RUNNING TITLE: Voluntary action control and stuttering

Children who stutter show reduced action-related activity in the rostral cingulate zone

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Abstract

Previous studies have indicated that children who stutter show not only speech-related problems, but also wider difficulties in self-control. In this study we test the novel hypothesis that children who stutter may experience difficulties with inhibitory control over voluntary actions. We used functional MRI to compare brain activity between children who stutter and children who do not stutter in a task that captures key cognitive aspects of voluntary action control. Participants performed a rolling marble task, in which they were instructed to press a key to stop a rolling marble from crashing on some of the trials (instructed action condition). They were also asked to choose voluntarily whether to execute or inhibit this prepotent response in other trials (volition condition). Children who stutter reported less motor and cognitive impulsivity and had shorter stop-signal reaction times when controlled for IQ, consistent with greater inhibition, compared to children who do not stutter. At the neural level, children who stutter showed decreased activation in the rostral cingulate zone during voluntary action selection compared to children who do not stutter. This effect was more pronounced for children who were rated as showing more stuttered syllables in the stutter screening, and was furthermore correlated with stop-signal reaction times and impulsivity ratings. These findings suggest that stuttering in childhood could reflect wider difficulties in self-control, also in the non-verbal domain. Understanding these neural mechanisms could potentially lead to more focused treatments of stuttering.

Keywords: stuttering, voluntary action control, rostral cingulate zone

1. Introduction

Stuttering is a speech problem characterized by blocks, repetitions, or prolongations of speech segments (WHO, 2007). One percent of all adults suffer from developmental stuttering, which is defined as stuttering that develops during childhood without obvious neurological origin (Bloodstein & Ratner, 2008). Stuttering has negative emotional, psychological and social consequences for preschool children, as reported by their parents (Langevin, Packman, & Onslow, 2010). Quality of life is reduced when stuttering persists after preschool into adolescence and adulthood (Davis, Howell, & Cooke, 2002; Koedoot, Bouwmans, Franken, & Stolk, 2011; Yaruss, 2010). Thus, this developmental disorder has severe consequences for daily life functioning, but the underlying cognitive and neural mechanisms remain poorly understood.

Recently, it was found that children who stutter (CWS) show abnormalities not only in speaking, but also in self-control more generally. These studies reported that CWS showed less attentional control compared to children who do not stutter (CWNS) (Eggers, De Nil, & Van den Bergh, 2009, 2012; Kaganovich, Wray, & Weber-Fox, 2010). Parents and teachers also reported more attentional problems in CWS than in CWNS (Eggers et al., 2009; Eggers, De Nil, & Van den Bergh, 2010; Felsenfeld, van Beijsterveldt, & Boomsma, 2010; Karrass et al., 2006; Schwenk, Conture, & Walden, 2007). Furthermore, CWS had more difficulty with inhibitory control than CWNS based on parent-report questionnaires (Eggers et al., 2009, 2010), and performance on the Go/NoGo task (Eggers, De Nil, & Van den Bergh, 2013). Other studies, however, failed to find differences between CWS and CWNS in parent-rated attentional focusing, impulsivity and inhibitory control (Anderson & Wagovich, 2010). Taken together, self-control may be a key dimension in understanding the underlying mechanisms of stuttering, but prior studies report inconsistent findings and a comprehensive study on self-control in relation to stuttering is lacking.

Self-control is often studied by focusing on inhibition in response to external cues, for example in the stop-signal reaction time task (Band, van der Molen, & Logan, 2003; Logan & Cowan, 1984). However, self-control in daily life is mostly internally triggered, suggesting an important role for *voluntary* action control. This can be further subdivided into voluntary action selection (choosing what action to make), action initiation, and voluntary inhibition (choosing, at given moment, to suppress action, rather than acting). Previous studies in adults have shown that voluntary action selection was related to activity in the rostral cingulate zone (RCZ) (Brass & Haggard, 2008; Brass, Lynn, Demanet, & Rigoni, 2013; Demanet, De Baene, Arrington, & Brass, 2013). Voluntary control of inhibition remains a controversial idea, but has been linked to an internal decision to inhibit an action that has already been prepared. Several studies linked this form of inhibition to activation of the dorso-frontal median cortex (dFMC) (Brass & Haggard, 2008; Brass et al., 2013; Filevich, Kühn, & Haggard, 2012). Thus, these studies suggest that two important regions in the medial frontal cortex, the RCZ and the dFMC, are critically involved in voluntary action selection and voluntary inhibition, respectively. Regions in the lateral prefrontal cortex have also been implicated in self-control. An fMRI study showed that 10-12-year-old typically developing children recruited the right inferior frontal gyrus (IFG) more during voluntary inhibition than adults (Schel, Ridderinkhof, & Crone, 2014). Consistent with this finding, studies of stimulus-driven inhibition demonstrated ongoing changes in the same network (Casey, Thomas, Davidson, Kunz, & Franzen, 2002; Crone & Dahl, 2012; Durston et al., 2006; Luna, Padmanabhan, & O'Hearn, 2010).

One might hypothesize that developmental stuttering could be related to protracted or deviant development of the brain. Most studies have revealed that stuttering is related to increased activation in certain brain regions, often interpreted as compensatory activity. For instance, during speech perception, adults who stutter (AWS) showed increased activity in the

right IFG and left Heschl's gyrus (Halag-Milo et al., 2016) and left anterior insula (Lu et al., 2016), but decreased activity in several motor regions and angular gyrus (Chang, Kenney, Loucks, & Ludlow, 2009) compared to adults who do not stutter (AWNS). During speech production, increased activity was found in primary motor and auditory regions (Chang et al., 2009). A conjunction analysis that focused on both speech perception and speech production revealed coincident activity in speech motor areas (Lu et al., 2016). CWS showed increased activity in the anterior insula and cingulate sulcus during speech production (Watkins, Smith, Davis, & Howell, 2008). The latter region may be closely related to the RCZ, given that both are located in the medial frontal cortex. Prior research has also related stuttering symptoms to a non-speech related executive function task, the Simon spatial incompatibility task. CWS and AWS showed more activity in frontostriatal regions when resolving conflict, but less activity in the dorsolateral prefrontal cortex (dlPFC) when adapting to changes in conflict compared to CWNS and AWNS. These differences were interpreted as suggesting failure to recruit control-related regions in some task conditions, and possibly a compensatory mechanism for other task conditions (Liu et al., 2014). Interestingly, this study showed that activity in the ACC was negatively correlated with the severity of stuttering symptoms, possibly reflecting a failure to recruit conflict related regions to resolve stuttering (Liu et al., 2014).

Even though almost no studies examined functional brain activation in children who stutter, some hypotheses can be derived from studies that related stuttering in children to structural brain measures. Structural brain imaging studies reported that CWS and children who recovered from stuttering showed reduced grey matter volume in the left IFG and bilateral temporal brain areas, areas that are related to speech (Chang, Erickson, Ambrose, Hasegawa-Johnson, & Ludlow, 2008), as well as the auditory areas, supplementary motor area (SMA) and putamen (Chang, 2014). The latter two regions are possibly related to initiation and timing of speech motor control (Chang, 2014). Taken together, prior studies

show some differences in brain activity during several aspects of cognitive control in CWS and AWS (Liu et al., 2014), and structural brain development studies indicate differences in neural trajectories in CWS (Chang, 2014; Chang et al., 2008), but it is currently unknown how difficulties in self-control in CWS are related to differences in brain activity.

The goal of the present study was therefore to compare neural responses between CWS and CWNS during voluntary action control. We used an adapted version of the marble task (Schel, Windhorst, van der Molen, & Crone, 2013) to measure brain activity during voluntary action control in CWS and CWNS between the ages of 9 and 14 years. In this task, participants could choose to execute (voluntary action selection) or inhibit (voluntary inhibition) a key press to stop a marble from rolling down the ramp (Kühn, Haggard, & Brass, 2009; Schel, Kühn, et al., 2014). These choice trials were interleaved with trials in which a stimulus instructed participants to stop the marble. The speed of the marble required rapid responding in instructed trials. As a result the action response became prepotent, and the voluntary inhibition response became, in turn, an exercise of self-control over a prepotent action tendency. Our first hypothesis was that CWS would show impaired voluntary action selection, based on behavioral studies that show that CWS have poorer attentional control (Eggers et al., 2009, 2012; Kaganovich et al., 2010; Karrass et al., 2006; Schwenk et al., 2007). We expected that this would be accompanied by aberrant activation of the RCZ (Brass & Haggard, 2008; Brass et al., 2013; Demanet et al., 2013). Our second hypothesis was that CWS would show specific deficits in voluntary inhibition based on behavioral studies showing less inhibitory control in CWS (Eggers et al., 2009, 2010, 2013). We expected that this would be accompanied by differential activation in the inhibition network including the dFMC, IFG/pre-SMA and the putamen (Brass & Haggard, 2008; Brass et al., 2013; Filevich et al., 2012; Schel, Ridderinkhof, et al., 2014). All participants also performed a stop-signal task (Logan & Cowan, 1984) to obtain a behavioral measure of stimulus-driven inhibition and

to further test for difficulties in self-control. In addition, all participants filled out the Barrett Impulsiveness Scale (Patton, Stanford, & Barratt, 1995), to test whether CWS and CWNS differed in impulsivity.

2. Material and methods

2.1 Participants

Seventeen CWS and nineteen CWNS between the ages of 9 and 14 years participated in this study. Care was taken to recruit a similar number of boys and girls in this study. CWS were diagnosed and referred to us by speech therapists[1] and CWNS were recruited from schools in the local area and through recruitment websites. The control group data was published previously in a study about developmental effects in voluntary action control (Schel, Ridderinkhof, et al., 2014). All children were right-handed, had normal or corrected-to-normal vision, and none of the children had a current or past neurological or psychiatric disorder. Table 1 displays the means and standard deviations of CWS and CWNS across several background variables. CWS and CWNS did not differ in age, F (1, 34) = 0.44, p = 0.51, and the distribution of gender was the same in both groups, $X^2(1) = 0.47$, $p = 0.53$. Informed consent was signed by parents for children under 12 years, and by both parents and participants for children over 12 years. The study was approved by the Internal Review board at Leiden University Medical Center.

To check for differences in cognitive functioning, all participants performed two subtests of the Wechsler Intelligence Scale for Children (WISC) (Wechsler, 1991). Estimated IQ scores were within the normal range. However, estimated IQ was lower in CWS than in CWNS, F (1, 34) = 10.83, p = 0.002. Therefore, we performed all analyses also with IQ added as a covariate and we report the results of both analyses.

[1] It should be noted that no speech-language tests were conducted, so the children may have other disorders.

All children were screened for stuttering. We collected two speech samples of 300 syllables per child, while reading aloud a story and while having a conversation with the experimenter. Two independent trained analysts scored these speech samples. CWS stuttered significantly more syllables (range 1.07 – 14.32) than CWNS (range 0.16 – 1.47) across the two speech samples, F (1, 34) = 18.58, $p < 0.001$. The interanalyst reliability was computed using a Pearson correlation of the average percentage of stuttered syllables across the two speech samples. This interanalyst reliability was good, $r = 0.98$. Additionally, Table 1 shows the percentage of stuttered syllables for reading and conversation separately, mean age of onset of stuttering and results from self-report and parent-report questions about stuttering.[2]

Table 1

Means and standard deviations for background variables, and results of the self-reported and parent-reported questions about stuttering.

		CWS		CWNS	
		M	*SD*	*M*	*SD*
Age (at time of scanning)		11.29	1.26	11.05	0.91
IQ		98.53	13.29	111.32	9.94
Percentage stuttered syllables (reading and conversation)		5.31	4.71	0.64	0.41
Percentage stuttered syllables (reading)		5.33	4.88	0.72	0.51
Percentage stuttered syllables (conversation)		5.28	6.06	0.55	0.43
Age of stuttering onset		5.41	2.26		
		number of subjects		number of subjects	
Boys		10		9	
Self-reported stuttering		16			
Self-reported stuttering severity	Light	4			
	Medium	9			
	Severe	2			

[2] Both analysts indicated that three children stuttered less than 3% of the syllables on both speech samples. When we excluded these children, the results remained largely the same. Only three results changed: (a) After correction for IQ, there was no difference between white and green trials across all participants, F (1, 30) = 2.05, $p = 0.16$ (instead of being marginally significant in the original analysis); (b) RCZ activation during voluntary action selection was only marginally significant related to SSRT, $r = 0.32$, $p = 0.08$ (instead of being significant in the original analysis); (c) After correction for IQ, RCZ activation during voluntary action selection was also related to RT in green trials, $r = 0.40$, $p = 0.02$ (instead of being not significant in the original analysis).

Parent-reported stuttering		17	0
Parent-reported stuttering severity	Light	8	
	Medium	7	
	Severe	1	
Treated for stuttering		14	0

Note: data on self-reported stuttering was missing for 1 CWS, data on self-reported stuttering severity was missing for 2 CWS, data on parent-reported stuttering severity was missing for 1 CWS, data on treatment for stuttering was missing for 3 CWS.

2.2 Task

The marble task (Kühn et al., 2009) was adapted to measure voluntary action control in children using fMRI (see Figure 1). This version (Schel et al., 2013) consisted of two conditions: a green marble condition, and a white marble condition. Each trial started with a fixation cross, presented between 1400 and 2000 ms (random variation, jitter). A white marble was then shown at the beginning of a ramp. The marble started to roll down the ramp after 1400-2000 ms. In the green marble condition, the color of the marble changed to green when it started to roll down the ramp. Participants had to press a key with their right index finger to stop the green marble from rolling down the ramp. If the participants responded in time, they were shown a feedback screen with the marble at the point at which they had stopped it. These trials measured stimulus-driven action and were called Green-Go trials. If the participants were too late, they were shown a feedback screen with a green marble shattered beneath the ramp (Green-Omission trials).

In the white marble condition, the color of the marble did not change when it started rolling down the ramp. The marble rolled considerably slower in this condition, to give participants enough time to voluntarily decide between executing and inhibiting a key press with the right index finger (Kühn et al., 2009). When the key was pressed, participants were shown a feedback screen with the marble undamaged at the point at which they had stopped it. These trials measured voluntary action selection and were called White-Go trials. When the key press was inhibited, participants were shown a feedback screen with the marble

undamaged beneath the ramp. These trials measured voluntary inhibition and were called White-NoGo trials.

All participants were instructed to distribute their responses equally between execution and inhibition of the key press in the white marble condition. To make sure that participants could generally monitor their performance, they were shown during the breaks how many marbles they had collected in two buckets. The left bucket was "filled" with the marbles that were stopped (White-Go trials), and the right bucket was "filled" with the marbles that were not stopped (White-NoGo trials). Participants were instructed to decide anew on each white trial whether to act or inhibit, and not to use a sequencing strategy to predecide.

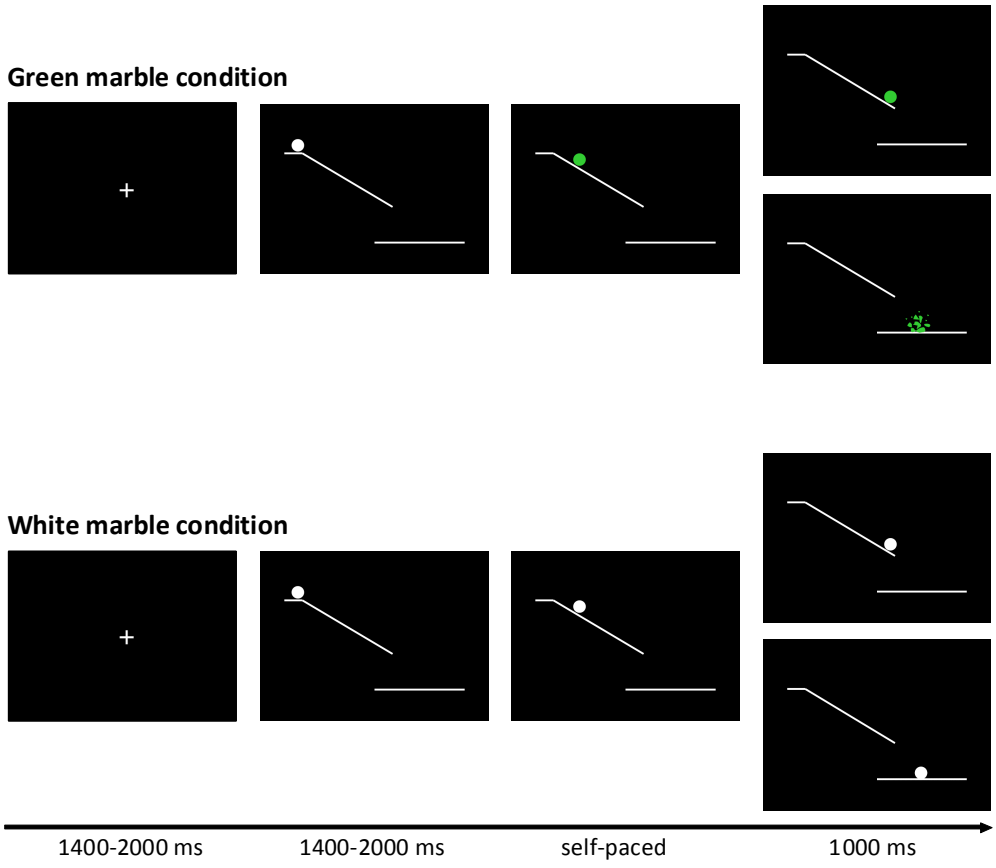


Figure 1. Schematic overview of the marble task.

Maximal trial length in the green marble condition varied between 320 and 1280 ms, dependent on a staircase procedure. After the fixation cross and start screen, we showed 16

static pictures of the marble at different positions of the ramp at a high speed, which was experienced as motion. At the start of the experiment, these static pictures were each shown for 30 ms. When the participants was able to stop the marble in time, the duration per static picture was decreased with 10 ms. When a participant was not able to stop the marble in time, the time duration per static picture was increased with 10 ms. Maximal trial length in the white marble condition varied between 800 and 1760 ms, because the static pictures in the white trials always took 30 ms longer than the green trials. The marble task consisted of three blocks of 80 trials. Each block consisted of 48 green trials and 32 white trials in pseudo-randomized order. Each white trial was preceded by 0, 1, 2 or 3 green trials. Pressing the key was viewed as a prepotent response, because there were more green trials than white trials, and because green trials had shorter durations. Furthermore, participants could not predict which condition would come, which prevented strategic responding (deciding in advance of trials). Table 2 shows the mean number of trials per group per condition. CWS and CWNS did not differ in the number of trials per condition, all *p*s > 0.33. Between the blocks, there were breaks in which the experimenter checked on the participants. In total, the task took approximately 15 minutes to complete.

Table 2

Means, standard deviations and range for number of trials per condition, for CWS and CWNS separately.

	CWS			CWNS		
	M	*SD*	*Range*	*M*	*SD*	*Range*
Green-Go trials	80.12	7.00	72-93	82.58	7.90	72-99
Green-Omission trials	63.41	7.79	48-72	61.42	7.90	45-72
White-Go trials	58.76	7.81	37-73	56.89	9.63	31-69
White-NoGo trials	36.94	7.80	23-59	39.11	9.63	27-65

2.3 Stop-signal task

We also administered the stop-signal task (Logan & Cowan, 1984) to obtain a measure of stimulus-driven inhibition and to test for differences in self-control. During this task, participants responded as fast as possible to the direction of a green left or right pointing arrow (i.e., right key press after right pointing arrow). In 25% of the trials, the arrow turned red, and participants had to inhibit their reaction. Participants performed two blocks of 128 trials (96 green trials, and 32 stop trials) (see Schel, Kühn, et al. (2014) for the details of this task and the calculation of the stop-signal reaction time [SSRT]). One CWS was excluded because s/he was not successful in 90% of the stop trials, three CWS performed only the first block of the task.

2.4 Barratt Impulsiveness Scale

After the scanning session, participants filled out the Barratt Impulsiveness Scale (BIS-11) (Patton et al., 1995) which was rephrased in an age-appropriate style. This questionnaire measures impulsive traits and consists of three subscales: motor impulsivity ("I act without thinking"), cognitive impulsivity ("I have difficulties sitting still in the classroom"), and non-planning impulsivity ("I'm not interested in the future, but in today").

2.5 Procedure

When the participants arrived in the lab, the MRI procedure was explained to them. We showed the participants a mock scanner and let them listen to the sounds of an MRI scanner. In this way, the participants were familiarized with the scanning procedure. Before scanning, we explained the marble task and the stop-signal task to the participants and they performed ten practice trials of the marble task and twelve practice trials of the stop-signal task. Care was taken that all participants understood the task instructions and were able to perform the task. Subsequently, all participants performed the marble task and the stop-signal

task in the MRI scanner. After scanning, all participants filled out the BIS-11, and performed the subscales 'vocabulary' and 'block design' of the Dutch version of the WISC (Kort et al., 2005) to obtain an estimate of their IQ. They also participated in the stutter screening.

2.6 Data acquisition

Behavioral data and timing of the stimuli were obtained using E-prime (Schneider, Eschman, & Zuccolotto, 2002). Scanning was performed using a 3.0T Philips Achieva scanner with a standard whole-head coil at the Leiden University Medical Center. We used foam inserts to reduce head movements in the scanner. The participants viewed the marble task via a mirror on a screen at the head of the magnet. They responded with their right index finger by pressing a key on a response box attached to their right upper leg. Functional data were acquired using T2*-weighted Echo-Planar Images (TR=2.2 s, TE=30 ms, sequential acquisition, 38 slices of 2.75 mm, slice matrix=80×80, in-plane resolution 2.75 mm, slice gap=0.28 mm, field of view=220) during three functional runs. The first two volumes of each run were discarded to allow for equilibration of T1 saturation effects. After the functional runs, a high resolution 3D T1-FFE scan for anatomical reference was obtained (TR=9.760 ms, TE=4.59 ma, flip angle=8 degrees, 140 slices, 0.875 X 0.875 X 1.2 mm^3 voxels, field of view = 224 x 168 x 177 mm^3).

2.7 Data analysis

The behavioral data were analyzed using IBM SPSS Statistics 23.0. We used analysis of variance to compare demographic variables and task performance between CWS and CWNS. We used the Random Number Generation 2 (RNG2) index using the RgCalc program (Towse & Neil, 1998), to compare the use of strategies between CWS and CWNS in the voluntary condition. We set alpha at 0.05.

The fMRI data were preprocessed and analyzed using SPM8 software (Welcome Department of Cognitive Neurology, London) implemented in MATLAB (Mathworks, Sherborn, MA). During fMRI preprocessing, the functional images were realigned using the middle slice as reference. For two participants, we deleted the last two scans of each run due to excessive motion (>3 mm). CWS (M = 0.12, SD = 0.04) and CWNS (M = 0.13, SD = 0.03) did not differ in their motion during the scanning session, F (1, 35) = 0.82, p = 0.37. We also performed all the analyses with motion regressors added to the model, to make sure effects were not driven by possible motion effects. The results were highly similar with and without motion regressors added. The images were spatially normalized to the T1 scan of the participant and then spatially normalized to an MNI template. Finally, they were spatially smoothed with a Gaussian kernel (8 mm, full-width at half-maximum). The normalization algorithm used a 12-parameter affine transformation together with a non-linear transformation involving cosine basic functions, and resampled the volumes to 3 mm cubic voxels. The fMRI time series data were modelled by a series of events convolved with a canonical hemodynamic response function. The onset of each trial was modeled as a zero duration event at the onset of marble motion. These events were divided into four conditions: Green-Go, Green-Omission, White-Go and White-NoGo.

Individual participants' data were analyzed using the general linear model in SPM8. First, whole brain contrasts for the total group (n = 36) between the different conditions were computed by performing t-tests, treating participants as a random effect. Analyses were performed using FWE voxel level correction ($p < 0.05$). Voluntary action selection was measured with the contrast White-Go > Green-Go (in which the selected response was voluntary action). The decision process of voluntary inhibition was measured with the contrast White-NoGo > Green-Go (in which the selected response was voluntary inhibition). The late decision outcome of voluntary inhibition was measured using the contrast White-

NoGo > White-Go (in which we compared voluntary inhibition with voluntary action selection). Stimulus-driven action was measured with the contrasts Green-Go > White-Go and Green-Go > White-NoGo.

To test for group differences at the whole brain level, we performed a two-sample t-test between CWS and CWNS for the same five contrasts. Given the exploratory focus, these analyses were performed at cluster size of 25 voxels, to balance between Type 1 and Type 2 errors ($p < 0.005$ uncorrected, >25 contiguous voxels). If there was a significant group difference, we used the MARSBAR toolbox for SPM8 (Brett, Anton, Valabregue, & Poline, 2002) to extract regions of interest (ROIs) from interaction effects observed in this two-sample t-test. We extracted contrast values from this ROI for CWS and CWNS to examine possible effects further.

3. Results

3.1 Behavioral results

CWS and CWNS showed the same percentage of key presses in green trials (Green-Go), F (1, 34) = 0.70, $p = 0.41$ (see Figure 2). As instructed, both groups chose to press the key in approximately 50 percent of the white trials, CWS and CWNS did not differ from each other, F (1, 34) = 0.49, $p = 0.49$ (see Table 2 for the percentage of key presses in green and white trials). To check whether the choices in the white trials of CWS and CWNS followed a pattern, we computed the RNG2 index using the RgCalc program (Towse & Neil, 1998). When we compared the RNG2 index of CWS, CWNS and a randomly generated data set (n = 24), there was a main effect, F (2, 57) = 9.45, $p < 0.001$. The RNG2 index of the randomly generated data set (average $M = 0.80$, $SD = 0.002$) was smaller than the RNG2 index of CWS ($M = 0.81$, $SD = 0.01$) and CWNS ($M = 0.81$, $SD = 0.002$), respectively t (16.67) = 3.56, p = 0.002 and t (19.62) = 3.84, $p = 0.001$. However, this difference was very small and indicated

that participants were close to being random and had not used simple alternating strategies. In addition, individual children did not show extreme RNG2 values (+/- 3 SD from the mean) and none of the children reported after the experiment that they had used a simple alternating strategy. There was no difference in RNG2 index between CWS and CWNS, t (34) = -0.77, p = 0.45. In line with the assumption that the decision process takes time, reaction times on the white trials were slower than on the green trials, F (1, 34) = 77.94, $p < 0.001$. There was no difference in reaction times between CWS and CWNS, F (1, 34) = 0.18, p = 0.67.

In the stop-signal task, CWS and CWNS successfully stopped their response in an equal number of stop trials, F (1, 33) = 0.86, p = 0.36. There was no difference in SSRT between CWS and CWNS, F (1, 33) = 1.68, p = 0.20. Finally, results of the BIS-11 revealed that CWS showed less motor and cognitive impulsivity than CWNS, respectively F (1, 34) = 11.42, p = 0.002 and F (1, 34) = 5.98, p = 0.02 (see Table 3). There was no difference in non-planning impulsivity between CWS and CWNS, F (1, 34) = 0.03, p = 0.87.

After correction for IQ, results remained largely the same, except for three measures. The difference in reaction time on white and green trials across all participants was only marginally significant when IQ was added as a covariate, F (1, 33) = 3.25, p = 0.08. There was still no difference between CWS and CWNS, F (1, 33) = 0.01, p = 0.93. CWS showed a faster SSRT than CWNS when IQ was added as a covariate, F (1, 32) = 4.28, p = 0.047, and cognitive impulsivity was only marginally lower in CWS when IQ was added as a covariate, F (1, 33) = 3.27, p = 0.08.

Table 3

Means and standard errors of the behavioral measures for CWS and CWNS separately.

Behavioral measure		CWS		CWNS	
		M	*SE*	*M*	*SE*
Marble task	% Green-Go	55.85	1.26	57.35	1.26
	% White-Go	61.40	1.97	59.27	2.30
	RT Green-Go	331.33	9.65	326.18	9.12
	RT White-Go	385.95	13.85	378.05	13.10
	RNG2 index	0.81	0.01	0.81	0.002
Stop-signal task	% Successful stops	50.49	1.37	48.71	1.33
	SSRT	265.32	13.54	289.12	12.43
BIS-11	Motor impulsivity	1.75	0.04	2.01	0.06
	Cognitive impulsivity	1.85	0.08	2.19	0.11
	Nonplanning impulsivity	2.16	0.07	2.14	0.10

Note: CWS = children who stutter; CWNS = children who do not stutter; RT = reaction time; RNG = random number generation; SSRT = stop-signal reaction time; BIS-11 = Barratt impulsiveness scale.

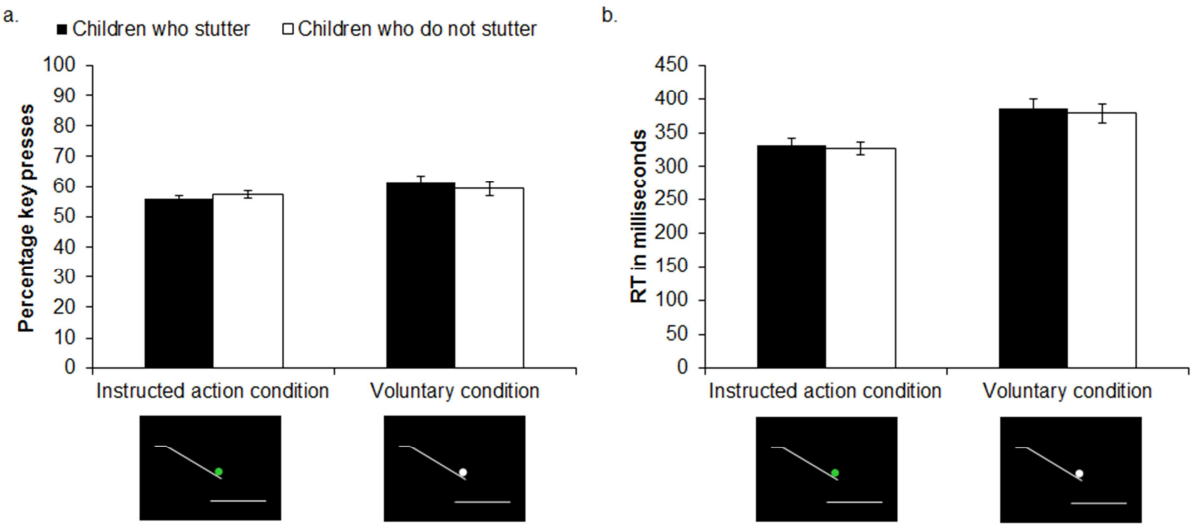


Figure 2. (a) Percentage of key presses in the instructed action and voluntary condition for children who stutter and children who do not stutter separately. (b) Reaction time on the

instructed action and voluntary condition for children who stutter and children who do not stutter separately.

3.2 fMRI results: main effects

First, we tested for main effects of task in voluntary action selection. To examine which brain regions participants recruited during the decision process of selecting an action, we used the contrast White-Go > Green-Go (voluntary action selection vs. stimulus-driven action). Consistent with prior research, this contrast revealed activated clusters with peak values in right RCZ, left and right insula lobe, right precuneus, right middle frontal gyrus, right supramarginal gyrus, and left supplementary motor area ($p < 0.05$, FWE voxel level corrected; see Figure 3a and Supplementary Table 1).

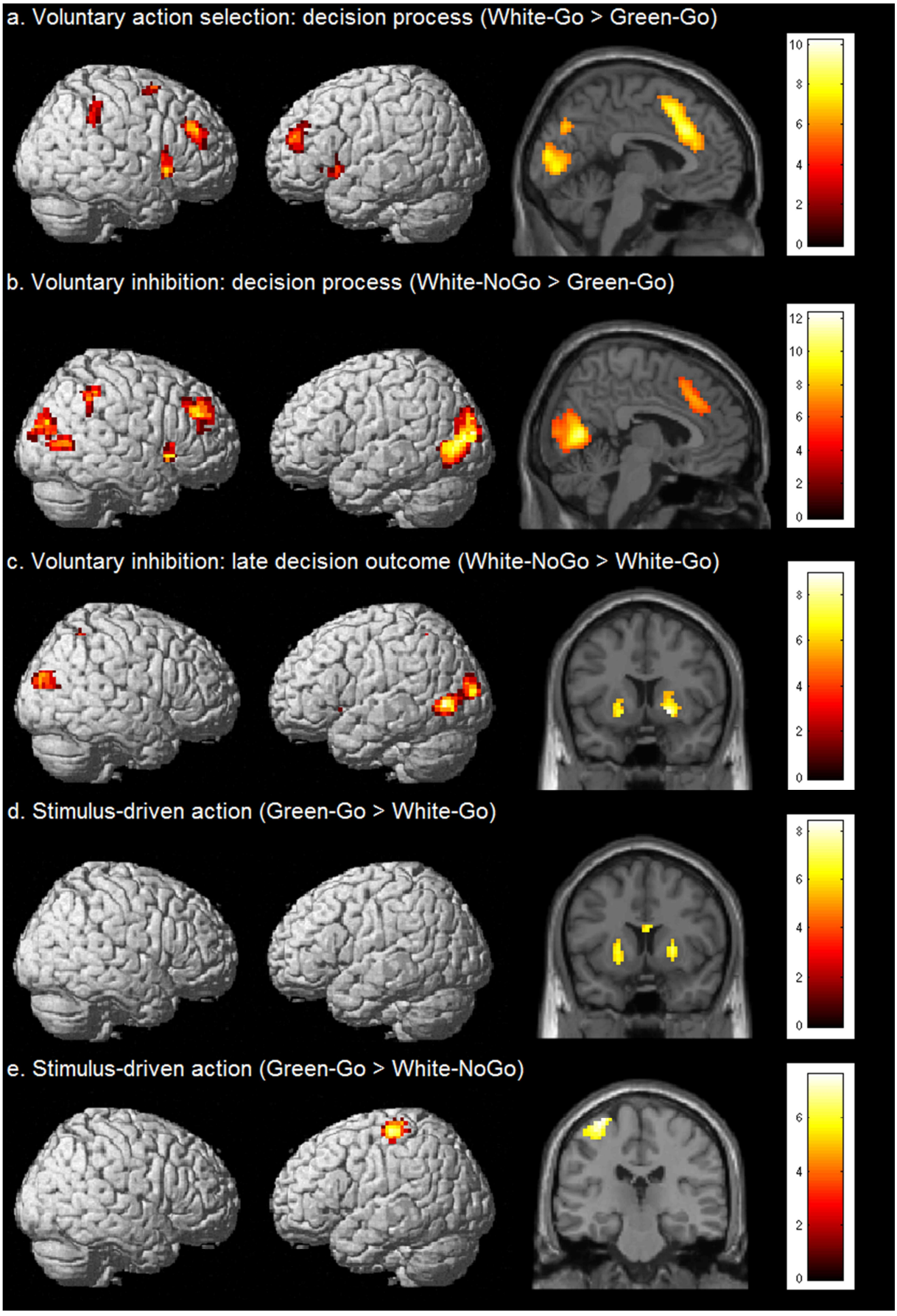
Second, to examine which brain regions participants recruited during the decision process of choosing to inhibit, we used the contrast White-NoGo > Green-Go (voluntary inhibition vs. stimulus-driven action). This contrast revealed activated clusters with peak values in right calcarine gyrus, right insula lobe, right middle cingulate cortex, right middle frontal gyrus, and right inferior parietal lobe ($p < 0.05$, FWE voxel level corrected; see Figure 3b and Supplementary Table 1).

Third, to examine which brain regions participants recruited during the late decision outcome of voluntary inhibition compared to voluntary action, we used the contrast White-NoGo > White-Go (voluntary inhibition vs. voluntary action). This contrast revealed activated clusters with peak values in left and right putamen, left middle occipital gyrus, right superior occipital gyrus, right lingual gyrus, right superior parietal lobule, left inferior parietal lobule ($p < 0.05$, FWE voxel level corrected; see Figure 3c and Supplementary Table 1).

Fourth, to examine which brain regions participants recruited during stimulus-driven action compared to voluntary action selection, we used the contrast Green-Go > White-Go

(stimulus-driven action vs. voluntary action selection). This contrast revealed activated clusters with peak values in left and right putamen, and corpus callosum ($p < 0.05$, FWE voxel level corrected; see Figure 3d and Supplementary Table 1).

Fifth, to examine which brain regions participants recruited during stimulus-driven action compared to voluntary inhibition, we used the contrast Green-Go > White-NoGo (stimulus-driven action vs. voluntary inhibition). This contrast revealed an activated cluster with a peak value in the left postcentral gyrus ($p < 0.05$, FWE voxel level corrected, see Figure 3e and Supplementary Table 1).


a. Voluntary action selection: decision process (White-Go > Green-Go)
10
8
6
4
2
0
b. Voluntary inhibition: decision process (White-NoGo > Green-Go)
12
10
8
6
4
2
0
c. Voluntary inhibition: late decision outcome (White-NoGo > White-Go)
8
6
4
2
0
d. Stimulus-driven action (Green-Go > White-Go)
8
6
4
2
0
e. Stimulus-driven action (Green-Go > White-NoGo)
6
4
2
0

1

Figure 3.Whole brain contrasts for all participants (n = 36) for (A) the decision process of voluntary action selection, (B) the decision process of voluntary inhibition, (C) the late decision outcome of voluntary inhibition, and (D, E) stimulus-driven action ($p < 0.05$, FWE voxel-level corrected).

3.3 fMRI results: group differences

Next, we tested for differences in stimulus-driven and voluntary action control between CWS and CWNS at the whole-brain level using a two-sample t-test including Group. We focused on five contrasts examining voluntary action selection (White-Go > Green-Go), the decision process of voluntary inhibition (White-NoGo > Green-Go), the late decision outcome of voluntary inhibition (White-NoGo > White-Go), and stimulus-driven action (Green-Go > White-Go, Green-Go > White-NoGo) ($p < 0.005$ uncorrected, >25 contiguous voxels). No group differences were found for the contrasts White-NoGo > Green-Go, White-NoGo > White-Go, Green-Go > White-Go, and Green-Go > White-NoGo. The contrast White-Go > Green-Go (voluntary action selection) x Group (CWNS > CWS) revealed a significant difference between CWS and CWNS, only in the RCZ (see Figure 4). This cluster overlapped with the cluster that was observed in the analyses across groups (see Figure 3a).

We extracted this region of the RCZ from the two-sample t-test during voluntary action selection, and examined this effect further using an ROI analysis. As can be seen in Figure 4, CWS showed decreased activation during voluntary action selection compared to CWNS. This effect remained significant when IQ was added as a covariate, F (1, 33) = 7.28, p = 0.01.

To further interpret the role of this region in action selection, we tested how activation was related to individual differences in IQ, stuttered syllables, SSRT on the stop-signal task and BIS-11 impulsivity scores. These correlation analyses showed that increased activation in

the RCZ during voluntary action selection was related to higher IQ (r = 0.43, p = 0.01), fewer stuttered syllables (r = -0.39, p = 0.02), slower SSRT (r = 0.34, p = 0.047), more motor impulsivity (r = 0.42, p = 0.01), and more cognitive impulsivity (r = 0.44, p = 0.01). After correction for IQ, the correlations between RCZ activation during voluntary action selection and SSRT (r = 0.46, p = 0.01), motor impulsivity (r = 0.42, p = 0.01), and cognitive impulsivity (r = 0.36, p = 0.04) remained significant.

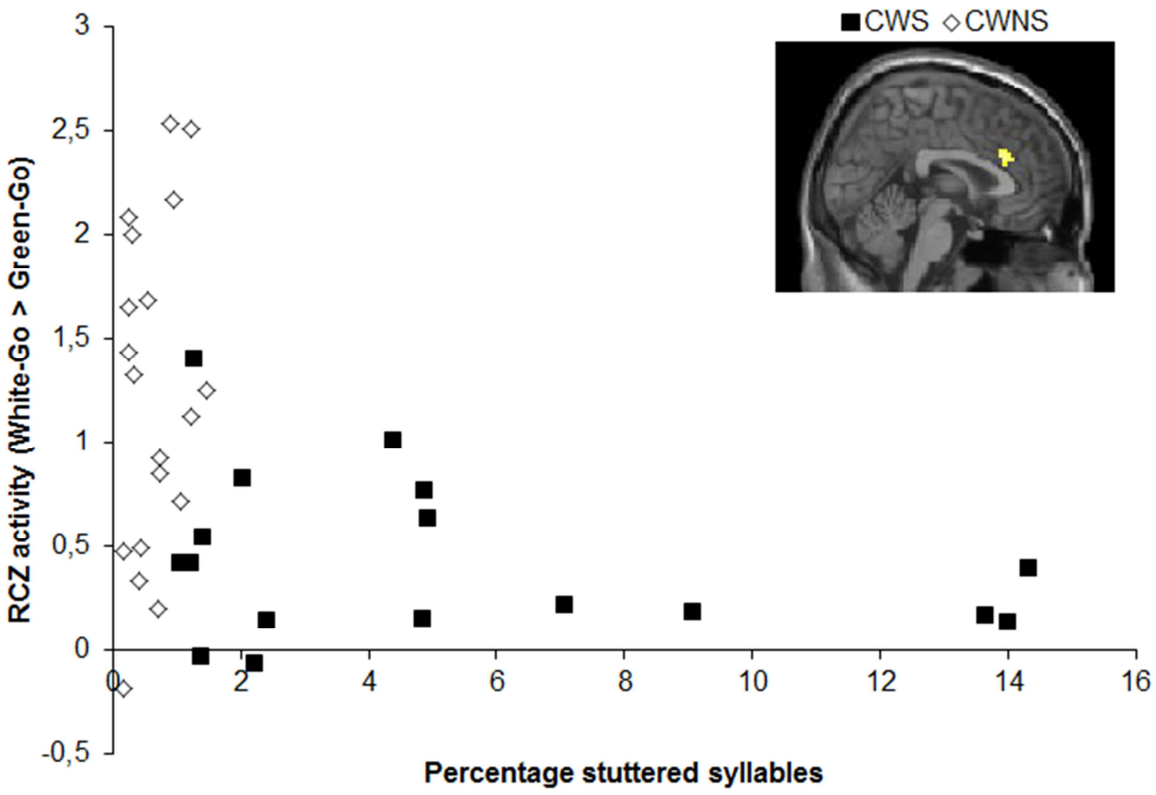


Figure 4. RCZ (center of mass: 5.33 26.4 21.8, volume: 2619 mm) activity during voluntary action selection (White-Go > Green-Go) in CWS and CWNS, relation with percentage stuttered syllables.

4. Discussion

We aimed to compare neural mechanisms of voluntary action control between CWS and CWNS. All children performed a marble task (Schel et al., 2013), in which they could

freely choose to execute or inhibit a prepotent response on each white trial. CWS and CWNS did not differ in their behavior during the marble task. However, CWS showed decreased motor and cognitive impulsivity on the BIS-11 questionnaire, and faster stop-signal reaction times when controlling for IQ. fMRI results revealed that CWS showed decreased activation of the RCZ during voluntary action selection. Together, these results suggest that CWS are more inhibited, or less impulsive, compared to CWNS, which may reflect problems with action selection more generally.

The neural findings revealed that CWS showed less activation in the RCZ during voluntary action selection compared to CWNS, and this result remained significant when controlling for IQ. In adults, activation in the RCZ is related to the decision process of selecting a response (Brass & Haggard, 2008; Brass et al., 2013; Demanet et al., 2013). The RCZ was also activated during voluntary action selection in typically developing children (Schel, Ridderinkhof, et al., 2014). Differences in brain activation between CWS and CWNS were found in the absence of behavioral differences. The task was selected such that it could be performed well by children of both groups, which allowed us to test for neural differences that were not caused by performance differences. The results indicate that even though performance was the same, the underlying processes in CWS were different.

One interpretation of decreased RCZ activation in CWS is that when making voluntary choices, activity in RCZ is less involved in resolving conflict. Other studies have shown that activation in the RCZ is also decreased when choices are influenced by external information (even when this information was unconscious) (Demanet et al., 2013; Teuchies et al., 2016). Indeed, distractibility was related to the presence of speech-language dissociation in CWS, but not in CWNS (Clark, Conture, Walden, & Lambert, 2015). In addition, several behavioral studies have shown that CWS showed less efficient orienting of attention than CWNS (Eggers et al., 2012), and less attentional control capacity (Eggers et al., 2009; Felsenfeld et al., 2010;

Kaganovich et al., 2010; Karrass et al., 2006; Schwenk et al., 2007). This may be associated with less RCZ activation during voluntary action selection. Another interpretation of decreased RCZ activation in CWS is that this might be a kind of compensatory function, since decreased RCZ activation was related to faster SSRT and less motor and cognitive impulsivity. Both interpretations should be investigated in future studies.

Two other studies have found increased activity in brain regions near the RCZ in relation to stuttering (Liu et al., 2014; Watkins et al., 2008). First, in a Simon spatial incompatibility task, CWS and AWS showed increased activity in the ACC during conflict resolution compared to CWNS and AWNS. Moreover, increased activity in the ACC was related to decreased stuttering severity in CWS and AWS, interpreted as a compensatory role of the ACC (Liu et al., 2014). The study of Liu et al. (2014) used conflict-laded stimuli, whereas there was no conflict in the present study – the response in voluntary action trials was the same as the prepotent response in stimulus-driven action trials. In addition, Liu et al. (2014) included both children and adults, whereas we included only children. Therefore, it is difficult to directly compare the results of both studies. Second, in a speech task, CWS showed more activity during speech production in the cingulate sulcus compared to CWNS (Watkins et al., 2008). This area might be closely related to the RCZ found in our and previous studies, which would suggest that CWS show aberrant brain activity when voluntarily selecting their verbal and non-verbal actions. It is not clear whether these findings are indicative of a primary disorder in voluntary control, or are a consequence of stuttering. For example, reduced residual capacity for voluntary control could also be due to the increased effort associated with speaking in CWS (Ingham, Warner, Byrd, & Cotton, 2006).

Several remaining questions deserve attention in future research. Decreased RCZ activation was specific to voluntary action selection, because CWS did not differ from CWNS during voluntary inhibition (during neither the decision process, nor the late decision

outcome). In addition, in the current study, CWS scored lower than CWNS on motor and cognitive impulsivity on a standard impulsivity scale (Patton et al., 1995), and also had faster SSRTs, after controlling for IQ. In contrast, previous studies have shown that CWS had impaired inhibition in a Go/NoGo task (Eggers et al., 2013) and lower levels of inhibitory control according to their parents (Eggers et al., 2009, 2010). This discrepancy in findings could be related to the type of task that is used. We measured impulsivity with a self-report questionnaire, whereas other studies used parent-report questionnaires (Eggers et al., 2009, 2010) or task data (Eggers et al., 2013). It is possible that CWS are not aware of their own problems with impulsivity or inhibitory control. Moreover, previous studies have been done in young children between 3 and 10 years (Eggers et al., 2009, 2010, 2013), whereas we have included children from 9 to 14 years old. This could also have caused differences between our and previous findings. Finally, CWS only had faster SSRTs when IQ was added as a covariate. To our knowledge, prior behavioral studies did not specifically control for IQ, which may have affected the results. Future research should also examine whether there are differences in the neural correlates of externally driven inhibition in CWS, since the current study indicated that CWS showed faster SSRTs after controlling for IQ than CWNS (which may be indicative of too much self-control).

To our knowledge, our study is the first to investigate neural mechanisms of self-control in CWS in a non-verbal, cognitive control task. One limitation of our study is the difference between groups in estimated IQ. Despite this, almost all effects remained when statistically correcting for IQ. A question for future research concerns possible developmental effects on self-control, since self-control and related brain regions develop during childhood (Casey et al., 2002; Cohen et al., 2010; Crone & Dahl, 2012; Durston et al., 2006; Luna et al., 2010; Schel, Ridderinkhof, et al., 2014). In the current study the sample size was too small to test for age differences, but future studies should use longitudinal measures to capture

changes within both groups over time. Strengths of this study were the specific whole-brain effects and post hoc correlates with individual differences in stuttering scores and impulsivity measures. Replication of these effects in a further sample would be valuable. Nevertheless, these effects provide important starting points for future research to test for differences between CWS and CWNS in non-verbal tasks. A greater understanding of the underlying mechanisms of verbal and non-verbal problems in CWS could help in advancing the treatment of stuttering.

Acknowledgements

This work was supported by the Dutch Science Foundation (NWO, grant number 461-090525) as part of the EUROVETO project (09-ERCP-020) of the European Science Foundation.

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1 Supplementary Table 1

2 Brain regions revealed by whole brain contrasts across all participants (n = 36).

Contrast	Brain region	MNI			K	Z
		x	y	z		
White-Go > Green-Go	Right rostral cingulate zone	6	24	33	764	6.91
	Left supplementary motor area	-27	45	24	142	6.16
	Left insula lobe	-33	18	-6	112	6.05
	Right precuneus	12	-69	39	716	5.95
	Right insula lobe	45	15	-3	147	5.69
	Right middle frontal gyrus	36	36	30	138	5.40
	Right supramarginal gyrus	48	-42	39	62	5.32
White-NoGo > Green-Go	Right calcarine gyrus	12	-69	6	2323	7.61
	Right insula lobe	36	12	-3	100	5.89
	Right middle cingulate cortex	6	27	36	220	5.76
	Right middle frontal gyrus	45	36	33	152	5.55
	Right inferior parietal lobule	45	-42	48	72	5.12
White-NoGo > White-Go	Right putamen	31	9	-6	111	6.41
	Left middle occipital gyrus	-48	-72	3	194	6.00
	Right superior occipital gyrus	27	-78	2	119	5.87
	Left putamen	-21	12	0	41	5.46
	Right lingual gyrus	18	-72	-6	47	5.33
	Right superior parietal lobule	30	-54	57	10	5.11
	Left inferior parietal lobule	-27	-51	54	12	5.06
Green-Go > White-Go	Corpus callosum	3	3	21	67	6.17
	Right putamen	24	9	3	35	5.52
	Left putamen	-21	9	0	28	5.27
Green-Go > White-NoGo	Left postcentral gyrus	-30	-27	69	119	5.81

3