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Ventral striatum and stuttering: Robust evidence from a case-control study applying DARTEL

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ABSTRACT

A prominent theory of developmental stuttering highlights (dys-)function of the basal ganglia (and in particular the ventral striatum) as a main neural mechanism behind this speech disorder. Although the theory is intriguing, studies on gray matter volume differences in the basal ganglia between people who stutter and control persons have reported heterogeneous findings, either showing more or less gray matter volume of the aforementioned brain structure across the brain's hemispheres. Moreover, some studies did not observe any differences at all.

From today's perspective several of the earlier studies are rather underpowered and also used less powerful statistical approaches to investigate differences in brain structure between people who stutter and controls. Therefore, the present study contrasted a comparably larger sample of $n = 36$ people who stutter with $n = 34$ control persons and applied the state of the art DARTEL algorithm (Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra) to analyze the available brain data. In the present data set stuttering was associated with *higher* gray matter volume of the right caudate and putamen region of the basal ganglia in patients. Our observation strongly supports a recent finding reporting a larger nucleus accumbens in the right hemisphere in people who stutter when compared to control persons. The present findings are discussed in the context of both compensatory effects of the brain and putative therapeutic effects due to treatment of stuttering.

1. Introduction

Idiopathic or developmental stuttering represents a speech disorder with a prevalence of about 1% in the general population (Bloodstein and Bernstein Ratner, 2008). The core symptoms of the disorder are believed to be neurological in origin (Rosenfield, 2001; Qiao et al., 2017). This has led to a growing number of neuroimaging studies on developmental stuttering (for review and meta-analyses see Chang et al., 2018; Craig-McQuaide et al., 2014; Etchell et al., 2018; Neef et al., 2015). These studies provide convergent evidence from different imaging modalities that left hemisphere motor and auditory areas and their interconnecting fiber tracts are of major relevance for the disorder. Such deficits are often interpreted as neurofunctional impairment in the integration of auditory feedback in speech motor planning (Chang et al., 2018). Speech motor planning, however, does not only rely on cortical areas. Particularly the subcortical nuclei of the basal ganglia structure play an important role by providing precise timing signals within the speech production network (Kotz and Schwartze, 2010). Timing and motor control processes are also clearly involved in fluent speech production and are thought to be disrupted in stuttering. It has therefore been proposed that the basal ganglia play a major role in idiopathic stuttering as well (Alm, 2004). This idea is supported by computational modeling (Civier et al., 2013) and by empirical evidence that points towards impaired performance by people who stutter on behavioral tasks that rely strongly on the basal ganglia structures such as the *Stop Signal Reaction Time Task* (Markett

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Table 1
Structural MRI studies contrasting persons who stutter with control persons*.

Authors	Number of participants	Children vs. adults	Therapy status	Image processing	Findings concerning basal ganglia
Beal et al. (2013)	11 people who stutter (boys) vs. 11 control persons (boys)	Children Age range between 6 and 12 years	Unknown	VBM with VBM8 toolbox in SPM8, DARTEL normalization with customized pediatric template	Less gray matter volume in the left putamen in people who stutter compared to controls (x = −15, y = 14, z = 0)
Foundas et al. (2013)	13 people who stutter (boys) vs. 14 controls persons (boys)	Children PWS: 10.10 (SD = 2) vs. Controls: 10 0.20 (SD = 1.60)	Unknown	Manual volumetric tracing.	Less gray matter volume of the right caudate nucleus in people who stutter compared to the controls (no coordinates provided)
Lu et al. (2010)	12 people who stutter (10 males, 2 females) vs. 12 control persons (8 males, 4 females)	Adults PWS: 24.5 vs. Controls: 24	Recruited while being on a waiting list at the Stuttering Therapy Center in Beijing, China	SPM5's unified segmentation and spatial normalization.	Higher gray matter volume of the left putamen in people who stutter compared to controls (x = −29, y = −9, z = 0)
Neef et al. (2018)	33 people who stutter (17 males, 18 females) vs. 34 matched controls (16 males, 17 females)	Adults PWS: median-age 36 years vs. Controls: median-age 35.5	PWS were recruited from stuttering help groups.	Automatized subcortical segmentation with FSL's FIRST. Volumetric and surface mesh analysis.	Enlarged volume and surface of the right nucleus accumbens in PWS (x = 12, y = 9, z = −9).
Sowman et al. (2017)	27 people who stutter (20 males, 7 females) vs. 27 controls (20 males, 7 females)	Adults PWS: 45.9 (SD = 16) vs. Controls: 47.1 (SD = 15)	25 PWS underwent treatment	VBM with VBM8 toolbox in SPM8, DARTEL normalization	Lower gray matter volume of the left caudate nucleus/putamen in people who stutter compared to controls (x = −18, y = 12, z = 16.5)

* Only studies are depicted in the table reporting differences in the basal ganglia when contrasting people who stutter and controls. Studies by Beal et al. (2007) [SPM's unified segmentation and normalization (SPM5)], Chang et al. (2008) ['optimized' VBM], Jäncke et al. (2004) ['optimized' VBM in SPM99], Kell et al. (2009) [SPM's unified segmentation and DARTEL normalization] and Song et al. (2007) could not find a difference between people who stutter and control persons in this brain area.

et al., 2016a) and the *GoNogo task* (Eggers et al., 2013). Furthermore, molecular studies have implicated dopamine – a key neurotransmitter of the basal ganglia – in stuttering (Lan et al., 2009; Montag et al., 2012, Stager et al., 2005). In line with the theory, a few sMRI studies have also reported altered structural properties of the basal ganglia in people who stutter. These neuroimaging studies, however, are at least in part inconsistent with regard to the direction of findings (i.e, increased or decreased tissue concentration in people wo stutter), lateralisation (i.e. left or right hemisphere), and the exact location within the basal ganglia (for a summary see Table 1). When reviewing and discussing the available body of work, Sowman et al. (2017) mentioned that most sMRI studies on stuttering so far lack a sufficient sample size and therefore statistical power to find robust effects for stuttering. Shen and Sterr (2013), for instance, report that a minimum of 25 participants in each group would be needed for meaningful results in sMRI studies with case-control designs that apply voxel-based morphometry (VBM) with the DARTEL algorithm. DARTEL is an image processing algorithm for the co-registration and spatial normalization of MR images (Ashburner, 2007). DARTEL belongs to a family of deformable algorithms that was shown to be superior to traditional approaches (Yassa and Stark, 2009). In a comparative evaluation, DARTEL ranked among the best performing algorithms, and particularly outperformed traditional approaches (Klein et al., 2009). Compared to the traditional SPM approach, DARTEL models anatomical features with a higher degree of detail (Kurth et al., 2015). The majority of previous structural MRI studies on stuttering have used older algorithms for spatial normalization which raises concerns on sensitivity and statistical power, particularly given the often moderate sample sizes. As can be seen in Table 1, the sample size criterion of $N > 25$ is only met by the more recent reports by Sowman et al. (2017) and by Neef et al. (2018).

Given the clear theoretical implications of the basal ganglia in idiopathic stuttering and the inconsistent evidence from sMRI studies so far, our present study aims to revisit the question if people who stutter differ in gray matter volume of the basal ganglia.

2. Methods

2.1. Participants

74 participants took part in this study: 37 people who stutter (aged 19 to 62 years, mean age = 34.00, SD = 11.87; 24 males, 13 females; 33 right-handed, 2 left-handed, 2 ambidextrous persons) and 37 aged-, gender- and handedness-matched controls (aged 19 to 61 years, mean age = 34.14, SD = 11.72). Data from 70 participants (36 adults who stutter (AWS) and 34 controls) were used in the final analysis because four datasets were excluded during the recommended quality control steps of the MRI images (see MRI acquisition). 36 AWS consisted of 23 males and 13 females (mean-age = 33.47, SD = 11.58) and 34 controls of 22 males and 12 females (mean-age = 32.44, SD = 10.57).

People who stutter were recruited through the infrastructure of the German Stuttering Association (local self-help groups, annual meetings, and an advertisement in the association journal) and with the help of specialized therapy providers who contacted former patients via mailing lists. People who stutter were required to meet the following eligibility criteria before being accepted to the study: (1) age 18 years and over; (2) the nature of stuttering must be developmental in origin (not related to known neurological causes) with the onset before age ten; (3) no other speech, language or hearing disorder than stuttering; (4) no neurological or psychiatric disorders. Controls were selected from the structural neuroimaging data base of the Life and Brain Center in Bonn, Germany and met the following inclusion criteria: (1) age 18 years and over; (2) no personal or family history of stuttering; (3) no other speech, language or hearing disorder; (4) no neurological or psychiatric disorders. Finally, participants in the people who stutter group had been diagnosed with stuttering by a speech therapist. Such diagnostic information was not available for one participant who only

self-identified as a person who stutters but who showed disfluencies in our own assessments. We decided to include this person in our sample as excluding the person did not affect the results. All eligibility criteria in this study were determined by self-reports. Both people who stutter and controls were native German speakers. Imaging was performed at the Life & Brain Center in Bonn, Germany. Informed written consent was obtained from all participants in advance. Participants were compensated with 10 EUR/h of their time. The study protocol was approved by the ethics review board at the University Hospital, Bonn, and adhered to the principles laid out in the Declaration of Helsinki and its amendments.

2.2. Clinical and behavioral assessments

Stuttering severity in the people who stutter was assessed with the Stuttering Severity Instrument, Third Edition (SSI-III; Riley, 1994; German version Sandrieser and Schneider, 2008). Speech samples of all people who stutter were audio-visually recorded (digital voice recorder: Olympus VN-2100PC and a Sony video camera) before the scanning session in a separate room in the presence of one of the experimenters (B·B).

Speech samples included an unstructured interview about the home town of the participants and their way to work (about 10 minutes) as well as a standardized reading task (232 syllables). For the offline analysis of disfluencies the first 200 syllables of the two speaking tasks (interview and text) were transcribed syllable by syllable and then scored independently by two trained raters who specialize in stuttering therapy (authors T.M., B.B.). The percent of stuttered syllables (% SS) was calculated based on the syllables that included any type of stuttering-like disfluencies (SLD; Sandrieser and Schneider, 2008). Furthermore, the estimated duration of the three longest blocks as well as the observation of physical concomitants based on the video recordings were included for the estimate of the individualized total score of stuttering severity (SSI total score, Riley, 1994; Sandrieser and Schneider, 2008).

The independently scored stuttering severity measurements had excellent inter-rater reliability (% SS for the unstructured interview: ICC = 0.999, $p < .001$; % SS for the reading task: ICC = 0.998, $p < .001$; duration of blocks: ICC = 0.994, $p < .001$; physical concomitants: ICC = 0.924, $p < .001$).

The SSI-III total scores varied from very mild to severe (mean = 14.72, SD = 11.73), which represents a wide range of symptom severity at the time of assessment. Of note, 12 people who stutter had a SSI-III total score lower than 10. They were still included in the study because they perceived themselves as people who stutter, had previously been diagnosed with stuttering, and self-rated their current stuttering severity higher than 0 on a 11-point scale (0 = no stuttering, 10 extreme stuttering). Finally, the videos of $n = 6$ participants could not be analyzed due to technical problems with the recordings. In consequence, no complete SSI-III could be calculated for these participants, because the variable “physical concomitants” could not be assessed. Finally, the structural MRI scan of author B.B., a person who stutters himself, was also included in the present study without including data on SSI-III (he knew about the design of the study which precluded speech assessment).

2.2.1. Descriptive statistics for stuttering severity

Among people who stutter self-assessed stuttering severity of M = 4.64 (SD = 2.16) was observed (possible range between 0 and 10, with 10 being the highest self-assessed stuttering severity; available for all $n = 36$ AWS (adults how stutter). The objective speech analysis ($n = 35$) pointed towards M = 15.54 (SD = 25.47) percent of stuttered syllables (%SS) in the unstructured interview and M = 12.20 (SD = 23.76) %SS in the reading task. The combination of %SS in the unstructured interview and reading task resulted in M = 27.74 (SD = 45.47) %SS. The mean length of three longest stuttering symptoms was 1.91 seconds (SD = 2.45). Analysis of the physical concomitants in $n = 29$ AWS resulted in M = 2.28 (SD = 2.39). Due to six missing video recordings the objective stuttering severity was only available in n = 29 participants (SSI-III, M = 14.72, SD = 11.73). Age was not associated with the here reported variables. Gender influenced several stuttering variables significantly. Given the skewed gender ratio we do not follow up on this lead further. Analyzing the stuttering severity measures in either the male or female subsample did not yield in different results.

2.3. MRI acquisition

Three dimensional high-resolution T1-weighted images were acquired on a 3 T Siemens Trio MRI scanner equipped with a 12 channel head coil using a Magnetization Prepared Rapid Gradient Echo (MP-RAGE) sequence with 160 sagittal slices of 1 mm slice thickness (in-plane resolution 1 mm × 1 mm, field of view 256 × 256 mm, TR = 1300 ms, TE = 3.97 ms, TI = 650 ms, flip angle 10°).

2.4. Voxel based morphometry

Voxel-based morphometry was carried out using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/) as described previously (Markett et al., 2013; 2016b). Preprocessing included the segmentation of images into gray and white matter tissue, and cerebrospinal fluid. To denoise the data, we applied a spatial adaptive non-local means (SANLM) filter during segmentation with an optimal weighting estimated internally, and a Markov random field (MRF) filter with a medium weighting of 0.15. Subsequently, images were normalized using the high-dimensional diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) algorithm. During normalization, only non-linear transformations were modulated so that voxels carried information on volume. This also restricted the analysis to relative differences irrespective of individual brain size. Finally, images were smoothed using a Gaussian filter with 8 mm full width at half maximum. Quality checks on the preprocessed data were performed as follows: Data were visually inspected by displaying one slice of each normalized and bias-corrected image to identify wrongly-oriented images or gross artifacts. As a second step, the covariance matrix between normalized gray matter segments was inspected for outliers. Images of one adult who stuttered and three control participants did not pass these quality control steps and were excluded from statistical analyses.

2.5. Statistical analyses

Whole-brain group differences in gray matter volume were assessed by a general linear model fitted in Statistical Non-Parametric Mapping (SnPM, http://warwick.ac.uk/tenichols/snpm). We decided to use non-parametric permutation based testing because non-parametric approaches to MRI data achieve a better balance between false-positive and false-negative findings than parametric tests (Eklund et al., 2016). Group differences were assessed by linearly weighted contrasts at the whole brain level. Despite our clear hypothesis regarding the basal ganglia, we refrained from any a priori regions of interest to provide unbiased results and better compatibility with prior whole brain studies. Participant's sex, age, and handedness were treated as nuisance covariates. Statistical significance was assessed based on 5000 permutations. The family-wise error was kept below $p < .05$ at the voxel level. Associations with clinical variables were explored by correlating individual summary scores with extracted parameter estimates from significant clusters.

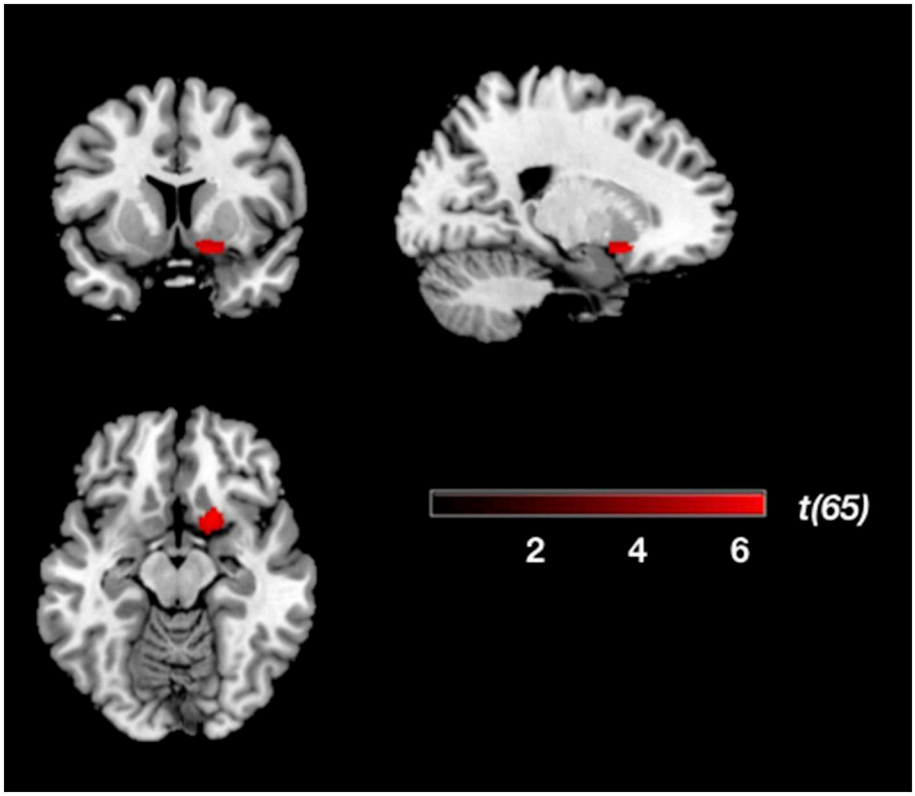

Fig. 1. Higher gray matter volume of the ventral striatum in persons who stutter compared to controls.

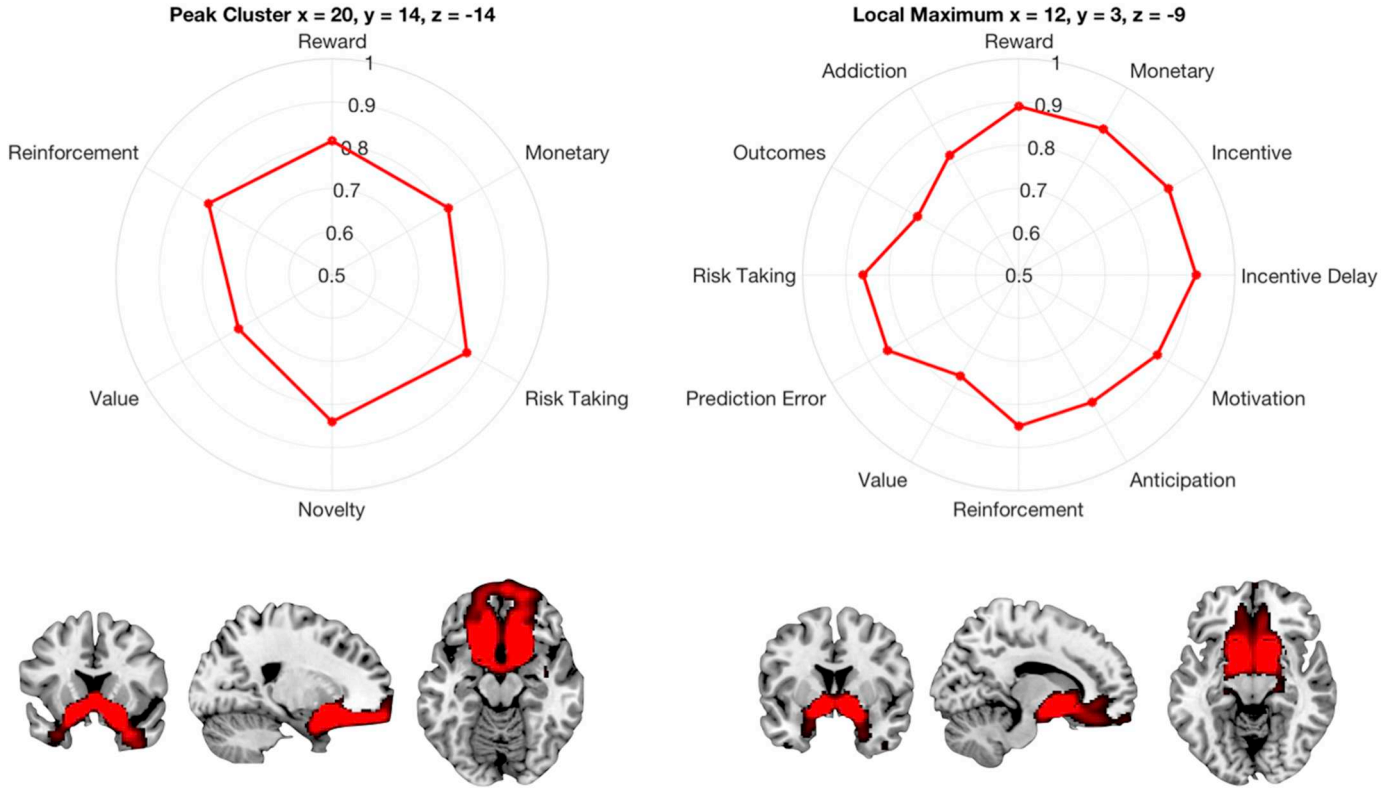

Fig. 2. Top panels show the results of the functional decoding analysis. The statistics in the circular plots are posterior probabilities. In the Neurosynth framework, these probabilities indicate the probability that a study refers to this term given functional activation at this voxel location. The bottom panels show functional resting state connectivity networks centered around the two voxel locations as seed regions. Connectivity maps implicate the orbitofrontal cortex as the most likely projection side of the ventral striatal cluster. Data are taken from Neurosynth.

3. Results

3.1. Comparing gray matter volumes of the AWS group with the control group

Contrasting the two groups revealed one cluster (k = 264 voxels) of increased gray matter volume in the right basal ganglia (putamen and caudate) of adults who stutter (compared to controls, see Fig. 1). The cluster's global maximum was at MNI x = 20, y = 14, z = −14 (t(65) = 6.4, p = .0006, FWE-corrected). A local maximum within the same cluster was found at MNI x = 12, y = 3, z = −9 (t(65) = 5.36, p = .0126, FWE-corrected).

3.2. Correlations between the extracted parameters from the significant basal ganglia cluster and stuttering severity

No significant associations between gray matter volume of the significant basal ganglia cluster and stuttering severity measures were observed. For the variables with available data for n = 35 (objective speech analysis), all p's were higher than .42. For the variables with available data for n = 29 (physical concomitants and SSI-III total scores) all p's were higher than .71. Finally, self-assessed stuttering severity was not significantly correlated with gray matter volumes (r = .23, p = .19; rho = .28, p = .10). Of note, splitting the sample into a male and female subsample for the correlational analysis did also not yield any significant associations.

3.3. Functional decoding

We queried the neurosynth database (neurosynth.org) for a data-driven characterization of our VBM finding. Neurosynth is a publicly accessible database that currently lists the results from > 14,000 functional MRI investigations. Neurosynth can be queried for the functional decoding of voxel locations in MNI space (Yarkoni et al., 2011). We probed both voxel locations (peak coordinate and local maximum) and retained terms with a) a significant meta-analytical z-statistic, and that b) referred to psychological and not anatomical terms. Results are shown in Fig. 2. We limited the display to a maximum of twelve terms. Results unequivocally suggested an association with reward and motivation related functions. For reference, we also plot resting-state functional connectivity maps of the two voxel locations, as obtained through neurosynth. The functional connectivity maps clearly implicate the orbitofrontal cortex as a likely projection area.

3.4. Correspondence with previous findings

One previous neuromorphometric study has implicated the ventral striatum and particularly the nucleus accumbens region in stuttering (Neef et al., 2018). We obtained a list of all significant voxel MNI coordinates from the first author (Nicole Neef, personal communication) to test for precise spatial overlap of our present finding. Despite the difference in methodology (surface analysis restricted to the nucleus accumbens vs. unconstrained gray matter based VBM), we found an exact overlap of 18 voxels between the Neef et al. results and our cluster in the ventral striatum.

4. Discussion

The present study used voxel-based morphometry with the DARTEL algorithm in a case-control design to revisit structural gray matter differences between people who stutter and control persons, in particular with a focus on the basal ganglia. Such differences are widely believed to be a core neural underpinning of stuttering. Empirical investigations, however, have repeatedly provided inconsistent results. Our results suggest increased gray matter volume in the right ventral striatum in people who stutter. Even though we used a different methodological approach than Neef et al. (2018), our results can be regarded a direct replication of their finding of increased (surface-) volume of the right hemisphere's nucleus accumbens in people who stutter. We will first discuss our current finding in the context of previous evidence on the involvement of the basal ganglia structure in stuttering, followed by a discussion of our functional decoding analysis that points towards reward and motivation related processes, and conclude with a methodological discussion regarding inconsistencies with previous neuromorphometric studies.

Alm (2004) has argued that the basal ganglia circuits play a key role in the mechanisms of stuttering. This argument was based on an extensive review of the neuroscience literature on stuttering and included evidence from behavioral, neuropsychological, neuroimaging, and pharmacological studies. The basal ganglia circuits consist of parallel loops that funnel input from cortical regions back to the cortex via thalamic projections. Different loops can be dissociated based on interconnected cortical regions and segregate in at least three functional domains: motor, cognitive, and limbic (Alexander et al., 1986; Smith et al., 2004; Utter and Basso, 2008). The role of the basal ganglia circuitry has been particularly detailed regarding its relevance for motor function. Here, the basal ganglia facilitate smooth and fluid movements by activating relevant and inhibiting irrelevant motor programs (Mink, 1996). Neurally plausible computational models have detailed how these mechanisms could contribute to disfluencies in speech production (Civier et al., 2013), and behavioral evidence suggests a generalized deficit in producing smooth motor sequences in people who stutter (Smits-Bandstra and De Nil, 2007). Given the large body of work that point towards the basal ganglia as key structures in stuttering, it is surprising that large meta-analyses on functional and structural neuroimaging studies on stuttering have primarily highlighted different brain regions: The first meta-analysis on stuttering that applied activation likelihood estimation (ALE) techniques proposed a “neural signature of stuttering” consisting of over-activation of right inferior premotor cortices, the insula, cerebellum, and an under-activation of auditory cortices (Brown et al., 2005). These findings have been in parts replicated in later ALE meta-analyses, and extended to the supplementary motor area (Budde et al., 2014; Belyk et al., 2017). While many studies on stuttering report subcortical activation foci, spatial concordance across reports is low (Budde et al., 2014). An ALE-based meta-analysis on structural connectivity has implicated left-lateralized cortico-cortico- and callossal connections in stuttering, and did not find evidence for involvement of fiber tracts passing through the basal ganglia (Neef et al., 2015). A more recent combined functional and structural connectivity study found evidence for increased functional but decreased structural connectivity between the right (but not the left) nucleus accumbens with orbitofrontal as well as caudal visual areas (Sitek et al., 2016). Even though the results were reported on a lenient statistical threshold, they do point towards the same structure as our current report.

So while the history of the study of the basal ganglia in stuttering is quite long and a large body of literature seems to be supportive of this idea, the precise location is disputed and meta-analytic evidence so far has been disappointing. This is in line with our observation of the VBM literature that we have detailed in the introduction. By analyzing a larger number of participants than most older studies, by using state-of-the-art segmentation and normalization strategies, by applying more robust non-parametric statistical tests, and by means of precise replication of a previous report (Neef et al., 2018), we are confident to provide reliable evidence for neurostructural alterations in the right ventral striatum. The location of our finding is noteworthy, as previous work on basal ganglia involvement in stuttering has mainly focused on motor function. The ventral striatum region belongs to the limbic subdivision of the basal ganglia circuit which is involved in reward and motivational functions. This interpretation is further corroborated by meta-analytical functional decoding (see Fig. 2) which exclusively

found associations with reward-related terms. Furthermore, the functional connectivity of our peak coordinate with orbitofrontal regions suggest an involvement in the medial forebrain bundle and the brain's motivation system (Coenen et al., 2018). In fact, the ventral striatum and the associated limbic loop of the basal ganglia have been described as an interface between motivation and movement (Haber and Knutson, 2010). Neef et al. (2018) were the first to report structural alterations in the right ventral striatum of adults who stutter. They refer to comparative evolutionary neuroscience theories (e.g. Syal and Finlay, 2011) and discuss their finding with the idea that speech is a motor act that is goal-directed and mediated by reward. Reward-related aspects of speech production could account for the motivational and social modulation of stuttering (Yaruss and Quesal, 2006) and are very well in line with the notion that speaking and telling is considered a joyful act (Neef et al., 2018). The possible involvement of the ventral striatum in speech production and its social modulation is suggested by animal literatures that report the homologue of the ventral striatum in birds to be involved in song, and particularly in the modulation of song production in social goal-directed context (Yanagihara and Hessler, 2006). Neef et al. (2018) warrant caution in their report that their results should be regarded preliminary until successful replication. With our present study, we provide such replication which points towards reward and motivational aspects in speech production and stuttering and encourages further investigations in a less explored and potentially new mechanism underlying disfluency disorders.

The validity of morphometric analyses depends crucially on the accuracy of inter-subject alignment and a precise matching of brain anatomy in standard space. Our processing pipeline included tissue segmentation with an adaptive maximum a posteriori technique and partial volume estimation, together with denoising methods and DARTEL normalization. These steps represent an advancement of processing methodology when compared to earlier studies on stuttering. Newer approaches towards spatial normalization based on information from multimodal imaging have been shown to be more advantageous when analyzing cortical regions (Haxby et al., 2011; Robinson et al., 2014; Glasser et al., 2016). Volumetric analyses like ours, however, are still recommended when subcortical structures like the basal ganglia are in the focus. A further issue in individual differences research with MRI is statistical power and sample size. Dubois and Adolphs (2016) provide simulation results that show how the number of false positive findings in MRI studies is inversely related to sample size. Given that most previous studies on the basal ganglia and stuttering have used very small sample sizes and often older and less accurate processing pipelines, there is reason to believe that inconsistencies in the literature and the inconsistency of the present with most previous findings stems from methodological and statistical issues. Our own sample consisted of 74 participants of whom 70 were entered into the analysis after quality control. This is actually not a large sample when looking at the current standards in the neuroimaging community, and power problems might still apply here as well. However, it is one of the two largest morphological study on stuttering so far (together with the Neef et al. study), and most importantly comes to the same conclusion as the other study. Our findings also in parts overlap with those from Lu et al. (2010) who report higher gray matter volumes of the putamen region. In their study, however, higher volume was observed in the left hemisphere, whereas we found the mentioned differences in the right hemisphere. Of importance, two studies investigating children came to a different observation than our work. Beal et al. (2013) and Foundas et al. (2013) report lower gray matter of the left putamen and right caudate in children who stutter. But it needs to be mentioned that these works are underpowered from the current perspective.

Although the motivation/reward aspects in the context of language production as discussed by Neef et al. (2018) and in our work is intriguing, it does not explain why persons who stutter are associated with larger gray matter volume of the ventral striatum in the right hemisphere. Although our work is of cross-sectional nature and cannot answer this question, it is conceivable that such differences – in particular when contrasting findings of works conducted in adults and children (effects in the opposite direction) - represent an adaption of the adult brain. It has been suggested that the brain responds to its own speech deficit with efforts to “repair” the dysfunction over the course of life (Kell et al., 2009). Therefore, higher volumes could be interpreted as compensatory mechanism of the brain that might be beneficial to counteract speech problems. All participants (but one) of the present sample had already undergone speech therapy to a certain degree, potentially amplifying such compensatory efforts through the therapeutic intervention. This explanation, however, is weakened by the findings by Sowman et al. (2017) who report lower gray matter volumes of the left caudate in a sample of people who stutter who were about ten years older than the participants from the present study. If aging and life-long adaptation would lead to larger volumes, it should be expected that such an effect was even more pronounced in higher age. Clearly, sufficiently powered longitudinal studies are needed to explore the developmental trajectories of structural alterations in people who stutter over the lifespan. Such studies could also aim at a systematic assessment of lateralization. Our present study suggests increased gray matter volume of the right ventral striatum (as the work by Neef et al., 2018) while Sowman et al. (2017) report a decrease in the left hemisphere. As Sowman et al.'s participants have been in the middle of their 40ies, it would be interesting to know how ventral striatum volumes develop in the present sample in the next ten years. Again, only longitudinal studies will help to get the full picture, here.

Speech is usually lateralized in the brain, and it is therefore conceivable that different compensatory mechanisms lead to different adaptations e.g. structural adaptation across hemispheres. Despite the inconsistencies between the present and Neef et al.'s work and the studies by others, we want to point out that the present study (together with the one by Neef et al. (2018)) used the largest sample so far, and found a very robust group difference that survived FWE-correction at the voxel level using permutation testing, a statistical approach that is thought to be superior to parametric testing (Eklund et al., 2016).

This being said, some limitations of the present study need to be mentioned. The information on stuttering severity derived from objective language analysis in recorded interviews was not correlated with ventral areas of the striatum. Such a correlation would have strengthened our findings, as an inverse association between stuttering severity and gray matter volumes could have been interpreted as evidence for the suggested structural adaptation of the adult brain to speech dysfunctions (Kell et al., 2009). But also a positive association between basal ganglia/ventral striatum gray matter volumes and stuttering severity would have been meaningful (note that Neef et al. also did not observe any of such associations in their work). Unfortunately, we weren't able to obtain complete SSI-III scores in a relatively large number of people who stutter for technical reasons. A final limitation needs to be mentioned: the control persons did not undergo speech analysis and we only relied on self-report that they did not stutter.

In sum, it presently remains unclear how structural alterations of the basal ganglia contribute to the etiology and pathogenesis of stuttering. Nevertheless, the ventral striatum of the basal ganglia seems to play an important part when putting the pieces of the puzzle together. Future work should include more thorough clinical assessments, functional imaging assays and strategies for connectivity mapping, but also neuropsychological tests that tap into the function of the basal ganglia/ventral striatum circuit. Although the present work includes the so far largest sample size, it is still relatively small. Therefore, future studies need to even enlarge the sample size to be able to carve out the most robust effects.

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