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The neural correlates of developmental stuttering: A brief overview of the literature

Developmental stuttering (DS) is a disruption of the rhythmic flow of speech, and its aetiology is still obscure. Neuroimaging/neurophysiological techniques have been used to study, the neural system of people with DS highlighting the presence of widespread structural/functional abnormalities, especially in the motor system. Reduced white matter integrity and altered functioning of the basal ganglia-thalamo-cortical circuit play a key role in DS. Evidence from transcranial magnetic stimulation suggests the presence of an altered interplay between excitatory and inhibitory signals, especially in the left motor cortices; findings of neurophysiological indexes obtained from non-speech related muscles, support the theory that stuttering is the overt symptom of a more general motor disorder. Further investigations need to be conducted to better elucidate the neural basis of this disorder, in order to find better rehabilitative solutions.

Key words: Stuttering, connectivity, motor cortex, basal ganglia, transcranial magnetic stimulation.

1. *What is stuttering?*

Stuttering is a particular condition in which the normal rhythmic flow of speech is disrupted by frequent pauses, blocks, hesitations, repetitions of syllables, words, and sounds. It may result in a highly negative impact on the quality of life and daily activities of people who stutter, affecting not only their spoken communication attitudes but also their emotional stability and mental health status (Craig, Blumgart & Tran, 2009). Stuttering may be associated with lower social interaction capacities, educational and occupational disadvantages, self-imposed isolation and elevated levels of social anxiety (see Craig, Tran, 2014; Iverach, Rapee, 2014). Developmental stuttering (DS) is the most common form of the disturbances and includes all cases with gradual onset in childhood that are not the result of an acquired brain damage (Costa, Kroll, 2000); disfluencies occur predominantly at the beginning of words and phrases (Bloodstein, 1995) and they are characterized by possible adaptation phenomena (Craig-McQuaide, Akram, Zrinzo & Tripoliti, 2014). The overt symptoms of stuttering are also usually accompanied by spasms and associated movements of various muscular districts (especially facial muscles), that may initially help people with DS to overcame the disfluencies (Riva-Posse, Busto-Marolt, Schteinschnaider, Martinez-Echenique, Cammarota & Merello, 2008). DS is a relatively frequent disorder in childhood, especially in males. In many cases, it recovers either naturally or as result of a specific clinical/behaviour-

al treatment (see Yairi, Ambrose, 2013). However, due to the complex nature of speech production the exact aetiology of DS has not yet been fully understood: multifactorial components, as well as genetic predispositions, seem to play an important role in the pathophysiology of this complex disorder (Neef, Anwander & Friederici, 2015a). Epidemiological twin studies, adoption studies, family aggregation studies and different sex ratios suggest a possible influence of genetic components in stuttering (see Yairi, Ambrose, 2013). For example, mutations in proteins involved in the lysosomal enzyme-targeting pathway (Kang, Riazuddin, Mundorff, Krasnewich, Friedman, Mullikin & Drayna, 2010) have been identified in people with DS: protein trafficking plays a key role in the biogenesis and maintenance of myelin sheaths and thus the white matter abnormalities described in DS (e.g. Sommer, Koch, Paulus, Weiller & Buchel, 2002; Watkins, Smith, Davis & Howell, 2008; see below) could be related to those mutations (see also Buchel, Watkins, 2010). In this regard, a mouse model genetically engineered to carry one of these mutations has been created: with respect to the littermate wild type controls, mutant puppies show stuttering-like behaviours, emitting fewer vocalizations with longer pauses between them (Barnes, Wozniak, Gutierrez, Han, Drayna & Holy, 2016). Over the years, scientists from different fields, ranging from psychology to linguistics, from biomechanics to neuroscience, have proposed different theories to describe the causal role of DS (Neef *et al.*, 2015a). One of the older and most influential theories of DS pathophysiology suggests that stuttering may occur as a result of an incomplete dominance of the speech and motor centres of the left hemisphere over the right homologue areas (Travis, 1978). In this context, it has been widely shown that stuttering improves during various "fluency-inducing conditions", such as singing, choral speech and external rhythmic cues (e.g. speaking with a metronome); these empirical observations suggest that the disorder has its origin in the central nervous system, likely at a speech motor planning level, rather than in the peripheral nervous system or in abnormalities of the vocal apparatus (see Craig-McQuaide *et al.*, 2014). In fact, the occurrence of stuttering during direct intra-operative electrical stimulation of brain regions such as supplementary motor area (Penfield, Welch, 1951) and/or thalamus (Ojemann, Ward, 1971) indicates the implication of a cortico-subcortical circuit in the disorder. This is further supported by the evidence of stuttering occurrence in fluent speakers after the stimulation of the left frontal aslant tract (Kemerdere, Champfleur, Deverdun, Cochereau, Moritz-Gasser, Herbert & Duffau, 2016) which connects the pars opercularis of the inferior frontal gyrus and the anterior supplementary motor/pre-supplementary motor areas (see Catani, Dell'Acqua, Vergani, Malik, Hodge, Roy, Valabregue & Thiebaut de Schotten, 2012). All this evidence sustains also the suggestion that stuttering may be related to a series of disturbances that involve also the auditory-motor integration level (useful for speech), especially in adults (e.g. Daliri, Max, 2015). As a consequence, the most relevant vision includes, at the moment, the proposal that stuttering should be more properly viewed as a disconnection syndrome (see below and Sommer *et al.*, 2002), also characterized by the aberrant function-

ing of the basal ganglia system (see below and Alm, 2004). In this context, in the present work, we will briefly review the available neurophysiological evidence in DS, trying to combine it with one of the more recent computational models of DS (Civier, Bullock, Max & Guenther, 2013), in order to propose new suggestions for research, and toward more effective rehabilitative solutions.

2. *Neuroimaging correlates of developmental stuttering*

Numerous non-invasive brain imaging studies have provided advanced structural and functional descriptions of the neural system of people with DS, and they have highly contributed to define some neural markers of DS. Techniques such as functional magnetic resonance, diffusion tensor imaging and positron emission tomography, were able to individuate widespread white matter abnormalities and metabolism alterations in DS: reduced levels of white matter are present bilaterally in many brain regions, such as in the posterior inferior frontal gyrus, in precentral gyrus, in ventral premotor cortex, in the cerebral peduncles (see Watkins *et al.*, 2008), in the arcuate fasciculus, in the left angular gyrus, in the left corticospinal tract and in the left corticobulbar tract (see Connally, Ward, Howell & Watkins, 2014). In this context, especially during speech production, people with DS show lower neural activity in the left ventral premotor cortex, the left and antero-medial Heschl's gyrus, left and right sensorimotor cortex and in the rolandic opercular cortex (Watkins *et al.*, 2008). Interestingly, reduced white matter integrity is present in the left rolandic operculum, immediately below the motor representations of tongue, larynx and pharynx (see also Sommer *et al.*, 2002), while a prominent increase in white matter volume is present in various regions of the right hemisphere, likely as the result of compensatory mechanisms, in the superior temporal gyrus, the inferior frontal gyrus including the pars opercularis, and in the sensorimotor areas including hand and mouth motor representations (Jäncke, Hänggi & Steinmetz, 2004). An increased mean diffusivity is also present, bilaterally, in the frontal aslant tract (Kronfeld-Duenias, Amir, Ezrati-Vinacour, Civier & Ben-Shachar, 2016). Other regions characterized by white matter abnormalities include chorona radiata, left superior longitudinal fasciculus (Chang, Zhu, Choo & Angstadt, 2015), corpus callosum and thalamo-cortical circuits (Choo, Kraft, Olivero, Ambrose, Sharma, Chang & Loucks, 2011). Similarly, in the adult population of DS decreased/increased volumes of grey matter may be evident in basal ganglia, cerebellum, inferior frontal gyrus, middle temporal gyri, pre- and post-central gyri and superior temporal gyri, in both hemispheres (see Beal, Gracco, Lafaille & Denil, 2007; Lu, Chen, Ning, Ding, Guo, Peng, Yang, Li & Lin, 2010; Song, Peng, Jin, Yao, Ning, Guo & Zhang, 2007). The major part of available data has been obtained from the adult population, while a reduced amount of studies have been conducted in children with DS. Also in this population differences in neural networks with respect to fluent speakers have been highlighted: a decrease in gray matter volume is present, in DS, in the left and right inferior frontal gyri, left anterior cingulate gyrus, right tem-

poral regions and, bilaterally, in the supplementary motor area (Chang, Erickson, Ambrose, Hsegawa-Johnson & Ludlow, 2008). A reduction is evident also in the left putamen (Beal, Gracco, Brettschneider, Kroll & Denil, 2013). Conversely, grey matter volume is increased, in the right hemisphere, in the middle frontal gyrus, in the post-central gyrus, in the superior temporal gyrus, in the inferior parietal lobule and in the rolandic operculum in DS children (Beal *et al.*, 2013). Reduced white matter integrity in the tract underlying the left rolandic opercular region is also present in DS children but not associated with higher white matter volumes in right hemisphere speech regions, suggesting that the anatomical increase present in adults may be the result of compensatory mechanisms (see Chang *et al.*, 2008). In fact, in DS there is an overactivation of the right hemisphere motor systems, including primary motor cortex, supplementary motor area, superior lateral premotor regions and cerebellum (Fox, Ingham, Ingham, Hirsch, Downs, Martin, Jerabek, Glass & Lancaster, 1996). Moreover, a greater activity is present in the left and right midbrain, at the level of the substantia nigra, in the subthalamic nucleus, peduncolo-pontine nucleus and red nucleus, as well as in the left and right posterior lobe of the cerebellum (Watkins *et al.*, 2008). Close to the right anterior insula, a systematic activation of the right frontal operculum (the right hemisphere homologue of Broca's area), may be evident in DS, especially during speech tasks (Preibisch, Neumann, Raab, Euler, von Gudenberg, Lanfermann & Giraud, 2003). The negative correlation between neural activation of this brain region and stuttering severity helps to exclude a direct causal role of this cortical area in DS but favours a vision that claims a compensatory activity of right frontal operculum in the disturbance. These findings sustain the idea of a compensatory role of the right hemisphere in DS (see Kell, Neumann, von Kriegstein, Poserienske, von Gudenberg & Euler, 2009) that may develop during a life of stuttering (see also Ingham, Grafton, Bothe & Ingham, 2012). Metabolism abnormalities are also present in DS: glucose hypometabolism has been highlighted in the neural system of people with DS in Wernicke's area, Broca's area, medial cerebellum, superior frontal cortices, ventral posterior cingulated cortex, frontal orbital cortex, anterior prefrontal cortex and angular gyrus; moreover in DS, the left caudate nucleus is nearly 50% less active both during stuttering and fluency-enhanced conditions (Wu, Maguire, Riley, Fallon, Lacasse, Chin, Klein, Tang, Cadwell & Lottenberg, 1995). The reduced glucose uptake seems in part related to an altered dopamine metabolism which may be present in people with DS: an increased dopamine uptake activity is present in DS in the left caudate tail, and in the right ventro-medial prefrontal cortex, which is an area functionally connected to the supplementary motor area. Other regions of enhanced uptake activity include the amygdala, the left insular cortex, the right deep orbital cortex, left insular cortex and the left pulvinar (Wu, Maguire, Riley, Lee, Keator, Tang, Fallon & Najafi, 1997). This is indirectly supported by the evidence of fluency enhancements after the administration of dopamine D2 antagonists such as haloperidol (Murray, Kelly, Campbell & Stefanik, 1977), risperidone (Maguire, Riley, Franklin & Gottshalk, 2000) and olanzapine (Maguire,

Riley, Franklin, Maguire, Nguyen & Brojeni, 2004). Similarly, paroxetine, a selective serotonin reuptake inhibitor, is also effective in the management of stuttering symptoms (Busan, Battaglini, Borelli, Evaristo, Monti & Pelamatti, 2009) probably via a serotonin mediated and indirect anti-dopaminergic mechanism (Schreiber, Pick, 1997). As a consequence, it is evident that one of the main neural mechanisms related to DS may rely on the possible dysfunction of the basal ganglia system. For this reason, in the following section, we will try to focus our attention on possible dysfunctional cortico-basal-thalamo-cortical mechanisms in DS.

3. *Cortico-basal-thalamo-cortical networks in stuttering*

Stuttering shares a series of characteristics with various basal ganglia-related disorders such as Parkinson's Disease, attention deficit and hyperactivity disorders, Tourette's Syndrome and focal dystonia. In this context, acquired neurogenic stuttering often occurs after lesions of basal nuclei (see Craig-McQuaide *et al.*, 2014). An abnormal activity of basal ganglia (see the previous section but see also Alm, 2004), along with a consequent impairment of the cortico-basal-thalamo-cortical network that is mainly able to reach supplementary motor area complex, seems to play a key role in DS. In fact, fluent speech production is a highly demanding motor task that requires the punctual motor planning and execution of articulated movements through the integration of excitatory and inhibitory neural signals useful for the correct coordination of the muscles of speech apparatus. Supplementary motor area is involved in planning and execution of voluntary movements as well as in word production: anterior pre-supplementary motor area may have a role in lexical selection process, while its posterior portion may have a role in linear sequence encoding; finally, the "proper" supplementary motor area is fundamental in articulation of motor output (Alario, Chainay, Lehericy & Cohen, 2006). Basal ganglia are strongly involved in neural activity related for example to motor control of voluntary movements, learning, cognitive and limbic functions (Graybiel, 2000). An anomalous activation of basal ganglia in DS is often reported (e.g. Watkins *et al.*, 2008; Lu *et al.*, 2010): stuttering severity positively correlates with bilateral caudate nucleus activity and negatively correlates with left substantia nigra activity (Giraud, Neumann, Bachoud-Levi, von Gudenberg, Euler, Lanfermann & Preibisch, 2008). Weaker connectivity is present in DS when considering regions of the posterior middle temporal gyrus and the putamen, whereas a stronger connectivity is present from putamen to the thalamus and from this latter region to temporal cortices and supplementary motor area, as well as between them (Lu *et al.*, 2010). As a consequence, the understanding of DS neurophysiology may take advantage from the utilization of techniques that have been already extensively used in other basal ganglia related motor disorders (e.g Parkinson's Disease, dystonia and Tourette's Syndrome), such as transcranial magnetic stimulation (TMS).

4. *Electro/magneto-neurophysiological correlates of developmental stuttering*

The aforementioned findings, mainly obtained by using neuroimaging techniques such as functional magnetic resonance and positron emission tomography, have shed light on different aspects of DS neurophysiopathology. Similarly, non-invasive brain stimulation tools such as transcranial magnetic stimulation (TMS) have been employed to investigate the functioning of the motor system in adults with DS. TMS provides useful information on the excitability of motor cortex, cortico-spinal and cortico-bulbar physiology and on the role of the intracortical networks in the modulation of the final motor output (see Kobayashi, Pascual-Leone, 2003). Only few authors have employed, at the moment, TMS in DS, often concentrating on non-speech related muscles (see Sommer, Wischer, Tergau & Paulus, 2003; Alm, Karlsonn, Sundberg & Axelson, 2013), probably due to the challenging methods required to record motor evoked potentials (MEPs) directly from the speech apparatus (see D'Ausilio, Jarmolowska, Busan, Bufalari & Craighero, 2011). Early findings from TMS highlighted that indexes of intracortical inhibition (ICI) and facilitation (ICF), recorded from right hand muscles when stimulating only the left motor cortex, are normal in DS, but an increased resting and active motor threshold in the left motor cortex is evident, suggesting that a dysfunction at a cortico-spinal level is present (Sommer *et al.*, 2003). In this regard, evidence from recruitment curves suggests that left hand cortical excitability is lower in DS probably due to a reduced number of cortical projecting neurons or due to a reduced strength of the cortico-spinal pathway (Busan, D'Ausilio, Borelli, Monti, Pelamatti, Pizzolato & Fadiga, 2013). The same study also highlighted that cortical silent period duration is normal in bilateral hand motor cortex in DS supporting the evidence that, when compared to fluent speakers, no differences are present in terms of intracortical inhibition in people with DS. In every case, a negative correlation between silent period duration and stuttering severity was also evident in the right hemisphere of stuttering males. Fluent speakers usually show lower motor thresholds (i.e. increased excitability) in the left hemisphere, while in DS the pattern is usually reversed: motor thresholds tend to be higher in the left hemisphere, in comparison to their own right and to the left hemisphere of fluent speakers (Alm *et al.*, 2013). Hand motor cortex in DS seems also characterized by the absence of an aberrant interhemispheric inhibition (IHI) and ipsilateral cortical silent period duration (Sommer, Knappmayer, Hunter, Gudenberg, Neef & Paulus, 2009). On the other hand, the chronic administration of paroxetine decreases TMS-evoked silent period (i.e. an index of intracortical inhibition) duration registered from right hand muscles and reduces DS associated spasms and movements (Busan *et al.*, 2009). In fluent speakers, a sub-threshold repetitive TMS (rTMS; 1 Hz for 20 min) over the left dorsolateral premotor (dPM) cortex during auditory paced finger tapping tasks, prolongs ipsilateral hand asynchrony, while right stimulation is ineffective; in DS the pattern is reversed: rTMS over the right dPM cortex increases contralateral asynchrony but no effects were present after left dPM stimulation (Neef, Jung, Rothkegel, Pollok, von Gudenberg, Paulus & Sommer, 2011a). This evidence suggests an altered control of timed non-speech movements in DS (Neef *et al.*, 2011a). On the other

hand, the stimulation of cortical representations of primary motor cortex representations of tongue muscle performed during no concurrent speech tasks has pointed out the presence of alterations in motor intracortical networks. More specifically, different asymmetries are present in terms of motor thresholds: in fluent speakers, tongue motor cortex excitability is increased in the left hemisphere while in DS left motor cortex excitability is decreased and right is increased (Barwood, Murdoch, Gozee & Riek, 2013; Busan, Del Ben, Bernardini, Natarelli, Bencich, Monti, Manganotti & Battaglini, 2016). Neef, Paulus, Neef, von Gudenberg & Sommer (2011b) evaluated a series of neurophysiological indexes where the main outcome is the presence of a bilaterally reduced intracortical facilitation and a reduced short term intracortical inhibition in the right hemisphere: these findings suggest the presence of alterations in intracortical modulation of inhibitory and facilitatory circuits underlying tongue motor representations in DS. More recently, Busan *et al.* (2016) have further investigated cortico-bulbar excitability and intracortical inhibition in DS, mainly focusing on neurophysiological indexes not previously evaluated: in adults with DS, silent period threshold of the left hemisphere is higher in comparison to their own right; moreover, silent period duration is prolonged in the left hemisphere compared to the left hemisphere of fluent speakers. The pathophysiological mechanism underlying enhanced intracortical inhibition in stuttering is not clear, but a possible explanation of this pattern of findings can be the presence of an imbalance between excitatory and inhibitory inputs to the motor cortex, probably in relation with an abnormal activity of inhibiting interneurons, influencing the final level of excitability of motor cortex. The prolonged cortical silent period duration can be the result of a decrease in excitation modulated by afferent pathways to motor cortex as a result of widespread white matter abnormalities already described in the DS neural system (see Watkins *et al.*, 2008; Connally *et al.*, 2014), favouring a prolonged GABA-mediated inhibition on pyramidal cells. Moreover, stuttering severity positively correlates with silent period durations of right hand muscles, and negatively with left hand muscles: the associations of higher stuttering severity with higher intracortical inhibition in the left hemisphere and lower intracortical inhibition in the right one, also in cortical areas that are not directly involved in speech muscle control, support the idea that stuttering may be only the overt symptom of a more general motor disorder (Busan *et al.*, 2013; Busan *et al.*, 2016). Finally, TMS applied during speech tasks highlighted that, in fluent speakers, a conspicuous increase of motor cortex excitability (facilitation) is present in the left hemisphere tongue motor cortex during a speech transition phase, but not in DS (Neef, Hoang, Neef, Paulus & Sommer, 2015b). Thus, it is evident that TMS studies led to further highlight the presence of an altered functioning of the motor system in DS; however, it would be interesting to investigate this aberrant modulation of excitatory and inhibitory networks also in different populations of people who stutter, and in particular in children, in order to elucidate if such neurophysiological abnormalities are present since stuttering onset or they may be the result of compensatory mechanisms. Also electroencephalography (EEG) and magnetoencephalography (MEG) have further highlighted neural differences between DS and fluent speak-

ers. Altered oscillations in the beta frequency band (about 13-30Hz), which are associated with motor activity, are often reported in DS: hyperactivity in the cortical beta band may be present in adults during aloud reading, but it is reduced in delayed auditory feedback conditions (Rastatter, Stuast & Kalinowski, 1998). On the contrary, reduced beta band activity may be present in children (Özge, Toros & Cömelekoglu, 2004). Again, it has been proposed that this hyperactivation in adults likely reflects a compensatory mechanism for hypoactivity in beta oscillations, starting from basal ganglia (Etchell, Johnson & Sowman, 2014). Intrahemispheric alterations in resting state are mainly present for high frequencies band (beta and gamma -i.e. > 30 Hz-): functional connectivity for high frequencies oscillations is mainly decreased, in DS, between Broca's area and right motor cortex, between right premotor cortex and left and right pars opercularis and right motor cortex, between left premotor area and Broca's area (beta), and between left motor and premotor area and Broca's area (gamma) (Joos, De Ridder, Boey & Vanneste, 2014). Finally, MEG showed in DS a relevant suppression of beta rhythms during the preparation stage of overt speech production and a consequent higher synchronization in mouth motor cortex, bilaterally (Mersov, Jobst, Cheyne & De Nil, 2016). Moreover, before stuttering occurs, the left inferior frontal and orbitofrontal cortices are less active, while an extra-activation may be present in the homologous right hemisphere regions and, bilaterally, in sensorimotor and auditory cortical regions (Sowman, Crain, Harrison & Johnson, 2012).

5. *A computational model of stuttering*

In light of the above reported evidence, functional and structural abnormalities of DS may be also verified by using computational models. In this view, a recently implemented "stuttering" version of the neuro-computational speech production model GODIVA (Gradient Order Directions Into Velocities of Articulators) (see for descriptions Bohland, Bullock & Guenther, 2010; Civier *et al.*, 2013) has been employed to test the main hypothesis of a causal disruption in DS (i.e. the basal ganglia dysfunction hypothesis and the white matter disruption hypothesis). Interestingly, in comparison with the normal performance of the "healthy" model, the GODIVA model with basal ganglia dysfunction (i.e. elevated levels of dopamine in this region) reads out the motor program for the word initial syllable with a significant neural delay. Differently, in the simulation of white matter fibre impairment, the motor program for the word second syllable is readout with delay. As a consequence, this computational simulation of DS seems to support both hypothesis and may suggest different neural substrates for different DS symptoms (e.g. blocks vs. repetitions): high levels of dopamine and basal ganglia dysfunctions are associated with stuttering occurrence especially in the first syllable of the word/sentence, whereas the white matter hypothesis may be associated with stuttering occurrence mainly in the following part of the word/utterance (Civier *et al.*, 2013). This may open the discussion to the possibility that different subgroups of stuttering may exist.

6. *Different stuttering subgroups from a neural point of view?*

From a structural and functional point of view, neuroimaging and neurophysiological studies have shown that neural differences may exist also among the stuttering population: for example, between children with DS and those who recovered, as well as between children and adults with DS (see Chang *et al.*, 2008). Interestingly, different neurophysiological profiles are present also between males and females with stuttering (e.g. Busan *et al.*, 2013; Ingham, Fox, Ingham, Xiong, Zamarripa, Hardies & Lancaster, 2004). Moreover, findings of the previously reported studies are often difficult to reproduce and sometimes discordant, especially in adults, which undergo a series of modifications and adaptations in their neural system, likely to overcome stuttering. It has been hypothesized that the population of adults with DS can be divided into subgroups also from a clinical/behavioural point of view (see Alm, 2004 for a review): for example, one subgroup may be characterized by individuals with a genetic predisposition to DS, while others may be composed of people who suffered from early neural injuries (Poulos, Webster, 1991). Another possible classification is based on the level of secondary concomitants and anxiety (e.g. higher anxiety and a higher incidence of attention deficit and hyperactivity vs. lower anxiety and higher familiar history of DS) (Alm, Risberg, 2007) Finally, evidence of different responses to pharmacological treatment may suggest a possible and further subdivision.

7. *Conclusions and future perspectives in stuttering research*

The present work is a very brief (and partial) overview on DS neurophysiology, and it has been proposed based on the currently available literature. It is evident that the exact aetiology of DS is not completely clear; however, clinical observations along with neuroimaging and neurophysiological studies have provided evidence that an abnormal functioning of the brain, and especially of the motor system, is present. The main features of DS seem to include alterations in brain regions useful to prepare, execute and control motor acts; in particular, a widespread reduced white matter integrity, an abnormal functioning of the cortico-basal-thalamo-cortical circuit, a strong activation of right hemisphere during speech, and an altered balance between excitatory and inhibitory neural signals in motor cortex have been highlighted. It is still not clear if these abnormalities are specific features of DS or the result of compensatory mechanisms due to a lifetime stuttering. In this regard, subgroups of people with DS may share different neurophysiological profiles. The future research in neurophysiology of DS should attempt to answer to every remaining question by using different techniques and different approaches (see Busan, Battaglini & Sommer, 2017), in order to define more focused and effective treatments ranging from pharmacological to neuromodulatory (see Chesters, Watkins & Möttönen, 2017) and behavioural ones (Ingham, Ingham, Euler & Neumann, *forthcoming*).

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