# Speaking-related changes in cortical functional connectivity associated with assisted and spontaneous recovery from developmental stuttering

Kell, Christian A.; Neumann, Katrin; Behrens, Marion; von Gudenberg, Alexander W.; Giraud Mamessier, Anne-Lise

**How to cite**

KELL, Christian A. et al. Speaking-related changes in cortical functional connectivity associated with assisted and spontaneous recovery from developmental stuttering. In: Journal of Fluency Disorders, 2018, vol. 55, p. 135–144. doi: 10.1016/j.jfludis.2017.02.001

This publication URL: https://archive-ouverte.unige.ch/unige:99627

Publication DOI: 10.1016/j.jfludis.2017.02.001

# Manuscript Details

| | |
|---|---|
| **Manuscript number** | JFD_2016_74 |
| **Title** | Speaking-related changes in cortical functional connectivity associated with assisted and spontaneous recovery from developmental stuttering |
| **Article type** | Research Paper |


**Abstract**

We previously reported speaking-related activity changes associated with assisted recovery induced by a fluency shaping therapy program and unassisted recovery from developmental stuttering (Kell et al., Brain 2009). While assisted recovery re-lateralized activity to the left hemisphere, unassisted recovery was specifically associated with the activation of the left BA 47/12 in the lateral orbitofrontal cortex. These findings suggested plastic changes in speaking-related functional connectivity between left hemispheric speech network nodes. We reanalyzed these data involving 13 stuttering men before and after fluency shaping, 13 men who recovered spontaneously from their stuttering, and 13 male control participants, and examined functional connectivity during overt vs. covert reading by means of psychophysiological interactions computed across left cortical regions involved in articulation control. Persistent stuttering was associated with reduced auditory-motor coupling and enhanced integration of somatosensory feedback between the supramarginal gyrus and the prefrontal cortex. Assisted recovery reduced this hyper-connectivity and increased functional connectivity between the articulatory motor cortex and the auditory feedback processing anterior superior temporal gyrus. In spontaneous recovery, both auditory-motor coupling and integration of somatosensory feedback were normalized. In addition, activity in the left orbitofrontal cortex and superior cerebellum appeared uncoupled from the rest of the speech production network. These data suggest that therapy and spontaneous recovery normalizes the left hemispheric speaking-related activity via an improvement of auditory-motor mapping. By contrast, long-lasting unassisted recovery from stuttering is additionally supported by a functional isolation of the superior cerebellum from the rest of the speech production network, through the pivotal left BA 47/12.



| | |
|---|---|
| **Keywords** | Psychophysiological interactions; speech production; overt reading; auditory-motor interactions, left inferior frontal gyrus |



| | |
|---|---|
| **Corresponding Author** | Christian Kell |
| **Order of Authors** | Christian Kell, Katrin Neumann, Marion Behrens, Alexander w. von Gudenberg, Anne-Lise Giraud |


## Submission Files Included in this PDF

**File Name [File Type]**

cover.docx [Cover Letter]

authordeclaration.jpg [Conflict of Interest]

Response to Reviewers.docx [Response to Reviewers (without Author Details)]

manuscript.docx [Manuscript (without Author Details)]

Figure1rev.tif [Figure]

Figure2rev.tif [Figure]

bionotes.docx [Author Biography]

Highlights.docx [Highlights]

titlepage.docx [Title Page (with Author Details)]

To view all the submission files, including those not included in the PDF, click on the manuscript title on your EVISE Homepage, then click 'Download zip file'.

GOETHE UNIVERSITY
FRANKFURT
MEDICAL FACULTY

Dr. Christian Kell – Klinik für Neurologie · Schleusenweg 2-16 · 60528 Frankfurt

To Professor Pascal van Lieshout

Editor of the

Journal of Fluency Disorders

**Dr. Christian Kell**

**Consultant in Neurology**
**Group leader**
**Cognitive Neuroscience Group**
Schleusenweg 2 – 16, Haus 95
60528 Frankfurt am Main
Germany

(+49) 069 - 6301 - 5739
www.brainclocks.com
c.kell@em.uni-frankfurt.de

15.12.2016

Dear Professor van Lieshout,

we thank you for the opportunity to revise our manuscript entitled „Speaking-related changes in cortical functional connectivity associated with assisted and spontaneous recovery from developmental stuttering" by the authors Kell, Neumann, Behrens, von Gudenberg, and Giraud.
The reviewers did a great job by providing numerous constructive remarks. It thus took us a while to re-analyze the data, slightly update the results and Figures (based on the use of different covariates as suggested by Reviewer 2), and rewrite the Introduction and Discussion based on both Reviewers suggestions.

We dealt with all their remarks, hopefully convincingly, and we hope that this version is now acceptable for publication.

Yours faithfully,

Christian Kell

BIC
Brain Imaging Center
Frankfurt am Main

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email from the Journal of Fluency Disorders (c.kell@em.uni-frankfurt.de).

Signed by all authors as follows:

C. Kell 7.10.16

K. Rebers 07.10.16

Alexandra v. Gudenberg 8.10.16

Anne-Lise Giraud 9.10.2016

Katrin Neumann

## Response to Reviewers

We thank both reviewers for their careful evaluation of the manuscript. We have re-analyzed the data, updated all results, and re-written parts of the Introduction and Discussion based on their suggestions. Please find our answers below.

## Reviewer #1

### INTRODUCTION

Comment: The authors claim that "relapses are frequent" and "rarely adults who stutter recover spontaneously", "fluency induction due to scanner noise", and statements about subjects not entering a consistent "default mode". Can they provide citations for each of these statements? I have heard them made before, but it would be good if they can include references.

Answer: These references have been added.

Comment: The background appears to be somewhat lacking. Inclusion of several other studies could improve the depth of the manuscript. The authors state that, "Neuroplasticity is often associated with changes in the interaction between brain areas that complement changes in regional activity". The authors should probably mention/cite recent review/meta-analyses of stuttering including but not limited to (e.g Belyk 2015, Budde 2014, Etchell 2016 this issue). They should also provide more background on structural connectivity in stuttering adults (e.g. the DTI meta analysis by Neef et al., 2015) because structure underpins function. Individual studies examining either treatment effects (e.g. Giraud et al., 2008; Toyomura et al., 2015), functional connectivity relevant for the current work (e.g. Chang et al., 2016 this issue, Yang et al., 2016) or comparisons of persistent and recovered stutterers (e.g. Chang et al., 2015, Usler and Weber Fox 2015), even if the latter studies focus on children could also be mentioned.

Answer: We now mention the proposed studies on activity changes in adult people who stutter. Because we did not have access to the not yet published other manuscript of this special issue, we could not cite them, unfortunately. In case the Senior Editor agrees, we will add the relevant co-papers when correcting the proofs.

Comment: The authors seem to be performing a 'double subtraction' analysis. That is, the difference between in PPI during overt and covert reading (conditions) between their groups (controls, recovered stutterers and persistent stutterers (before and after therapy). If this understanding is correct, then it might be helpful to include a diagram of this (to accompany what is written in the text) or make the text more explicit because it is sometimes unclear as to precisely what the authors are comparing.

Answer: We added: "Our results of such a double subtraction approach thus represent group differences in PPIs elicited by overt vs. covert reading, i.e. functional connectivity that is modulated by the sensorimotor aspects of speech production."

## METHODS

Comment: The authors might want to include information about the age of the participants in the study rather than just referring to their previous work.

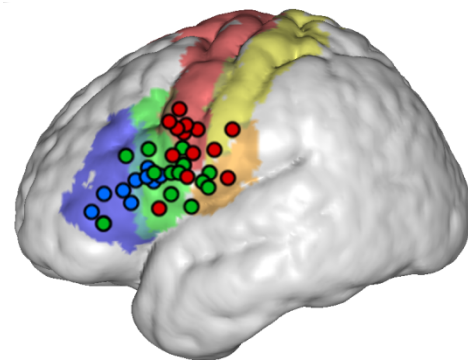
Answer: We now provide this information in the methods section and the statistics, which drew our attention to a mistake in the previous manuscript. We now report group comparisons using age as covariate in the group comparisons with RS (please see also our answers to Reviewer 2 comment #5.

Comment: Asking PS after therapy to not use the newly acquired speaking technique appears very strange to me. It potentially confounds the neural activation and patterns of connectivity even if they did not report active suppression of the speaking technique. I suspect it was to make the pre/post scans more comparable and attributable to the effect of therapy rather than the use of the fluency inducing technique, but this might be wrong. Please provide more information.

Answer: This is an important point but participants did not need to actively suppress the trained technique. Please see also our comments below. We now write: "PS after therapy were asked to refrain from using the newly acquired technique inside the scanner, and read freely as they did before the therapy. Due to the masking scanner noise, application of the newly acquired technique was not necessary and PS reported that they did not need to actively suppress the newly acquired speaking technique inside the scanner. This was expected, because even after the intensive therapy course, participants need to consciously remind them to actively use the technique when speaking. As a consequence, pre- and post therapy imaging data are well comparable, because they do not represent different ways of speaking. Contrasting both time points against each other may reveal state-independent therapy-related changes in functional connectivity."

Comment: A radius of 10mm around the group maxmia appears to be quite large particularly given the spatial resolution of fMRI (~1-2mm). Was this chosen a priori or post hoc and did using a smaller radius exclude too many results?

Answer: The spatial resolution of our data was 3x3x3mm. The radius thus included three voxels in each direction which - given the smoothing kernel of 8mm - seems fine. Subject exclusion for PPI analyses due to difficulties with seed definition is critical because seeds need to be clearly defined. The sphere dimensions thus need to be adjusted depending on the regions that are studied. In one of our former studies on PPIs of the planum temporale, we used spheres of 20mm and included only those maxima that were located ventral of the Sylvian fissure, because the planum temporale extends more than 3cm in the rostro-caudal axis (Kell et al., Cerebral Cortex 2011). For those regions studied here, an a priori defined sphere of 10mm provides a fine trade-off between regional specificity and sensitivity, because interindividual variability in structure-function relationships is large. Please see this illustration of interindividual variability of three different functional speech and language sites during direct cortical electrical stimulation (unpublished results):



Comment: The authors state, “We … calculated PPIs only on the residuals of the general linear models by adjusting for task-related activations.” Please provide more details about this procedure. Did the authors first get the residuals of the GLM containing only task regressors, and then use the residuals images calculated the PPIs?

Answer: The PPIs are calculated only on the residuals of the GLMs by adjusting for effects of interests, which is a standard setting in SPM’s PPI pipeline. There is no need to use ResMS images for such analyses. This is documented in the quoted Friston paper. We clarified this in the manuscript.

Comment: Did the authors collect data on respiration or account for the effects of respiration? If they did collect respiration data and it was not already performed, the authors could use RETROICOR to remove physiological noises associated with speaking.

Answer: We did not collect respiration data. Breathing artifacts were accounted for by high pass filtering the data. We thank the reviewer for pointing out this additional opportunity that we will consider in future studies.

Comment: The authors indicate they investigated group differences in connectivity in selected seed volumes by testing for significant modulation at $p<0.05$ FWE corrected. Please provide more details. Was this corrected at the voxel level, or the cluster level? If it was at the cluster level, please provide the cluster size threshold. Additionally, the authors also probably need to control for false positives due to multiple comparisons from different seeds. Could they provide more details as it is not clear whether or not this was done.

Answer: We applied a voxel-level correction for multiple comparisons within the sphere volumes. We limited the number of studied regions as much as possible and thus included only left hemisphere brain regions and excluded further potential seeds in the basal ganglia or cerebellum. Nevertheless, a correction for number of studied connections using an additional Bonferroni correction on top of the small volume correction would not be possible (see Tables) and is not standard. We now write: “In particular, we investigated group differences in functional connectivity between the selected seed volumes in the left hemisphere by testing for a significant speaking-related modulation (overt vs. covert reading) at $p<0.05$, FWE corrected on the voxel level within the 10 mm spheres around group coordinates that already served for seed identification (Arnold, Gehrig, Gispert, Seifried, & Kell, 2013). The results are not additionally corrected for the number of studied connections.”

Comment: Please provide the procedure to calculate the r values in Table 1. Were they the peak r in each regions or average across all voxels in each region? Was the same method used to extract the individual r values for the correlation analysis with stuttering severity?

Answer: These are peak voxel beta estimates for the PPI regressor in each target region for each seed. Yes, these were the values that were used for correlation. This has been clarified in the text.

Comment: the authors indicate that the stuttering severity ranged from 1.4% to 13.9%. Could they provide more detail regarding how this was measured (i.e. what inventory/questionnaire)?

Answer: It is Journal policy to avoid redundancies with previous publications. We refer to the way it is measured in our previous publication that is cited at the appropriate place in the manuscript. In our previous publication, we write: "Stuttering severity, speech rate and speech naturalness were assessed before the MRI session by digital audio recordings of the subjects' speech (at least 300 analysable syllables) in four speaking situations: (i) an open conversation with a therapist; (ii) reading a standard newspaper text; (iii) calling an unknown person by telephone; and (iv) interviewing a passer-by on the street. Quality criteria of these measures are reported elsewhere (Euler and von Gudenberg, 2000), with a place-to-place inter-rater agreement of 78.8% and a split-half reliability between r = 0.83 (telephone call) and r = 0.99 (interviewing a passer-by). Stuttering severity was defined as the percentage of stuttered syllables according to the guidelines by Boberg and Kully (1994). This dysfluency measure contains only the number of unambiguous moments of stuttering (Jones et al., 2000) and incorporates syllable repetitions and audible and inaudible sound prolongations (Conture, 2001). The measure does not include normal dysfluencies such as interjections, whole-word repetitions, revisions and phrase-repetitions. The scores of the percent stuttered syllables were the non-weighted means of the percent stuttered syllables at the four measurement occasions and were used subsequently for parametric analysis of the MRI dataset."

Comment: It would also be important to explicitly state whether or not the speakers explicitly instructed to NOT use fluency inducing techniques learnt in therapy when taking speech (like they were during scanning). Because otherwise, this could create an inconsistency between the patterns of connectivity observed during the fMRI experiment and stuttering severity.

Answer: As mentioned before, it is normal during the intensive therapy course that participants do not use the technique during the whole therapy week. Outside of training sessions, they often refrain from using the technique, because it is tiring. We thus do not judge this point critical. In contrast, therapy-associated changes beyond the direct change in behavior are actually more directly related with plasticity.

Comment: The authors claim, "Because the comparison was based on only 12 vs. 12 participants, we could not correct it for multiple comparisons". I do not understand why only using 12 participants in each group prevents correction for multiple comparisons. Could the authors please provide some clarification as to why this is the case? Is it that the authors attempted correcting and the results were not statistically significant?

Answer: Indeed. We believe not reporting these subthreshold results would render the interpretation of the data more difficult. We now write: "The observation strongly suggested a positive PPI between the activated BA 47/12 in RS and another region outside the pre-specified seeds. We thus investigated the RS-specific functional connectivity of the left BA 47/12 by contrasting it with the one of fluent controls and searching whole brain voxel-wise for increased functional connectivity with left BA 47/12 in RS based on positive PPIs. The whole brain group comparison did not reveal significant positive connectivity when a voxel-wise correction for multiple comparisons was applied. Yet, when the original threshold of $p<0.001$, uncorrected, as in (Kell et al., 2009), was applied for the PPI*group interaction, there was increased connectivity between the left BA 47/12 and the superior cerebellum, a region that has previously been associated with compensation attempts and therapy effects in PS (Etchell, Johnson, & Sowman, 2014; Lu et al., 2012; Sitek et al., 2016; Yang et al., 2016). We thus decided to report this effect although it is not corrected for multiple comparisons."

Comment: The authors then go on to state that, "because the only two regions that this contrast revealed….the risk of reporting false positives is reduced". Something appears to be off with the phrasing. The current study is independent of the other cited studies which does not reduce the risk of reporting false positives in this study per se. I understand the authors are trying to say (i.e. that because of the consistency of the studies we can be more confident the current results are not false positives) but they might want to reconsider the phrasing slightly.

Answer: We deleted this phrase.

## RESULTS

Comment: The results are difficult to follow. The authors seem to go from discussing within and between group differences within a few sentences. If possible a little more structure might improve the flow of the section and make it considerably easier to understand the manuscript

Answer: We now clarified the structure and provided more information.

## DISCUSSION

Comment: Perhaps the authors would like to discuss the relationship between functional connectivity between the left IFG and SMA in relation to structural connectivity of the frontal aslant tract (specifically papers by Kronfeld et al., 2016 and Kemedere et al., 2016). This could perhaps be beneficial to the manuscript.

Answer: Due to the slightly changed results based on our re-analysis (see our comments to Reviewer 2), this connection is not any more in the focus of the discussion.

Comment: Please provide a little bit more information on the statement, "Indeed PS are not impaired when detecting passive articulatory movements". Is this an impairment in reaction time? Accuracy? Neural activation? Connectivity? Another group?

Answer: We now write: “Indeed, PS show normal kinesthetic acuity and movement detection thresholds when detecting passive articulatory movements (Daliri, Prokopenko, & Max, 2013). “

Comment: The statement about the correlation between stuttering severity and the connection between the left SMG and BA44 should perhaps, be qualified with information about the degree of significance.

Answer: We now write: “The therapy-related connectivity reduction between the left SMG and BA 44 and the fact that fluency-shaping therapy abolished a pre-therapeutic weak correlation of this connectivity measure from stuttering severity both suggest that normalizing the reliance on somatosensory feedback restores fluency.”

Comment: The authors state that, “This suggests the use of somatosensory feedback by different components of the PS speech production network has both beneficial and deleterious effects on stuttering symptoms”. Could the authors elaborate on this apparent contradiction given (as they state) over reliance on sensory feedback can lead to disfluencies? Specifically, how could a greater reliance on sensory feedback be beneficial?

We now write: “Functional connectivity between the left SMG and SMA correlated positively with stuttering severity in PS, whereas connectivity between the left SMG and BA 44 correlated negatively. This suggests that different components of the PS’ speech production network are differently sensitive to somatosensory feedback information. It seems that somatosensory feedback integration in the SMA has negative consequences on stuttering while integration in Broca’s region could potentially be beneficial. Overall, the observed hyper-connectivity of the left SMG in PS compared to controls suggests a functional over-reliance on somatosensory feedback in PS. Such an over-reliance was not only observed during fMRI, which could mask auditory feedback and induce a shift towards somatosensory feedback control, but also behaviorally (Hutchinson & Ringel, 1975) and electrophysiologically (van Lieshout, Hulstijn, & Peters, 1996a, 1996b).”

Comment: The authors state, “Reduction of stuttering was also observed in other fluency inducing conditions….” They could mention Toyomura et al., 2015 and mention this study with respect to brain activation elsewhere.

Answer: We included this citation. Thanks for pointing this out.

Comment: The authors state that “PWS cannot detect unexpected, rapid changes in auditory feedback as well as fluent controls…electrophysiological responses to brief auditory stimuli during speech planning are less strongly modulated in people who stutter”. Other studies the authors might wish to cite include, Mock et al., 2016 as well as Vanhoutte et al., 2015, 2016. Also, difficulties detecting/processing brief auditory stimuli dot not just occur during speech planning/production, but also during passive listening to sounds (see Etchell et al., 2016).

Answer: We thank the Reviewer for pointing these references out. We included the Mock quote because of its direct relevance for auditory processing while Vanhoutte’s publications investigate non-auditory aspects of speech planning, which is not in the

focus of the discussion. Unfortunately, the Etchell 2016 publication was not yet available.

Comment: The authors state that “Because activation levels and structure in this region were not modified by therapy, we interpret the anomalies in this brain region as directly related with the pathophysiology underlying developmental stuttering”. This interpretation, though definitely acceptable, is debatable from a theoretical standpoint. I am genuinely curious to know why the authors think regions involved in the pathophysiology of stuttering not be altered by therapy.

Answer: Because of the sub-threshold effect in the re-analysis, this section has been deleted. Regarding your question: Given the observation of structurally abnormally developed cortex that is directly related with stuttering severity years after stuttering onset it is likely that people who stutter cannot plastically modify this region once it has developed the way it has. Consequently, plasticity is more likely to occur somewhere else. It may well be that in children with transient stuttering, plasticity occurs exactly in the dorsal IFG.

Comment: The authors state, “A functional connection between these two regions…”. Please note that works have discussed the compensatory role of the cerebellum in stuttering (Alm et al., 2007; Etchell et al., 2014 and Yang et al., 2016).

Answer: We included Etchell et al., 2014 and also re-referenced Yang et al., 2016 in this context. We now quoted Alm’s contribution with respect to the role of the basal ganglia.

Comment: The sentence beginning with, “The orbitofrontal cortex…” is not clear. Please rephrase.

Answer: Deleted.

Comment: The terms sex and gender are often used interchangeably. However, “Gender differences” are technically sociological/psychological and “sex differences” are technically biological. This is picky, but assuming the authors were referring to biological sex rather than gender identification, the authors should probably change the terminology.

Answer: Done.

TABLE 1/2

Comment: From my understanding, PPI is *not* a method of effective connectivity. However, the rows and columns for some cells in both Tables (e.g. table 1, BA44 and SMG) are not the same as the rows and columns for SMG and BA44). This creates the impression that there is some form of directionality when this might not be the case. Could the authors please fix this? (Potentially by putting all values on one side of the graph and blacking out the other).

Answer: It is a common observation that PPIs are found in one but not the other direction depending on the studied seed. This is likely because the input and output regions do not map exactly onto the same voxel. Consequently, it is standard practice to

study PPIs between local maxima as seeds and spheres in the target region. While some authors have used this "asymmetry" to argue for directionality, we believe that you cannot interpret such findings in that way. Nevertheless, we represent the data here as they are and thus do not black the other side out, because it represents the detailed results of the analyses. We now write more clearly in the Table legend: "Table 1. Stronger PPIs (peak voxel values for the contrast overt vs. covert reading) between left perisylvian regions in PS before therapy compared to fluent control participants. Seed regions are indicated in the first row and target regions in the subsequent rows. Significant group differences at $p<0.05$ FWE small volume corrected for multiple comparisons are indicated by their T and p value."

FIGURE 3

It is just a suggestion, but the authors might want to provide axial and coronal views as well.

Answer: We now provide an axial view of the cerebellar changes in Figure 2.

Reviewer #2

This is a very nice study, carefully conducted and clearly explained. In terms of the results, I very much like the finding in the group of Persistent stuttering and the changes in connectivity observed following successful fluency shaping therapy to assist in recovery. I find the results in the spontaneous recovery group interesting but less relevant because this is such an unusual group – spontaneous recovery being so rare in adults. It is difficult to know in this group whether the differences in connectivity pre-exist the spontaneous recovery, are the cause of it, or are caused by the recovery mediated elsewhere. I think the manuscript needs to acknowledge these alternatives (or argue for or against some of them) but I would not like to distract from the main (and in my view most interesting) findings in the assisted group both before and after therapy. In the discussion, the authors address this point but I don't think it is obvious what is meant, so I would specifically like them to do so in the discussion of the recovered data.

Answer: Done. We now write in the specified section: "Due to the recruitment of RS years after recovery, we cannot disentangle whether this plasticity is a pre-requisite for recovery or the result of neuroplasticity."

Below are some minor concerns that the authors may wish to address that in my view would improve the manuscript.

1) Throughout – although the use of Brodmann Areas is accurate and precise and less vague than alternative terms, I think these are obscure to the majority of readers of this journal and should have some context provided. So for example in the abstract you say "unassisted recovery was specifically associated with activation of left BA 47/12" – I think it is important to highlight that this is in an anterior portion of the left inferior frontal gyrus, and possibly even more specifically "pars orbitalis" though the relevance of this to most readers might also not be obvious. I see this was done in the introduction, so perhaps it is only necessary to adjust the abstract (see point 3 below also).

Answer: We now provide a better description at numerous places in the manuscript. In the abstract, we now write: "While assisted recovery re-lateralized activity to the left hemisphere, unassisted recovery was specifically associated with the activation of the left BA 47/12 in the lateral orbitofrontal cortex."

2) Abstract – I think that the explanation that the anterior superior temporal gyrus is "a region that is sensitive to slow acoustic variations of the auditory feedback" is out of place and unnecessary here. It is also not the obvious/go to function that I would think of when describing this region. Auditory cortex or associative auditory cortex would be fine but then again other areas do not have their functions listed e.g. supramarginal gyrus – so perhaps just delete.

Answer: Corrected. We now write: "Persistent stuttering was associated with reduced auditory-motor coupling and enhanced integration of somatosensory feedback between the supramarginal gyrus and the prefrontal cortex. Assisted recovery reduced this hyper-connectivity and increased functional connectivity between the articulatory motor cortex and the auditory feedback processing anterior superior temporal gyrus. In spontaneous recovery, both auditory-motor coupling and integration of somatosensory feedback were normalized."

3) Abstract (see above) – dorsal BA 44/45 – should also be explained/renamed – "dorsal part of the posterior inferior frontal gyrus, functionally referred to a Broca's area" or some combination of these terms.

Answer: This result is now subthreshold due to the new analysis that were inspired by the Reviewer's comment #5.

4) Methods 2.2 – It is surprising that one participant per group showed no speaking-related activations. I am not sure I would agree that their data should be excluded from this analysis when it contributed to the previous publication. Is it possible that the activation is just sub-threshold – or what other explanation is there for the lack of activity??? I think this needs further justification or discussion.

Answer: As already pointed out in response to Reviewer 1's comment, seed definition is key in functional connectivity studies. Indeed, one subject in each group did not have sufficient supra-threshold local maxima in the spheres of interest to justify inclusion in this analysis. Likely, in these rare cases (<10% of cases) the local maximum is further apart than 1cm, indicating that these subjects contributed to group activation with a rather large cluster of activity. For functional connectivity analyses, it is standard to include those subjects who show also a local maximum in the region of interest.

We now write: "For group comparisons of network connections, it is critical that the participants contribute equally to all connections because otherwise group differences could arise from different sampling. We thus included only those participants who showed local maxima in all spheres of interest (spheres of a radius of 10 mm centered on the group maxima). Because one subject in each group had no local maximum in at least one of the pre-defined spheres, this resulted in an exclusion of one participant per group, leaving 12 subjects per group for further analyses."

5) Methods 2.2 – it is said that there were significant differences in handedness score – please elaborate – between which groups? Also then the lateralization quotient was used as a covariate in the connectivity analyses – what is the quotient? Why was it used? Did it make a difference to the results? What was the relationship between the quotient and the connectivity measures if any? I don't really understand the logic of including this covariate as also only one hemisphere was analysed. Please discuss.

Answer: This was a mistake in the previous manuscript. Actually, there was an age difference between controls and RS and no other significant group difference in handedness or age. We corrected this, re-analyzed the data and present now the largely similar results. Only the previous recovery-related effect in the left dorsal inferior frontal cortex has been largely affected by the covariate "age" and is now sub-threshold. We apologize for this error in the previous version of the manuscript.

6) Methods – is a 10mm sphere one with a radius or diameter of 10mm??

Answer: Radius, this is now stated more clearly. See also Answer to Reviewer 1.

7) Results – the significant correlations with stuttering severity are very interesting – would it be possible to see the scatter plots to determine what the relationship looks like?

Answer: Done. Please see Inserts in Fig. 1

8) Results 3.1 – I am sure this is a typo but what does it mean that "Therapy stashed away the correlation"?

Answer: This has been deleted.

9) Discussion 4.1 – I disagree with the interpretation of the Cai et al., 2014 study that "PS cannot detect unexpected, rapid changes in auditory feedback" – that study showed that they did respond to such changes but at a later point relative to the controls. It was not a detection task – failure to respond could be just that i.e. maybe they cannot use the auditory feedback to rapidly update their speech production. It is too simplistic to claim they cannot detect rapid changes in auditory feedback on the basis of this study.

Answer: We agree with the reviewer and changed the wording to: "On the other hand, PS adapt more slowly and less well to unexpected, rapid changes in auditory feedback as well as fluent controls (Cai, Beal, Ghosh, Guenther, & Perkell, 2014; Cai et al., 2012; Loucks, Chon, & Han, 2012)".

Once again, thank you for your help in improving this manuscript.

# Speaking-related changes in cortical functional connectivity associated with assisted and spontaneous recovery from developmental stuttering

Abstract

We previously reported speaking-related activity changes associated with assisted recovery induced by a fluency shaping therapy program and unassisted recovery from developmental stuttering (Kell et al., Brain 2009). While assisted recovery re-lateralized activity to the left hemisphere, unassisted recovery was specifically associated with the activation of the left BA 47/12 in the lateral orbitofrontal cortex. These findings suggested plastic changes in speaking-related functional connectivity between left hemispheric speech network nodes.

We reanalyzed these data involving 13 stuttering men before and after fluency shaping, 13 men who recovered spontaneously from their stuttering, and 13 male control participants, and examined functional connectivity during overt vs. covert reading by means of psychophysiological interactions computed across left cortical regions involved in articulation control.

Persistent stuttering was associated with reduced auditory-motor coupling and enhanced integration of somatosensory feedback between the supramarginal gyrus and the prefrontal cortex. Assisted recovery reduced this hyper-connectivity and increased functional connectivity between the articulatory motor cortex and the auditory feedback processing anterior superior temporal gyrus. In spontaneous recovery, both auditory-motor coupling and integration of somatosensory feedback were normalized. In addition, activity in the left orbitofrontal cortex and superior cerebellum appeared uncoupled from the rest of the speech production network.

These data suggest that therapy and spontaneous recovery normalizes the left hemispheric speaking-related activity via an improvement of auditory-motor mapping. By contrast, long-lasting unassisted recovery from stuttering is additionally supported by a functional isolation of the superior cerebellum from the rest of the speech production network, through the pivotal left BA 47/12.

Keywords

Psychophysiological interactions; speech production; overt reading; auditory-motor interactions, left inferior frontal gyrus

## 1. Introduction

Developmental stuttering is a speech and language disorder that often requires considerable attention and heavy rehabilitation if children do not spontaneously recover. This speech disorder is neurobiologically characterized by an over-activation of right hemispheric brain areas during speech production (Belyk, Kraft, & Brown, 2015; Brown, Ingham, Ingham, Laird, & Fox, 2005; Budde, Barron, & Fox, 2014; Kell et al., 2009; Neumann et al., 2003). Several behavioral stuttering therapies exist that promise a reduction in symptoms. However, relapses are frequent (Bloodstein & Bernstein Ratner, 2008, pp. 384-6), suggesting that therapy-induced plasticity cannot support full recovery. Rarely, adults who stutter recover spontaneously, i.e. without any therapeutic intervention (Finn, 2004). Exploring these rare cases of recovered adults who have stuttered in the past (RS) using neuroimaging and comparing them with adults who persisted in stuttering (PS) before and after stuttering therapy as well as with fluent control participants may provide crucial information about the type of plasticity that is required for long-term recovery.

We previously reported brain activity during overt reading in the aforementioned groups, and observed that a fluency shaping therapy program that softens speech onsets, slows speech down, and modulates prosody abolished right-hemispheric over-activations and re-lateralized activity to a functionally normalized left hemisphere in male PS (Kell et al., 2009). Unassisted recovery in male RS was specifically associated with activation of the left BA 47/12, at the border between the orbital part of the inferior frontal gyrus (IFG) and orbitofrontal cortex. These findings, however, did not permit to fully apprehend the neural underpinnings of optimal recovery, as we did not report recovery-related changes in functional connectivity. Neuroplasticity is often associated with changes in the interaction between brain areas that complement changes in regional activity. Comprehensive interpretation of recovery-associated changes indeed requires taking into account changes at the level of inter-regional functional connectivity.

Several functional connectivity studies have already been performed in PS, either during speaking (Chang, Horwitz, Ostuni, Reynolds, & Ludlow, 2011; Lu et al., 2010; Watkins, 2011) or while resting silently inside the scanner (Lu et al., 2012; Sitek et al., 2016,Yang, Jia, Siok, & Tan, 2016). Both approaches have their advantages and drawbacks. Speaking constitutes a controlled experimental condition, yet it represents a state-dependent measure that can potentially be affected by movement and by the influence of the scanning conditions on fluency (e.g., fluency induction due to the masking effect (Bloodstein & Bernstein Ratner, 2008, pp. 295-6 and pp. 392-3) by scanner noise). Resting state measurements are appealing because they potentially unravel trait-dependent differences. Yet, during resting state, subjects do not necessarily enter a consistent 'default mode', because participants may differ largely in covert behavior or vigilance (Tagliazucchi & Laufs, 2014). Altogether, functional connectivity studies in adults who stutter revealed abnormal connectivity between Broca's region and the premotor cortex (Chang et al., 2011) or the rest of the resting state language network in the bilateral fronto-temporo-parietal cortex (Lu et al., 2012), reduced auditory-motor coupling (Watkins, 2011), a hyper-connectivity in right homologue areas (Chang et al., 2011), and enhanced, compensatory cerebello-orbitofrontal connectivity (Sitek et al., 2016). Auditory-motor hypo-connectivity was confirmed in boys who stutter together with connectivity changes of the putamen (Chang & Zhu, 2013).

To our knowledge, only one study investigated therapy-associated changes in functional connectivity (Lu et al., 2012). In this study, therapy focused on changing the manner of

speaking. Therapy reduced resting state functional connectivity between the superior cerebellum and the rest of the resting state language network, suggesting that intensive stuttering therapy uncoupled the superior cerebellum from language processing even during (covert speech in) the resting session.

Here, we re-analyzed the data from our previous study and investigated the connectivity changes associated with speech articulation in persistent stuttering, assisted recovery by a fluency-shaping intensive therapy that restructures speech as a whole (global speech restructuring), and by spontaneous recovery in adulthood. We focused on connectivity changes in the left hemisphere, where we previously observed plastic changes in assisted and spontaneous stuttering recovery (Kell et al., 2009). Based on these former experimental findings and on theoretical observations that parameter changes in both the feedforward control system and the auditory-motor mapping in the GODIVA model (Bohland, Bullock, & Guenther, 2010) induce dysfluencies (Civier, Bullock, Max, & Guenther, 2013; Civier, Tasko, & Guenther, 2010), we hypothesized that neuroplasticity associated with recovery should translate into connectivity alterations in these components. While connectivity changes in assisted recovery point to the way therapy reduces symptoms, findings in spontaneous recovery may reveal how neuroplasticity remedies stuttering in the long-term. In this regard, the functional connectivity of the only region that specifically activated in RS, namely BA 47/12, was of interest.

We investigated psychophysiological interactions (PPI) reflecting the functional connectivity between brain regions that is modulated by a psychological factor. In our case, we used the contrast overt > covert reading as psychological variable, which centers the analyses on sensorimotor aspects of articulation and controls for visual input (reading) of linguistic material. We compared speaking-related PPI maps of untreated PS compared to fluent controls to identify the abnormal functional connectivity profile in our sample of male adults who stutter. We subsequently studied therapy-induced changes in functional connectivity of PS and the connectivity profile associated with spontaneous recovery in RS compared to fluent controls.

## 2. Methods

We re-analyzed the dataset published in (Kell et al., 2009) for group differences in speaking-related functional connectivity changes between left hemispheric cortical regions involved in speaking. The study was approved by the ethics committee of the Medical Faculty of Goethe University (277/04). For details on participants' characteristics, study design, data acquisition and preprocessing see (Kell et al., 2009). In brief, we investigated 13 male participants with persistent stuttering (PS, mean age 27) directly before and after a fluency-shaping intensive therapy course that efficiently reduced stuttering severity by changing the way of speaking through softening speech onsets, slowing speech down, and modulating speech prosody. We compared their brain activity when overtly reading German declarative sentences with the activity of 13 male people who recovered spontaneously from their stuttering in adulthood (RS, mean age 40) and 13 fluent male control participants (mean age 30). RS were older than PS (two sample t-test: $p=0.007$) or fluent controls (two sample t-test: $p=0.008$), because it was impossible to recruit RS directly after their recovery. Importantly, the fMRI data were recorded using continuous acquisition, which resulted in quasi-constant scanner noise. This, together with the isolation inside the bore, induced fluency already before therapy. As a consequence, we could compare brain activity during overt reading between the

groups because they all spoke fluently and showed comparable behavior during scanning. Fluency-inducing conditions thus allowed studying trait- rather than state-related group differences (for meta-analyses on trait- vs. state-related activation differences, please see Belyk et al., 2015; Budde et al., 2014). PS after therapy were asked to refrain from using the newly acquired technique inside the scanner, and read freely as they did before the therapy. Due to the masking scanner noise, application of the newly acquired technique was not necessary and PS reported that they did not need to actively suppress the newly acquired speaking technique inside the scanner. This was expected, because even after the intensive therapy course, participants need to consciously remind them and actively use the technique when speaking. As a consequence, pre- and post therapy imaging data are well comparable, because they do not represent different ways of speaking. Contrasting both time points against each other may reveal state-independent therapy-related changes in functional connectivity.

### 2.1 Seed definition

Because we observed a therapy-associated re-lateralization of speaking-related activity from the right to the left hemisphere in PS and largely normal activity in the left perisylvian network in RS (Kell et al., 2009), we hypothesized there was considerable recovery-associated plasticity in the left hemisphere in terms of altered functional connectivity between brain regions involved in the neural control of articulation. We thus focused on functional connectivity changes between left hemispheric components of the GODIVA model (Bohland et al., 2010), which besides inferior frontal, motor, auditory, and somatosensory cortices incorporates the supplementary motor area (SMA). Because the left BA 47/12 was the only region that dissociated RS from PS and fluent controls (Kell et al., 2009), this area was also included in the functional connectivity analysis.
Based on significant group activations across groups in one sample t-tests of the contrast overt > covert reading ($p<0.05$, FWE corrected), we identified the left pars opercularis of the IFG (BA44, MNI -62, 12, 10), left articulatory motor cortex (BA6, MNI -62, 0, 20), and the SMA (BA6, MNI -6, 12, 38) as seeds for functional connectivity analyses. We recently showed that activity in the left supramarginal gyrus (SMG, MNI -50, -38, 28) likely reflects somatosensory feedback processing during articulation and processing of auditory feedback primarily occurs in the anterior parts of the superior temporal gyrus (aSTG, MNI -54, -4, 0) and posterior superior temporal sulcus (pSTS, MNI -66, -28, 2, Kell et al., 2016). The aSTG and pSTS differ in their sensitivity to auditory feedback: The aSTG is more sensitive to slowly varying acoustic features and the pSTS more sensitive to more rapidly changing acoustic features (Kell et al., 2016). We thus studied functional connectivity of these seeds separately. While the identification of the aforementioned seeds were based on group activations of all participants, the left BA 47/12 coordinate (MNI -40, 28, -18) was obtained from a one sample t-test of overt > covert reading in RS. We hypothesized that speaking-related functional connectivity of this region in RS compared to the physiological connectivity in fluent controls would highlight neural plasticity specifically associated with unassisted recovery.

### 2.2 Psychophysiological interactions

For group comparisons of network connections, it is critical that the participants contribute equally to all connections because otherwise group differences could arise

from different sampling. We thus included only those participants who showed local maxima in all spheres of interest (spheres of a radius of 10 mm centered on the group maxima). Because one subject in each group had no local maximum in at least one of the pre-defined spheres, this resulted in an exclusion of one participant per group, leaving 12 subjects per group for further analyses. Age was entered in the group comparisons with RS as covariate.

Changes in functional connectivity could result from mere changes in regional brain activity, if such effects are not accounted for. This is particularly relevant for overt articulation, during which movement artifacts could affect the signal to noise ratio. We thus used a special echo planar imaging sequence that was shown to be robust against movement artifacts during 3 s of overt speech (Preibisch et al., 2003), included realignment parameters as effects of no interest in the design matrices, and calculated PPIs only on the residuals of the general linear models by adjusting for task-related activations / effects of interest (Friston et al., 1997). The PPI analyses were performed similarly as in our previous reports on overt reading (Keller & Kell, 2016; Pichon & Kell, 2013). In particular, we investigated group differences in functional connectivity between the selected seed volumes in the left hemisphere by testing for a significant speaking-related modulation (overt vs. covert reading) at $p<0.05$, FWE corrected on the voxel level within the 10 mm spheres around group coordinates that already served for seed identification (Arnold, Gehrig, Gispert, Seifried, & Kell, 2013). The results are not additionally corrected for the number of studied connections. The individual seed's PPI maps based on the psychological variable overt vs. covert reading were contrasted against each other using two sample t-tests (for the comparison between groups) and paired t-tests (for the within subjects analyses of therapy effects). We report peak voxel values of group differences in the text and the Table. Our results of such a double subtraction approach thus represent group differences in PPIs elicited by overt vs. covert reading, i.e. group differences in functional connectivity that is modulated by the sensorimotor aspects of speech production. Unless indicated otherwise, p values are corrected for multiple comparisons in the search volume.

### 2.3 Correlation analyses with stuttering severity

Stuttering severity during free speech before therapy ranged from 1.4 % to 13.9 % stuttered syllables (for details, see Kell et al., 2009). This inter-individual variability allowed investigating a relationship between the observed functional connectivity changes and stuttering severity before therapy. To this end, beta values for each connection that showed significant group differences were extracted from peak voxels in the individual PPI maps of PS and correlated in SPSS with % stuttered syllables during free speech outside the scanner prior to therapy using non-parametric Spearman correlations. Such an approach does not suffer from double dipping, because the extracted values are not used to study group differences but rather to explain inter-individual variability. Correlations between functional connectivity measures and stuttering severity were considered significant at $p<0.05$.

### 2.4 Post hoc analyses of left BA 47/12 connectivity in RS

The left BA 47/12 activated strongly in RS but not in any other participant group (Kell et al., 2009). We observed a reduced speaking-related functional connectivity of this activated region with the SMA in RS compared to fluent controls (see Results). RS likely do not activate a region that fluent controls do not involve in the neural control of

speaking solely to hypo-connect it with a speech-relevant region (Bohland, Bullock, & Guenther, 2010). The observation strongly suggested a positive PPI between the activated BA 47/12 in RS and another region outside the pre-specified seeds. We thus investigated the RS-specific functional connectivity of the left BA 47/12 by contrasting it with the one of fluent controls and searching whole brain voxel-wise for increased functional connectivity with left BA 47/12 in RS based on positive PPIs. The whole brain group comparison did not reveal significant positive connectivity when a voxel-wise correction for multiple comparisons was applied. Yet, when the original threshold of $p<0.001$, uncorrected, as in (Kell et al., 2009) was applied for the PPI*group interaction, there was increased connectivity between the left BA 47/12 and the superior cerebellum, a region that has previously been associated with compensation attempts and therapy effects in PS (Etchell, Johnson, & Sowman, 2014; Lu et al., 2012; Sitek et al., 2016; Yang et al., 2016). We thus report this effect although it is not corrected for multiple comparisons.

## 3. Results

### 3.1 Functional connectivity changes in PS compared to fluent controls

During scanning, both PS and control participants spoke fluently. Despite comparable behavior, there were considerable functional connectivity group differences during speaking prior to therapy. Compared to fluent controls, the coupling between the pSTS and the articulatory motor cortex was reduced in PS before therapy ($T=3.3$, $p=0.044$, dashed connection in Figure 1), which confirms previous findings of reduced auditory-motor coupling in boys who stutter during resting state (Chang & Zhu, 2013) and during speaking in adult PS (Watkins, 2011). In parallel, there was significant hyper-connectivity of the posterior STS with the BA 47 in the IFG and the SMG, and hyper-connectivity of the SMG with both the BA 44 and 47 in the IFG and the SMA compared to fluent controls (yellow connections in Figure 1, see also Table).

### 3.2 Correlation between functional connectivity and stuttering severity in PS

In PS, functional connectivity between the SMG and the SMA correlated positively with stuttering severity outside the scanner ($rho=0.622$, $p=0.031$) while there was a negative correlation with stuttering severity and the functional connectivity between the SMG and BA 44 in the IFG ($rho=-0.58$, $p=0.048$, see inserts in Figure 1).

### 3.3 Therapy effects in PS

The fluency-shaping therapy reduced the described dorsal hyper-connectivity, particularly between the SMG and BA44 ($T=4.65$, $p=0.02$, blue asterisk in Figure 1) so that the group comparison between PS after therapy and fluent controls did not reveal any significant differences. Therapy abolished the correlation between functional connectivity of the SMG and pre-therapy stuttering severity (all $p>0.05$). However, it increased PS' speaking-related functional connectivity between the anterior auditory-feedback processing region in the aSTG and the articulatory motor cortex ($T=3.84$, $p=0.049$, blue connection in Figure 1).

### 3.4 Functional connectivity changes in RS compared to PS and fluent controls

Compared with untreated PS, who showed enhanced connectivity between left BA 47/12 and the SMG, this connectivity was less strong in RS ($T=4.88$, $p=0.003$, yellow/red dashed connection in Figure 2). Spontaneously RS did not differ significantly from fluent controls in functional temporo-frontal connectivity and thus showed normalized auditory-motor and somatosensory-motor mapping during speaking. Yet, the speaking-related functional connectivity of left orbitofrontal BA 47/12 differed considerably from fluent control participants. Note that only RS activated this region significantly (Kell et al., 2009). Yet, this activation was not associated with increased connectivity between left BA 47/12 and the speech production network. Instead, this region showed lower PPI values with the left SMA in RS compared to fluent controls ($T=3.37$, $p=0.044$, see red dashed connection in Figure 2).
This observation justified the question as to why this orbitofrontal region was activated when it actually was disconnected from task-relevant cortical areas. We thus examined positive PPIs in RS between left BA 47/12 and the rest of the brain that were significantly different from fluent controls. Compared to fluent controls, the left BA 47/12 during articulation connected more strongly to caudal parts of the bilateral superior cerebellum (MNI -34, -82, -20, $T=4.61$, uncorrected $p<0.001$, and MNI 24, -90, -20, $T=3.94$, uncorrected $p<0.001$, red clusters in the insert in Figure 2).

## 4. Discussion

Connectivity of the speech articulatory network within the left hemisphere was remarkably different in PS relative to fluent control participants. These alterations were largely attenuated after therapy. Importantly, because of the fluency-inducing conditions inside the scanner, these effects are unlikely to be accounted for by mere behavioral differences, due to either dysfluencies prior to therapy and/or to the active use of the fluency shaping technique after therapy. More reasonably, these differences reflect profound changes in the way PS use the articulatory cortical network depending on whether they still stutter or were helped out of stuttering by the fluency-shaping therapy.

### 4.1 Therapy-assisted repair of impaired auditory-motor coupling during speaking

Auditory-motor coupling in PS was reduced during speaking, confirming earlier observations made both during speaking (Watkins, 2011) and in resting children (Chang & Zhu, 2013). Also structural connectivity between the left auditory and motor cortex is reduced (Neef, Anwander, & Friederici, 2015). These findings together with our observations suggest reduced auditory-motor coupling is a trait-related feature of developmental stuttering. The reduced auditory-motor coupling was observed in the pSTS, a region that is sensitive to fast acoustic modulations in the auditory feedback during articulation, particularly those that underlie consonant processing (Kell et al., 2016). Since we previously reported increased articulation-related activity in auditory cortex in PS in the same dataset (Kell et al., 2009), these new connectivity findings suggest reduced monitoring of rapidly changing auditory feedback features in PS. We also found that untreated PS had enhanced connectivity between the feedforward control system in the left IFG, the SMA and the somatosensory feedback processing system in the left SMG (for details on auditory and somatosensory feedback processing

in fluent controls, please see Kell et al., 2016). Functional connectivity between the left SMG and SMA correlated positively with stuttering severity in PS, whereas connectivity between the left SMG and BA 44 correlated negatively. This suggests that different components of the PS' speech production network are differently sensitive to somatosensory feedback information. It seems that somatosensory feedback integration in the SMA has negative consequences on stuttering while integration in Broca's region could potentially be beneficial. Overall, the observed hyper-connectivity of the left SMG in PS compared to controls suggests a functional over-reliance on somatosensory feedback in PS. Such an over-reliance was not only observed during fMRI, which could mask auditory feedback and induce a shift towards somatosensory feedback control, but also behaviorally (Hutchinson & Ringel, 1975) and electrophysiologically (van Lieshout, Hulstijn, & Peters, 1996a, 1996b). This suggests an intact somatosensory system in PS. Indeed, PS show normal kinesthetic acuity and movement detection thresholds when detecting passive articulatory movements (Daliri, Prokopenko, & Max, 2013).

The therapy-related connectivity reduction between the left SMG and BA 44 and the fact that fluency-shaping therapy abolished a pre-therapeutic weak correlation of this connectivity measure from stuttering severity both suggest that normalizing the over-reliance on somatosensory feedback restores fluency. This could potentially follow from a more efficient auditory-motor mapping induced by therapy. Accordingly, therapy increased functional connectivity between the articulatory motor cortex and the aSTG, a region that is sensitive to acoustic voice parameters like slow modulations of the fundamental frequency during the articulation of sentences (Kell et al., 2016). This suggests that fluency-shaping therapy reinforces the mapping of slowly varying acoustic parameters onto motor representations. This interpretation is consistent with the fact that fluency shaping therapy relies on a reduction in speech rate with a softening of speech edges to reduce stuttering. Since post-therapy PS did not explicitly use the newly acquired speaking technique inside the scanner, the results suggest that the altered auditory-motor mapping has at least partially been automatized.

Reduction of stuttering was also observed in other fluency-inducing situations that slow down temporal modulations of auditory feedback, like speaking in synchrony with a metronome, chorus reading, speaking with delayed auditory feedback, or singing (Bloodstein & Bernstein Ratner, 2008; Bothe, Davidow, Bramlett, & Ingham, 2006; Christenfeld, 1996; Toyomura, Fujii, & Kuriki, 2011). On the other hand, PS adapt more slowly and less well to unexpected, rapid changes in auditory feedback as well as fluent controls (Cai, Beal, Ghosh, Guenther, & Perkell, 2014; Cai et al., 2012; Loucks, Chon, & Han, 2012). Electrophysiological responses to brief auditory stimuli during speech planning are less strongly modulated in people who stutter (Daliri & Max, 2015) and this impairment correlates with stuttering severity (Mock, Foundas, & Golob, 2016). Together with the current observation, these findings indicate that the use of fast auditory feedback modulations is impaired in people who stutter, whereas slow acoustic cues such as prosodic modulations of the voice can actively be utilized to induce fluency. This interpretation is supported by recent behavioral observations (Cai et al., 2014) and neuroimaging findings (Neumann et al., 2016) and specifies a previous proposal that PS rely overly on auditory feedback in general (Civier et al., 2010).

### 4.2 Unassisted recovery proceeds by functionally disconnecting the caudal superior cerebellum from the rest of the speech production system

Unlike PS, RS showed normalized auditory-motor mapping during speaking. The only region where neural activity distinguished RS from PS and fluent controls was the left

BA 47/12, at the border between the pars orbitalis of the IFG and the orbitofrontal cortex (Kell et al., 2009). RS activated this region, but, functionally, it appeared less strongly connected with the rest of the speech production network, particularly the SMA and the somatosensory feedback processing SMG. This suggests that left BA 47/12 did not modulate the speech production system to improve its functioning, but played another role in unassisted recovery. Interestingly, the functional disconnection from the speech production network included not only the left orbitofrontal cortex but also caudal parts of the superior cerebellum. A functional connection between these two regions has recently been related to compensation attempts in PS (Sitek et al., 2016), and efficient stuttering therapy was shown to disconnect the superior cerebellum from the speech production system during rest (Lu et al., 2012). We show here that the cortical normalization of auditory-motor mapping can lead to long-lasting recovery in case it is accompanied by plasticity involving the superior cerebellum and left orbitofrontal cortex. Due to the recruitment of RS years after recovery, we cannot disentangle whether this plasticity is a pre-requisite for recovery or rather the result of neuroplasticity.

The orbitofrontal cortex generates arguably a predictive internal model of action-related outcomes that emulates rewarding values as a function of current state and previous experience (Koechlin, 2016). The observed disconnection of this left orbitofrontal-cerebellar network from the rest of the speech production system in RS may hence point to a change in the executive control of speaking. It is thus tempting to speculate that some aspect of sensory feedback that is processed by the caudal parts of the superior cerebellum is devalued, or at least prevented from evaluating speech outcome in RS. Given the diminished connectivity between left BA 47/12 and the somatosensory feedback processing SMG, it is likely that this feature is somatosensory in nature. Because RS show normal functional connectivity between ventral BA 44 and the auditory feedback processing aSTG as well as the pSTS and the somatosensory feedback processing SMG, we propose that speech production can only normalize in the long-term if the superior cerebellar influence on the speech production network is reduced.

### 4.3 Limitations

The presented sample size is small, because we studied only men due to previously reported sex differences in stuttering (Ingham et al., 2004), and due to the rarity of spontaneously RS. Despite the limited size of our sample, we were able to detect significant group differences, even though type two errors may have occurred.

Further, the observed group differences occurred in a fluency-inducing condition inside the scanner. We therefore cannot completely rule out that the observed functional connectivity effects follow from the fluency-inducing situation instead of representing trait-related changes. To back-up our interpretations, wherever possible, we related the present observations to similar findings during resting state or behavioral or electrophysiological investigations without auditory masking.

We explored functional connectivity changes in the left hemisphere. Our study thus does not focus on cortico-subcortical interactions with the basal ganglia, regions that also show activity and connectivity changes that are modulated by stuttering therapy (Alm, 2004; Giraud et al., 2008; Kell et al., 2009; Toyomura, Fujii, & Kuriki, 2015).

Finally, the timing of spontaneous recovery was not controlled, and it may well be that the observed differences relative to controls and PS may represent pre-existing differences rather than recovery-associated consequences.

## 4.4 Conclusions

We confirmed impaired auditory-motor mapping in PS. Importantly, the observed impairment involved the posterior auditory association cortex, a region that is sensitive to rapid changes in the auditory feedback. Assisted recovery with fluency-shaping therapy was associated with a switch from an over-reliance on somatosensory feedback to auditory-motor mapping involving the anterior part of the auditory association cortex that is sensitive to slowly changing acoustic features of the auditory feedback. Behavioral data indicate that, while PS process the fast acoustic modulations provided by the auditory feedback less efficiently than fluent controls, they can successfully make use of slower acoustic components, and are even able to capitalize on this dissociation to reduce stuttering by slowing down speech, softening speech onsets, and changing prosody. Although the studied therapy program efficiently reduced stuttering to nearly zero, people who stutter need to work hard to maintain the therapeutic success. Consequently, the observed therapy-associated changes reflect only partly automatized symptom-reducing strategies, and do not unravel the neuroplastic changes that are required to obtain long-lasting recovery.

Spontaneous, long-term recovery in adults who stutter instead revealed key plasticity. RS also showed a normalization of auditory-motor and somatosensory-motor mapping. Yet, in addition, the orbitofrontal cortex was involved in dampening the influence of the caudal superior cerebellum on the speech production network. Our results hence suggest that speech production can normalize in RS once superior cerebellar influences are short-circuited by means of a functional disconnection. Our findings provide testable hypotheses for neuromodulatory approaches in the treatment of developmental stuttering. Specifically, the caudal superior cerebellum can easily be targeted by neurostimulation procedures like transcranial direct current stimulation, and inhibition of this region's activity should be able to reduce stuttering symptoms in case it is paired with fluency-shaping therapy that normalize activity in the rest of the speech production system.

References


Alm, P. A. (2004). Stuttering and the basal ganglia circuits: a critical review of possible relations. [Research Support, Non-U.S. Gov't Review]. *J Commun Disord, 37*(4), 325-369. doi: 10.1016/j.jcomdis.2004.03.001

Arnold, C., Gehrig, J., Gispert, S., Seifried, C., & Kell, C. A. (2013). Pathomechanisms and compensatory efforts related to Parkinsonian speech. *Neuroimage Clin, 4*, 82-97. doi: 10.1016/j.nicl.2013.10.016

Belyk, M., Kraft, S. J., & Brown, S. (2015). Stuttering as a trait or state - an ALE meta-analysis of neuroimaging studies. [Meta-Analysis Research Support, Non-U.S. Gov't]. *Eur J Neurosci, 41*(2), 275-284. doi: 10.1111/ejn.12765

Bloodstein, O., & Bernstein Ratner, N. (2008). *A Handbook on Stuttering*. New York, NY: Cengage Learning.

Bohland, J. W., Bullock, D., & Guenther, F. H. (2010). Neural representations and mechanisms for the performance of simple speech sequences. [Research Support, N.I.H., Extramural Research Support, U.S. Gov't, Non-P.H.S.]. *J Cogn Neurosci, 22*(7), 1504-1529. doi: 10.1162/jocn.2009.21306

Bothe, A. K., Davidow, J. H., Bramlett, R. E., & Ingham, R. J. (2006). Stuttering treatment research 1970-2005: I. Systematic review incorporating trial quality assessment of behavioral, cognitive, and related approaches. [Research Support, N.I.H., Extramural Review]. *Am J Speech Lang Pathol, 15*(4), 321-341. doi: 10.1044/1058-0360(2006/031)

Brown, S., Ingham, R. J., Ingham, J. C., Laird, A. R., & Fox, P. T. (2005). Stuttered and fluent speech production: an ALE meta-analysis of functional neuroimaging studies. *Hum Brain Mapp, 25*(1), 105-117.

Budde, K. S., Barron, D. S., & Fox, P. T. (2014). Stuttering, induced fluency, and natural fluency: a hierarchical series of activation likelihood estimation meta-analyses. [Meta-Analysis Research Support, N.I.H., Extramural]. *Brain Lang, 139*, 99-107. doi: 10.1016/j.bandl.2014.10.002

Cai, S., Beal, D. S., Ghosh, S. S., Guenther, F. H., & Perkell, J. S. (2014). Impaired timing adjustments in response to time-varying auditory perturbation during connected speech production in persons who stutter. [Research Support, N.I.H., Extramural]. *Brain Lang, 129*, 24-29. doi: 10.1016/j.bandl.2014.01.002

Cai, S., Beal, D. S., Ghosh, S. S., Tiede, M. K., Guenther, F. H., & Perkell, J. S. (2012). Weak responses to auditory feedback perturbation during articulation in persons who stutter: evidence for abnormal auditory-motor transformation. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S.]. *PLoS One, 7*(7), e41830. doi: 10.1371/journal.pone.0041830

Chang, S. E., Horwitz, B., Ostuni, J., Reynolds, R., & Ludlow, C. L. (2011). Evidence of left inferior frontal-premotor structural and functional connectivity deficits in adults who stutter. [Research Support, N.I.H., Extramural Research Support, N.I.H., Intramural]. *Cereb Cortex, 21*(11), 2507-2518. doi: 10.1093/cercor/bhr028

Chang, S. E., & Zhu, D. C. (2013). Neural network connectivity differences in children who stutter. [Research Support, N.I.H., Extramural]. *Brain, 136*(Pt 12), 3709-3726. doi: 10.1093/brain/awt275

Christenfeld, N. (1996). Effects of a metronome on the filled pauses of fluent speakers. [Comparative Study]. *J Speech Hear Res, 39*(6), 1232-1238.

Civier, O., Bullock, D., Max, L., & Guenther, F. H. (2013). Computational modeling of stuttering caused by impairments in a basal ganglia thalamo-cortical circuit

involved in syllable selection and initiation. [Research Support, N.I.H., Extramural]. *Brain Lang, 126*(3), 263-278. doi: 10.1016/j.bandl.2013.05.016

Civier, O., Tasko, S. M., & Guenther, F. H. (2010). Overreliance on auditory feedback may lead to sound/syllable repetitions: simulations of stuttering and fluency-inducing conditions with a neural model of speech production. [Research Support, N.I.H., Extramural Research Support, U.S. Gov't, Non-P.H.S.]. *J Fluency Disord, 35*(3), 246-279. doi: 10.1016/j.jfludis.2010.05.002

Daliri, A., & Max, L. (2015). Modulation of auditory processing during speech movement planning is limited in adults who stutter. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Brain Lang, 143*, 59-68. doi: 10.1016/j.bandl.2015.03.002

Daliri, A., Prokopenko, R. A., & Max, L. (2013). Afferent and efferent aspects of mandibular sensorimotor control in adults who stutter. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *J Speech Lang Hear Res, 56*(6), 1774-1788. doi: 10.1044/1092-4388(2013/12-0134)

Etchell, A. C., Johnson, B. W., & Sowman, P. F. (2014). Behavioral and multimodal neuroimaging evidence for a deficit in brain timing networks in stuttering: a hypothesis and theory. *Front Hum Neurosci, 8*, 467. doi: 10.3389/fnhum.2014.00467

Finn, P. (2004). Self-change from stuttering during adolescence and adulthood. In A. K. Bothe (Ed.), *Evidence-based treatment of stuttering: Empirical bases and applications* (pp. 117-136). Mahwah, NJ: Lawrence Erlbaum.

Friston, K. J., Buechel, C., Fink, G. R., Morris, J., Rolls, E., & Dolan, R. J. (1997). Psychophysiological and modulatory interactions in neuroimaging. *Neuroimage, 6*(3), 218-229.

Giraud, A. L., Neumann, K., Bachoud-Levi, A. C., von Gudenberg, A. W., Euler, H. A., Lanfermann, H., & Preibisch, C. (2008). Severity of dysfluency correlates with basal ganglia activity in persistent developmental stuttering. [Research Support, Non-U.S. Gov't]. *Brain Lang, 104*(2), 190-199. doi: 10.1016/j.bandl.2007.04.005

Hutchinson, J. M., & Ringel, R. L. (1975). The effect of oral sensory deprivation on stuttering behavior. [Clinical Trial Controlled Clinical Trial Research Support, Non-U.S. Gov't]. *J Commun Disord, 8*(3), 249-258.

Ingham, R. J., Fox, P. T., Ingham, J. C., Xiong, J., Zamarripa, F., Hardies, L. J., & Lancaster, J. L. (2004). Brain correlates of stuttering and syllable production: gender comparison and replication. [Comparative Study Research Support, U.S. Gov't, P.H.S.]. *J Speech Lang Hear Res, 47*(2), 321-341. doi: 10.1044/1092-4388(2004/026)

Kell, C. A., Darquea, M., Behrens, M., Cordani, L., Keller, C., & Fuchs, S. (2016). Phonetic detail and lateralization of reading-related inner speech and of auditory and somatosensory feedback processing during overt reading. *Hum Brain Mapp*. doi: 10.1002/hbm.23398

Kell, C. A., Neumann, K., von Kriegstein, K., Posenenske, C., von Gudenberg, A. W., Euler, H., & Giraud, A. L. (2009). How the brain repairs stuttering. *Brain, 132*(Pt 10), 2747-2760.

Keller, C., & Kell, C. A. (2016). Asymmetric intra- and interhemispheric interactions during covert and overt sentence reading. *Neuropsychologia*. doi: 10.1016/j.neuropsychologia.2016.04.002

Koechlin, E. (2016). Prefrontal executive function and adaptive behavior in complex environments. [Review]. *Curr Opin Neurobiol, 37*, 1-6. doi: 10.1016/j.conb.2015.11.004

Loucks, T., Chon, H., & Han, W. (2012). Audiovocal integration in adults who stutter. [Comparative Study Research Support, N.I.H., Extramural]. *Int J Lang Commun Disord, 47*(4), 451-456. doi: 10.1111/j.1460-6984.2011.00111.x

Lu, C., Chen, C., Peng, D., You, W., Zhang, X., Ding, G., . . . Howell, P. (2012). Neural anomaly and reorganization in speakers who stutter: A short-term intervention study. *Neurology, 79*(7), 625-632.

Lu, C., Peng, D., Chen, C., Ning, N., Ding, G., Li, K., . . . Lin, C. (2010). Altered effective connectivity and anomalous anatomy in the basal ganglia-thalamocortical circuit of stuttering speakers. [Research Support, Non-U.S. Gov't]. *Cortex, 46*(1), 49-67. doi: 10.1016/j.cortex.2009.02.017

Mock, J. R., Foundas, A. L., & Golob, E. J. (2016). Cortical activity during cued picture naming predicts individual differences in stuttering frequency. *Clin Neurophysiol, 127*(9), 3093-3101. doi: 10.1016/j.clinph.2016.06.005

Neef, N. E., Anwander, A., & Friederici, A. D. (2015). The Neurobiological Grounding of Persistent Stuttering: from Structure to Function. [Research Support, Non-U.S. Gov't Review]. *Curr Neurol Neurosci Rep, 15*(9), 63. doi: 10.1007/s11910-015-0579-4

Neumann, K., Euler, H., Kob, M., von Gudenberg, A. W., Giraud, A. L., & Kell, C. A. (2016). Functional anomalies associated with prosody deficits and their assisted and unassisted recession in persons who stutter. *J Fluency Disord, this issue*.

Neumann, K., Euler, H. A., von Gudenberg, A. W., Giraud, A. L., Lanfermann, H., Gall, V., & Preibisch, C. (2003). The nature and treatment of stuttering as revealed by fMRI A within- and between-group comparison. [Comparative Study]. *J Fluency Disord, 28*(4), 381-409; quiz 409-410.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*(1), 97-113.

Pichon, S., & Kell, C. A. (2013). Affective and sensorimotor components of emotional prosody generation. [Research Support, Non-U.S. Gov't]. *J Neurosci, 33*(4), 1640-1650. doi: 10.1523/JNEUROSCI.3530-12.2013

Preibisch, C., Raab, P., Neumann, K., Euler, H. A., von Gudenberg, A. W., Gall, V., . . . Zanella, F. (2003). Event-related fMRI for the suppression of speech-associated artifacts in stuttering. *Neuroimage, 19*(3), 1076-1084.

Sitek, K. R., Cai, S., Beal, D. S., Perkell, J. S., Guenther, F. H., & Ghosh, S. S. (2016). Decreased Cerebellar-Orbitofrontal Connectivity Correlates with Stuttering Severity: Whole-Brain Functional and Structural Connectivity Associations with Persistent Developmental Stuttering. *Front Hum Neurosci, 10*, 190. doi: 10.3389/fnhum.2016.00190

Tagliazucchi, E., & Laufs, H. (2014). Decoding wakefulness levels from typical fMRI resting-state data reveals reliable drifts between wakefulness and sleep. [Randomized Controlled Trial Research Support, Non-U.S. Gov't]. *Neuron, 82*(3), 695-708. doi: 10.1016/j.neuron.2014.03.020

Toyomura, A., Fujii, T., & Kuriki, S. (2011). Effect of external auditory pacing on the neural activity of stuttering speakers. [Research Support, Non-U.S. Gov't]. *Neuroimage, 57*(4), 1507-1516. doi: 10.1016/j.neuroimage.2011.05.039

Toyomura, A., Fujii, T., & Kuriki, S. (2015). Effect of an 8-week practice of externally triggered speech on basal ganglia activity of stuttering and fluent speakers. [Research Support, Non-U.S. Gov't]. *Neuroimage, 109*, 458-468. doi: 10.1016/j.neuroimage.2015.01.024

van Lieshout, P. H., Hulstijn, W., & Peters, H. F. (1996a). From planning to articulation in speech production: what differentiates a person who stutters from a person who

does not stutter? [Comparative Study Research Support, Non-U.S. Gov't]. *J Speech Hear Res, 39*(3), 546-564.
van Lieshout, P. H., Hulstijn, W., & Peters, H. F. (1996b). Speech production in people who stutter: testing the motor plan assembly hypothesis. [Comparative Study]. *J Speech Hear Res, 39*(1), 76-92.
Watkins, K. (2011). Developmental disorders of speech and language: from genes to brain structure and function. [Review]. *Prog Brain Res, 189*, 225-238. doi: 10.1016/B978-0-444-53884-0.00027-0
Yang, Y., Jia, F., Siok, W. T., & Tan, L. H. (2016). Altered functional connectivity in persistent developmental stuttering. [Research Support, Non-U.S. Gov't]. *Sci Rep, 6*, 19128. doi: 10.1038/srep19128

Figure legends

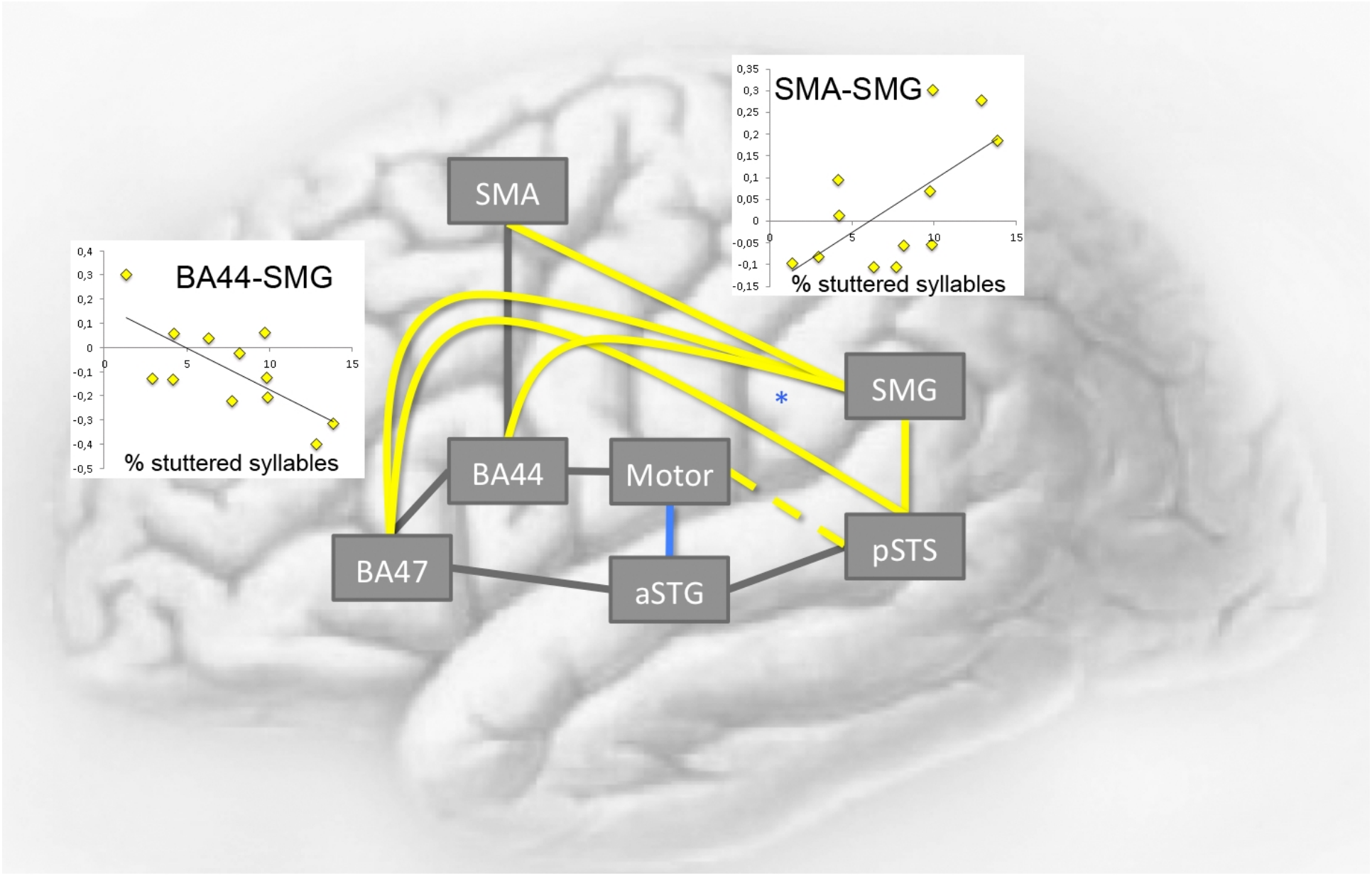
Figure 1. Group differences in speaking-related functional connectivity in persistent stuttering. PS before therapy showed diminished auditory-motor coupling between the posterior superior temporal sulcus (pSTS) and the articulatory motor cortex compared to fluent controls (dashed yellow connection). Compared to fluent controls, PS before therapy hyper-connected (yellow connections) the somatosensory feedback processing supramarginal gyrus (SMG) with the supplementary motor area (SMA), BA 44 and BA 47/12. Hyper-connectivity was also observed between the pSTS and both SMG and BA 47/12. Therapy reduced hyper-connectivity between the SMG and BA 44 (blue star) and increased auditory-motor coupling between the anterior superior temporal gyrus (aSTG) and the articulatory motor cortex (blue connection). All results are significant at $p<0.05$, FWE corrected for multiple comparisons in the search volumes.
The inserts illustrate the across-subjects correlations of functional connectivity (the y-axes represent the individual beta estimates of the PPI regressors) between the BA 44 and the SMG and the SMA and SMG, respectively, with stuttering severity. For statistics, please see text.

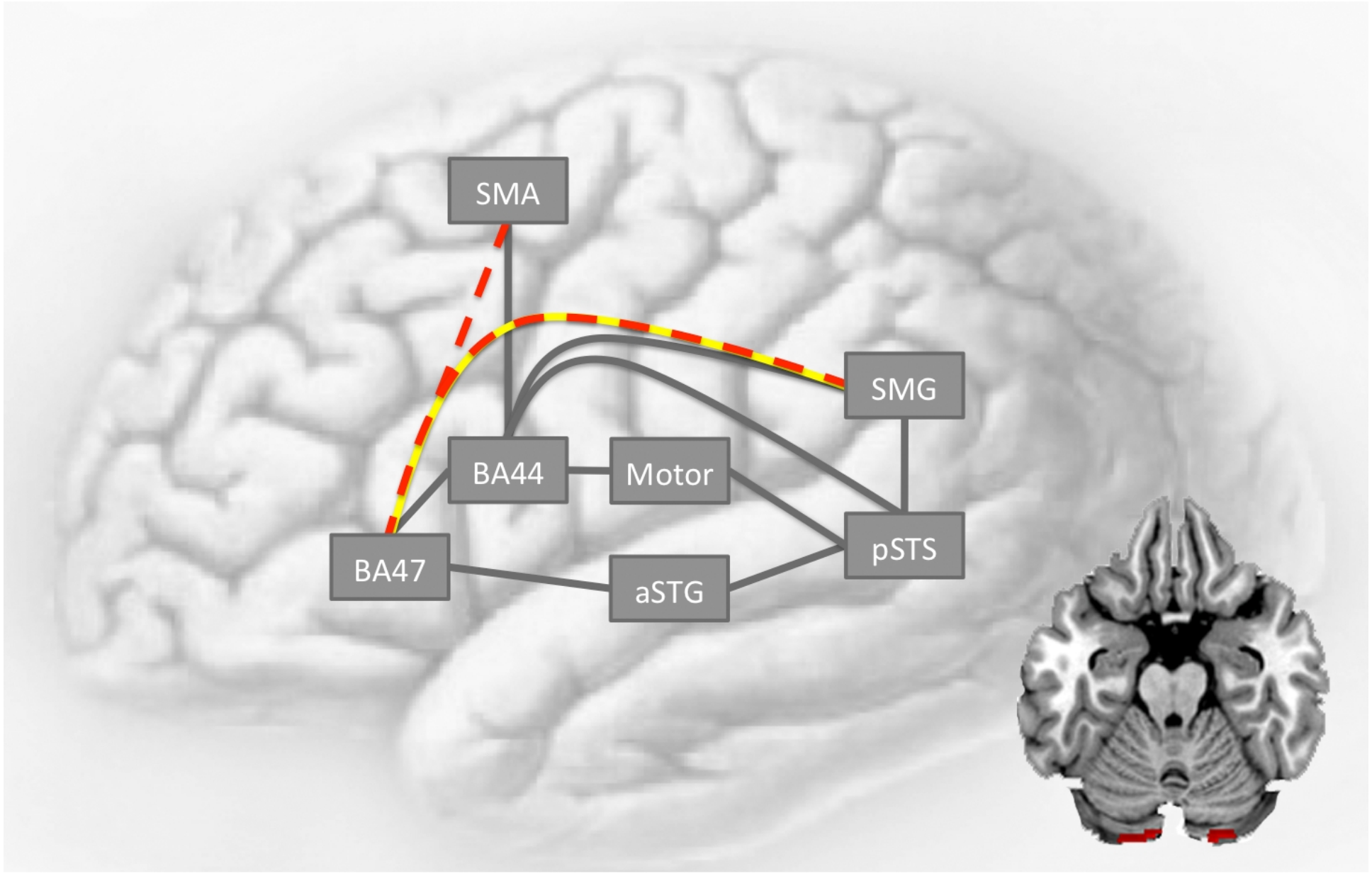
Figure 2. Group differences in speaking-related functional connectivity in unassisted recovery from stuttering in adulthood. Overall, connectivity within the speech production network appeared normalized. Yet, compared with fluent controls, RS showed diminished functional connectivity between left BA 47/12 and the supplementary motor area (SMA, dashed red connection). Compared to PS before therapy, RS connected BA 47/12 less strongly with the somatosensory processing supramarginal gyrus (SMG, yellow/red dashed line). All group differences are significant at $p<0.05$, FWE corrected for multiple comparisons in the search volumes.
The insert illustrates the increased functional connectivity between left BA 47/12 and the caudal superior cerebellum at $p<0.001$, uncorrected (red clusters).
aSTG: Anterior superior temporal gyrus. pSTS: Posterior superior temporal sulcus.

Table

| | BA 44 | BA 47 | M1 | SMA | SMG | aSTG | pSTS |
|---|---|---|---|---|---|---|---|
| BA 44 | - | | | | 3.47 (0.036) | | |
| BA 47 | | - | | | 4.75 (0.003) | | 3.84 (0.017) |
| M1 | | | - | | | | |
| SMA | | | | - | 4.22 (0.01) | | |
| SMG | | | | | - | | |
| aSTG | | | | | | - | |
| pSTS | | | | | 4.01 (0.014) | | - |

Table. Stronger PPIs (peak voxel values for the contrast overt vs. covert reading) between left perisylvian regions in PS before therapy compared to fluent control participants. Seed regions are indicated in the first row and target regions in the subsequent rows. Significant group differences at $p<0.05$ FWE small volume corrected for multiple comparisons are indicated by their T and p value.


SMA-SMG
% stuttered syllables
BA44-SMG
% stuttered syllables
SMA
SMG
BA44
Motor
BA47
aSTG
pSTS
*


SMA
SMG
BA44
Motor
pSTS
BA47
aSTG

Bio-Notes

Christian Kell, M.D. is a neurologist and group leader of a Cognitive Neuroscience group at the Brain Imaging Center of Goethe University Frankfurt. Besides other research interests (see www.brainclocks.com), he investigates neural plasticity in speech and language disorders, including developmental stuttering, Parkinson's disease, and tumor aphasia.

Katrin Neumann, M.D. is professor of phoniatrics and pediatric audiology and otolaryngologist. She is head of the Dept. of Phoniatrics and Pediatric Audiology and the Hearing and Cochlea Implant Center at the ENT clinic of the St. Elisabeth-Hospital, University of Bochum, Germany. She is member of the WHO Expert Advisory Board for the WHO program for prevention of deafness and hearing loss. One of her research focuses is the examination of speech, language, and hearing processes, in particular with neuroimaging techniques. She is associate editor of the Journal of Fluency disorders.

Marion Behrens works as a clinical neuropsychologist at the University Medical Center Mainz, Germany. She uses brain imaging to study the neural basis of aesthetic experiences in Dr. Kell's Cognitive Neuroscience group at Goethe University Frankfurt.

Alexander W. von Gudenberg, M.D. is a general practitioner with additional training in speech, language, and voice disorders and the head of the Kasseler Stottertherapie, the therapy program that was investigated in this study. He is head of the Parlo Institute since 5 years. He performs both basic and clinical research in speech and language disorders.

Anne-Lise Giraud, PhD. is professor at the Neuroscience Department of the Medical Center of Geneva University. She specialized in auditory and speech sciences...

Highlights

- Men who stutter show reduced motor coupling to the posterior auditory cortex
- Men who stutter rely overly on somatosensory feedback during speaking
- Therapy re-establishes motor coupling with the anterior auditory cortex
- Also spontaneous recovery normalizes auditory-motor coupling
- Recovery disengages the caudal superior cerebellum from controlling speech

# Speaking-related changes in cortical functional connectivity associated with assisted and spontaneous recovery from developmental stuttering

Christian A. Kell[a], Katrin Neumann[b], Marion Behrens[a,c], Alexander W. von Gudenberg[d], Anne-Lise Giraud[e]

[a] Brain Imaging Center and Department of Neurology, Goethe University, Frankfurt, Germany

[b] Department of Phoniatrics, Ruhr University, Bochum, Germany

[c] Department of Neurology, University Medical Center, Mainz, Germany

[d] Institut der Kasseler Stottertherapie, Bad Emstal, Germany

[e] Département des Neuroscience Fondamentales, Université de Genève, Switzerland

Corresponding author: Christian A. Kell, Department of Neurology, Schleusenweg 2-16, 60528 Frankfurt, Germany, c.kell@em.uni-frankfurt.de

## Abstract

We previously reported speaking-related activity changes associated with assisted recovery induced by a fluency shaping therapy program and unassisted recovery from developmental stuttering (Kell et al., Brain 2009). While assisted recovery re-lateralized activity to the left hemisphere, unassisted recovery was specifically associated with the activation of the left BA 47/12 in the lateral orbitofrontal cortex. These findings suggested plastic changes in speaking-related functional connectivity between left hemispheric speech network nodes.

We reanalyzed these data involving 13 stuttering men before and after fluency shaping, 13 men who recovered spontaneously from their stuttering, and 13 male control participants, and examined functional connectivity during overt vs. covert reading by means of psychophysiological interactions computed across left cortical regions involved in articulation control.

Persistent stuttering was associated with reduced auditory-motor coupling and enhanced integration of somatosensory feedback between the supramarginal gyrus and the prefrontal cortex. Assisted recovery reduced this hyper-connectivity and increased functional connectivity between the articulatory motor cortex and the auditory feedback processing anterior superior temporal gyrus. In spontaneous recovery, both auditory-motor coupling and integration of somatosensory feedback were normalized. In addition, activity in the left orbitofrontal cortex and superior cerebellum appeared uncoupled from the rest of the speech production network.

These data suggest that therapy and spontaneous recovery normalizes the left hemispheric speaking-related activity via an improvement of auditory-motor mapping. By contrast, long-lasting unassisted recovery from stuttering is additionally supported by a functional isolation of the superior cerebellum from the rest of the speech production network, through the pivotal left BA 47/12.

Keywords

Psychophysiological interactions; speech production; overt reading; auditory-motor interactions, left inferior frontal gyrus