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Editorial

From locations to networks: Can brain imaging inform treatment of stuttering?

Ninety years ago Orton (1927) postulated that developmental stuttering was associated with aberrant functional lateralization of cortical networks. He suggested that these cortical disruptions lead to inefficient activation of motor control regions that in turn produce prolongations, repetitions, and blocks at the level of speech production. These behavioral abnormalities are characteristic of the speech dysfluencies seen in children, adolescents, and adults with a diagnosis of developmental stuttering. Despite this early speculation about the biological basis of stuttering, it was not until the mid-1980s that empirical studies began to focus on brain structural and functional systems in people who stutter (PWS). The advent of advanced brain imaging technologies and the continued development of non-invasive neuroimaging methods has yielded important and significant results.

Early neuroimaging studies on stuttering focused mainly on certain cerebral regions or connections which were either pre-defined as regions of interest or guided by theoretical considerations or previous findings. Over the years, a more systemic view indicated that a "locationist's" perspective does not sufficiently reflect the complex networks involved in stuttering. The "locationistic" approach leads to variable findings that may not adequately reflect the complex structural architecture and functional organization of the brain (Chang et al., this issue). It also misses "uninteresting" regions (related to e.g., attention, temperament, emotion). However, the "… brain is not a set of isolated regions, but rather comprises intrinsically connected networks that underpin distinct but related functions" (Chang et al., this issue). This special issue of the *Journal of Fluency Disorders*, titled Neuroimaging in Stuttering Research, looks on the functional and structural architecture of speech fluency generating cerebral networks from this contemporary, systemic perspective and reveals an outlook on target networks for treatment. It includes seven empirical studies, one systematic and one narrative review that build on the knowledge gained in the past thirty years.

Etchell, Civier, Ballard, and Sowman (this issue) provide a systematic review on the current literature of neuroimaging findings in stuttering. It is organized by both methodology (fMRI, structural MRI, diffusion MRI PET, EEG, MEG, TMS) and population (adults, children). It is the largest comprehensive overview of the neuroimaging literature on developmental stuttering published between 1995 and 2016 and summarizes the content of 111 articles out of 359 identified publications. The review informs about the widespread abnormalities in the structural architecture and functional organization of the brains of stuttering persons that are evident in speech and non-speech tasks.

Stuttering involves widespread cerebral networks associated not only with sensorimotor functions but also with emotional and social-motivational factors. The findings of the group of Neef et al. (this issue) open a new view on this complex disorder by demonstrating structural changes in the limbic system of PWS. Using MRI, the group looked for volumetric alterations in cortical and subcortical structures of the limbic system in AWS and found an enlarged right nucleus accumbens and a smaller substantia nigra in PWS. The nucleus accumbens as part of the basal ganglia belongs to the mesolimbic system. It functions as a motivation-to-movement interface, controlled by the substantia nigra. The sustantia nigra is another part of the basal ganglia that mainly works in the extrapyramidal motor system and has been reported before as functioning abnormally in stuttering, together with thalamus and cerebellum, in mediating sensorimotor functions. Alterations in the motivation-to-movement interface seem plausible in stuttering, in the light that stuttering may establish a considerable obstacle to speak and communicate. The findings of Neef and her group indicates a complex neurobiological framework of stuttering that integrates sensorimotor and social-motivational neuroanatomical circuitries. But it cannot be derived from the data which component plays a rather causal and which one a rather consequential role.

Another indication for such an extended network implicated in stuttering comes from Chang et al. (this issue). In their paper titled "Anomalous network architecture of the resting brain in children who stutter", this group studied intrinsic connectivity networks (ICNs), including neural systems that support internally directed mentation (default mode network; DMN), attention and executive control, sensorimotor processes, and vision in a relatively large sample of children who stutter (CWS) (n = 42, 30 boys, ages 3–10)

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compared to an age-matched group of children who do not stutter (CWNS) (n = 42, 20 boys) recruited from an ongoing longitudinal whole brain study. The primary goal was to identify predictors of stuttering persistence. A retrospective analysis found that 15 children recovered from stuttering, and 24 developed a persistent pattern of dysfluency. Three could not be categorized because of attrition. Results showed that the intra-network connectivity in the DMN and its connections with executive control and attention networks predicted persistent stuttering, although it is important to note that the recovery rate in this sample is lower than expected, perhaps because of the retrospective classification method.

Gough et al. (this issue) and colleagues examined the structural integrity of the planum temporale, a language-related posterior cortical region, in adults with a diagnosis of persistent development stuttering (AWS) (n = 67, 54 males) compared to a group of fluent age-matched controls (n = 63, 47 males) in their paper titled "Planum temporale asymmetry in people who stutter." The main goal was to determine whether AWS have a reduced leftward or reversed asymmetry compared to controls. Two measurement techniques were used including a manual-based region-of-interest approach and an automated method. There was no significant group effect for the size and asymmetry of this structure using the manual and the automated measure. A secondary goal was to determine whether there was a relationship between stuttering severity and anatomical asymmetry among the AWS; results showed no significant effects. There were two other interesting findings. First, there was a sex-linked difference within the stutter group showing a tendency towards an atypical rightward asymmetry in women compared to men. Second, a development effect was found, as expected, in the control group who showed an increase in the degree of the typical leftward asymmetry with age compared to the AWS, who did not show this developmental change. Future longitudinal studies should examine the development of this structure in the language dominant hemisphere including an analysis of white matter connections to frontal language zones and to homologous regions in the contralateral hemisphere. Perhaps such studies will show that there is a subgroup of PWS with vulnerability within the speech-language network; this vulnerability may be partially mediated by a sex-linked factor.

In the article titled: "White matter pathways in persistent developmental stuttering: lessons from tractography," Kronfeld-Duenias, Civier, Amir, Ezrati-Vinacour, and Ben-Shachar (this issue) used diffusion magnetic resonance imaging (dMRI) to study the integrity of 18 major white matter pathways in AWS (n = 25; 19 males) compared to an age-matched group of controls (n = 19; 16 males). The authors postulated that the biological basis of stuttering could be linked to white matter anomalies. This represents one important approach as early imaging studies in both AWS (Sommer, Koch, Paulus, Weiller, & Buchel, 2002) and CWS (Chang, Erickson, Ambrose, Hasegawa-Johnson, & Ludlow, 2008) showed reduced fractional anisotropy (FA) in left hemispheric pathways that connect portions of the frontal language zones to the representations for the face and larynx within the primary motor cortex. Their study includes a comprehensive review of the methodology and summarizes past studies in PWS. Results of the dMRI study showed involvement of the right inferior longitudinal fasciculus (ILF), a major intra-hemispheric pathway that connects posterior cortical association areas to prefrontal regions, and the right cingulum, a pathway that connects orbitofrontal regions to the anterior temporal pole. Functionally distinct pathways are segregated within the ILF with distinct hemispheric differences. The involvement of these right hemispheric pathways in AWS, including the right ILF and right cingulum, could be associated with deficits in attention, emotion regulation, and working memory. It is interesting that the earlier findings of white matter defects in frontal pathways were not replicated (Chang et al., 2008; Sommer et al., 2002). These current results are compelling, but do not answer the question of whether these aberrant white matter pathways are a neural risk or a result of the maintenance and exacerbation of stuttering behaviors. This question holds true in general for imaging studies involving participants who already have some history of actual stuttering. It may be assumed with caution that a negative deviation from the norm rather reflects a pathological entity, while a surplus in functional brain substance might signal adaptive changes.

The group of Mersov, Cheyne, Jobst, and De Nil (this issue) was interested in the difference between the cortical speech motor activity associated with fluent and disfluent speech production. Using MEG, the authors explored the neural differences in motor preparation prior to speaking between fluent and stuttered utterances in AWS. They detected a suppression of beta oscillatory activity prior to speech onset in the bilateral precentral gyrus but with no differences between stuttered and fluent utterances, possibly due to a relatively low and variable number of stuttered trials analyzed in this preliminary study. The trends they found, however, make the applied methodology a promising approach for studies of neural processes associated with stuttered and fluent speech.

Brain imaging and brain stimulation studies were reviewed in the article by Ingham, Ingham, Euler, and Neumann (this issue) titled: "Stuttering treatment and brain research: a still unfolding relationship." The authors discuss this challenging area of research. Although neuroimaging studies have considerably increased the knowledge on the neural correlates of stuttering, they have not much contributed to the advancement of stuttering treatment so far and neural stimulation has had a limited application to date in the treatment of stuttering. Descriptions of what happens by a therapy need to be followed by more predictive approaches now and studies on methods that will induce neuroplasticity are overdue. The emerging area of empirical treatment studies using neuroimaging methods requires careful pre-treatment testing in PWS and the use of valid post-treatment outcome measures. Studies should, if possible, include placebo (sham)-controlled conditions with stringent analysis approaches. The precise quantification of the behaviors of interest will need to be benchmarked with reliability measures. If the underlying theoretical model is that stuttering therapies induce changes in brain architecture, then these studies will need to start with hypothesis driven models of neural networks implicated in the target therapy.

Kell, Neumann, Behrens, Wolff von Gudenberg, and Giraud (this issue) reanalyzed a formerly studied sample of male adults who stutter (AWS) before and after a fluency shaping therapy and compared the functional connectivity between left-hemispheric speech network nodes with that one of formerly stuttering males who had recovered spontaneously from stuttering and with that one of typically fluent males. In the former study, Kell et al. (2009) had shown a re-lateralized activity to the left hemisphere after treatment and that unassisted recovery was specifically associated with the activation of the left BA 47/12 in the lateral orbitofrontal cortex. In the re-analysis, the authors confirmed former indications that untreated stuttering goes along with a reduced auditory-motor