the left sensorimotor hand area with a significant difference between the TD and DLD groups (TD > DLD; $p < 0.001$, threshold extent $k \geq 77$; Supplementary Fig. 3). There were no significant differences in group activation patterns between the TD and the 22q11DS group or between children with DLD and children with 22q11DS.

3.6. Lateralization index

For the SR task, mean Lateralization Indices (LIs) in the language-ROI were positive, indicating left-lateralized language-related activation in most participants of all groups (Fig. 4; Supplementary Table 4). Interestingly, also within the motor-ROI, most LIs were positive and

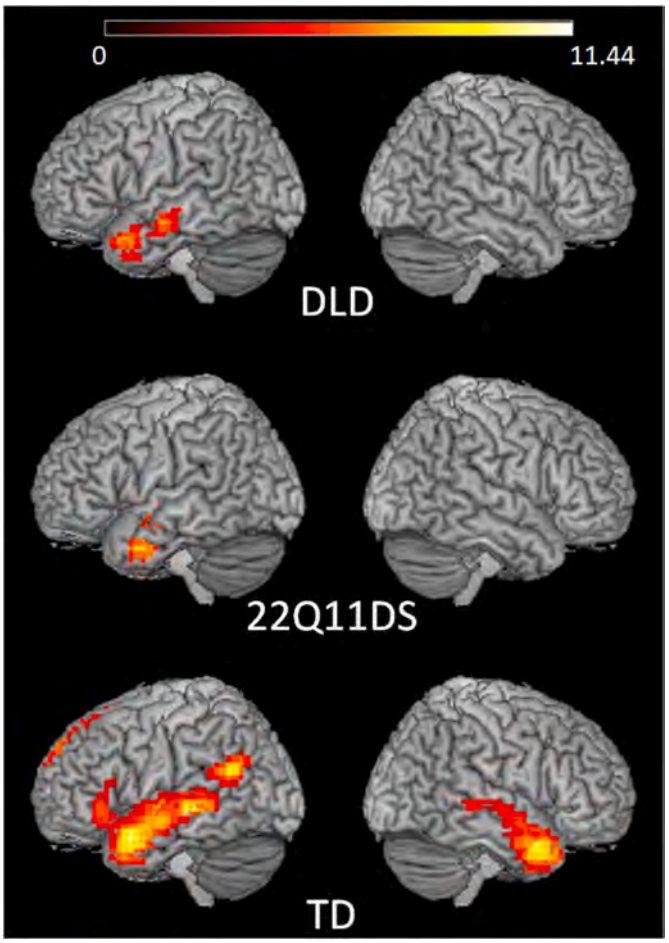

Fig. 2. SR task activation pattern. Group activation patterns of the SR task for children with DLD (n = 13; T = 3.93; p < 0.001; threshold extent k ≥ 37), 22q11DS (n = 9; T = 4.5; p < 0.001; threshold extent k ≥ 43) and TD children (n = 20; T = 3.58; p < 0.001; threshold extent k ≥ 35). The color scale indicates T-values. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

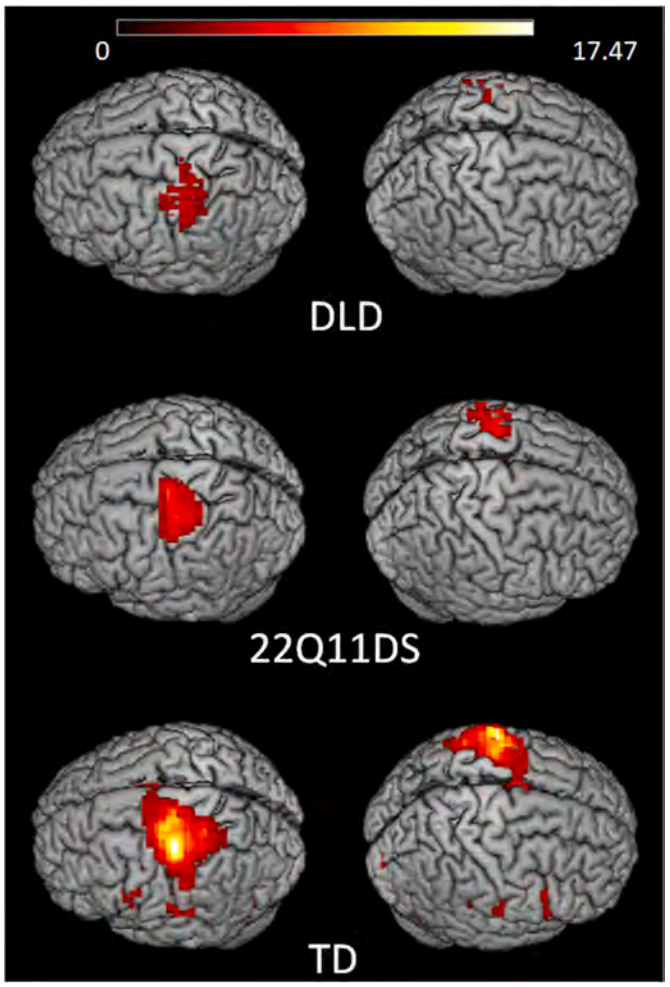

Fig. 3. HM activation. Group activation patterns of the HM task for children with DLD (n = 14; T = 3.85; p < 0.001; threshold extent k ≥ 43), 22q11DS (n = 11; T = 4.14; p < 0.001; threshold extent k ≥ 31) and TD children (n = 15; T = 3.79; p < 0.001; threshold extent k ≥ 39). The color scale indicates T-values. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

largely in the same range as values obtained for the language-ROI. There was no significant difference between groups in the SR task LIs in either of the two ROIs (one-way ANOVAs; language-ROI: F (2,39) = 0.30, p = 0.75; motor-ROI: F (2,39) = 0.99, p = 0.38).

The HM task resulted in left lateralized activation in the motor-ROI in all three groups, whereas LIs in the language-ROI were, on average, close to 0 (Fig. 4; Supplementary Table 4). There were no significant differences in HM task LIs between the three groups in the two ROIs (one-way ANOVAs; language-ROI: F (2,37) = 0.06, p = 0.94; motor-ROI: F (2,37) = 1.25, p = 0.30).

To investigate potential differences between groups in the LIs of different sub-areas of the language network, we compared LIs of the SR task for each of the five different language sub-ROIs (Supplementary Table 5). There was no significant difference in the LIs across groups during performance of the SR task in any of the sub-ROIs, neither when all participants (with both positive and negative LIs) were taken into account, nor when only participants with positive (i.e. typical or left lateralized) LIs were included (see Supplementary Table 5 for values per sub-ROI and the results of the one-way ANOVAs).

3.7. Activation levels: beta values

We computed, per participant and per task, the mean beta value for each of the five language sub-ROIs and the motor-ROI (Fig. 5), using either the 10% voxels with the highest beta value, or the 10% voxels with the lowest beta values. For the SR task, for the top 10% voxels, there were significant effects of group for the Anterior Temporal, Broca and Wernicke sub-ROIs of the left hemisphere (independent ANOVAs, p < 0.05, Bonferroni corrected for 12 comparisons; Supplementary Table 6). Posthoc comparisons revealed that for left-Broca, SR-task-related activation in the TD group was significantly higher than in the 22q11DS group (post-hoc Bonferroni test, p = 0.002). For left Anterior Temporal and left Wernicke, the TD group activation was significantly higher than that of both language-impaired groups (p < 0.01 in all cases). Mean beta values did not differ between the two language-impaired groups in the left Anterior Temporal, Broca or Wernicke sub-ROI (p > 0.5).

Other differences between groups observed for the SR task (i.e. top 10% voxels: right Broca, right Wernicke, right Anterior temporal; bottom 10% voxels: left Wernicke, left Caudate, right Motor) were significant in one-way ANOVA analyses (Supplementary Table 6), but none of these effects survived Bonferroni correction for multiple comparisons. Also for the HM task there were no significant differences between groups for either the top 10% or bottom 10% beta values after Bonferroni correction.

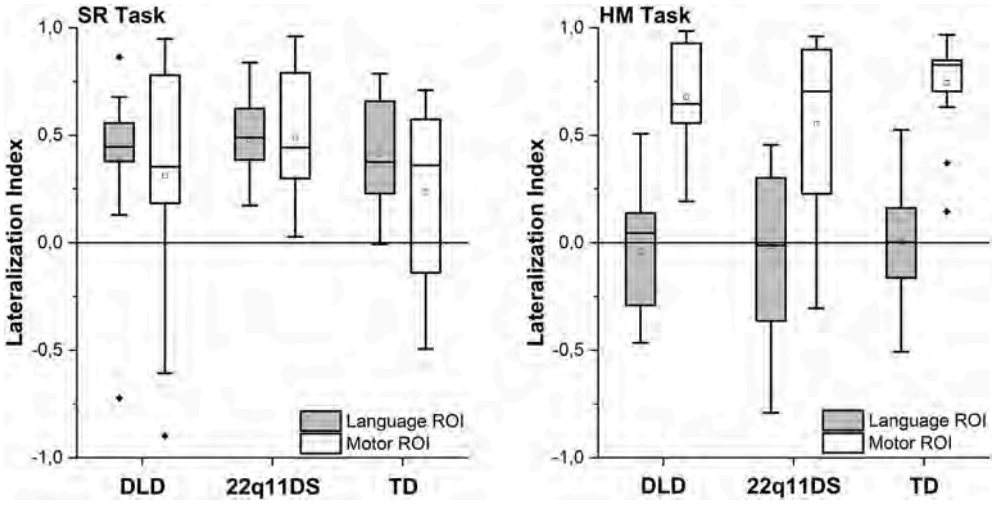

Fig. 4. Lateralization Index. Boxplots for the Lateralization Indices for the SR task (left) and the HM task (right) in the three groups. Grey boxes represent values for the language-ROI, white boxes for the motor-ROI.

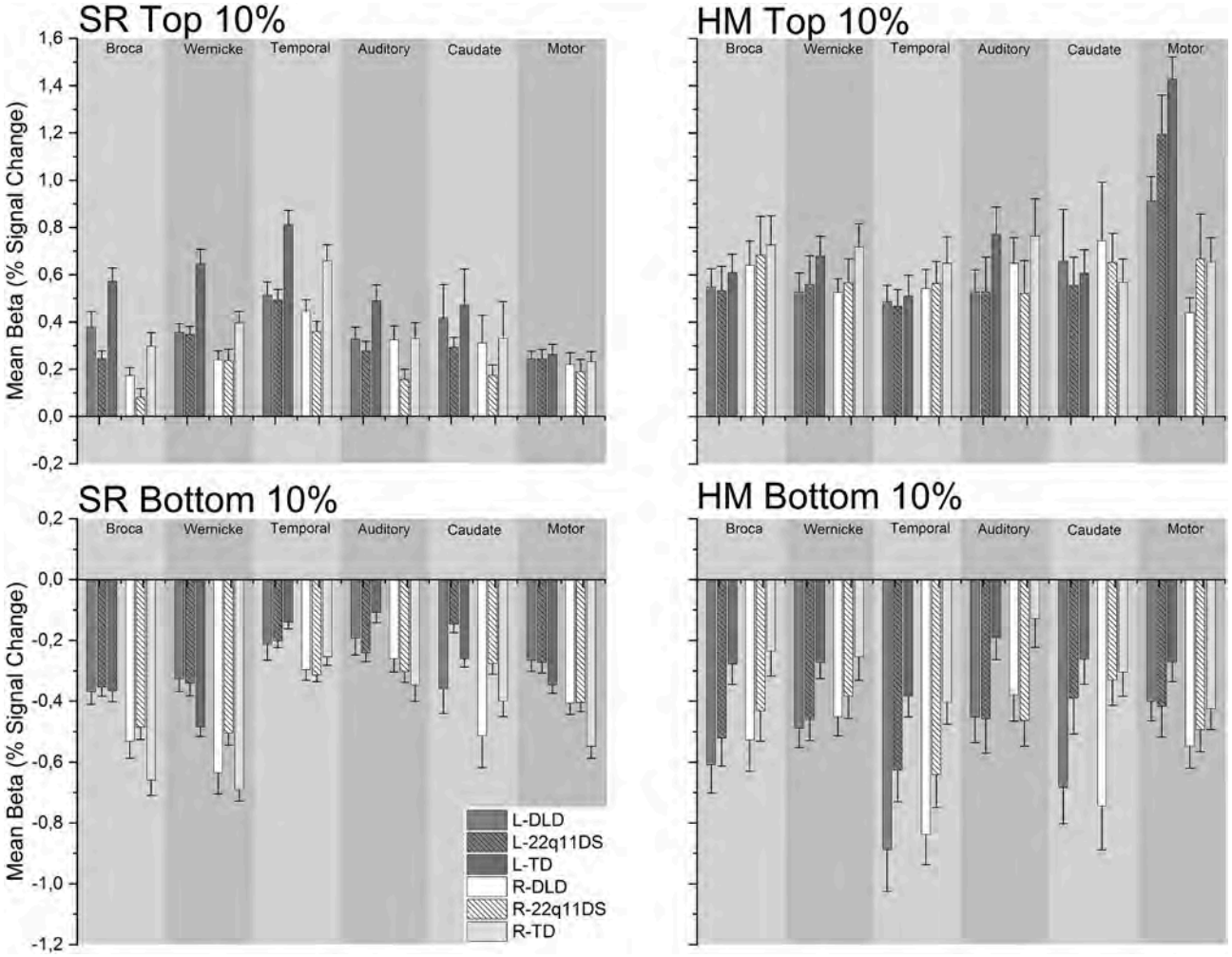

Fig. 5. Beta values. Upper panels: Mean (over participants; ±SEM) beta values, per sub-ROI, hemisphere and group, for the top 10% voxels of the SR task (left) and the HM task (right). Grey bars indicate values of the left hemisphere. White bars indicate values of the right hemisphere. Per sub-ROI and hemisphere, 3 bars are given, the left-most (without additional shading) represents the DLD group, the middle (striped bar) the 22q11DS group and the right (dotted bar) the TD group. Bottom panels: idem, but for the bottom 10% voxels. L = left hemisphere, R = right hemisphere.

3.8. Relation between beta values and IQ and language scores

For the left Anterior Temporal, Broca and Wernicke sub-ROIs (the three areas with a significant group effect for the beta values of the SR task), we investigated whether or not there was a relation between the mean beta values obtained in the SR task on the one hand and group, IQ, sentence repetition and PPVT score on the other. We only analyzed the relation for the top 10% of beta values since there was no significant group effect on the bottom 10% beta values in any ROI for the SR task. Notably, since IQ and language scores were not available for the TD children, this group was not included in this analysis. This also applied to one DLD participant. The overall fit of the model using the group variable and the behavioral measures to predict the top 10% betas was only significant for the left Broca sub-ROI (F (10,1 per each variable) = 4.92, p = 0.009, adjusted R^2 = 0.66). In left Broca, the relationship between the sentence repetition scores and the top 10% beta values was significant at $p < 0.05$. In addition, in the same area, there was a significant interaction effect of group*IQ, group*PPVT and IQ*PPVT scores (all significant at $p < 0.05$, Supplementary Table 7). Notably, after correction for multiple (n = 3 sub-ROIs) comparisons, only the effect of group*PPVT score remained significant. Other regions did not show a significant relation between the mean beta values and a combination of group (only 22q11DS and DLD included), IQ and language scores.

The analysis of the direction for the interactions between the group and the language scores showed opposite trends for the DLD and 22q11DS groups: for the DLD group, lower PPVT values were associated with higher betas, and higher PPVT values were associated with lower betas. The 22q11DS group showed the opposite relationship between the PPVT language scores and the beta values in the left Broca sub-ROI (Fig. 6).

4. Discussion

In this fMRI study, we investigated brain activation of two groups of language-impaired children, namely children with Developmental Language Disorder (DLD) and children with 22q11.2 Deletion Syndrome (22q11DS), and compared the results to data of a group of typically developing (TD) children acquired earlier within another study (Charbonnier et al., 2020). The data reveal that, during performance of a spoken language processing or a hand-movement task, both groups of language-impaired children showed activity in brain areas that were also found to be activated in TD children and lateralization values did not differ between the three groups. However, in language-impaired children, the level of language task-related activation (beta value) was lower than that of TD children in several nodes of the language network. Interestingly, in one of these nodes, left-Broca, the two language impaired groups showed an opposite relationship between beta values and language performance scores on the PPVT task.

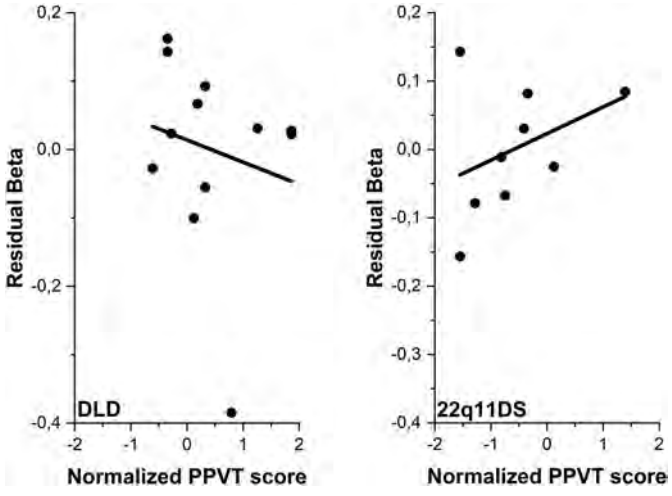

Fig. 6. Interactions between PPVT language scores, groups and betas in left Broca. The plots show the distribution of residual mean betas (based on top 10% voxels; y-axis) over the normalized PPVT language scores (x-axis) per group. The residual betas were obtained from first fitting the model on all variables and their pairwise interactions except for the interaction of interest (group*PPVT for top 10%). Because the model also fits the constant term, the residual betas appear to be zero-centered.

4.1. IQ and language performance

The data showed that the language-impaired participants were representative for children with either 22q11DS or DLD with regard to their intelligence and language skills. The sentence repetition task is a measure used by clinicians to identify children with a language impairment (Klem et al., 2015), and indeed participants with DLD obtained scores markedly lower than the age-adequate average (below the normal range for their age). In addition, absence of intellectual problems among the DLD participants of this study is in correspondence with the literature (Bishop et al., 2017). Interestingly, in our study, children with DLD scored in the average range on the PPVT. This may be explained by the fact that impaired language domains can differ across children with DLD and some children with DLD mainly have problems with expressive language (Bishop et al., 2017; Conti-Ramsden and Durkin, 2012). Moreover, average scores on a receptive vocabulary task have been previously reported in Dutch children with DLD (Blom and Boerma, 2016; Duinmeijer et al., 2012). As expected, children with 22q11DS in our sample presented, on average, with a level of borderline intellectual function (McDonald-McGinn et al., 2015) and scored lower than the age-adequate range on the sentence repetition task and PPVT, which is in line with earlier studies reporting weak vocabulary and grammatical skills in this population (Solot et al., 2019; Van den Heuvel et al., 2018).

4.2. Brain activation patterns and laterality

The brain activation patterns associated with the SR and the HM task of children with language impairment showed hotspots at locations that corresponded to those found in TD children. In addition, the data showed that both language-impaired groups had levels of motor and language lateralization that were not significantly different from that of TD children, in the motor- and language-ROI as well as in the language sub-ROIs. Taken together, we did not find evidence for fundamental spatial alterations in the motor or language networks of children with DLD and children with 22q11DS. As far as we are aware, there are no published studies on the language laterality of individuals with 22q11DS. For DLD, previous fMRI literature on language laterality has been inconsistent, with several studies showing decreased left-right asymmetry (Badcock et al., 2012; de Guibert et al., 2011) and others stating clear left-right asymmetry (Ellis Weismer et al., 2005; Hugdahl et al., 2004; Krishnan et al., 2021) in people with DLD. A recent twin study used functional transcranial Doppler ultrasound to assess language lateralization in large groups (n > 100) of typically developing children and children with DLD, and found no evidence for atypical language laterality in children with DLD (Wilson and Bishop, 2018). Our findings, showing similar levels of language lateralization in children with DLD and TD children, are in agreement with that finding and add to it that also at a more spatially detailed level (i.e. in different sub-ROIs of the language network), language laterality is highly similar between these groups, and to that of children with 22q11DS.

Perhaps surprisingly, in all three groups, the motor-ROI showed leftward lateralization during performance of the SR task. Although the group maps did not show supra-threshold activity in this area, the left-right asymmetry observed in the majority of the participants does indicate some level of involvement of the sensorimotor areas during the story listening task. This finding is in agreement with earlier reports on the involvement of the motor areas in language comprehension, which

has been linked especially to the processing of action words (Buccino et al., 2005; Hauk et al., 2004; Vukovic et al., 2017).

4.3. Activation levels

Children with DLD and children with 22q11DS had significantly lower language-related activation in several nodes of the language network than TD children. Several phenomena should be considered for the interpretation of this observation. First, effects of head motion and task activity both predominantly occur at the lower end of the frequency power spectrum of the time-series, so that head motion is prone to affect task-beta estimates. These effects are random across subjects and thereby represent a source of noise in the second level analysis, attenuating the power of group-studies. In this study, head motion did not differ between groups, as indicated by the comparable number of scans excluded for excessive motion. Also the proportion of statistical power remaining after scan exclusion was not significantly different between groups. Based on these data, we consider it unlikely that differences in head motion caused the lower activation in the language areas of language impaired children. Second, task compliance may potentially affect activation patterns. The SR task was designed to keep the children attentive, but the nature of this task prohibited monitoring of task compliance during the scan. It should be noted, however, that levels of anxiety and enjoyment did not differ between groups, and also task performance (accuracy and reaction time) during the HM task was not significantly different between groups, indicating that all groups were similarly involved during the fMRI session at large. In addition, our finding that all groups showed clearly left-lateralized activation in language areas during the SR task, but not the HM task, suggests that, on average, children were actively processing the spoken language information during the SR task. A third factor to take into account is that children may have hearing loss that negatively affects their ability to hear the speech of the SR task. Indeed, previous research has shown a relationship between fMRI activation in the auditory cortex and sound volume (Bilecen et al., 2002; Röhl and Uppenkamp, 2012). Hearing impairment is quite common in children with 22q11DS (Van Eynde et al., 2016), but a diagnosis with DLD precludes hearing impairment as the cause of the language problems (Bishop et al., 2017). In our study, all but one of the participants (a child with 22q11DS) had hearing loss that was lower than 25 dB, which corresponds to Grade 0 (no impairment), of the WHO grades of hearing impairment (WHO, 1991). Taking these three factors into account, we propose that the lower language activation in the brain of both groups of children with language impairment is of neurophysiological origin and is associated with their language problems, not with any language-external factor.

The lower levels of activity we observed in the left-Anterior Temporal and the left-Wernicke sub-ROI of children with DLD correspond to earlier reports on dampened language-related activity in peri-Sylvian regions of people with DLD (Badcock et al., 2012; de Guibert et al., 2011; Hugdahl et al., 2004). Others did not find a significant difference in language activation patterns of TD children and children with DLD, but did report less detectable activity in cortical language areas of children with DLD (Pigdon et al., 2020). Interestingly, our finding that also children with 22q11DS demonstrate a decrease of language-related activity in the left-Anterior Temporal and the left-Wernicke sub-ROIs, suggests that similar brain areas are involved in the language impairment of 22q11DS and DLD.

Current views on language processing in the brain indicate that the Wernicke sub-ROI that we looked at in the current study, which encompasses (parts of) the posterior superior temporal gyrus, supramarginal gyrus and angular gyrus, is mainly associated with phonological (Binder, 2017; Middlebrooks et al., 2017) and semantic processing (angular gyrus (Binder et al., 2009)). The anterior temporal areas, including the temporal pole, superior temporal gyrus/sulcus and middle temporal gyrus, on the other hand, are thought to play an important role in speech processing and speech comprehension (Price, 2012; Scott et al., 2000; Specht, 2014). Processing of both syntactic structure (word order) and semantics (word meaning) have been associated with the anterior and middle temporal regions, with a possible emphasis on syntactic processing in the superior temporal gyrus (Friederici, 2012; Humphries et al., 2006), whereas semantic processing seems to occur more in the middle temporal gyrus (Binder et al., 2009; Friederici, 2012). Given the size of the sub-ROIs used in the current study, it is difficult to draw conclusions about which aspect of spoken language processing is associated with the lower activation in the left-Anterior Temporal and the left-Wernicke sub-ROIs of language-impaired children. Consequently, we are not in a position to determine if the language difficulties in DLD and 22q11DS are due to a common underlying mechanism. Interestingly, the fact that both groups showed a decrease in fMRI activity levels in these areas, as well as below average sentence repetition scores, suggests that these measures are related. However, our post-hoc analysis did not reveal any significant relationship between group, IQ or language scores and the beta values in left-Wernicke and left-Anterior Temporal regions and this topic therefore deserves further investigation.

In children with 22q11DS, but not children with DLD, activation in the left-Broca sub-ROI was significantly lower than that of TD children. The findings for children with DLD are in agreement with a recent study on somewhat older children with DLD who performed a verb generation task (Krishnan et al., 2021). Notably, in our study, children with 22q11DS also scored lower on the PPVT than children with DLD, with most DLD children scoring within the normal (or even above-normal in two cases) range, whereas most 22q11DS children scored below average on the PPVT. Our post-hoc analysis on the relation between beta values and behavioral scores revealed an interaction effect for group*PPVT in left-Broca, such that for children with DLD, smaller task-related neural activity changes (lower beta values) were associated with higher PPVT scores, whereas children with 22q11DS showed the opposite: larger task-related neural signal changes occurred in those with higher PPVT scores. This is interesting, since word comprehension plays an important role in both the SR task and in the PPVT. We hypothesize that (perceived) task difficulty may relate to this observation. In general, increasing language task difficulty has been associated with increased activation in language areas (Just et al., 1996; Keller et al., 2001; Yeatman et al., 2010). Interestingly, however, for working memory tasks, it has been demonstrated that the relation between task-load and fMRI activation has an inverted U-shape, in that with increasing task-load, fMRI activation increases up to a certain point, after which activation levels decrease with further increments in task difficulty (Callicott et al., 1999; Jansma et al., 2004; Van Snellenberg et al., 2015). Importantly, it has been proposed that the decreasing slope is not necessarily related to participants simply giving up on the task, but that this effect is caused by participants using alternative or additional cognitive processes. It could be speculated that this phenomenon is also present for language tasks and that children with DLD are on the rising phase of the inverted U-shape, whereas children with 22q11DS (most of whom have relatively low PPVT scores and therefore may perceive the SR as being more difficult to understand) are on the decreasing slope. Alternatively, the different relationship between language performance and fMRI activation may reflect a difference in developmental stage. Earlier research suggests that children and adults (Krishnan et al., 2015) and children with higher and moderate grammatical knowledge (Knoll et al., 2012) differ in their relationship between activity in frontal areas and language skills. Clearly, this topic deserves further investigation.

With respect to the HM task-related activity levels, we found it interesting that there was a cluster of voxels in the left sensorimotor hand area with a significant difference between TD children and children with DLD. Also, in the ROI analysis, the left motor-ROI showed a trend for less activation (lower top 10% beta values) in children with language impairment, compared to TD children, whereas de-activation in several language sub-ROIs seemed a bit stronger (lower bottom 10% beta values). These latter effects did, however, not survive

Bonferroni correction for multiple comparisons. Yet, we do believe that further investigation of motor-related activity patterns of children with DLD and with 22q11DS may be interesting, especially since for both groups, there are indications for the occurrence of motor-impairment (Oskarsdóttir et al., 2005; Preis et al., 1997).

4.4. Limitations

This study has several limitations. First, it cannot be excluded that one or more DLD participants of the current study also have 22q11 deletion syndrome. We consider this possibility highly unlikely, however, since the diagnosis of DLD is based on the exclusion of any physical and developmental symptoms in other domains than language, whereas such symptoms are associated with 22q11DS. Second, the sample sizes of the language-impaired groups were relatively limited, and smaller than that of the TD group. Although sample size differences prohibit proper comparison of the group activation patterns, they do not negatively affect the interpretation of the laterality indices and beta values, which were computed for each participant individually. Our observation of an interaction effect between beta values and PPVT scores, however, needs further validation in a follow-up study with larger sample sizes. Third, since this study focused on language-laterality and activation levels in relatively large ROIs, we used a conservative voxel size (4 mm isotropic) and smoothing kernel (8 mm). A more in-depth investigation on the detailed representation of language-sub-functions in these groups could benefit from a follow-up study where the acquisition and analyses parameters are geared towards higher spatial resolution. Fourth, hearing, IQ and language performance data was not available for the TD children because, for this group, we used data acquired for another study. All children of this group attended regular schools, however, and were not reported to have any relevant medical issues. Overall, we believe this group can therefore be considered as typically developing. Of note, one TD participant was dyslectic. Since dyslexia has been associated with hypo- and hyperactivation in several brain regions (Hancock et al., 2017), we checked whether or not leaving out this child from the statistical analysis of the SR task would affect the results. Importantly, the findings on SR lateralization index and beta values did not change by excluding this child and we therefore decided not to exclude this participant from the manuscript.

5. Conclusions

Our observation that children with DLD and children with 22q11DS show decreased levels of activity in the Anterior Temporal and Wernicke sub-ROIs suggests that the language impairment of both groups involves similar cortical areas. The difference between the two groups in the relationship between fMRI activity in Broca's area and PPVT scores may be indicative of a difference in the severity of the impairment, but it cannot be excluded that the two groups differ in a more fundamental level in this respect. Our findings do not exclude the existence of (partially) overlapping neural mechanisms underlying the language impairment of children with 22q11DS and children with DLD, and therefore suggest that further characterization of 22q11DS may also be informative for understanding DLD. However, a definitive answer to this question requires further an in-depth investigation of the relationship between neural activity and language performance in these two groups.

Declarations of competing interest

Nick Ramsey is shareholder in Braincarta, a clinical fMRI company. Braincarta was not involved in this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuropsychologia.2021.107907.

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