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Neuropsychological Profile of Childhood Apraxia of Speech: Implicit Learning and Executive Functions

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DOTTORANDA
Dott.ssa Clara Bombonato

TUTOR
Prof.ssa Roberta Battini

CO-TUTOR
Dott.ssa Anna Maria Chilosi

Anna Chilosi

COORDINATORE
Prof. Maria Pia Amato

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Summary

The purpose of this thesis is to analyze the neuropsychological profile of children with idiopathic Childhood Apraxia of Speech (CAS), in particular in relation to transversal processes such as implicit learning and Executive Functions (EFs). Treatment implications are also investigated through a systematic review and metanalysis.

In the first study, implicit learning processes were investigated in twenty-five children with CAS, aged between 4 and 12 years and matched for IQ and age to a control group of 25 typically developing children. Implicit learning of participants was assessed by the Serial Reaction Time Task. Children with CAS did not show implicit learning, as documented by the absence of differences between Reaction Times in the sequenced block and the random block, usually considered as a measure of implicit learning effect.

The second study aimed at defining the EF profile in a group of 30 preschool children with idiopathic CAS, investigating the relationship between EFs, speech severity and connectivity of the Frontal Aslant Tract (FAT), a white matter tract involved in the neural circuits of both speech and EFs. The results showed the presence of multiple alterations in the EF profile, mainly in its basic components, such as inhibition and working memory. A significant reduction in Fractional Anisotropy (FA) in left pre-Supplementary Motor Area (preSMA) and Supplementary Motor Area (SMA) components of FAT, compared to TD children, was found. Only speech severity correlated and predicted FA value along FAT in both of its components investigated (SMA and pre-SMA) and EF impairment moderated this relation. In particular, a significant role of visuo-spatial working memory in moderating the relationship between speech severity and FA value along FAT in the left SMA component was found.

Our findings support the conceptualization of CAS not only as a motor-speech disorder, but also involving transversal processes such as implicit learning and Executive Functions, in a composite and complex picture. The results obtained underline the importance of a comprehensive multidisciplinary assessment, which becomes mandatory in order to provide a more in-depth characterization of the disorder and define the most appropriate therapy interventions.

Finally, as a consequence of the results obtained from the previous study, a systematic review and meta-analysis of the literature about the potential of EF treatments to produce enhancements of skills not directly trained, defined as far effects, has been conducted.

Despite less considered, these trainings could be extremely relevant to reduce the negative impact of a disorder’s core symptomatology. The study aimed to investigate the far effect outcomes after EF training in children with different types of neurodevelopmental disorders. 17 studies met the inclusion criteria for the systematic review, while 15 studies were selected in the metanalysis. An overall statistically significant effect size was found in the majority of far effect outcome measures considered in the studies. In particular, trainings on executive functions determine significant far effects on daily life functioning and clinical symptoms. Despite a high variability of the results, intensity, frequency, and the laboratory/life contexts dimension seem to be the most influential variables in determining far effects. This systematic review and metanalysis highlights the need to measure the far effects of executive function training in neurodevelopmental disorders, selecting treatments not only on directly targeted processes, but also according to far impacts on the functional weakness of the disorder.

General Introduction and outline of the thesis

Clara Bombonato

General Introduction and outline of the thesis

Childhood Apraxia of Speech

The Technical Report on Childhood Apraxia of Speech of the American Speech-Language-Hearing Association (ASHA, 2007) defines *Childhood apraxia of speech* (*CAS*) as a "neurological childhood speech sound disorder in which the precision and consistency of movements underlying speech are impaired in the absence of neuromuscular deficits (e.g., abnormal reflexes, abnormal tone)". The same movements that can be performed correctly automatically in the context of habitual activities, in fact, are difficult to be performed in voluntary motor.

With regard to the differential diagnosis, etiology, prevalence and neuropsychological correlates of the disorder, the literature data are scarce and discordant. The first definitions, relating to an adult patient, date back to a late nineteenth-century case report (Hughlings-Jackson, 1878) while Morley, Court, Miller and Garside describe for the first time in 1954 a phono-articulatory disorder with features similar to CAS in childhood. Despite the subsequent interest in the field of developmental neuroscience, unanimous agreement has not yet been reached regarding the terminology used to refer to this symptomatology. In addition to the term CAS considered official, the Technical Report on Childhood Apraxia of Speech (ASHA, 2007) reports, in fact, the presence in the literature of about 50 other labels used.

CAS may be either a result of known neurological impairment, symptomatic of neurometabolic pathologies such as galactosemia (Shriberg, Potter, et al., 2011) and creatine transporter deficiency (Battini et al., 2007), or be associated with syndromic conditions (Wilson et al., 2019), as well as occur in the context of neurodevelopmental disorders such as Autism Spectrum Disorder (ASD; Shriberg, Paul, et al., 2011), Intellectual Disability (ID; Chilosi et al., 2022; Shriberg, Strand, et al., 2019) and Attention Deficit Hyperactivity Disorder (ADHD; Chilosi et al., 2022), or as an idiopathic neurogenic speech sound disorder (Chilosi et al., 2015). Similarly, it can be present as a pure form or it can be associated either with motor programming disorders affecting other body districts (Sabbadini, 2005) or with Developmental Coordination Disorder (DCD, American Psychiatric Association, 2013).

Although still scarce, epidemiological data suggest a lower incidence compared to other phono-articulatory and linguistic disorders. Shriberg, Aram and Kwiatkowski (1997) estimate a prevalence of 1-2 children in 1000, while in a study conducted on a clinical population of a large number of children evaluated for speech and language delay, the prevalence rises to 4.3% (Delaney & Kent, 2004). In a more recent analysis, it is reported that 2.4% of children with phono-articulatory disorders have idiopathic CAS (Shriberg, Kwiatkowski, et al., 2019). Children with CAS were reported to have a higher likelihood of concomitant language, reading, and/or spelling disorders (Lewis, Freebairn, Hansen, Gerry Taylor, et al., 2004; Lewis & Ekelman, 2007).

As regards to the genetic contribution, the starting point is represented by the studies on the KE family (Lai et al., 2001), in which sixteen out of thirty members were affected by speech apraxia with varying degrees of severity in the absence of other neurodevelopmental disorders. A mutation in the FOXP2 gene located on chromosome 7q3 was initially identified by Hurst et al. in 1990, and subsequently, familial and de novo mutations in the same gene have been described. However, large-scale studies have revealed that these mutations are present in only a small percentage of individuals with CAS in the general population, ranging from 2% to 4% as reported by MacDermot et al. in 2005. The heterogeneity of the genetic patterns associated with CAS was then confirmed with the spread of the Array-CHG (Comparative Genomic Hybridization) technique, which made it possible to identify numerous copy-number variations in different chromosomal regions (Fedorenko et al., 2016).

Speech and Language Profile

The main feature of CAS, namely the precision and consistency of speech movements impaired due to issues with speech motor planning and programming, consists in three core symptoms:

a) Inconsistent errors on consonants and vowels in repeated productions of syllables or words: different productions not functional to a progressively better approximation of the target for the same phonological target. In a group of Italian-speaking children with CAS (Chilosi et al., 2015), high percentages of inaccurate productions were reported in both a naming task and a repeat task of bi- and trisyllabic sequences, with a high percentage of inconsistent errors (64%);

b) Lengthened and disrupted coarticulatory transitions between sounds and syllables: the difficulties in programming and controlling articulatory transitions produce the phenomena of syllabic segmentation, the scanning of the target word into syllables, and articulatory groping, the vain search for the appropriate articulatory scheme during attempts to pronounce sounds, syllables or words;

c) Inappropriate prosody, speed, intonation and rhythm of speech: prolongation and pauses between phones, syllables or words, atypical accentuation (Shriberg et al., 2003), reduction of speed, rhythm and fluence, sometimes with alterations of the voice timbre.

ASHA (2007) points out that these characteristics, however, are neither necessary nor sufficient to diagnose CAS and their frequency can vary according to the age and severity of the disorder (Lewis, Freebairn, Hansen, Iyengar, et al., 2004; Lewis et al., 2019). Together with these pivotal criteria, in fact, the literature highlights a wider set of recurring characteristics:

- Abnormal babbling (late, scarce, little varied, sometimes absent)
- Incomplete and / or atypical phonetic, consonant and vowel inventory
- Slow and poor lexical development
- Gap between understanding and production due to a greater deficit in production
- Non-verbal oro-motor skills often deficient
- Automatic / voluntary dissociation
- Groping
- Mixed phonological errors: substitutions, distortions, omissions of consonants, vowels, or syllables, with contraction of the polysyllabic chain
- Increase in errors as the length / complexity of the target increases
- Slow speech, deficit in diadochokinesis
- Reading and writing difficulties.

These characteristics compromise the intelligibility of the child’s speech. In Murray, McCabe, Heard and Ballard (2015), two checklists containing the main diagnostic criteria of CAS are compared. The first refers to the three aforementioned macro-criteria of ASHA (2007), the second refers to 10 criteria proposed by Strand, listed below (Table 1.1). The authors indicate that the diagnosis of CAS should require the presence of all 3 ASHA criteria and at least 4 of the 10 Strand criteria.

Table 1.1 The three diagnostic criteria of ASHA (2007) and the10 criteria proposed by Strand (Murray et al., 2015)

Technical Report (ASHA, 2007)	**Strand's 10-point checklist**
1. Inconsistent errors on consonants and vowels in repeated productions of syllables or words 2. Lengthened and disrupted coarticulatory transitions between sounds and syllables 3. Inappropriate prosody, especially in the realization of lexical or phrasal stress	1. Difficulty in achieving initial articulatory configurations and transitions into vowels 2. Syllable segregation 3. Lexical stress errors or equal stress 4. Vowel or consonant distortions including distorted substitutions 5. Groping (nonspeech) 6. Intrusive schwa 7. Voicing errors 8. Slow rate 9. Slow DDK rate 10. Increased difficulty with longer or more phonetically complex words

Cognitive Profile

As described above, to formulate a diagnosis of CAS there is a consensus on the need to identify some main symptoms affecting speech (ASHA, 2007;Murray et al., 2015), while there are no shared criteria based on the presence of non-related to speech symptoms and which can instead characterize children with CAS, directing their diagnosis. To date, in fact, the behavioral manifestations and neuropsychological correlates of the disorder are still to be defined with certainty. However, the fact that CAS is a speech disorder does not preclude that there may be additional problems also in other functional areas, since, on the one hand, verbal skills develop in interaction with other cognitive functions, and on the other hand impaired development of other functions may contribute to the manifestation of the linguistic disorder (Bishop, 1997).

The literature contributions on the cognitive and neuropsychological profile of DVE are scarce and incomparable, both for the different areas investigated and, above all, for the differences in the selection criteria of the subjects. In older works, in which subjects with CAS were studied together with Speech Sound Disorders (SSD) of other nature, difficulties in spatial and sequential memory (Dewey et al., 1988) and phonological working memory (Raine et al., 1991) were documented, the latter due to the low rhythm of articulation (Hulme & Roodenrys, 1995).

Subsequently, the difficulty in working memory was described on several levels, which involve, in addition to motor planning and realization deficits, a problem of verbal representation in the aspects of perception and auditory coding, coding and maintenance in working memory and transcoding (Lewis, Avrich, Freebairn, Taylor, et al., 2011; Shriberg et al., 2012). Such difficulties seem to persist into adulthood (Kenney et al., 2006), and could reflect a global sequential processing deficit that affects speech development as well as cognitive and linguistic processing (Peter et al., 2013). Other works (Lewis, Avrich, Freebairn, Taylor, et al., 2011) confirm the presence of phonological working memory difficulties, underlining however the presence of a constellation of deficits (motor skills, phonological awareness, vocabulary, rapid naming), which represent the endophenotypes underlying the early expression of CAS and the subsequent difficulties experienced in school age by children affected by this pathology.

Nijland, Terband, & Maassen (2015) analyzed cognitive functions in three domains (complex sensorimotor and sequential memory functions, simple sensorimotor functions, and unrelated control functions such as attention and spatial memory) in a group of children with CAS compared with typically developing peers. Confirming that CAS is a disorder that not only affects speech motor control difficulties, but also implies difficulties in non-verbal sequential functioning, children with CAS showed lower scores in all domains than children with typical development. Complex sensorimotor and sequential memory functions seem to remain deficient even when CAS children were compared to younger children with typical development, while the simple sensorimotor functions not related to speech (attention and spatial memory) showed a developmental delay and were comparable to those of younger children with typical development (Nijland et al., 2015).

Through questionnaires and observations, subsequent works described cognitive and learning difficulties, attention, social communication, temperament and behavioral regulation in children with CAS (Teverovsky et al., 2009; Velleman & Mervis, 2011). Phonological awareness difficulties are also reported (J. Preston & Edwards, 2010; Raitano et al., 2004), leading to written language learning difficulties in school age, especially if the disorder is persistent and associated with a broader linguistic impairment (Lewis, Avrich, Freebairn, Hansen, et al., 2011; Lewis et al., 2000, 2006; Lewis, Freebairn, Hansen, Iyengar, et al., 2004; Smith et al., 2005).

However, in many of these papers the subjects with CAS were not differentiated from those with SSD of other nature and / or a distinction was not made between subjects with idiopathic disorder and subjects with disorders associated with other overt pathologies. Furthermore, the cited studies concern non-Italian-speaking subjects, since there are no contributions on the cognitive and neuropsychological profiles of Italian children with CAS as yet.

In a work conducted at the IRCCS Stella Maris (Casalini and Comparini, 2014) the cognitive profile of children with CAS was studied through the analysis and comparison of the neuropsychological profiles of subjects with SSD of different nature, in order to highlight any non-purely linguistic aspects that characterize or differentiate the disorders and that can help the differential diagnosis. Assessment of cognitive level, visual-motor integration, working memory and attention were administered both in verbal and visuo-spatial modality. The results indicate that children with CAS differ from children with SSD of other nature in various non-verbal skills, such as non-verbal intelligence, visuo-motor skills, visual-spatial working memory and attention, demonstrating a lower efficiency of non-verbal processing, in particular when the motor component is involved. Regarding verbal cognitive processes, children with CAS differ from children with SSD of other nature in phonological working memory skills. Comparing working memory skills, a difference in the profiles also emerged: not only children with CAS show more reduced memory skills but also a greater fall in the recall of longer words. In addition to difficulties in coding and linguistic representation, children with CAS appear to have difficulties in maintaining through internal rehearsal processes, which might constitute a more specific aspect of the disease.

The extension of the difficulties to several cognitive areas with linguistic and non-linguistic mediation would highlight a reduced “specificity” of the disorder, justifying the interpretation of CAS as a “composite condition” characterized by a pathological interaction between motor and linguistic functions, in which a central impairment of motor programming would have a cascade effect not only on the acquisition of speech and language (Liberman & Mattingly, 1985) but also on the efficiency of the more global neuropsychological functioning.

Moreover, the general slowdown in a wide range of skills, not only linguistic but also non-linguistic, leads to hypothesize the presence of a processing deficit not specific to the verbal sector, which involves general domain processes transversal to language, motor and instrumental. learning

These results laid the foundations for this work, suggesting the usefulness of examining transversal processes such as Executive Functions (EFs) and implicit learning in children with CAS.

Neurobiological bases

In recent years, the identification and understanding of the neuroanatomical correlates of CAS have met with great interest. The application of conventional neuroimaging techniques, however, did not produce significant results, as the majority of patients with CAS did not demonstrate evident brain changes on Magnetic Resonance (MR) (F. J. Liégeois & Morgan, 2012). The lack of results also emerged from the study of the neuro-functional bases of the KE family using conventional imaging (F. Liégeois et al., 2011), while, in a study conducted at the IRCCS Stella Maris Foundation (Chilosi et al., 2015) on a group of 26 children with idiopathic CAS aged between 4 and 8 years, only minor anomalies were detected (in order of frequency: arachnoid cysts, low position of cerebellar amygdales, enlargement of the retrocerebellar subarachnoid space, partial thinning of the corpus callosum, central venous dysplasia) in the absence of abnormalities of major brain metabolites, supporting the hypothesis that children with idiopathic CAS do not present macroscopic abnormalities typically found in adults with stroke or acquired verbal dyspraxia.

The neuroanatomical alterations underlying CAS, therefore, could be present at a level that conventional MR techniques are not able to grasp, paving the way for the use of advanced imaging techniques, which allow investigating brain development at a microscopic level, in functional, volumetric, and white matter integrity terms.

With reference to the KE family, Voxel Based Morphometry (VMB) techniques have shown, in the presence of CAS, a reduction of the volume in the caudate nucleus bilaterally. This alteration has been correlated to clinical measures of the oro-motor and oro-articulatory control deficit (Belton et al., 2003; Watkins et al., 2002). A reduction of gray matter was also found in the inferior frontal gyrus (Broca's area), in the precentral gyrus, in the temporal pole, in the head of the caudate nucleus and in some cerebellar ventral lobules. On the other hand, an increase in the volume of gray matter was also found in the posterior portion of the superior temporal gyrus (Wernike's area), the angular gyrus and the putamen (Belton et al., 2003). Further studies conducted using the Positron Emission Tomography (PET) technique have shown an over-activation of the caudate nucleus, of the inferior frontal cortex and of the premotor cortex, tracing this hyperactivation to a need for increased neural activity to maintain a certain functional level in underdeveloped structures (Watkins et al., 2002). The results relating to the KE family, while opening the way to the microstructural investigation of the neural basis of CAS, are scarcely generalizable, given the specificity of the disorder linked to the FOXP2 gene.

More recently, Tkach and collaborators (2011) assessed a group of children with articulatory disorder during an articulatory task in functional MR (fMR), finding hypoactivation in the middle right lower frontal and temporal gyrus, and bilateral hyperactivation in the pre and supplementary motor cortex, inferior parietal, supramarginal gyrus and cerebellum. Hypoactivation was correlated with a deficit in the phonological processing loop and speech reduction, while hyperactivation with a compensatory recruitment mechanism (Tkach et al., 2011). Subsequently, Preston and colleagues (2014) identified a hyperactivation of brain areas involved in auditory-motor representation and in the processing of complex words on the articulatory plane (Hickok & Poeppel, 2004; Shalom & Poeppel, 2008), including the superior temporal gyrus bilaterally, right supramarginal gyrus, right precentral and post-central gyrus in children showing persistent phonological errors (Preston et al., 2014), and a hypoactivation of the left middle temporal gyrus, involved in lexical mapping.

Therefore, the results of the aforementioned studies support an alteration in the circuits underlying the acoustic-phonological discrimination (input) that negatively affects the processing of language sounds and their realization (output).

Studies that have analyzed children with CAS more specifically agree with a thickening of the supramarginal gyrus (Kadis et al., 2014). This area would play a significant role in the acquisition and adaptation of sensorimotor patterns useful for articulatory control of language, representing a connection system between frontal and motor areas. Furthermore, a reduction in cortical thickness at the level of the left posterior superior temporal gyrus (Wernicke’s area) is demonstrated following a specific treatment period of motor-articulatory control (Hayden, 2006; Namasivayam et al., 2013). According to the authors, the thickening of the supramarginal gyrus area could represent an alteration in the phenomenon of synaptic pruning in the first year of life, with a consequent failure to reduce cortical thickness and therefore a reduced synaptic functional specificity. This phenomenon, according to the authors, could represent a specific marker of CAS.

In a recent study conducted at the IRCCS Stella Maris Foundation (Conti et al., 2020), two clinical groups (CAS and Autism Spectrum Disorder - ASD) and a control group were compared through morphometric Magnetic Resonance Imaging (MRI)-based measures, in order to evaluate any differences in the volume and thickness of cortical and subcortical structures in different conditions. In children with CAS, in particular, an increase in the volume of the supramarginal gyrus emerged, in line with what was previously found (Kadis et al., 2014), and at the level of the inferior frontal gyrus (Broca's area), in agreement with the alteration found in the KE family.

In addition to morphometric studies and as a consequence of the results on a possible early alteration of brain development and synaptogenesis in CAS, diffusion techniques in MR (Diffusion Tensor Imaging - DTI) were applied to study structural connectivity in children with CAS (Fiori et al., 2016). The results highlight the presence of connectivity alterations in both hemispheres, in particular with reference to three circuits. Subnetwork 1 concerned the altered connectivity in the temporal regions of the left hemisphere, whose role had already been hypothesized in CAS (Ashtari et al., 2004; Guenther et al., 2006; Guenther & Hickok, 2015; Kadis et al., 2014; J. L. Preston et al., 2014; Tkach et al., 2011) in relation to phonemic discrimination, to higher-order auditory processing useful for the comparison between the model provided by the premotor cortex and the one actually produced, and to phonological and syntactic processing in articulatory control based on feedback. Subnetwork 2 encompassed intra- and inter-hemispheric connections, including the left precuneus, the right supplementary motor area, the left cuneus and the right cerebellum. The results are in agreement with previous studies that had hypothesized the involvement of these regions in conceptual planning during lexical research (Grande et al., 2012) and in general in integrated functions (Cavanna & Trimble, 2006) known as high-level functions. The third altered subnetwork (Subnetwork 3) included intra-hemispheric connections among the right angular gyrus, the superior temporal gyrus and the inferior occipital gyrus, according to previous hypotheses on bilateral language involvement in CAS (Liégeois & Morgan, 2012) in regions crucial for representation and semantic processing. The neuroanatomical results were also analyzed in relation to their possible functional meaning, producing preliminary correlation results between the deficit in diadochokinesis (DDK rate) and the alteration of fronto-temporal connectivity (Fiori et al., 2016). In a subsequent study conducted on 10 children with idiopathic CAS (Fiori et al., 2021), white matter microstructural changes were evaluated after a PROMPT-type motor treatment in comparison to a language, nonspeech oral motor treatment. In both groups, language improvements correlated with changes in the left ventral corticobulbar tract. The PROMPT group also showed an increase in Fractional Anisotropy (FA) and a decrease in Mean Diffusivity (MD) in the left dorsal corticobulbar tract.

Although these results open an important path to understanding the neuro-functional basis of CAS and especially to the possible structural changes as a result of specific treatments, further studies involving a larger population are needed to confirm the findings about the neuroanatomical correlates of the disorder and to explain the complex relationship between disease and treatment in CAS, taking into account not only the specific alterations at the level of speech and language, but also a complex cognitive-linguistic profile in which different processes can interact and contribute to determining the disorder. The purpose of this thesis will be based precisely on these assumptions.

Outline of the thesis

The purpose of this thesis is to analyze the cognitive profile of children with idiopathic CAS, in particular in relation to transversal processes such as implicit learning and Executive Functions (EFs).

The first study investigated implicit learning process by using a Serial Reaction Time Task. In the original research study, we report the analysis of the EF profile in relation to connectivity alterations highlighted through the Diffusion Tensor Imaging (DTI) MRI technique. Treatment implications are also investigated through a systematic review and metanalysis on the effect of higher-order skill empowerment in specific disorders, in order to identify preferential treatment for each specific condition and the specific characteristics that allow an effective improvement of clinical symptoms.

In addition to a general introduction and discussions, the present thesis is composed of two chapters, of which the second is divided into two sub-sections:

1) **Chapter 1**: **Implicit Learning.** Implicit learning in children with Childhood Apraxia of Speech.

2) **Chapter 2***:* **Executive Functions**.

2.1 Relationship among Connectivity of the Frontal Aslant Tract, Executive Functions, and Speech and Language Impairment in Children with Childhood Apraxia of Speech.

2.2 Literature review and metanalysis. Far transfer effects of trainings on executive functions in neurodevelopmental disorders: a systematic review and metanalysis.

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Chapter 1

Implicit learning in children with Childhood Apraxia of Speech

Clara Bombonato
Claudia Casalini
Chiara Pecini
Giulia Angelucci
Stefano Vicari
Irina Podda
Paola Cipriani
Anna M. Chilosi
Deny Menghini

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Abstract

Background: Childhood Apraxia of Speech is a severe and persistent clinical subtype of Speech Sound Disorder. Given the difficulties in the acquisition, programming and control of the movements underlying speech and the slowdown in a wide range of non-linguistic skills, the difficulty in implicit learning of sequential information could play a role in the disorder, contributing to understand its etiopathological mechanisms and behavioral manifestations.

Aims: The present study was aimed at investigating implicit learning in children with Childhood Apraxia of Speech.

Methods and Procedures: Twenty-five children with Childhood Apraxia of Speech, aged between 4 and 12 years, were matched for IQ and age to a control group of 25 typically developing children. Implicit learning of participants was assessed by Serial Reaction Time Task.

Outcome and Results: Children with Childhood Apraxia of Speech did not show implicit learning, as documented by the absence of differences between reaction times in the sequenced block and the random block, usually considered as a measure of implicit learning effect.

Conclusion and Implications: Our results underline an implicit learning deficit in children with Childhood Apraxia of Speech, supporting the concept of a disorder not only confined to the speech domain, but also involving non-linguistic skills, in a composite and complex picture.

What this paper adds: This paper provides data on the presence of an implicit learning deficit in children with Childhood Apraxia of Speech, contributing to define the neuropsychological profile of the disorder, not limited to the speech and language domains. To our knowledge this is the first study that evaluated implicit learning in Childhood Apraxia of Speech through a Serial Reaction Time Task that does not require motor precision or verbal processing.

1. Introduction

Implicit memory is defined as the knowledge of a know-how which permits to acquire the acquisition of motor or cognitive skills automatically and progressively by practice, including context-dependent sequential or probabilistically structured information, without the awareness of what is being learned (Gabrieli, 1998; Eichenbaum & Cohen, 2000; Henke, 2010). This knowledge underlines aspects of implicit rule learning and is particularly important for acquiring and performing procedures that include serial, abstract, sensorimotor or cognitive sequences. These procedures can be processed automatically and rapidly after a relatively slow learning phase in which considerable repetition or practice is required (Packard & Knowlton, 2002; Lum, Ullman & Conti-Ramsden, 2013).

It has been hypothesized that, together with explicit and conscious declarative memory, the implicit and unconscious procedural memory system is involved in language and speech acquisition (Ullman, 2004; Ullman & Pierpont, 2005). In language, idiosyncratic mappings (involved in the acquisition of vocabulary and more general semantic knowledge) have been associated with declarative memory, whereas learning and the use of rule-governed aspects of grammar (syntax, morphology and phonology) have been linked with implicit and procedural memory (Ullman 2001, 2004). More specifically, it appears that the implicit memory system is involved in the learning, storage and retrieval of the statistically regular, rule-based, features of grammar and phonology (Gomez & Gerken, 1999; Ullman, 2004). According to the perspective that language acquisition is based to some extent on the computation of the statistical properties of the linguistic input (Aslin & Newport, 2008), poor implicit learning mechanisms could then explain the grammar deficits in children with Language Impairment (LI).

Since most of the skills that require procedural learning involve motor actions (Knowlton et al., 2017), procedural learning in language development might affect the acquisition of new sequential skills to produce words and sentences, including the ability to control speech movements with an appropriate degree of variability. Therefore, it can be hypothesized that implicit learning plays a role not only in the extraction of statistically regular sequences from the linguistic input, but also in the automatization of motor plans for speech output. Moreover, the procedural learning hypothesis could be of relevance for understanding not only linguistic difficulties but also deficits in automatizing voluntary motor sequences to produce and combine speech movements, which is a characteristic of Childhood Apraxia of Speech (CAS).

CAS is a motor speech disorder, whose core deficit involves the planning and programming of the spatio-temporal parameters of speech movement sequences in the absence of neuromuscular deficits (ASHA, 2007). The main feature of CAS is that the precision and consistency of speech movements are impaired due to issues with speech motor planning and programming. In particular, according to the ASHA consensus criteria, three features are characteristic of CAS: 1) inconsistent errors on consonants and vowels during repeated productions of syllables or words, 2) lengthened and disrupted co-articulatory transitions between sounds and syllables, 3) inappropriate prosody, especially in the realization of lexical or phrasal stress (ASHA, 2007). CAS may occur as isolated or associated with other disorders. It can appear as an idiopathic disorder in otherwise healthy children (Chilosi et al., 2015) but it may be also symptomatic of neurometabolic pathologies, such as galactosemia (Shriberg et al., 2011) and creatine transporter deficiency (Battini et al., 2007), or associated with syndromic conditions (Wilson et al., 2019).

To date, the underlying neural mechanisms of idiopathic CAS remain largely unknown (Liégeois et al., 2014) and, although subtle brain abnormalities have been hypothesized (Liégeois & Morgan, 2012; Fiori et al., 2016; Conti et al., 2020), the etiological factors still need to be defined. Moreover, there are only a few studies describing cognitive processes possibly underlying CAS, that showed the presence of a constellation of deficits. Some older works, which studied children with CAS together with heterogeneous groups of children with Speech Sound Disorders (SSD), found deficits in spatial and sequential memory (Dewey et al., 1988), as well as in phonological working memory (Raine et al., 1991; Hulme & Roodenrys, 1995). More recently (Shriberg et al., 2012), 40 children with CAS were tested by a non-word repetition task and difficulties at multiple levels were described: in planning and motor execution, in verbal representation, in perception and auditory coding (substitution errors of consonants within the same class), in working memory (increasing errors in the repetition of longer non-words compared to shorter ones), and in transcoding (sound addition errors).

Beside phonological working memory deficits in children with CAS, other authors also found deficits in motor skills (Iuzzini-Siegel, 2019), phonological awareness, vocabulary and rapid naming (Lewis et al., 2011), suggesting the presence of difficulties not only limited to speech and language domains.

Short-term verbal and non-verbal memory difficulties seem to persist into adulthood in individuals with a history of CAS (Kenney et al., 2006). Sequencing errors in the repetition of non-words and polysyllabic words in adults have been interpreted as a global deficit of sequential processing that influences not only speech and linguistic skills, but also further cognitive domains (Peter et al., 2013). Deficits in sensorimotor and sequential memory functions were found in a group of 17 children with CAS evaluated twice, at a 15-month interval, in three non-linguistic areas (Nijland et al., 2015): complex sensorimotor and sequential memory skills, simple sensorimotor skills and control skills such as attention and spatial memory. Children with CAS showed lower scores in all domains compared to typically developing (TD) children at both evaluations. Moreover, children with CAS showed deficits in complex sensorimotor and sequential memory skills even when compared to younger TD children, whilst in simple sensorimotor skills, attention and spatial memory children with CAS showed lower performance compared only to age-matched TD children.

Considering these previously reported studies, deficits in the acquisition and control of sequential memory skills could play a role in CAS. Nevertheless, to date only a recent study has directly investigated implicit learning in children with CAS (Iuzzini-Seigel, 2021). In this study 13 children with CAS were compared to 15 TD children and to 20 peers with SSD on a Serial Reaction Time Task (SRTT) in which motor responses were requested. Results showed that children with CAS were slower than the other two groups, needed more repetitions of the sequenced trials to gain procedural learning, but did not differ from the control groups in procedural learning.

The present study aimed at investigating implicit learning in a group of children with idiopathic CAS, looking for deficits that may contribute to the cognitive endophenotype of this disorder.

After considering that children with CAS may manifest difficulties in programming the movements underlying speech, and that their motor difficulties could extend also to non-verbal aspects, we tested implicit learning through a modified version of the SRTT (Nissen & Bullemer, 1987), in which motor precision would not influence the response. This modified version of SRTT was already employed in previous studies of our research group, documenting implicit learning deficits in children with dyslexia (Vicari et al., 2003), genetic disorders, such as Williams syndrome (Vicari, Verucci & Carlesimo, 2007), and Duchenne muscular dystrophy (Vicari et al., 2018).

We hypothesized that children with CAS may manifest a deficit in implicit learning and this deficit may interfere with the automatization of grammar patterns and of motor plans for speech output.

2. Materials and Methods

2.1 Participants

The assessment was conducted on 25 children who received a diagnosis of CAS at the Neurolinguistic and Neuropsychological Unit of IRCCS Stella Maris. The group included 3 girls and 22 boys, confirming the highest prevalence of CAS in males (ASHA, 2007). The children were aged between 4.3 and 12.8 years (mean age = 7.2 years; SD = 2.5). Identification of patients with CAS was based on a comprehensive clinical and instrumental assessment (see below), which represents the standard clinical protocol adopted by our facility for the assessment of complex neuropsychological and neurodevelopmental disorders. Eligibility criteria required Italian as the only or primary language spoken at home, age at clinical evaluation ≥4 years and the ability to complete a full neurological and speech and language assessment. Exclusion criteria were orofacial structural abnormalities, audiological deficits, epilepsy, known neurological and neurometabolic disorders, dysarthria and comorbid Attention Deficit/Hyperactivity Disorder and Developmental Coordination Disorder.

The diagnosis of CAS was carried out by a multidisciplinary team in accordance with the three ASHA criteria (2007) and with any combination of at least seven out of the twelve speech features listed in Namasivayam et al. (2015) and detectable across at least three contexts that varied in difficulty. The identification of the diagnostic features was based on formal testing and on perceptual analysis of video-recorded speech samples by two independent observers with expertise in developmental motor speech disorders.

Twenty-five TD children (4 girls and 21 boys) from local schools (last year of kindergarten and primary school), without evidence of intellectual, neurological and psychiatric disorders, were selected as the control group. Moreover, for none of these children parents and teachers expressed concerns regarding their speech and language development. The two groups did not differ for chronological age (CAS: M = 7.2, SD =

2.5; Controls: M = 7.1, SD = 1.8; t(48)=0.3; p=0.76; eta-squared=0.002), gender distribution and non-verbal intelligence (t(48)=-0.36; p=0.72; eta-squared=0.003).

G-power was used for calculating the sample size. The power was estimated at 95% with a minimum of 25 participants in each group with a two-sided significance level of 0.05 to be achieved.

Written parental informed consent and child assent for the participation in this study and data publication were obtained in all cases. The study was approved by the Ethics Committee of the IRCCS Fondazione Stella Maris (Number 13/2013) and by the Regional Pediatric Ethics Committee (CEP) 19-03-2018/RF2016-02361560.

2.2 Procedures and measures

2.2.1 Clinical assessment

To rule out the presence of co-occurring complex neurodevelopmental disorders all cases underwent standard neurological and psychiatric examination by a specialized team. DSM-5 clinical diagnostic criteria and specific assessment procedures were applied.

Cognitive non-verbal abilities of participants with CAS were assessed by using Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III; Wechsler, 2008), or Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV; Wechsler, 2012), depending on the child's age. In typically developing children, cognitive non-verbal abilities were assessed by using the Coloured Progressive Matrices (CPM; Raven, 2008).

2.2.2 Speech and language assessment

Speech and language profiles were analyzed by two independent observers through formal testing and evaluation of spontaneous productions (Table 1). The assessment protocol included:

a) Parental report on the child's early vocal behavior, speech, language and early motor developmental milestones, as well as familial antecedents for oral/written language disorders. Family history was considered significant if one or more members of the nuclear family had a history of any type of speech-language and/or learning disorders.

b) Speech tasks: assessment of phonetic inventory, speech inaccuracy, inconsistency and syllable omissions, diadochokinetic rate (DDK). Since for these measures there were no standard scores from norm-referenced tests, data from 40 TD Italian children with a mean age of 4.7 years (SD 0.47) were used for reference. Verbal motor skills were evaluated through the administration of the Verbal Motor Production Assessment for Children (VMPAC, Hayden and Square, 1999) and speech intelligibility was assessed through the "Intelligibility in Context Scale" (McLeod et al., 2012, Italian version). To assess receptive and expressive language abilities, vocabulary and grammar tests were administered (Table 1).

Table 1. *Speech and language assessment procedures.*

	Procedure		**Reference data**	**Scoring**
	Parental report	Family history, child's pre-, peri- and post-natal clinically significant events, early vocal behavior and language milestones acquisition. Intelligibility of speech to familiar and unfamiliar adults (modified version of the questionnaire reported by Chilosi et al., 2009).		
Speech Assessment	*Phonetic inventory*	Repetition of 21 syllables containing all the Italian consonantal sounds.	40 TD children, mean age=4.7 yrs (SD= 0.47 yrs)	Mean number of phonemes: 19.2 (SD=0.9)
	Word Inaccuracy	46 probe words picture naming test (Chilosi & Podda, in preparation);	40 TD children, mean age=4.7 yrs (SD= 0.47 yrs)	Mean percentage of inaccurate productions: 8.8% (SD=10.7).
	Inconsistent errors on consonants and vowels	Same task as for inaccuracy. Scoring based on the percentage of variable phonetic errors on two repeated productions of the same word.	40 TD children mean age=4.7 (SD=0.47 yrs)	Mean percentage of inconsistent errors: 0.4% (SD= 1.3)

	Syllable omissions	Same task as for inaccuracy. Scoring based on the percentage of omitted syllables in words.	40 TD children mean age=4.7 (SD=0.47 yrs)	Mean percentage of omitted syllables: 0%
	DDK rate (maximum performance task)	Fast repetition of the trisyllabic non-word sequence /pataka/, scored as the number of repeated /pataka/ in 20 sec.	40 TD children (mean age=4.7 yrs (SD=0.9 yrs)	Mean number of repetitions: 23.18 (SD=4.5);
	Intelligibility	Intelligibility in Context Scale (McLeod et al., 2012, Italian version). Parental report on the child's intelligibility in different communicative contexts.		Qualitative rating scale ranging from 5 to 1 (5=always, 4= usually, 3= sometimes, 2= rarely, 1= never intelligible)
Language Assessment	*Expressive grammar*	Grid for the Analysis of Spontaneous Speech (GASS) Chilosi et al (2013)	Longitudinal sample: 6 TD children video recorded twice a month from 19 to 36 months (Cipriani et al., 1993) Cross-sectional sample: 50 t.d. children aged 26-44 mths (Chilosi et al., 2013)	12-18 months: Preverbal/Holophrastic level. 19–25 months: Presyntactic level, emergence of two- and three-word combinations. 20–26 months: Telegraphic level, emergence of morphosyntactically incomplete subject – verb-object structures 24–31 months: Grammatical stage 1, full control of morphology in simple sentences

				28–36 months: Grammatical stage 2, production of well-formed both simple and complex sentences
	Receptive grammar	TCGB, Test di Comprensione Grammaticale per Bambini (Grammar comprehension test for children) (Chilosi & Cipriani, 2005) TROG-2 Test for Reception of Grammar– Version 2. Dorothy VM Bishop (Italian Version: Suraniti, Ferri & Neri, 2009)	280 ss; age from 3.6 to 8 yrs 1276 ss (51% F, 49% M); age from 4 to 87 yrs	Standard scores Standard scores
	Receptive vocabulary	Test Fonolessicale-TFL (Vicari et al., 2007) and/or Peabody Picture Vocabulary Test (PPVT-R – Dunn & Dunn, 1997; Italian version – Stella et al., 2000), depending on the child's age and on the severity of the disorder.	TFL: 240 Italian children from 2.6 to 6 yrs PPVT: 2400 Italian children from 3.9 to 11.6 yrs	Percentile scores Standard scores
	Expressive vocabulary	Test Fonolessicale-TFL (Vicari et al., 2007) and/or One-Word Picture Vocabulary Test (Brizzolara, 1989), depending on the	TFL: 268 Italian children from 3 to 6 yrs One –Word Picture Vocabulary test: 154	Percentile scores Separate z-scores for high (52 items) and low (52 items) frequency words.

		child's age and on the severity of the disorder.	children from 4.6 to 10.8 yrs	

Abbreviations: TD: Typically Developing; DDK: Diadochokinetic

2.2.3 Implicit sequence learning evaluation

In the literature, several tasks have been proposed to study implicit learning, ranging from artificial grammar learning (Jiménez et al., 2020) to mirror drawing (Vicari et al., 2005), contextual cueing task (Chen et al., 2019) and motor SSRT (Menghini et al., 2006). SRTT is a button-press task commonly used to measure implicit visuo-motor sequence learning (Nissen & Bullemer, 1987; Howard &Howard, 1997). This task fits the criterion of implicit learning, in that most of the participants typically remain unaware of the underlying sequence, yet still show learning of it through their performance on the task (Willingham et al., 1989). As a rule, reaction times (RTs) decrease more quickly in response to structured sequences than to a random sequence, therefore suggesting that participants acquire implicit knowledge about the sequence structure (Kirsch & Hoffmann, 2012).

In the present study, we adopted a simplified version of the SRTT (Nissen & Bullemer, 1987) in which events are ordered according to a temporal (but not a spatial) sequence and that does not require precise motor responses (pressing a single key instead of 4 different keys). Even if in our participants comorbid Developmental Coordination Disorder was ruled out, children with CAS could still manifest subtle motor planning and programming difficulties, potentially interfering with the task.

Each participant sat in front of a portable computer screen at a distance of about 30 cm. A series of single colored circles appeared centrally on the white screen. Stimuli were presented in six blocks of 75 single colored circles (stimulus) with a diameter of 2.8 cm. The time intervals between two consecutive circle appearances, and the onset duration of each single colored stimulus, varied randomly from 0.5 to 2 sec. In the first block (R1) stimuli were randomly presented, from the 2nd to the 5th block (S2, S3, S4, S5) a five-element sequence (RED, BLUE, GREEN, RED, BLUE) was repeated 15 times in each block; in the last block (R2), stimuli were randomly presented. Participants had to press the spacebar as quickly as possible only when a green circle appeared on the screen, and they were not informed about the repetition of the five-element sequence. The software automatically recorded the RTs for each stimulus.

At the end of the test, in order to assess whether the child gained awareness of the repeated sequence presented in blocks S2-S5, the following questions were asked: “Did you notice if the colors appeared in a specific order?”; “Could you tell me or try to guess the sequence?”. The only child who demonstrated explicit learning of the sequence, reporting the correct order in which the stimuli were presented in the blocks of the repeated sequences, was excluded from the analysis.

All procedures were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

2.3.4 Statistical analyses

The median RTs obtained by the two groups in the 6 blocks of the SRTT were compared by using a 2 x 6 repeated measured ANOVA with Group (CAS vs Controls) as between factor and Block (from R1 to R2) as within factor. Post-hoc analyses were conducted by means of the Tukey’s HSD (Honestly Significant Difference) test. The effect size of the 2 x 6 repeated measured ANOVA was calculated using the partial eta-squared coefficient. The effect size of the post-hoc analyses was calculated using Cohen’s *d*.

Non parametric correlation analyses (Spearman’s rho) were conducted between the implicit learning score and each speech and language measure.

Statistical analyses were performed by using STATISTICA 13.0 software (Statsoft, Tulsa, OK, USA).

3. Results

3.1 Clinical characteristics of children with CAS

3.1.1 Cognitive abilities

Children with CAS had a non-verbal intelligence index (PIQ or PRI) at the Wechsler Intelligence Scale (WPPSI-III or WISC-IV) within the normal limits (M = 104.04, SD = 15.54). The control group had a non-verbal IQ at the CPM within the normal limits (M = 105.6, SD = 10.03). No statistically significant differences were found between the two groups on non-verbal intelligence (t(48)=-0.36; p=0.72; eta-squared=0.003).

3.1.2 Speech profiles in children with CAS

The phonetic inventories of children with CAS were markedly reduced with a mean number of consonants of 13.2 (SD = 4.9), out of 21 consonantal sounds tested. The mean percentage of inaccurate speech productions in a single word-naming task was 59.76% with 24% of inconsistent errors in the same task. More than 60% of the children presented syllable omissions on polysyllabic words. On the McLeod et al. (2012) intelligibility scale, modified for Italian, the average score was 2.86 (SD = 1.35), thus showing a severely altered intelligibility as perceived by the communication partners in spontaneous production contexts. Concerning DDK rate, only twenty children were able to repeat the three-syllable non-word sequence /pataka/ over 20 seconds. Their mean rate was significantly slower (number of repetitions: M = 13.3, SD = 4.61) compared to the reference data (number of repetitions: M = 25.4, SD = 2.3) obtained from younger TD children.

As shown in Table 2, the mean z-scores of the Global Motor Control on the VMPAC were within the normal limits, thus excluding the presence of neuromotor deficits. Conversely, z-scores of the other areas of the VMPAC were 2 SD below the mean, a speech motor pattern consistent with the speech profile of CAS.

Table 2. *Mean z-scores of the group of children with CAS on the Verbal Motor Production Assessment for Children (VMPAC)*

VMPAC	**M (SD)**
Global Motor Control	-0.14 (0.74)
Focal Oromotor Control	-8.53 (4.71)
Sequencing	-2.61 (1.84)
Connected Speech and Language Control	-7.59 (3.51)
Speech Characteristics	-4.94 (5.01)

At the time of the assessment for implicit learning, the speech signs of CAS more frequently (80% or above) detectable across the whole sample were: inconsistent productions, difficulties in transitioning from one speech movement to another, errors with vowels, reduced consonantal repertoire, atypical phonological processes, syllable omissions, increasing difficulties in longer units, dysprosody, slow and/or scanned speech rate (Namasivayam et al., 2015).

3.1.3 *Language profiles in children with CAS*

Concerning receptive grammar, 72% of the children with CAS had normal (> 26° percentile) or borderline (between 25° and 6° percentile) scores, whereas 28% of the children showed a deficit (scores <5° percentile). Receptive lexicon was normal or borderline in 76% of children, whereas 24% of the children obtained deficit scores. At expressive grammar evaluation, 88% of the children scored below the 5° percentile. Expressive lexicon was deficient in 40% of the children. These results indicated that most of the children showed concomitant LI, mainly involving expressive grammar.

For a complete description of the measures of speech and language mentioned above see Table 1.

3.1.4 *Implicit sequence learning*

Violin plot of the distribution values of the median RTs obtained by the two groups in the 6 blocks of the SRTT are shown in Figure 1. The presence of implicit learning was verified by means of a 2 x 6 repeated measured ANOVA with Group as between factor and Block (from S1 to R2) as within factor. The Group effect was not statistically significant, (F(1,48)<0.001, p=.99, partial eta-squared <.001), documenting that the two groups did not differ in the median RTs. The Block effect was significant (F(5,240)=5.02, p=0.0002, partial eta-squared=0.09) with higher median RTs in R2 (M = 642.98 msec, SD = 142.69) than in S4 (M = 583.6 msec, SD = 132.16; Tukey's HSD test, p=0.021; Cohen's *d* = 4.25) and in S5 (M = 570.98 msec, SD = 143.61; Tukey's HSD test, p=0.002; Cohen's *d* = 0.5).

Also, the interaction Group x Block was statistically significant (F(5,240)=5.331, p=0.0001, partial eta-squared=0.1). Indeed, while in the group with CAS the response pattern was not modulated by the block presentation order, in the control group the performance was modulated throughout the blocks. The post-hoc analysis (Tukey's HSD test) of the TD group performance revealed a statistically significant increment (p=0.000021; Cohen's *d* = 0.86) in the RTs (from 519.88 msec, SD = 155.01 to 664.92 msec, SD = 180.23) between S5 and R2. This change between the last two blocks is usually considered the most reliable measure of sequence learning (Vicari, Bellucci & Carlesimo, 2001; Vicari et al., 2003; 2005; 2018) and it confirmed the presence of implicit learning in the control group. Conversely, in the group with CAS the RTs between S5 and R2 remained almost unvaried (p=1; Cohen's *d* = 0.009), passing from 622.08 msec (SD = 131.25) to 621.04 msec (SD = 90.79) (Figure 2).

Figure 1. *Average of the median RTs obtained by the two groups in the 6 blocks of the SRTT. Error bars refers to Standard Deviation.*

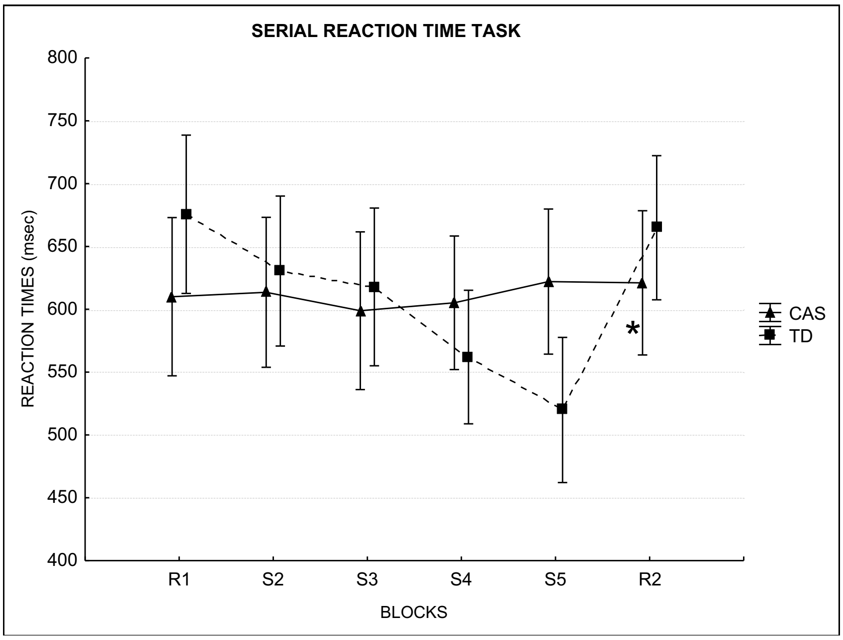
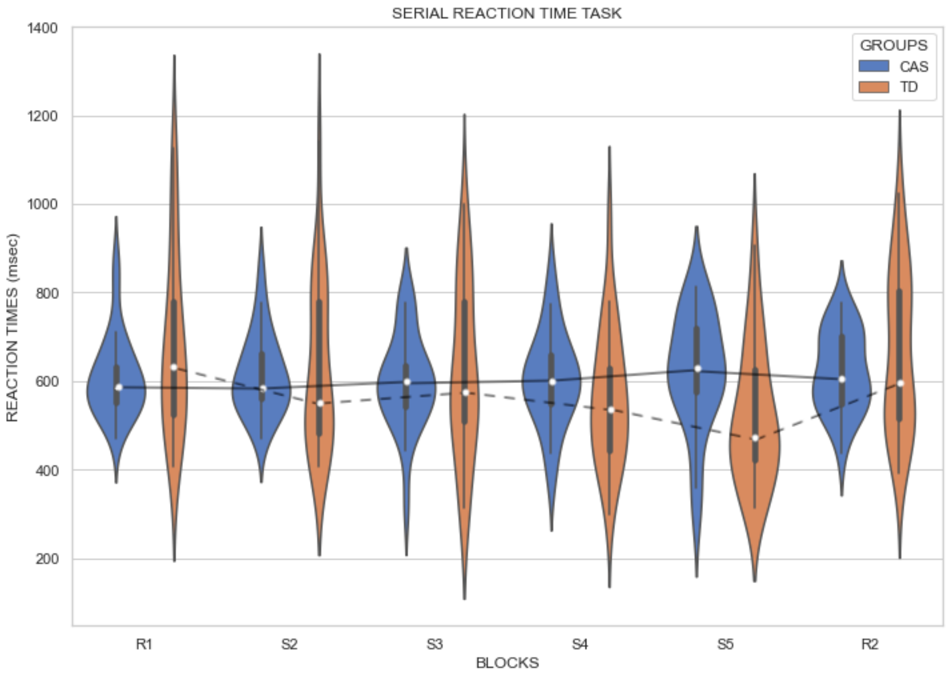


Figure 2 *Violin-plot of the distribution values of the median RTs obtained by the two groups in the 6 blocks of the SRTT.*



3.1.5 Relations between speech, language and implicit learning

Correlation analyses (Spearman's rho) were conducted between implicit learning score (reaction times change between S5 and R2), speech measures (phonetic inventory, inaccuracy and inconsistency, syllable omissions and DDK rate), the VMPAC speech motor measures and language measures (expressive and receptive vocabulary and grammar).

No significant correlations between the implicit learning score and each language, speech and VMPAC measures were found.

4. Discussion

Our study investigated the implicit learning of a group of children with CAS and TD controls by using a SRTT version in which no precise motor responses were requested.

This modified version of SRTT was already employed in previous studies, allowing us to test implicit learning in heterogeneous populations at different developmental stages, including children with complex neurodevelopmental disorders, as intellectual disability (Vicari et al., 2007) and learning difficulties (Vicari et al., 2003) or with motor deficits (Vicari et al., 2018).

The main reason for studying implicit memory in CAS was the need to investigate specific neuropsychological processes potentially related to the clinical manifestations of this disorder, and, in particular, the possible sequential processing impairment affecting the development of speech and linguistic skills (Lewis et al., 2011). Whilst a relatively wide body of literature is dedicated to the study of the speech characteristics of children with CAS, only recently their neuropsychological profile has started to gain attention from researchers. The presence of a general slowdown in a wide range of non-linguistic skills has been documented in children with CAS (Nijland et al., 2015). However, extra-linguistic deficits, involving procedural control and a more general impairment in the implicit learning of sequences, may play a role in the symptom complex of CAS. Accordingly, a recent case-control study (Iuzzini-Seigel, 2021) documented that children with CAS attained implicit learning but were slower and needed a higher exposure to repeated stimuli compared to TD children and peers with SSD.

The present study showed that children with CAS failed to learn a visuo-motor sequence, supporting the hypothesis of an implicit learning deficit in this population. As a matter of fact, the comparison between RTs of the last sequenced block (S5) and the random block (R2), usually taken as a measure of implicit learning effect, was significantly different between children with CAS and TD children. Whilst TD children significantly increased their RTs passing from S5 to R2, children with CAS did not significantly increase their RTs. Moreover, at the end of SRTT no participants included in the analysis reported the order in which the stimuli were presented in the blocks of repeated sequences, thus ruling out the contribution of explicit learning in the task execution. It is important to notice that the deficit of implicit learning of our children with CAS could not be linked to general motor difficulties, since RTs across the ordered blocks (S1 to S5) did not differ from those of controls.

Our results are only partially in line with those reported in the study by Iuzzini-Seigel (2021)~~,~~ as we found that our children with CAS did not differ from TD children in terms of speed, but they showed an atypical pattern of response. This may be possibly due to the administration of a different implicit learning task, which did not require either visual scanning or precise motor actions in order to progress across the blocks, as the stimulus was always presented in the middle of the screen. Although the present study supports the hypothesis that a deficit in implicit learning might mediate linguistic, motor and cognitive impairment in CAS, the question of the possible interaction between implicit learning deficit and the speech and language impairment remains open. On one hand, problems in processing and storing verbal information may depend on difficulties in phonological encoding, in speech motor planning and programming, as well as in altered explicit rehearsal strategies through articulatory processes. On the other hand, an implicit learning deficit in acquiring sensory–motor sequences could interfere with the processing of the sequential order of elements and, ultimately, with the acquisition of language rules. However, it is not clear if implicit learning deficits in CAS should be interpreted as a secondary effect of supramodal sequence processing alterations, rather than the consequence of speech motor deficits. Previous studies on families with a history of CAS (Peter et al., 2013; Button et al., 2013) have attributed language impairment to a secondary effect of a sequencing deficit. Peter et al. (2013), in particular, studied a multigenerational family with CAS, in which affected members showed a lower performance on tasks involving high loads of sequential processing than unaffected ones. In particular, the deficits shown by individuals with CAS were not only expressed in motor tasks, but also in working memory, and in long-term encoding, storage and maintenance. Moreover, Button et al. (2013) pointed out that the sequential processing deficit affects also performances in other modalities, such as written language.

In the present study statistical analysis did not show any significant correlation between the implicit learning deficit and the speech and language measures in our group of children with CAS. However, we cannot exclude that the implicit learning deficit, demonstrated by our participants, might affect their speech and language performances. A possible interpretation for the lack of statistical correlations might be the small sample size and the little variability of the speech and language scores. Furthermore, the speech and language assessment tasks may not capture the automatization processes, which are at the core of the implicit learning paradigm. Probably the study of the relationships between implicit learning and speech and language would benefit from the use of experimental speech and/or language tasks, which primarily involve the learning processes.

To clarify the nature of the implicit learning deficit in CAS, it would be of utmost importance to develop future research which compare different implicit learning tasks and stimulus types. Moreover, children with CAS with more heterogeneous speech and language characteristics and degree of severity should be included in further studies. One limitation of the present study is that the sample of participants is composed of children spanning a broad age range (5-12 years). Future investigations aiming to delineate the cognitive and linguistic profile of children with CAS should consider larger sample sizes and narrower age bands.

Since for these measures there were no standard scores from norm-referenced tests, data from 40 typically developing (TD) Italian children with a mean age of 4.7 years (SD 0.47) were used for reference. Despite this approach being a limitation of the present study, the results still still enabled us to identify clear speech deficits in children with CAS, even when compared to younger TD children.

Finally, longitudinal studies could allow us to better understand the relationship between the central disorder of motor planning and programming in children with CAS, language, and implicit learning deficits.

5. Conclusion

In conclusion, our study supports the hypothesis that speech and language deficits in children with CAS could stem from the alteration of shared mechanisms, involving not only sequential processing, as suggested by previous studies (Shriberg et al., 2012; Peter et al., 2013; Button et al., 2013), but also implicit learning, a fundamental process for the consolidation and automatization of patterned behaviors. The present study may contribute to the concept of CAS as a disorder not confined to the speech domain, but involving non-linguistic skills, in a composite and complex picture. Therefore, a comprehensive assessment of children with CAS becomes mandatory in order to provide a more in-depth characterization of the disorder and the most appropriate therapy interventions. We believe that present findings can promote intervention programs that consider the complex symptomatology of CAS, targeting motor speech and linguistic deficits together with central control processes with appropriate intensity, and providing dispensing and compensatory tools.

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Chapter 2

2.1

Relationship among Connectivity of the Frontal Aslant Tract, Executive Functions, and Speech and Language Impairment in Children with Childhood Apraxia of Speech

Clara Bombonato
Emilio Cipriano
Claudia Casalini
Chiara Pecini
Paola Cipriani
Irina Podda
Michela Tosetti
Laura Biagi
Paolo Bosco
Anna Maria Chilosi

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Abstract

Childhood apraxia of speech (CAS) is a subtype of motor speech disorder usually co-occurring with language impairment. A supramodal processing difficulty, involving executive functions (EFs), might contribute to the cognitive endophenotypes and behavioral manifestations. The present study aimed to profile the EFs in CAS, investigating the relationship between EFs, speech and language severity, and the connectivity of the frontal aslant tract (FAT), a white matter tract involved in both speech and EFs. A total of 30 preschool children with CAS underwent speech, language, and EF assessments and brain MRIs. Their FAT connectivity metrics were compared to those of 30 children without other neurodevelopmental disorders (NoNDs), who also underwent brain MRIs. Alterations in some basic EF components were found. Inhibition and working memory correlated with speech and language severity. Compared to NoND children, a weak, significant reduction in fractional anisotropy (FA) in the left presupplementary motor area (preSMA) FAT component was found. Only speech severity correlated and predicted FA values along with the FAT in both of its components, and visual-spatial working memory moderated the relationship between speech severity and FA in the left SMA. Our study supports the conceptualization of a composite and complex picture of CAS, not limited to the speech core deficit, but also involving high-order cognitive skills.

1. Introduction

Childhood apraxia of speech (CAS) is a subtype of developmental motor speech disorder in which the precision and consistency of movements underlying speech are impaired in the absence of neuromuscular deficits, as currently defined by the American Speech–Language–Hearing Association(Hammer et al., 2007). It is reported that 2.4% of children with speech sound disorders may be diagnosed with CAS, with a higher prevalence in males (Hammer et al., 2007; Shriberg et al., 2019). The CAS core deficit involves the planning and/or programming of the spatiotemporal parameters of movement sequences(Hammer et al., 2007). According to the ASHA consensus criteria, three features are characteristic of CAS: (a) inconsistent errors on consonants and vowels during repeated productions of syllables or words, (b) lengthened and disrupted co-articulatory transitions between sounds and syllables, and (c) inappropriate prosody, especially in the realization of lexical or phrasal stress. These symptoms, together with a reduced phonetic inventory, multiple speech sound errors, and disfluency result in an effortful, unintelligible speech that has a negative impact on the children's social communication and peer interactions. Children with CAS display altered speech timing and sequencing skills and show particular difficulties in dynamic transitions between articulatory postures and in combining smaller units of movement into larger ones. Difficulties in early oromotor and phono-articulatory aspects of speech acquisition in CAS may stem from weaker systematic mappings between articulatory gestures and their auditory effects (Maassen et al., 2010). Along with its isolated presentation, CAS usually co-occurs with language impairment (LI) (Chilosi et al., 2015, 2022; Lewis et al., 2004), particularly in the expressive domain (grammar and lexicon).

1.1 Executive Functions

In addition to the motor speech core deficit, some studies have shown the presence of other areas of cognitive difficulty in children with CAS. Shriberg and colleagues suggested that CAS is a multilevel disorder in which both planning/programming (transcoding) and auditory-perceptual (encoding) deficits are involved, together with memory processes (Shriberg et al., 2012). Moreover, the difficulty in working memory has been described on several levels (auditory coding, maintenance, and transcoding) (Lewis et al., 2011; Shriberg et al., 2012) and seems to persist into adulthood (Kenney et al., 2006). A constellation of other functional deficits (phonological awareness and rapid naming) seems to characterize these children, together with learning difficulties at school-age, especially if the disorder is persistent and associated with language impairment (Lewis et al., 2000, 2004, 2006, 2011; S. D. Smith et al., 2005). Moreover, difficulties in nonverbal sequential functioning have been described (Bombonato et al., 2022; Iuzzini-Seigel, 2021; Nijland et al., 2015), highlighting the presence of cognitive endophenotypes that support a broader conceptualization of the disorder.

Executive functions (EFs) have also been called into question in association with developmental language impairment (Bishop & Norbury, 2005; Duinmeijer et al., 2012; Henry et al., 2012; Marton, 2008; Montgomery et al., 2009). Early acquisition of good EFs represents a protective factor for the development and adaptation of human beings (Diamond, 2013), given that EFs often have a greater influence than IQ and socioeconomic status in predicting quality of life (Diamond & Ling, 2016). There is a debate about the nature of executive functions. Some cognitive models conceptualize EFs as a unitary construct (A. Baddeley, 2012; Kane & Engle, 2002), but the idea that EFs can be fractionated into different—although interrelated—functions is supported by most accepted developmental cognitive models (Diamond, 2013; Diamond & Ling, 2016; Friedman & Miyake, 2017; Miyake et al., 2000), claiming the presence of three core components—inhibition, updating working memory, and cognitive flexibility—which share a common purpose: the recruitment of attention and control over behavior in order to meet an adaptive goal. “Inhibition” refers to the deliberate control of prepotent responses and allows one to both resist temptations and impulsive actions (response inhibition) and to maintain focused attention by suppressing nonrelevant information (interference control). A lot of cognitive, behavioral, and emotional processes, such as abstract reasoning and self-regulation in affective and emotional contexts, require inhibitory control, which allows for more appropriate behaviors oriented to internal or external goals (Zelazo et al., 2005; Zelazo & Müller, 2002). “Updating working memory” refers to the ability to actively and dynamically code, maintain, monitor, update, and manipulate incoming verbal or visual-spatial information (A. Baddeley, 2003; A. D. Baddeley & Hitch, 1994; E. E. Smith & Jonides, 1999). Cognitive flexibility allows one to shift between mental sets and involves the ability to engage and disengage from different tasks, rules, or mental contents. It supports creative thinking and the capacity to solve problems in different ways or to see things from different perspectives. EFs develop from preschool-age to childhood and into adulthood (Hughes et al., 2009; Lehto et al., 2003; Somerville & Casey, 2010), following the maturation of prefrontal circuitries and their connections (Gilbert & Burgess, 2008).

1.2. Neuroanatomical Correlates of CAS

The frontal aslant tract is a brain white matter tract connecting the superior frontal gyrus (SFG), specifically the presupplementary motor area (preSMA), the supplementary motor area (SMA), and the lateral SFG to the pars opercularis and pars triangularis of the inferior frontal gyrus (IFG) and the anterior insula (La Corte et al., 2021). Over the last few years, research on the functional role of the FAT on speech and language processes has gained attention due to its well-known connections with "Broca's area" (Tremblay & Dick, 2016); with the preSMA and SMA regions, which have been associated with aphasia of the SMA (Ardila & Lopez, 1984); and with impaired speech production (Tremblay & Gracco, 2009). In vivo FAT reconstruction is possible thanks to diffusion weighting imaging (DWI). Recent research studies have investigated the functional role of the FAT, reporting an involvement of this tract's fibers with speech and language function in the left hemisphere, and an involvement of the right FAT in support of EFs (Dick et al., 2019). Neuroimaging studies have demonstrated that regions connected through the FAT play a key role in expressive language and motor speech. In fact, the left IFG has been associated with controlled lexical and phonological selection and retrieval (Dick et al., 2014; Katzev et al., 2013), and a lesion in this area seems to produce nonfluent aphasia symptoms (Pedersen et al., 1995). Studies on the mapping of the left IFG in healthy and in clinical adults demonstrated the role of this cortical area in language and motor speech processing and in phonatory control (Deletis et al., 2014; Rogić et al., 2014). Regions of the SMA and preSMA have been associated with high-order selection and execution in both speech and nonspeech domains (Tremblay & Gracco, 2010; Tremblay & Small, 2011), and a lesion in these areas can lead to motor and speech deficits, especially for volitional movements and speech (Bannur & Rajshekhar, 2000; Chivukula et al., 2018). The FAT is also associated with verbal fluency in persistent developmental stuttering (Kemerdere et al., 2016; Neef et al., 2016, 2018) and in typical development (Alario et al., 2006; Smirni et al., 2017), supporting its function in establishing preferred responses in the language (Dick et al., 2019) as well as the speech domains (Mandelli et al., 2014). In a case report using intraoperative electrical stimulation combined with diffusion tensor imaging fiber tracking, the stimulation of the FAT induced speech arrest, followed by its recovery when the stimulation was ended (Vassal et al., 2014). In a larger retrospective study, 17 adult patients who underwent awake craniotomy for left frontal lobe glioma showed a wide array of language and motor speech alterations, including speech arrest, stuttering, and vocalizations when the posterior part of the fronto-striatal and the FAT subsystem were stimulated (Corrivetti et al., 2019).The right IFG has also been identified as a region activated in executive function behaviors, especially in inhibitory control (Aron, 2007), with an impairment of the same function associated with lesions in this area (Aron et al., 2003, 2004). Motor stopping behaviors are sustained by a direct pathway from the right IFG and the subthalamic nucleus (Favre et al., 2013; Jahanshahi, 2013; Obeso et al., 2014; van Wouwe et al., 2017). However, the right preSMA and SMA also seem to play a role in inhibitory control in a more extended network, particularly in suppressing behaviors that conflict with a goal (Boehler et al., 2010; Wessel & Aron, 2017). The right SMA has also been proven to be implicated in working memory, particularly in the active mental manipulation of information (Cañas et al., 2018), as demonstrated by working memory deficits in patients with SMA lesions when compared with healthy controls.

Alterations in some areas belonging to the network connected by the FAT were found in CAS (Fiori et al., 2016). In particular, three intra- and interhemispheric sub-networks showed a reduction of fractional anisotropy (FA) in the CAS group, as compared to controls. Subnetwork 1 concerned the temporal regions of the left hemisphere, the role of which had already been hypothesized in CAS (Ashtari et al., 2004; Guenther & Hickok, 2015; Kadis et al., 2014; Preston et al., 2014; Tkach et al., 2011). Subnetwork 2 included intra- and interhemispheric connections, involving the left precuneus, the right supplementary motor area, the left cuneus, and the right cerebellum. The results are in agreement with previous studies that hypothesized the role of these regions in conceptual planning during lexical search (Grande et al., 2012) and in high-level integrated functions (Cavanna & Trimble, 2006). Subnetwork 3 included intrahemispheric connections among the right angular gyrus, the superior temporal gyrus, and the inferior occipital gyrus, pointing to bilateral language involvement in CAS (Liégeois & Morgan, 2012).

1.3 Aim of the Study

The present study aimed to investigate the EF profiles of a group of children with CAS with comorbid LI, hypothesizing that the presence of deficits may contribute to defining the cognitive endophenotype of this disorder. The study starts from the consideration of the involvement of the FAT as a key pathway for two important functional circuits: one related to motor speech control, and the other to executive functions. The two circuits are typically examined separately although motor speech and EFs possibly rely on overlapping mechanisms.

Moreover, given the presence of alterations of areas belonging to this circuit in CAS, a second aim of this study was to relate motor speech and the EF profile with structural connectivity information using diffusion MRI. We hypothesized that children with CAS may show impaired connectivity of the FAT, with that being more relevant in those with an alteration in the EF components.

2. Materials and Methods

2.1. Participants

A total of 30 children with CAS and co-occurrent LI, diagnosed at the Neurolinguistic and Neuropsychological Unit of IRCCS Stella Maris, were recruited. The group underwent a full speech, language, and EF assessment, as well as MRI examination.

The group of children with CAS included 6 girls and 24 boys. Children with CAS were aged between 4.3 years and 6.11 years (mean age = 6.6 years; SD = 0.7 years. All children with CAS were right-hand dominant except one child. The identification of patients with CAS was based on a comprehensive clinical and instrumental assessment (Bombonato et al., 2022), which is the standard clinical protocol for the assessment of complex neuropsychological and neurodevelopmental disorders adopted at the facility in which the study was conducted. Eligibility criteria required Italian as the only, or primary, language spoken at home, age at clinical evaluation ≥4 years, and the ability to complete full neurological and speech and language assessments. Exclusion criteria were orofacial structural abnormalities, audiological deficits, epilepsy, known neurological and neurometabolic disorders, dysarthria, and comorbid attention deficit/hyperactivity disorder, autism spectrum disorder, and/or developmental coordination disorder.

The diagnosis of CAS was carried out by a multidisciplinary team in accordance with the three aforementioned ASHA criteria (2007) and with any combination of at least 5 of the 10 points on Strand's checklist (Shriberg et al., 2011), detectable across at least three contexts that varied in difficulty. The identification of the diagnostic features was based on formal testing and on the perceptual analysis of videorecorded speech samples by two independent observers with expertise in developmental motor speech disorders. A group of 30 children with no speech and language concerns and no other neurodevelopmental disorders (NoND (mean age = 6.5 years; SD = 2.6 years), who had undergone a brain MRI for various reasons (including headache, seizures during fever, strabismus, cataract, paroxysmal vertigo, and diplopia) was also recruited in order to compare FAT connectivity measures between the two groups. The brain MRIs of the NoND group, as well as their neurological examination, were unremarkable.

Written parental informed consent and child assent for participation in the study and data publication were obtained in all cases. The study was approved by the Regional Pediatric Ethics Committee (CEP) 19-03-2018/RF2016-02361560.

2.2. Procedures and Measures

2.2.1. Clinical Assessment

To rule out the presence of co-occurring complex neurodevelopmental disorders, all cases underwent standard neurological and psychiatric examination by a specialized team. DSM-5 clinical diagnostic criteria and specific assessment procedures were applied.

The cognitive nonverbal abilities of participants with CAS (mean = 103.23; SD = 12.89) were assessed by using the Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III (Wechsler, 2022)).

2.2.2. Speech and Language Assessment

Speech and language profiles were analyzed by two independent observers through formal testing and evaluation of spontaneous productions. The assessment protocol included:

a) Parental report on the child's early vocal behavior, speech, language, and early motor developmental milestones, as well as familial antecedents for oral/written language disorders. Family history was considered significant if one or more members of the nuclear family had a history of any type of speech-language and/or learning disorders.

b) Speech tasks: assessment of phonetic inventory, speech inaccuracy, inconsistency, syllable omissions, and diadochokinetic rate (DDK). Since there are no standard scores from norm-referenced tests for these measures, data from 40 TD Italian children with a mean age of 4.7 years (SD 0.47 years) were used as a reference. Speech intelligibility was assessed through the Intelligibility in Context Scale (McLeod et al., 2012), Italian version).

c) Language assessment: standardized language tests for receptive and expressive vocabulary and grammar.

Detailed descriptions of the speech and language assessments are reported in a recent work (Bombonato et al., 2022).

In order to estimate the overall level of speech and language proficiency, two composite severity scores were calculated based on five speech and four language measures, provided by a speech therapist. Given that, depending on the children's ages and degrees of impairment, different standardized language tests were administered, to calculate the language composite severity score, we assigned for each measure: 0 when normal (>25th percentile or z-scores > -0.67), 0.5 when delayed (percentile scores between 6th and 25th or z-scores between -1.56 and -0.67), and 1 when deficient (≤5th percentile or z scores <-1.65). The maximum language composite severity score was 4, and 5 was the maximum speech severity score. On the basis of the speech and language severity scores, the sample was divided into two subgroups: 0–2.5: low language severity; 3–4: high language severity (20 children and 10 children, respectively); 0-3: low speech severity; 3.5–5: high speech severity (12 children and 18 children, respectively).

2.2.3. Executive Function Assessment

In order to obtain an overall evaluation aimed at the definition of a specific EF profile in children with CAS, an ad hoc evaluation protocol to investigate the different EF components was created, selecting tasks from standardized batteries for the Italian population, and taking into account the age range of the sample. The protocol consisted of the following tasks:

- Draw a Circle (FE-PS 2–6; (Usai et al., 2017)). The child is asked to inhibit the continuous motor response: the task requires tracing a circle with a finger on a white sheet of paper, adapting the execution speed to the examiner's request.

- Day and Night Stroop (FE-PS 2–6; (Usai et al., 2017)). The test involves the inhibition of the verbal response by suppressing a preponderant response prompted by a stimulus. The inhibition concerns the ability to block an automatic response and to manage the conflict between two response operations associated with the same stimulus. Both time and accuracy are measured.

- Flanker Task (FE-PS 2–6; (Usai et al., 2017)). The test assesses interference management: The child must indicate the direction of the central stimulus in the presence of interfering stimuli, which can be oriented either in the same direction as the target (congruence) or in the opposite direction (incongruence). Both time and accuracy are measured.

- Dimensional Change Card Sort (FE-PS 2–6; (Usai et al., 2017)). This test, which recalls the paradigm of the Dimensional Change Card Sort (DCCS), assesses the capacity for cognitive flexibility, inhibitory control, and working memory: The child must classify a series of cards, first by color, then by shape, and finally according to the color if the card has a black border and according to the shape if the card does not have a black border.

- Keep Truck (FE-PS 2–6; (Usai et al., 2017)) The test aims to evaluate the organization of information in working memory: The child is shown images belonging to five categories. Before the beginning of the test, the child is asked to pay attention to a particular category. A series of six images belonging to different categories are then shown, and the child must name them out loud. At the end of each series, the child is asked to remember the last image belonging to the designated category.

- Spin the Pots (BAFE, (Valeri et al., 2015). A visual research task that evaluates the visual-spatial working memory: The examiner places a red token under each of the eight pots arranged on a tray. The tray is then covered with a cloth and rotated. The child is asked to remove the cloth from the tray and find, one at a time, the tokens placed under each pot.

Scores obtained by the children with CAS were compared with standardized normative scores (Usai et al., 2017), considering as “deficits” those scores falling below the 5th percentile; as “immature” those scores below the 25th percentile; and as within the “normal” range those scores higher than the 25th percentile. In order to estimate the severity level of each EF component, each measure was assigned a score of 2 when normal (>25th percentile) and a score of 1 when deficient or delayed (<25th percentile).

2.3.4. Imaging Protocols

MRI data were acquired with a GE (General Electric Medical Systems, Chicago, IL) HDxt 1.5T Signa MRI system at IRCCS Stella Maris Foundation. The protocol included: (1) a 3D T1-weighted structural sequence (3D BRAVO) with 1 mm isotropic resolution (time of repetition (TR)/time of echo (TE) = 12.37/5.18 ms; flip angle (fa) = 13°; field of view (FoV) = 256 mm × 256 mm; matrix = 256 × 256; slice thickness = 1 mm); (2) a diffusion weighted imaging acquisition (DWI), by using a 2D single-shot spin-echo EPI sequence with a 3 mm isotropic resolution (TR/TE = 13,000/115.8 ms; fa = 90°; FoV = 240 mm × 240 mm; matrix = 80 × 80; slice thickness = 3 mm), including 30 noncollinear encoding directions with a b-value of 1000 s/mm2, and one additional volume without diffusion gradients (b = 0 s/ mm2).

2.3.5. MRI Analysis and Postprocessing

A total of 2 out of the 30 children with CAS were excluded from the MRI analysis because of excessive motion. The 3D T1-weighted images were processed using FreeSurfer (Conti et al., 2020). FreeSurfer was used for the preprocessing workflow for the structural MRI data to extract the white matter (WM), gray matter (GM), subcortical GM, and cerebrospinal fluid (CSF) structures (Fischl, 2012).

The preprocessing of the DWI data was performed using FSL 6.0.4 (Jenkinson et al., 2012) in particular for applying the corrections for head motion, induced eddy current, and EPI distortion. After preprocessing, the fractional anisotropy (FA) was extracted for each subject. FA is an invariant measure of the degree of diffusion anisotropy reflecting white matter integrity and varies between 0 and 1.

For the tracts of interest, their reconstructions were performed using the constrained spherical deconvolution (CSD) technique implemented in the MRtrix package (Tournier et al., 2004). The iFOD2 algorithm that facilitates more accurate fiber reconstruction in heavily curved regions was used with a maximum selected number of streamlines of 10,000 (Biagi et al., 2021). In order to correct and increase the anatomical plausibility of the reconstructed fibers, the anatomically-constrained tractography (ACT) method was applied by using the 5-tissue-type (5TT) images obtained via FreeSurfer segmentation, removing streamlines that are anatomically unfeasible (Horbruegger et al., 2019). For each tract, according to the literature, we manually identified specific regions of interest (ROI), to be used as a seed, inclusion, or exclusion region in tractography reconstruction.

The identified tract of interest was the frontal aslant tract (FAT), divided into supplementary motor area (SMA) and presupplementary motor area (preSMA) components. For both the SMA and preSMA components, a seed ROI was placed in the axial plane at the level of the inferior frontal gyrus pars opercularis (IFGop). The SMA-inclusion ROI was defined as rostral to the primary motor cortex and caudal to the vertical commissure anterior (VCA) line. The preSMA inclusion ROI was defined as rostral to the VCA line and caudal to the virtual line, passing through the genu of the corpus callosum (Broce et al., 2015).

Finally, the mean FA along each FAT component was calculated.

2.3.6. Statistical analyses

In order to compare the mean FA values along the FAT between CAS and TD children, ANCOVA analyses were performed using age, sex, number of tracts, and the tract volume as covariates. Descriptive and inferential statistics were conducted using Statistical Package for Social Science 2022, version 28.0.1.0 (142) (SPSS, IBM Corporation, Armonk, NY). First, data were analyzed to describe the distribution and the profile of the scores on the EF, speech, and language tasks. In order to identify the EF components most impaired in our sample, a nonparametric Friedman analysis was conducted. Point-biserial correlation analyses were used to investigate the relations between each EF task, speech and language severity, and FA values along the preSMA and SMA components of the FAT. On the basis of the correlation results, linear regression was used to determine the variance of FAT FA values explained by speech severity. Finally, to verify the interaction between speech severity and EF deficit on each task on the FA values of the FAT, a moderator model (Model 1; (Hayes, 2022)) was run using PROCESS v 4.0 SPSS. Regression analyses based on 5000 bootstrap samples were used to estimate path coefficients and confidence intervals for the regression equations (Hayes, 2022).

3. Results

3.1 *Speech profile*

Compared to what is expected in the typical population of the same age, the phonetic inventories of children with CAS were markedly reduced, with a mean number of consonants of 12.7 (SD = 4.09), out of 21 consonantal sounds assessed. The mean percentage of inaccurate speech productions in a single-word naming task was 61%, with a rating of 24% of inconsistency errors in the same task. On the McLeod and colleagues intelligibility scale (McLeod et al., 2012), modified for the Italian language, the average score was 2.32 (SD = 0.87), thus showing a severely altered level of intelligibility as perceived by the communication partners in spontaneous production contexts. Concerning the DDK rate, 24 children out of 30 were able to repeat the three-syllable nonword sequence /pataka/ over 20 seconds. Their mean rate was significantly slower (number of repetitions: M = 15.13, SD = 4.01) compared to the reference data (number of repetitions: M = 25, SD = 4.7). The speech profile results are summarized in Table 1.

Speech signs of CAS that were more frequently (80% or greater) detectable across the whole sample were: inconsistent productions, difficulties in transitioning from one speech movement to another, errors with vowels, reduced consonantal repertoire, atypical phonological processes, syllable omissions, increasing difficulties in longer units, dysprosody, and a slow and/or scanned speech rate.

Table 1. Speech profile results of children with CAS. Reference data are reported.

Speech assessment	CAS Group	Reference Data

protocol		
Phonetic inventory	*M* = 12.7 (*SD* = 4.09)	40 TD children, mean age = 4.7 years (*SD* = 0.47 years) Mean number of phonemes: 19.2 (*SD* = 0.9)
Word Inaccuracy	61%	40 TD children, mean age = 4.7 years (*SD* = 0.47 years) Mean percentage of inaccurate productions: 8.8% (*SD* = 10.7)
Inconsistent errors on consonants and vowels	24%	40 TD children mean age = 4.7 (*SD* = 0.47 years) Mean percentage of inconsistent errors: 0.4% (*SD* = 1.3)
DDK rate (maximum performance task)	*M* = 15.13 (*SD* = 4.01)	40 TD children (mean age = 4.7 years (*SD* = 0.9 years) Mean number of repetitions: 23.18 (*SD* = 4.5)
Intelligibility	*M* = 2.32 (*SD* = 0.87).	Qualitative rating scale ranging from 5 to 1 (5 = always, 4 = usually, 3 = sometimes, 2 = rarely, 1 = never intelligible)

3.2 *Language profile*

Concerning receptive grammar, 80% of the children with CAS had normal (> 25th percentile) or borderline (between 25th and 6th percentile) scores, whereas 20% of the children showed a deficit (scores <5th percentile). On expressive grammar evaluation, 87% of the children scored below the 5th percentile. The expressive lexicon was deficient in 17% of the children. The language profile results are summarized in Table 2.

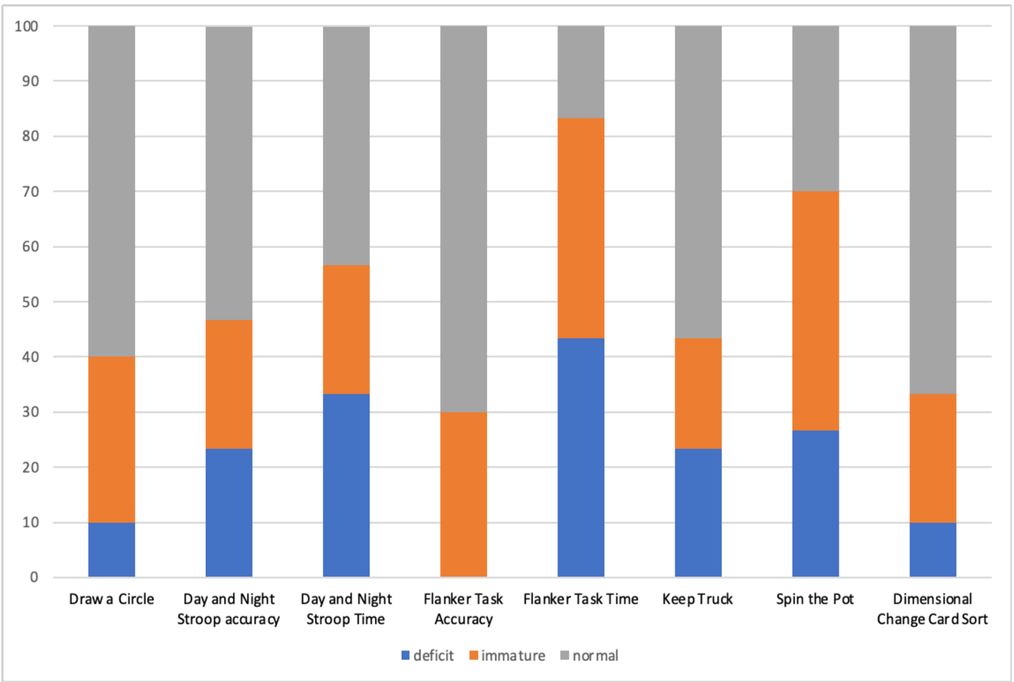
Language assessment protocol of CAS group	**% <5° percentile/ <-1.65 z score**	**Assessment measures**
Expressive Grammar	87%	Grid for the Analysis of Spontaneous Speech (GASS(Chilosi et al., 2013)
Receptive Grammar	20%	TCGB, Test di Comprensione Grammaticale per Bambini (Grammar comprehension test for children) (Chilosi & Cipriani, 2005) TROG-2 Test for Reception of Grammar, Version 2. (Bishop, 2009)
Receptive vocabulary	10%	Test Fonolessicale (TFL (Vicari et al., 2007),) and/or Peabody Picture Vocabulary Test (PPVT-R (Dunn, LM & Dunn, LM, 2000)), depending on the child's age and on the severity of the disorder
Expressive vocabulary	17%	Test Fonolessicale (TFL(Vicari et al., 2007) and/or One-Word Picture Vocabulary Test (Brizzolara, Daniela, 1989) depending on the child's age and on the severity of the disorder

Table 2. Language profile results of children with CAS. Assessment measures are reported.

3.3 *EF profile*

The Friedman test showed that the distribution of normal vs. impaired scores (immature + deficit) significantly differed among tasks (chi-squared (30) = 29.421; p < 0.001). As described below (Figure 1), the highest percentage of impaired scores was found in the Flanker Task and Spin the Pot task.

Figure 1. Frequency distribution of performance in each EF task.



In regard to response inhibition, in a task in which a motor response is required (Draw a Circle), 10% of the children showed a deficit and 30% had an immature performance, while 60% of the sample scored within the normal range. In a visual-verbal task (Day and Night Stroop), in the accuracy parameter, 23.4% of the sample obtained deficient scores, 23.3% demonstrated an immature performance, and 53.3% demonstrated a normal performance for their ages. Regarding the time parameter of the same task, 33.4% had deficient scores, 23.3% immature scores, and 43.3% normal scores. With regard to the ability to control interference, as assessed with a visual-spatial task (the Flanker Task), in the accuracy parameter, no child had a deficient score, 30% had immature scores, and 70% showed normal scores. Conversely, 43.3% had deficient scores for the time parameter, 40% showed an immature performance, and only 16.7% had a performance within the normal range. Concerning updating in working memory, in a visual-verbal task (Keep Truck), 23.3% of the sample obtained deficient scores, 20% showed an immature performance, and 56.7% scored within the norm for their ages. In a visual-spatial task (Spin the Pot), 26.7% scored in the deficit area, 43.3% obtained scores within the immaturity range, and 30% scored in the normal range. With regard to cognitive flexibility, in a visual-conceptual task (Dimensional Change Card Sort), 10% of the children with CAS obtained deficient scores, 23.3% showed an immature performance, and 66.7% scored within the norm for their ages.

The EF profile results are summarized in Table 3.

Table 3. EF profile results of children with CAS.

EF assessment protocol of CAS group	**%** **<5° percentile**	**%** **<10° percentile**	**%** **>25° percentile**
Motor Response Inhibition (Draw a Circle)	10%	30%	60%
Visual-Verbal Response Inhibition (Day and Night Stroop, accuracy)	23.4%	23.3%	53.3%
Visual-Verbal Response Inhibition (Day and Night Stroop, time)	33.4%	23.3%	43.3%
Visual-Spatial Control Interference (Flanker Task, accuracy)	0%	30%	70%
Visual-Spatial Control Interference (Flanker Task, time)	43.3%	40%	16.7%
Visual-Verbal Updating (Keep Truck)	23.3%	20%	56.7%
Visual-Spatial Updating (Spin the Pot)	26.7%	43.3%	30%
Visual Cognitive Flexibility (Dimensional Change Card Sort)	10%	23.3%	66.7%

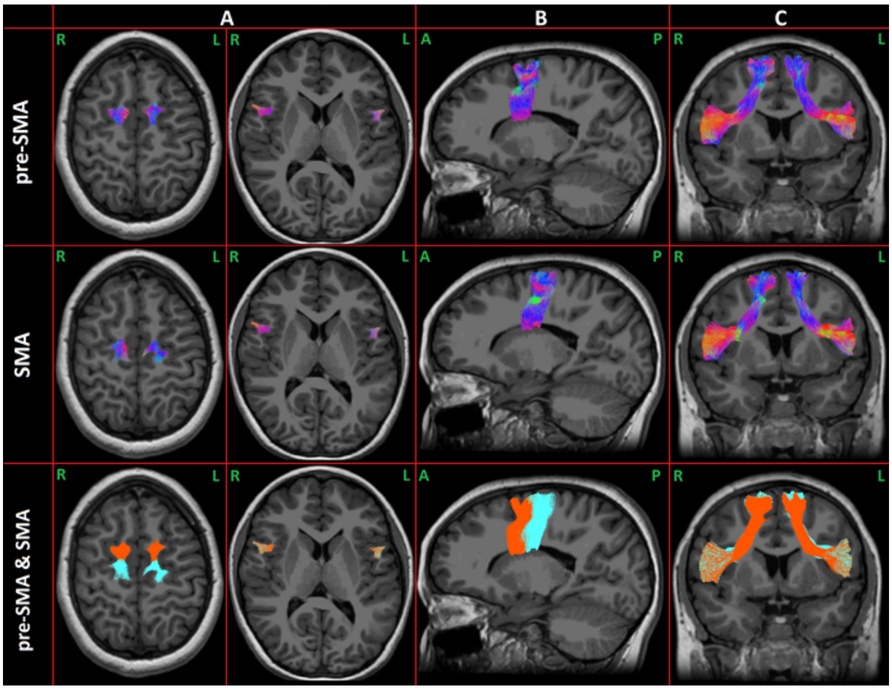
Covarying for age, gender, and handedness, language severity significantly correlates with accuracy on the Flanker Task ($r = 0.613$; $p < 0.005$) and Keep Truck task ($r = 0.627$; $p < 0.005$), while no significant correlation emerged between speech severity and EF measures.

3.4 FAT Reconstruction, Analysis, and Relations With Speech and Language

Each component of the FAT was extracted from each hemisphere of each CAS and TD subject. An example case is shown in Figure 2.

Figure 2. Example of the FAT: The first two rows represent the preSMA and SMA components. The direction of the tract is coded using RGB for the XYZ direction: red indicates the left–right

direction, green the anterior–posterior direction, and blue the superior–inferior one. In the last row are overlapped both the FAT components (orange for preSMA and light-blue for SMA). Panel (A) shows the top and the bottom of the tracts in the axial plane. In panels (B) and (C) ,the projections of the FAT in the sagittal and coronal planes are respectively represented.



The mean FA values along the FAT were compared between the CAS and TD children (see Table 4). A significant difference was found for the left component of the FAT preSMA (p < 0.05). Furthermore, this difference did not survive multiple comparison correction.

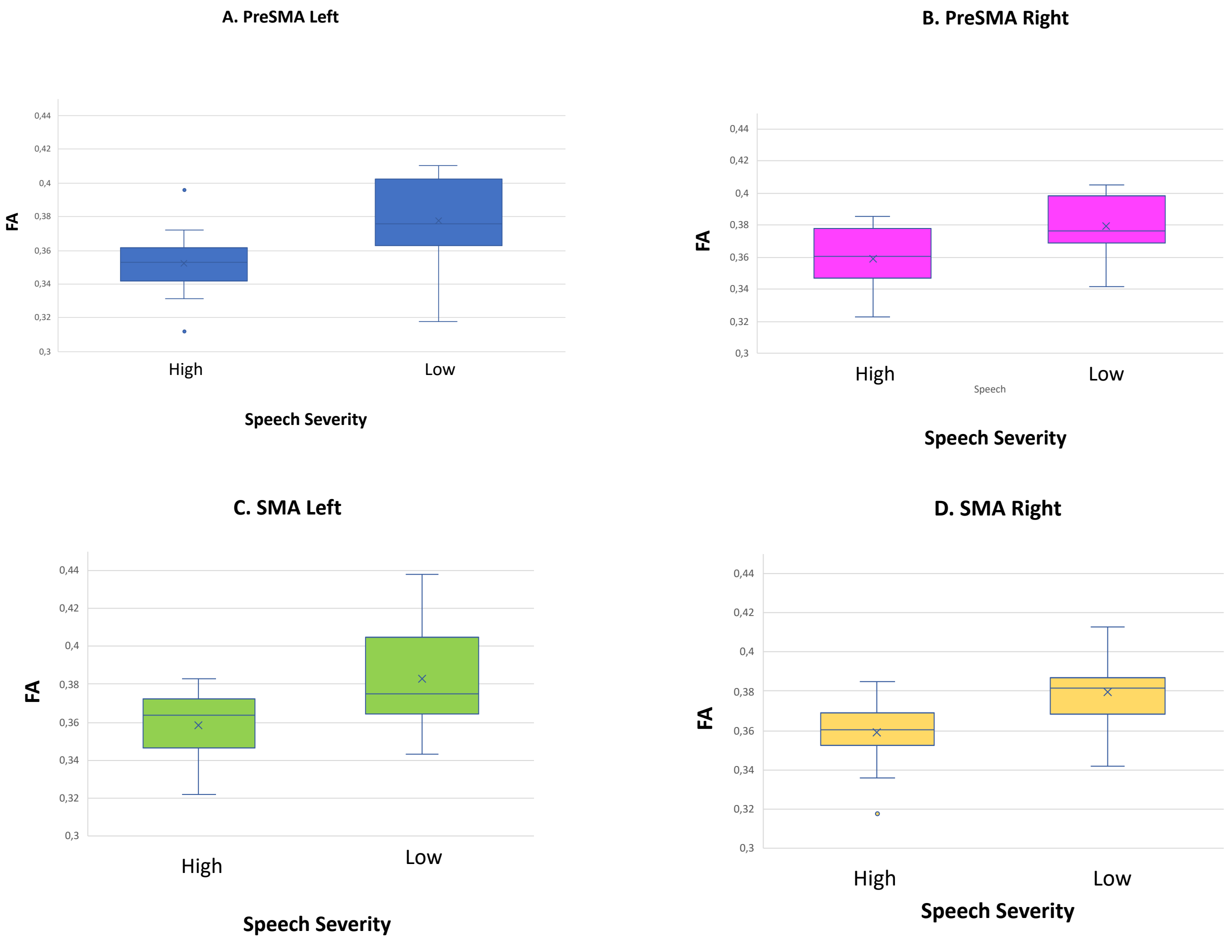
Table 4. Mean, Standard Deviation (SD), F, and *p*-value of the ANCOVA test for FA values of FAT components in CAS and TD children. * = statistically significant difference between groups (*p* < 0.05).

	CAS Mean (*SD*)	**TD Mean (*SD*)**	***F***	***p***
FA - left preSMA FAT	0.36 (0.02)	0.39 (0.02)	5.93	0.02*
FA - right preSMA FAT	0.37 (0.02)	0.37 (0.03)	0.01	0.90
FA - left SMA FAT	0.37 (0.02)	0.39 (0.02)	2.79	0.10
FA - right SMA FAT	0.37 (0.02)	0.37 (0.03)	1.71	0.19

Significant correlations emerged between speech severity and FA values along the preSMA component in the left hemisphere (r = 0.470; $p < 0.05$) (Figure 3A), in the right hemisphere (r = 0.519; $p < 0.01$) (Figure 3B), between speech severity and FA values along the SMA component in the left hemisphere (r = 0.481; $p < 0.05$) (Figure 3C), and in the right hemisphere (r = 0.557; $p < 0.01$) (Figure 3D), thus indicating a reduced white matter integrity in each FAT component in correspondence with greater speech severity. In order to confirm the expected changes on FA values along the FAT based on the severity of the disorder, linear regression analysis of speech severity on the FAT FA was conducted. Speech severity significantly predicted FA variance for each FAT component, with a percentage of explained variance ranging from 21% to 27% (preSMA left: $R^2 = 0.24$; $\beta = 0.49$; $p < 0.01$; preSMA right: $R^2 = 0.21$; $\beta = 0.46$; $p < 0.05$; SMA component: SMA left $R^2 = 0.22$; $\beta = 0.48$; $p < 0.05$; SMA right: $R^2 = 0.27$; $\beta = 0.52$; $p < 0.01$).

No significant correlations emerged between the FA value of the FAT in either the SMA or the preSMA components, nor in the language severity score, nor in the EF tasks.

Figure 3. Significant point-biserial correlation between Speech Severity and FA along the FAT in the preSMA component in left hemisphere **(A)**, FA along the FAT in the preSMA component in the right hemisphere **(B)**, FA along the FAT in the SMA component in the left hemisphere **(C),** and FA along the FAT in the SMA component in the right hemisphere **(D)**.



3.5 *Moderation Analysis*

A moderation test describes how the interaction between two different variables can influence the occurrence of an effect. In order to investigate whether EFs moderate the predictive role of speech severity on the FAT FA, a moderator analysis (Model 1,(Hayes, 2022)) was conducted for each EF and FAT component. The moderation analysis aimed to test the hypothesis that working memory, one of the most impaired EF components in our sample, and reported in the literature to be deficient in CAS (Kenney et al., 2006; Lewis et al., 2011; Shriberg et al., 2012), may moderate the relationship between speech severity and FA value of the FAT SMA component, which underlies several higher-order control functions during speech production. Its role is particularly relevant in complex speech activities [90], and its efficiency might be affected by the severity of the speech disorder, as well as by domain-general control difficulties in the continuous updating of motor plans.

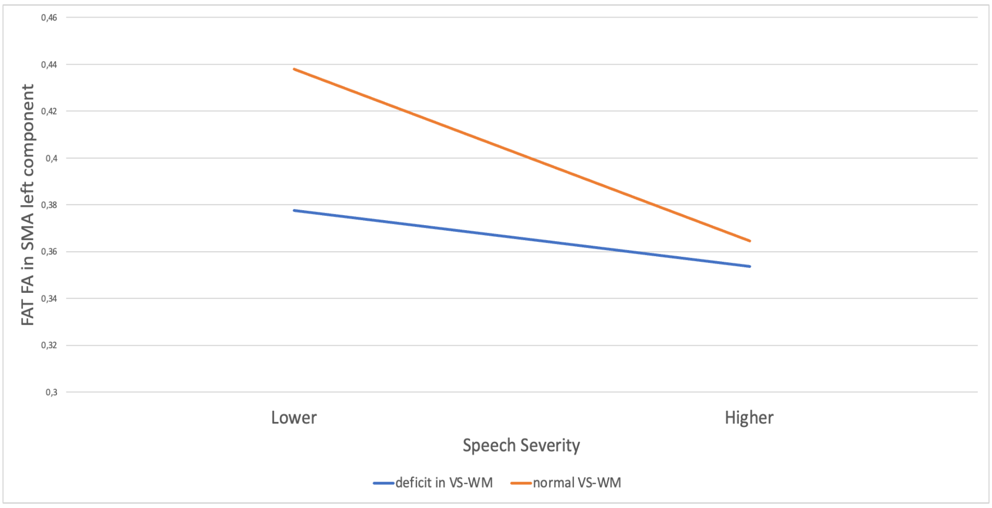
The moderation analyses showed that visual-spatial working memory significantly moderated the predictive role of speech severity on the FA value of the left FAT SMA component (B ≠ 0, SSxVS-WM $p < 0.05$; see Table 5); the R-squared increase due to the interaction was also significant ($R^2 = 0.10$, F (1. 24) = 4.45, p <0.05).

Table 5 Regression coefficients for moderation analysis on the FA value of the FAT in the left SMA component, including severity of speech as a predictive variable and visual-spatial working memory as a moderating variable.

	B	*S.E.*	*t*	*p*	*95% CI*
Speech severity (SS)	−0.025	−0.03	−0.89	0.38	−0.015–0.064
Visual-spatial working memory (VS-WM)	−0.039	0.03	−1.33	0.02	0.076–0.142-
SS x VS-WM	0.05	0.02	2.11	<0.05	−0.072–−0.029

The estimation of conditional effect of speech severity on the FA value along the FAT in the SMA left component at two levels (deficit/normal) of visual-spatial working memory showed that speech severity significantly affected the FA value along the FAT in the left SMA component at both visual-spatial working memory levels, although with a larger effect size for normal (β = −0.844) compared to deficient (β = −0.507) working memory ability, (Figure 4).

Figure 4. Interaction between severity of speech and Visual-Spatial Working Memory (VS-WM) on the FA value of the FAT in the left SMA component.



4. Discussion

While a relatively large body of literature is dedicated to the study of the speech characteristics of children with CAS, only recently has the neuropsychological profile started to gain attention from researchers. The existing literature on CAS reports a high rate of co-occurring cognitive–linguistic weaknesses in this population (Lewis et al., 2004; Bombonato et al., 2022; Iuzzini-Seigel, 2019 and 2021) and in our sample, children also showed co-occurring language impairments, mainly involving expressive grammar. However, less is known about the relationship of co-occurring deficits with the speech features that are central to a CAS diagnosis. The current study examined both the direct effect and the interaction of the core deficit of the disorder (the severity of speech) with higher-order cognitive processes (the executive functions) on brain connectivity in a fiber tract functionally relevant to the disorder, the frontal aslant tract (FAT). The main reason to study EFs in CAS was based on the need to investigate specific neuropsychological processes potentially related to the clinical manifestations.

The results of the present study showed the presence of a complex functional profile, characterized by difficulties not only in the speech domain, but also in specific EF components. Visual-spatial working memory, in particular, appears to be the most frequently compromised component in terms of accuracy. This result extends what was found by previous studies on phonological working memory (Lewis et al., 2011; Shriberg et al., 2012) and also to the visual-spatial processing mode, configuring the working memory impairment as a general domain deficit independent of the information processing mode (verbal vs. visual). The alteration found in a working memory task, in which information updating is highly required, demonstrates that, in these children, not only the articulatory repetition mechanism is compromised (Shriberg et al., 2012), but also the updating and the active manipulation of information are altered. The former contributes to the ability to retain information in the phonological circuit by keeping it "active" (Baddeley, 2007), while updating allows the modification of the contents of the memory to accommodate new input (Morris and Jones, 1990) Moreover, response inhibition and interference control were found to be frequently compromised in the speed parameter, the latter being deficient or immature in 83.3% of the sample, despite not being frequently compromised in the accuracy parameter, in which only 30% of the sample had a poor or immature performance. This adds to the literature that shows a general slowdown and slower performances in simple reaction time tasks in children with CAS, as compared to their peers with typical development or with other speech–sound disorders (Iuzzini-Seigel, 2021; Kim et al., 2015) . Our evidence suggests that, to achieve a satisfactory level of accuracy in suppressing interfering stimuli, children with CAS require a longer processing time. This could suggest and help to explain why these children require intense practice with numerous repetitions to achieve their treatment objectives (Case and Grigos, 2016; Edeal, 2011; Maas et al., 2014; Thomas et al., 2014) although it is not known how much practice they would require to reach the same processing times as their peers. Furthermore, the severity of the co-occurring language disorder was found to correlate with the accuracy of interference control, as also shown in children with isolated language disorder (Spaulding, 2010). Moreover, language severity scores correlated with verbal working memory update scores, pointing to the influence of linguistic difficulties, not only with short-term repetition or processing in phonological working memory (Montgomery et al., 2009; Duinmeijer et al., 2012; Marton et al., 2003; Archibald and Gathercole, 2006; Im-Bolter et al., 2006) but also with the semantic-lexical updating of information.

Therefore, with regard to the EF profile, multiple alterations are confirmed mainly in the basic components of EFs, such as inhibition and working memory, rather than in more complex components related to categorical abstraction and cognitive flexibility. Since the sample for our study was of preschool age, it is possible that the assessment tools were more sensitive to grasping difficulties in the components of EFs that develop early, rather than in those that tend to emerge later and require a wider developmental period (Diamond, 2013; Millet et al., 2012).

These results are clinically relevant as it is not commonplace to evaluate the profile of executive functions in children with CAS, while the investigation of these processes could provide relevant information for the definition of the functional profile.

Furthermore, EF impairment showed a complex pattern of relation with speech severity and neurofunctional findings. Through a diffusion MRI specific protocol, each component of the FAT was extracted. White matter integrity was compared between CAS and TD children, revealing a significant reduction in FA values in the left component of the FAT preSMA. Speech severity, but not language severity, correlated and predicted FA values along the FAT in both of its investigated components (the SMA and preSMA), and EF impairment moderated this relation. In particular, a significant role for visual-spatial working memory in moderating the relationship between speech severity and FA value along the FAT in the left SMA component was found. The relationship is sig-nificant for both deficient and normal levels of visual-spatial working memory, the latter with a larger effect size. Therefore, especially in conditions of lower speech severity, good visual-spatial working memory skills are associated with a greater integrity of the white matter in this area.

This result is of particular importance, as it underlines, on the one hand, the importance of the evaluation of executive functions in defining the functional profile of CAS and, on the other, it stimulates reflection on rehabilitation. Fractional anisotropy increase has been associated with neuroplastic effects induced by processes connected with learning (Rossi et al., 2017; Takebayashi et al., 2018; Tataranno et al., 2018) and in particular, in CAS, an improvement in speech has been demonstrated parallel to the increase in FA in the left ventral and right dorsal corti-cobulbar tracts following treatment focused on speech motor control, thus supporting the treatment-induced neuroplastic effect (Fiori, 2021). According to these results, we hypothesized a relationship between speech severity and FA in a specific white matter tract. However, as the relationship between cognitive and linguistic functions and FA of white matter tracts is not fully understood, further studies are needed to clarify the direction of this relationship. Following Fiori and colleagues' suggestion and, given that the role of the FAT has never been investigated in CAS but has been studied as a functionally relevant fiber pathway both in speech (Catani et al., 2013) and in executive functions (Dick et al., 2019), we decided to examine the role of these two processes and their functional relationship with the FAT in CAS. Our results support the presence of a direct role of speech severity on white matter integrity in the SMA component of the FAT, an area associated with selection and execution in the production of words and of oral motor gestures (Tremblay & Gracco, 2010; Tremblay & Small, 2011). However, new light has been shed on the role of higher-order skills, such as executive functions and, especially, on working memory and inhibition. A deficit in inhibiting the previous motor plans and updating new sequences (Mars et al., 2007), in fact, could affect the ability to program and plan the space-time parameters of movement sequences. Although further studies are necessary to confirm this assumption, we could argue that the enhancement of these abilities within a specific treatment could lead to a “far transfer effect” on the mitigation of the clinical manifestations of the disorder and on the generalization of learning, also verified at the neurofunctional level.

A limitation of the present study is the small sample size, mainly due to the low incidence of idiopathic CAS (Shriberg et al., 1997). Additional research with a larger sample is required to substantiate our results. A further limitation is the absence of a control group undergoing both the EF and speech and language evaluation protocol and the MRI acquisition, as the CAS children did. Another limitation was the relative homogeneity of our participants with CAS, who were characterized by a high rate of co-occurring language impairments. In order to verify the generalizability of our findings, a group with higher variability across their language skills should be included in further studies. Finally, longitudinal and pre/posttreatment studies could allow us to better understand the long-term consequences of the relationship between the core deficit of speech and executive functions in CAS.

5. Conclusions

In conclusion, our study extends the understanding of CAS, a persistent and severe developmental motor speech disorder, as a composite and complex condition, frequently involving higher order cognitive skills, such as EFs. In particular, the alterations in control inhibition and updating in working memory may play a critical role in maintaining the severity and persistence of the disorder over time. The results obtained underline the importance of a comprehensive multidisciplinary assessment, which becomes mandatory in order to provide a more in-depth characterization of the disorder and define the most appropriate therapy interventions. We believe that the present findings pave the way to future studies which consider the effect of higher-order skills empowerment in specific disorders in order to identify, on the one hand, the preferential treatment for each specific condition, and, on the other, which are the specific characteristics of the different treatments that allow an effective improvement of clinical symptoms.

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Chapter 2

2.2

Far transfer effects of trainings on executive functions in neurodevelopmental disorders: a systematic review and metanalysis

Clara Bombonato
Benedetta Del Lucchese
Costanza Ruffini
Maria Chiara Di Lieto
Paola Brovedani
Giuseppina Sgandurra
Giovanni Cioni
Chiara Pecini

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Abstract

Executive Functions are a set of interrelated, top-down processes essential for adaptive goal-directed behaviour, frequently impaired across different neurodevelopmental disorders with variable degrees of severity. Many executive-function-training studies in children with neurodevelopmental disorders have focused on near effects, investigating post-treatment improvements on directly trained processes, while enhancements of skills not directly trained, defined as far effects, are less considered, albeit these could be extremely relevant for reducing the negative impact of a disorder's core symptomatology. This systematic review and metanalysis aims to investigate the far effect outcomes after EF training in children with different types of neurodevelopmental disorders. 17 studies met the inclusion criteria for the systematic review, while 15 studies were selected in the metanalysis. An overall statistically significant effect size was found in the majority of far effect outcome measures considered in the studies. In particular, trainings on executive functions determine significant far effects on daily life functioning (0.46, 95% CI: [0.05-0.87]) and clinical symptoms (0.33, 95% CI: [0.15-0.51]). Despite a high variability of the results, intensity, frequency and the laboratory/life contexts dimension seem to be the most influential variables in determining far effects. This systematic review and metanalysis highlights the need to measure far effects of executive function training in neurodevelopmental disorders, selecting treatments not only on directly targeted processes, but also according to far impacts on the functional weakness of the disorder.

1. Introduction

1.1 Executive Functions: Definition

Executive Functions (EFs) represent a complex cognitive domain consisting of a set of top-down functions essential for adaptive goal-directed behaviour (Lehto et al., 2003; Miyake et al., 2000). EFs allow to formulate, plan, and organize ideas, cope with challenges and novelties, resist temptations and stay focused (Diamond, 2013). There is an ongoing debate as to the extent to which EFs can be fractionated or be unified into a single concept, both in adults and during development (for example, Morra et al., 2018). The model that may best explain executive functioning during development has been put forward by Adele Diamond (Diamond, 2013; Diamond & Ling, 2016), based on the conceptualizations of Miyake and colleagues (Friedman & Miyake, 2017; Miyake et al., 2000) . Three early and distinct, although interrelated, components are identified in this model: inhibition, working memory and cognitive flexibility, whose interaction allows for the development of higher order EFs such as reasoning, problem solving and planning.

Inhibitory control is the ability to voluntarily resist temptations and impulsive actions (i.e. response inhibition) and to maintain selective attention by suppressing non relevant information (i.e. interference control). Inhibitory control is a fundamental skill involved both in cognitive activities, such as abstract reasoning, and in affective and emotional challenges allowing for more appropriate behaviours geared to internal or external goals (Zelazo et al., 2005; Zelazo & Mller, 2002). Inhibitory control supports the development of self-regulation, which requires the ability to maintain optimal cognitive, emotional and motivational arousal levels.

Working memory is a complex and multi-component mental system where information can be temporarily stored. It refers to the ability to actively maintain, monitor, update and manipulate verbal or visual-spatial information (Baddeley, 2003; Baddeley & Hitch, 1994; Smith & Jonides, 1999).

Cognitive flexibility is the ability to shift among different tasks, rules or mental contents. It supports creative thinking and the capacity to solve problems in different ways or see things from different perspectives.

EFs develop from preschool-age to childhood and into adulthood (Hughes et al., 2009; Huizinga et al., 2006; Lehto et al., 2003; Somerville & Casey, 2010) following maturation of prefrontal circuitries and their connections (Gilbert & Burgess, 2008). A single-undifferentiated executive factor was found in younger children of preschool age (Wiebe et al., 2011), whereas two separate dimensions consisting of inhibition and working memory were identified in children older than 5 years of age (Lee et al., 2013; M. R. Miller et al., 2012; Usai et al., 2014). Cognitive flexibility emerges later in development (Lee et al., 2013; Lehto et al., 2003) after the inhibition and working memory abilities have been established. Subsequently, these three basic EF components support the emergence of more complex and high-level EFs, including abstract reasoning, problem solving and planning, also referred to as Fluid Intelligence (Collins & Koechlin, 2012; Diamond, 2013; Lunt et al., 2012).

EFs have also been differentiated into "cool" and "hot" processes (Zelazo & Carlson, 2012). The former domain, mainly subserved by the lateral prefrontal cortex, includes cognitive EF skills, elicited under relatively abstract, de-contextualized, non-affective conditions. Hot EF processes, mainly subserved by ventromedial prefrontal cortex and operating in motivationally and emotionally significant high-stakes situations, involve decision making, gratification delay and theory of mind (Wilson et al., 2018; Zelazo & Carlson, 2012).

In typically developing children, persistent difficulties affecting EFs, even if minor, represent a risk factor for development and can predict learning skills (Alloway & Alloway, 2010; Clark et al., 2014; LeFevre et al., 2013; Steele et al., 2012), academic achievement, job success, physical and mental wellbeing (McClelland et al., 2013; Moffitt et al., 2011; St Clair-Thompson & Gathercole, 2006).

1.2 EFs and Neurodevelopmental Disorders

It is currently well accepted that EFs are frequently impaired across different developmental disorders (Bausela Herreras et al., 2019; Pennington & Ozonoff, 1996). In some neurodevelopmental disorders an EF deficit may be a part of the core cognitive symptoms, while in others, a weakness of EFs is associated with specific deficits and help to define different subtypes of the disorder. Finally, poor executive abilities could be due to the reduced efficiency of other cognitive and sensory-motor functions.

A deficit in inhibition, and in particular in the ability to inhibit responses, was described as one of the core deficit of Attention Deficit Hyperactivity Disorder (ADHD) (Barkley, 2006, 2018). According to Barkley, a deficit in inhibition may cause, in turn, deficits in working memory, emotional regulation, reconstitution and internalization of language, leading to difficulties in the self-regulation of social interaction. Indeed, in ADHD other EFs are also compromised, notably working memory, divided attention, cognitive flexibility, planning, sustained attention and theory of mind (reviews: Elosúa et al., 2017; Jiménez-Figueroa et al., 2017; Lambek et al., 2011; Mary et al., 2016; Molnar, 2007; Pineda-Alhucema et al., 2018; Sergeant et al., 2002; Willcutt et al., 2005). In many studies, also the hot components of EF are impaired in individuals with ADHD, for example delay aversion, Theory of Mind and decision-making (reviews and meta-analysis: Bora and Pantelis, 2016; Groen et al., 2013; Mowinckel et al., 2015; Patros et al., 2016; empirical studies: Braaten and Rosén, 2000; Yang et al., 2011). Individuals with Intellectual Disability (ID) display worse EFs abilities than subjects with the same chronological and mental age (review and meta-analysis: Hronis et al., 2017; Spaniol and Danielsson, 2019; empirical studies: Costanzo et al., 2013; Danielsson et al., 2010; Tungate et al., 2021).

Children with Developmental Coordination Disorder (DCD) present EFs impairment in several domains, such as working memory (especially visuospatial), inhibitory control, attention, flexibility and metacognitive aspects of action planning (reviews and metanalysis: Leonard et al., 2015; Wilson et al., 2017, 2013; empirical studies: Piek and Dyck, 2004; Sartori et al., 2020). Moreover, some evidence supports deficits in hot executive functions in children with DCD, as they have a high sensitivity to immediate gratification and to distracting emotional stimuli that underly low decision-making skills in emotionally activating situations (Rahimi-Golkhandan et al., 2014, 2015, 2016). Some difficulties in EFs remain distinctive features of individuals with DCD even in middle childhood, adolescence and early adulthood and limit children’s ability to improve automatic motor control and motor skills in daily activities (Bernardi et al., 2018; Wilson et al., 2017).

Executive functions are fundamental for cognitive-linguistic translation (Berninger et al., 2012), the basis for language learning (Arrington et al., 2014; Berninger et al., 2012; Swanson, 2000; 2006), and appear to be in a reciprocal and complex relationship with language development (Bishop et al., 2013). It is therefore understandable that individuals with Developmental Language Disorders (DLDs) show cognitive difficulties that are not limited to the language domain. In particular, this clinical population presents difficulties with multiple components of EFs (meta-analysis and review: Kapa and Plante, 2015; Pauls and Archibald, 2016; empirical study: Andrés-Roqueta et al., 2021; Henry et al., 2012; Roello et al., 2015) and related functions such as processing speed (Miller et al., 2001), non-verbal reasoning (Gallinat & Spaulding, 2014), procedural memory (Lum et al., 2012), motor control (Finlay & McPhillips, 2013). The most compromised EFs in this disorder are inhibition (Marini et al., 2020; Pauls & Archibald, 2016), cognitive flexibility (Pauls & Archibald, 2016), working memory both phonological (Duinmeijer et al., 2012; Marini et al., 2014) and visuospatial (Vugs et al., 2013), updating (Marini et al., 2020) and attentional control in verbal and non-verbal tasks (Dispaldro et al., 2013; Duinmeijer et al., 2012; Ebert & Kohnert, 2011; Finneran et al., 2009; Montgomery, 2008; Montgomery et al., 2009; Spaulding et al., 2008). Learning to read, text comprehension and mathematical competences are linked to working memory, inhibition, cognitive flexibility, updating and attentional control and planning (Cartwright & Smith, 2017; Gilmore & Cragg, 2014; Zaccoletti & Mason, 2018).

Individuals with Specific Learning Disorder (SLD) are characterized by difficulties in executive functions domains such as planning, cognitive flexibility, verbal and visuospatial working memory, attentional control and inhibition (El Wafa et al., 2020; Schuchardt et al., 2008). Developmental Dyslexia is the most studied disorder in terms of executive dysfunctions. Impairments and/or weaknesses have been reported in visual-spatial (Altemeier et al., 2008; Helland & Asbjørnsen, 2000; Menghini et al., 2010) and auditory attention (Buchholz & McKone, 2004; Casco & Prunetti, 1996; Dufor et al., 2007; Facoetti et al., 2000; Valdois et al., 2004), shifting (Hari & Renvall, 2001; Laasonen et al., 2012), verbal categorical and phonological fluency, verbal and visual short-term memory, verbal and visual-spatial working memory (Varvara et al., 2014), inhibition of irrelevant information (Brosnan et al., 2002; Everatt et al., 1997; Reiter et al., 2005), maintaining relevant information in working memory (meta-analysis: (Booth et al., 2010). In particular, the working memory deficit is considered one of the major markers of Dyslexia, both in its verbal and visuospatial components (Bacon et al., 2013; Brosnan et al., 2002; Helland & Asbjrnsen, 2004; Martinussen & Tannock, 2006; Menghini et al., 2011; Poblano et al., 2000; Smith-Spark & Fisk, 2007; Swanson et al., 2009).

EFs have been found to be frequently impaired in children with Autism Spectrum Disorder (ASD), characterized by a deficit in cognitive flexibility, planning and inhibiting preponderant responses (Hill, 2004; Jiménez-Figueroa et al., 2017; Kenworthy et al., 2005; Landa & Goldberg, 2005; Lopez et al., 2005; Ozonoff et al., 1994; Rinehart et al., 2001; Robinson et al., 2009; Shu et al., 2001; Verté et al., 2005).

Finally, EFs are crucial for adaptive behaviour, in as much as efficient executive functioning during child development is able to predict health and well-being in adulthood (Moffitt et al., 2011). Considering that especially in childhood, EFs are indeed highly responsive to environmental influences (Jolles & Crone, 2012; Klingberg, 2010), it is important to identify early EF impairments in order to intervene and improve developmental trajectories.

1.3 EF interventions

Convergent evidence suggests that it is possible to improve EFs through cognitive training (Diamond & Lee, 2011) and some findings demonstrated a strengthening of the neural circuits underlying the trained EFs by intensive practice (Brehmer et al., 2011; Crespi et al., 2018; McNab et al., 2009; Rueda et al., 2012). Given the importance of EFs in development and their variability in the severity of their impairment in different neurodevelopmental disorders, many studies have analyzed the effectiveness of different approaches both for the enhancement of EFs and for the generalization effect on other cognitive and daily life functioning. Some key principles of clinical practice for an intervention to be helpful foresee contextual support and the use of compensatory aids, the use of problem-solving and metacognitive strategies aimed at improving specific task trained but also applicable to a variety of everyday situations (Krasny-Pacini et al., 2018).

Many types of EF intervention are reported in the literature: computerized training, non-computer games, physical activities, classroom curricula, art activities, mindfulness practices, and biofeedback. Computer-based programs, such as CogMed Working Memory Training (www.cogmed.com) and Braingame Brian (Prins et al., 2013), are among the most popular interventions used for the improvement of working memory and for the enhancement of inhibition and cognitive flexibility respectively. Evidence shows that although these treatments have a solid effect in improving the practiced skills, such as inhibition and working memory span (Beck et al., 2010; Chacko et al., 2014; Di Lieto et al., 2021; Gibson et al., 2011; Kidokoro et al., 2014; Klingberg et al., 2005; Løhaugen et al., 2011; Lundqvist et al., 2010; Melby-Lervåg et al., 2016), the improvements do not seem to transfer to untrained domains (Blair & Razza, 2007; Diamond, 2012; Diamond & Lee, 2011; Diamond & Ling, 2016), nor to untrained EF skills (Kassai et al., 2019), nor to everyday life contexts if the intervention is not included in these scenarios (Blair, 2017). The efficacy of EF treatments through physical activities (Best & Miller, 2010; Ng et al., 2017; Tomporowski et al., 2008) and non-computerized games (Tominey & McClelland, 2011) has also been demonstrated. The effectiveness of these interventions could depend on the activation of strategies and cognitive skills related to EFs. Furthermore, complex motor activity activates brain regions related to the prefrontal cortex which may produce immediate physiological responses (increased blood flow, oxygen and brain derived neurotrophic factor-BDNF) which in turn facilitate cognitive performance and learning (Best & Miller, 2010). The presence of cognitive challenges within physical activities requiring flexible adaptation of behaviour seems to produce greater effects on EFs than physical activities involving only aerobic components or automated motor responses (Best & Miller, 2010; Diamond, 2015). Other promising treatment approaches are classroom curricula specifically designed to promote EFs, such as Tools of the Mind (Bodrova & Leong, 2006). These approaches are inserted in the daily practice of children, facilitating the generalization of the skills learned and their application in new contexts. Furthermore, these programs do not require any specific materials, can be conducted in school by teachers and can include a large number of participants (Diamond & Lee, 2011). Not only specific curricula design to promote EF, but also some academic discipline as art activities (Diamond, 2012; Diamond & Lee, 2011; Diamond & Ling, 2016), such as music and drama, requiring inhibitory control and cognitive flexibility are able to produce benefits in EF skills (Schellenberg, 2004; Thibodeau et al., 2016). Another approach to foster children's EFs is providing them with strategies of self-regulation, both through teaching skills targeting metacognitive intervention, useful for daily life challenges, and through mindfulness practises. This latter activity requires attention (Zelazo & Lyons, 2012) and self-control, reducing anxiety and stress, in the meanwhile, working both on a cognitive and emotional level (Zenner et al., 2014).

Finally, also biofeedback, a technique that uses the electroencephalographic (EEG) or electromyographic (EMG) signal for learning voluntary self-control of some psychophysiological processes that are usually involuntary, are effective on attention and self-regulation, fostering self-teaching strategies to control physiological reactions (Niv, 2013). Neurofeedback training has also been reported to be effective in reducing clinical symptoms in children and adolescents with ADHD (Arns et al., 2009). However, a more recent meta-analysis highlighted the lack of efficacy of neurofeedback treatment tested by standardized tests on EFs in ADHD children (Louthrenoo et al., 2022). This inconsistency in the literature evidence could be due to the different outcome measures considered.

Despite the wide amount of data supporting the usefulness of EF training, the characteristics that make an EF intervention effective are not fully understood. The review by Diamond and Ling (2016) highlights that interventions involving socio-emotional components and physical exercise have the greatest effectiveness, as long as cognitive challenges are included within the proposed activities. Moreover, the exercises must be calibrated on the subject's abilities, as to represent a challenge rather than only skill practice. Other variables influencing the success of the training are the personal characteristics of the person conducting the program and the starting impairment level of the participants, as it seems that greater benefits are observed in conditions of greater initial EF impairment. Furthermore, Blair (2017) emphasizes the importance of placing the intervention within an everyday life context in order to increase ecological validity and generalization. However, interventions on EFs must not become a burden for the family system, already challenged by child’s difficulties, but have to involve the caregivers in an appealing way, favouring skills acquisition useful to support daily life functioning (Krasny-Pacini et al., 2018).

Since EFs are highly correlated with other cognitive functions, their impairment can determine cascade effects on other neuropsychological processes. For this reason, EF improvements could produce effects on functions untrained but correlated with EFs, resulting in important benefits for children's daily functioning. These non-specific effects have been defined by the literature as far-transfer effects, i.e. effects of training on different processes correlated with practiced skills (Melby-Lervåg & Hulme, 2013; Sala & Gobet, 2016, 2017), as opposed to near transfers, i.e. post-treatment improvements in tasks that require directly trained processes (Kassai et al., 2019; Melby-Lervåg & Hulme, 2013; Sala & Gobet, 2016, 2017). Transfer has been defined not only in terms of improvements in different tasks, but also in terms of improvement along time intervals and contextual similarity, and in each of these dimensions the transfer can be near or far (Klahr & Chen, 2011). Linked to the conceptualization of transfer in terms of context dimension, Diamond and Ling (2016) analysed the narrow transfers, i.e. improvements of the abilities trained within the treatment but in other contexts where the same skills are required. The authors argue that “people improve on the skills they practice and that transfers to other contexts where those same skills are needed [...]; improvement does not seem to transfer to other skills" (Diamond and Ling in Novick et al., 2020, pages 460-461). The question about the possibility of producing far transfer after EF training is still open, as pointed out by the review by Katz and Saha (2020) on children with developmental disorders (see Novick et al., 2020). Katz and Saha analysed many studies, showing the heterogeneity of results (Chooi & Thompson, 2012; Heinzel et al., 2014; Jaeggi et al., 2014; Kundu et al., 2013; Redick et al., 2013; Stephenson & Halpern, 2013; Thompson et al., 2013), varying from the absence of transfer effects (Melby-Lervåg & Hulme, 2013) to significant effects on skills far from those trained, as fluid intelligence (Au et al., 2015; Karbach & Verhaeghen, 2014). In order to disambiguate the question, it is necessary to develop and use dynamic outcome measures able to detect the effective EFs improvement after a treatment, as well as transfer effects on other processes, taking into account the ecological validity and the test-retest effect (Krasny-Pacini et al., 2018).

The present systematic review aims to investigate the presence of far-transfer effects following executive function training, limiting the analysis to children with neurodevelopmental disorders and considering as far-transfer effects any skill not directly trained by the treatment and assessed post intervention, also including executive functions, if different from those enhanced.

2. Method

2.1 Search strategy

The review authors undertook a comprehensive search of databases as MEDLINE Advanced PsycINFO, EMBASE, CINHAL and CENTRAL (Cochrane Controlled Registered Trials) in April 2020, in accordance with the PRISMA statement (Moher et al., 2009). The search strategy comprised keywords in different combinations referring to four main clusters: “executive functions", “neurodevelopmental disorders", “children” “intervention” and “far effects" including terms related to constructs and definitions (see Appendix 1 for complete search string and the Introduction for the definition of the specific terms). The keywords were selected based on the analysis of the literature on the effect of training in neurodevelopmental disorders (Kassai et al., 2019; Novick et al., 2020; Scionti et al., 2020; Takacs & Kassai, 2019). The selection of terms referring to executive functions was guided by the models suggested by Diamond (2013) and Miyake (2000). The latter one also includes emotional aspects such as emotion regulation and “hot” EF, which are considered also in this review as part of executive functions._Given the recent increased interest in studying the effects of EF training in children, the research was restricted to the period 2000-2020. In order to exclude non-peer reviewed studies, the authors included studies published in academic journals, reported in English and available for full text. The methodological quality of the included studies was assessed according to the National Health and Medical Research Council (NHMRC) Evidence Hierarchy (NHMRC, 2009).

2.2 Inclusion criteria

2.2.1 Type of participants

Published studies included samples of subjects in developmental age (5-18 years) diagnosed with Neurodevelopmental Disorders (according to ICD 11 or 10 or DSM 5 or IV TR) They included Learning Disorders, Developmental Coordination Disorder, Language Disorder, Autism Spectrum Disorder, Attention Deficit Hyperactivity Disorder and Intellectual Disabilities (or as defined by the ICD or DSM IV). The choice of age range was guided by evidence described above that EFs develop from the first year of life to late adolescence, with a peak of development during the first 5 years of life (Garon et al., 2008). Furthermore, it is possible that for some neurodevelopmental disorders a clear diagnosis cannot be formulated before the age of five, thus, it is from the end of the preschool ages that eventual alterations in EFs are expected and, in turn, interventions are needed.

2.2.2 Type of interventions

Selected studies focused on interventions aimed at improving any process belonging to the executive function domain (i.e. inhibition, working memory, shifting, planning, organization, problem solving, decision making, cognitive control, effortful control, self-regulation). Intervention could begin at any time during childhood and it could have been carried out either in an ecological context, such as home or school, or in an experimental context, such as a laboratory. The intervention had to be carried out by health professionals (such as psychologists, neuropsychiatrists or occupational therapists) or by education professionals (such as teachers or educators). Types of interventions could include any program assumed to work on EFs, such as neurocognitive stimulation, neurocognitive training, computer programs, scholastic and academic curricula, occupational therapy, neuropsychological rehabilitation, psychoeducation, mindfulness and physical activities. Any frequency, intensity and duration of training was included. Moreover, the studies included needed to have a pre-post treatment design or the presence of a control group (active or waitlist).

2.2.3 Type of outcomes

To be selected, studies must have measured far effect outcomes at the completion of the intervention.

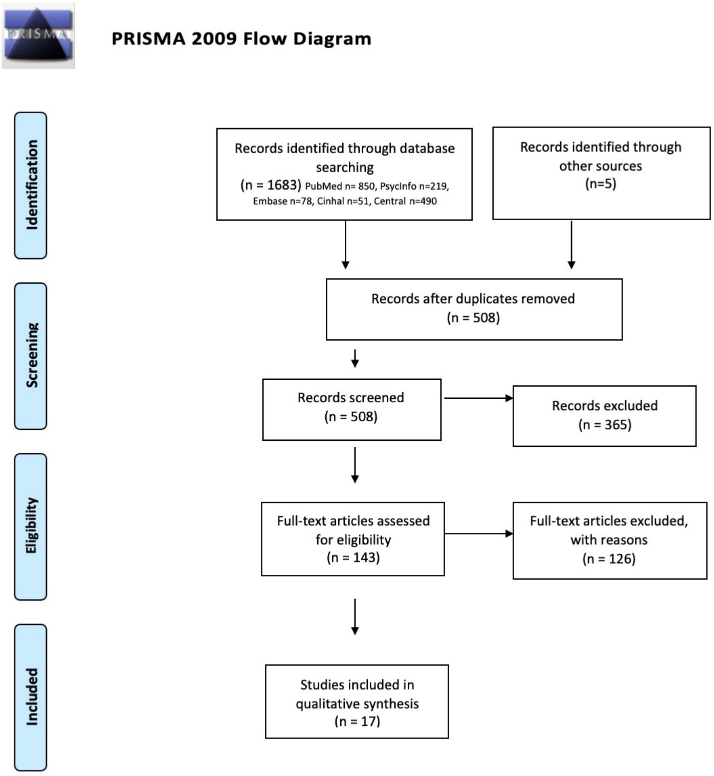
The outcome variables had to be measured with standardized, objective tests administered to the child (either commercial or prototypal/experimental) and with parent's and self-report questionnaires. These far effect measures included standardized neuropsychological and cognitive tests, achievement tests (math or reading or writing), quality of life questionnaires, self-regulation questionnaires, teachers' ratings (school readiness, general literacy skills, or math or reading or writing), report cards (literacy or math or reading or writing).

Studies were excluded if: (1) they included single case studies and reviews; (2) they were diagnostic or prognostic studies (2) participants' age was >18 or < 5 or not clearly defined; (3) they included participants with other medical, psychiatric or neurological conditions not included in the classification of neurodevelopmental disorders, (4) the training was not targeted on cognitive or neuropsychological domains, (5) there was no control group, (6) there were no far effect outcome measures.

2.3 Study selection process

The initial literature searches produced 1683 papers. Five of these studies were included by analysing the articles' bibliography. After removing duplicates, 508 articles were reviewed independently by three authors (XX1, XX2, XX3 for blind review) on the basis of the title and abstract with an inter-rater agreement of 100%. 143 full-text articles were selected and reviewed to identify those that met the inclusion criteria. When discrepancy arose, articles were discussed and re-reviewed to determine their inclusion or exclusion. The process led to the selection of 17 papers that met the inclusion criteria. The overall process for selecting studies is shown in Figure 1.

Figure 1. Study selection process following the PRISMA 2009 flow diagram



2.4 Meta-analysis

Far effect outcome measures of reviewed studies including control groups were analyzed. The data collected from the articles were analyzed using software R, version 4.1.2. All of the studies included different outcomes, divided and analyzed on the basis of 5 macro categories considered as far effects, detailed in paragraph 3.5. A multivariate random-effect linear model, making use of Hedges Estimator, was used to conduct a meta-analysis. Hedge's g values were calculated and, according to Cohen (Cohen, 1977), values of effect sizes between 0.2 and 0.5 were considered "small", between 0.5 and 0.8 "medium", and > 0.8 "large". Effect size estimates were pooled across studies to obtain an overall effect size.

3. Results

Seventeen studies were eligible for inclusion. The methodological quality of the included studies was independently assessed by the reviewers according to the National Health and Research Council (NHMRC). All studies were classified at level II, as Randomized Control Trials (Bigorra, Garolera, Guijarro, & Hervas, 2016; Bigorra, Garolera, Guijarro, & Hervás, 2016; Bowling et al., 2017; Chacko et al., 2014; de Vries et al., 2015; Dovis et al., 2015; Egeland et al., 2013; Esmaili et al., 2019; L. Kenworthy et al., 2014; H. Kirk et al., 2017; H. E. Kirk et al., 2016; Klingberg et al., 2005; Leins et al., 2007; S. D. Smith et al., 2020; Strehl et al., 2017; Weiss et al., 2018), except one that was classified at level III-1, as Pseudorandomized Control Trial (Beck et al., 2010).

3.1 Participants

Studies including children with neurodevelopmental disorders as the target population of the intervention were selected. In particular, samples were composed by children with Attention Deficit and Hyperactivity (ADHD) in ten studies (Beck et al., 2010; Bigorra, Garolera, Guijarro, & Hervas, 2016; Bigorra, Garolera, Guijarro, & Hervás, 2016; Chacko et al., 2014; Dovis et al., 2015; Egeland et al., 2013; Klingberg et al., 2005; Leins et al., 2007; S. D. Smith et al., 2020; Strehl et al., 2017), children with Autism Spectrum Disorder (ASD) in three studies, (de Vries et al., 2015; L. Kenworthy et al., 2014; Weiss et al., 2018), children with Intellectual and Developmental Disabilities (ID) in two studies (H. Kirk et al., 2017; H. E. Kirk et al., 2016) and children with Specific Learning Disabilities in one study (SLD) (Esmaili et al., 2019). Moreover, it was agreed to include one study that targets children with Behavioral Health Disorders (BHD) (Bowling et al., 2017), since, although not present in the main diagnostic classifications (DSM-5; ICD-10), a broad category including some of the neurodevelopmental disorders mentioned above (ASD, ADHD). The studies also varied in terms of the age range of the population (4-17 years) and sample size (50 to 150 subjects).

3.2 Study design

Regarding the study design, in fifteen studies, the population was divided into two groups. In five of these studies, the control group underwent a training equivalent to that of the experimental group but non-adaptive, therefore without the adjustment for difficulty (Bigorra, Garolera, Guijarro, & Hervas, 2016; Bigorra, Garolera, Guijarro, & Hervás, 2016; Chacko et al., 2014; H. Kirk et al., 2017; H. E. Kirk et al., 2016; Klingberg et al., 2005), in four studies the control group consisted in the waitlist (Beck et al., 2010; Bowling et al., 2017; Esmaili et al., 2019; Weiss et al., 2018), in three studies the experimental group's performance was compared with that of an active control group following an intervention not focused on EFs . Kenworthy et al., 2014; Leins et al., 2007; Strehl et al., 2017), and in two studies the control group received treatment as usual (Egeland et al., 2013; S. D. Smith et al., 2020). In two studies, the population was divided into three groups: two experimental groups and one control group, which underwent non-adaptive training (de Vries et al., 2015; Dovis et al., 2015).

3.3 Intervention

All the selected articles provided results about an intervention aimed at executive functions rehabilitation. Such treatments were undertaken in several ways. Specifically, most of the interventions included computer training activities (Beck et al., 2010; Bigorra, Garolera, Guijarro, & Hervas, 2016; Bigorra, Garolera, Guijarro, & Hervás, 2016; Chacko et al., 2014; de Vries et al., 2015; Dovis et al., 2015; Egeland et al., 2013; Kirk et al., 2017; . Kirk et al., 2016; Klingberg et al., 2005); in addition, among the selected articles there were two neurofeedback treatments (Leins et al., 2007; Strehl et al., 2017), two curriculum interventions delivered during school attendance (Kenworthy et al., 2014; Smith et al., 2020), an individualized manualized Cognitive Behavioural Therapy (CBT) intervention (Weiss et al., 2018), a training delivered through cooperative and collaborative group play activities at the clinic (Esmaili et al., 2019) and finally an intervention based on physical activity (Bowling et al., 2017).

In most studies, the intervention targeted cold components of executive functions, specifically working memory (Beck et al., 2010; Bigorra, Garolera, Guijarro, & Hervas, 2016; Bigorra, Garolera, Guijarro, & Hervás, 2016; Chacko et al., 2014; de Vries et al., 2015; Dovis et al., 2015; Egeland et al., 2013; Esmaili et al., 2019; Klingberg et al., 2005; Smith et al., 2020), inhibition (Dovis et al., 2015; Esmaili et al., 2019; Leins et al., 2007; Smith et al., 2020) and attentional control Kirk et al., 2017; H. E. Kirk et al., 2016; Leins et al., 2007; Smith et al., 2020), while others aimed at strengthening other executive functions such as planning, problem-solving, shifting, monitoring and cognitive flexibility (de Vries et al., 2015; Dovis et al., 2015; Esmaili et al., 2019; Kenworthy et al., 2014). Four studies targeted the hot components of executive functions, in particular self-regulation and emotional regulation, as intended by the Miyake model (2000) (Bowling et al., 2017; Esmaili et al., 2019; Strehl et al., 2017; Weiss et al., 2018).

These interventions were carried out in different settings; at home in ten studies (Beck et al., 2010; Bigorra, Garolera, Guijarro, & Hervas, 2016; Bigorra, Garolera, Guijarro, & Hervás, 2016; Chacko et al., 2014; de Vries et al., 2015; Dovis et al., 2015; Kirk et al., 2017; Kirk et al., 2016; Klingberg et al., 2005; Weiss et al., 2018), at school in five studies (Bowling et al., 2017; Egeland et al., 2013; Kenworthy et al., 2014; Smith et al., 2020; Weiss et al., 2018) and at the clinic in three studies (Esmaili et al., 2019; Leins et al., 2007; Strehl et al., 2017).

The duration of the interventions ranged from 5 weeks to 3 months; only one study involved a treatment in which the 28 sessions were spread over a year (Kenworthy et al., 2014).

The intensity of the intervention varied from 2 times a week to daily, twice a week in three studies (Bowling et al., 2017; Esmaili et al., 2019; Strehl et al., 2017), 3-4 times a week in one study (. Smith et al., 2020), 5 times a week in seven studies (Bigorra, Garolera, Guijarro, & Hervas, 2016; Bigorra, Garolera, Guijarro, & Hervás, 2016; Chacko et al., 2014. Kirk et al., 2017; Kirk et al., 2016; Klingberg et al., 2005; Leins et al., 2007). In one study, frequency of intervention corresponded to the total days of school attendance (Egeland et al., 2013). Of the articles examined, five studies did not report the frequency of intervention but the overall duration of the intervention: 6 weeks (de Vries et al., 2015), 10-14 weeks (Weiss et al., 2018), 28 sessions (Kenworthy et al., 2014), 25 sessions over 5-6 weeks (Beck et al., 2010) and the last one, 25 sessions over 5 weeks (Dovis et al., 2015). The duration of each single treatment session ranged from 20 minutes to 2 hours.

3.4 Far effect outcomes

According to the research questions of the studies, different far effects were measured. However, it was possible to outline some common aspects that had been investigated, regardless of the type and target of the author's intervention. Most of the authors investigated whether, as a consequence of training on specific executive functions, improvements were obtained on other executive functions not directly trained. For example, Bigorra and colleagues (2016a, 2016b) conducted two interventions on working memory and explored the far effect on inhibition, sustained attention, planning, cognitive flexibility, task switching (study 1) and decision making (study 2). De Vries and colleagues (2014) explored inhibition, sustained attention, working memory or cognitive flexibility and their intervention was directed to working memory or cognitive flexibility. Dovis and colleagues (2015) led a training on visuospatial working memory, inhibition and cognitive flexibility and studied the far effect on interference control, verbal short-term memory/working memory and complex reasoning. For Egeland and colleagues (2013) working memory was the target intervention and processing speed, attention, inhibitory control were assessed as far effects. Klingberg and colleagues (2005) implemented a working memory training and studied inhibition as a far effect. All these studies implemented neuropsychological outcome measures. Finally, Kirk and colleagues' (2017) intervention target was attentional control and response inhibition while Beck and colleagues' (2010) was working memory and both studies investigated parent and teacher-report child daily executive functioning as outcome measures.

Another common target of investigation was the study of any changes, following the training, in the disorder's specific symptomatology: ADHD symptoms (Beck et al., 2010; Bigorra, Garolera, Guijarro, & Hervás, 2016; Chacko et al., 2014; de Vries et al., 2015; Dovis et al., 2015; Egeland et al., 2013; Kirk et al., 2016; Klingberg et al., 2005; Leins et al., 2007; Smith et al., 2020; Strehl et al., 2017), autism symptoms (Kenworthy et al., 2014), mood (Weiss et al., 2018) referred by parents and teachers or by the clinician (Smith et al., 2020; Strehl et al., 2017; Weiss et al., 2018).

The majority of studies assessed the child's daily life functioning, including adaptive behaviour (Bigorra, Garolera, Guijarro, & Hervás, 2016; Dovis et al., 2015; Egeland et al., 2013; Kirk et al., 2017; Leins et al., 2007; Strehl et al., 2017; Weiss et al., 2018), quality of life (de Vries et al., 2015; Dovis et al., 2015; Esmaili et al., 2019; Strehl et al., 2017), classroom functioning (Bowling et al., 2017; Kenworthy et al., 2014), and social skills (Bigorra, Garolera, Guijarro, & Hervas, 2016; de Vries et al., 2015).

A recurring aspect that was investigated with direct outcome measures was the child's learning skills such as reading comprehension (Bigorra, Garolera, Guijarro, & Hervás, 2016), math, vocabulary, letter knowledge and rhyme detection (Kirk et al., 2017), reading and math (Egeland et al., 2013), word reading, sentence comprehension, spelling, and mathematical computation (Chacko et al., 2014).

Finally, a few studies explored other cognitive outcomes as far effect: memory (Egeland et al., 2013), complex non-verbal reasoning (Dovis et al., 2015; Klingberg et al., 2005; Strehl et al., 2017) and intelligence (Leins et al., 2007).

3.5 Efficacy on far effects

Results will be presented dividing the selected articles according to the EF component target of the intervention. Within each section, the studies will be reported analyzing the far effects investigated, which are categorized into 5 macro categories, agreed upon by the authors of this systematic review. These macro-categories grouped the different outcomes assessed as far effects (other executive functions, clinical symptoms, learning skills, daily life functioning and cognitive outcomes).

3.5.1 Intervention on attentional control and inhibition

Kirk et al. (2016), Kirk et al. (2017), Leins et al. (2006) analysed the effects of interventions targeting attention and inhibition (Table 1).

One study (Kirk et al., 2017) evaluated improvement of executive functions in daily life with parent and teacher report questionnaires, finding no significant far effect of the computerized attentional training on children with intellectual disability.

Two studies evaluated a reduction of ADHD symptomatology (rating scales) as a far effect of the interventions. Kirk et al. (2016) found no significant effects of the computerized attentional training in children with intellectual and developmental disabilities, while Leins et al. (2006), in children with ADHD found a significant reduction in symptoms after neurofeedback interventions in the two experimental groups, but in absence of a control group and without observing specific differences between the two types of treatment.

Only Kirk et al. (2017) considered the improvement in learning skills (defined as both academic skills and as abilities supporting learning) as a far effect, finding significant effects only for mathematic skills at the three-month follow-up, while no effects were found in cognitive skills underlying school learning, such as the receptive vocabulary and metaphonological skills neither at the post-test nor at the follow-up assessment.

The two studies, which evaluated children's daily life functioning through parent report questionnaires, did not find significant effects, neither in terms of improvement of behavioural and emotional problems (Kirk et al., 2017), nor of behavioural problems at home (Leins et al., 2007).

Leins et al. (2007) evaluated cognitive functioning (German intelligence test for children) as a far effect of the intervention, finding a significant increase in both neurofeedback intervention groups, however, these results were not compared with any control group.

Table 1. Studies implementing interventions on attentional control and inhibition

Legend: RCT Randomized Controlled Trial; ID Intellectual Disability; ADHD Attention Deficit Hyperactivity Disorder; EG Experimental Group; CG Control Gropu; DSM IV Diagnostic and Statistical Manual of mental disorders; WATT Wilding attention battery; TAP Testbatterie zur Aufmerksamkeitsprufung; GAN Give A Number ;TEMA Test of Early Mathematics Ability; PPVT-4 Peabody Picture Vocabulary Task-4; PAT Phonological Abilities Test; BRIEF Behavior Rating Inventory of Executive Functions; WMRS Working Memory Rating Scale;DBC-P Developmental Behavior Checklist Parent; SWAN Strengths and Weaknesses of ADHD symptoms and Normal behavior scale; ECBI Eyberg Child Behavior Inventory; HAWIK III The Hamburg-Wechsler intelligenztest fur Kinder.

Authors	**Study design**	**Diagnosis**	**Population**	**Age**	**Intervention**	**Target of intervention**	**Duration**	**Intensity**	**Assessment of near effect**	**Assessment of far effect**	**Near effects**	**Far effects**
Kirk et al., (2017)	RCT	ID	EG n=38, CG n=37 (non-adaptive training)	4-11 yrs	Training Attention and Learning Initiative (TALI): computer training at home	Selective attention, sustained attention, attentional control (conflict resolution; response inhibition)	5 wks (25 sessions)	20 minutes per day, 5 times a week	Not investigated	Learning skills: GAN, TEMA-3, PPVT-4, PAT (letter knowledge and rhyme detection subscales). Other executive Functions: BRIEF, WMRS. Daily life functioning: DBC-P	-	Yes, on mathematical learning skills (TEMA) at 3 months follow-up. No other learning skills, executive functions non-trained and daily life functioning.
Kirk et al., (2016)	RCT	ID	EG n=38, CG n=37 (non-adaptive training)	4-11 yrs	Training Attention and Learning Initiative (TALI): computer training at home	Selective attention, Sustained attention, attentional control (conflict resolution; response inhibition)	5 wks (25 sessions)	20 minutes per day, 5 times a week,	Selective attention, attentional control and sustained attention: WATT (visual search task; sustained attention task)	Clinical Symptoms: SWAN	Yes, on selective attention (Number of No on attentional control, selective attention (time) and sustained attention	No significant treatment effect found.
Leins et al., (2007)	RCT	ADHD	EG1 (SCP) n=19, EG2 (Theta/beta) n=19	8-13 yrs	Neurofeedback in clinic	Attention, inhibition	2 wks (10 sessions) for three treatment phases with a break of 4 to 6 weeks between each phase.	1 hr per session	Attention: TAP	Clinical symptoms: DSM-IV—questionnaires for parents and teachers, Conners' Rating Scale Daily life functioning: ECBI Cognitive outcomes: HAWIK-III	Yes, on attention for both EGs	No differences between EG on clinical symptoms (Conners' Rating Scale, DSM IV questionnaires), on daily life functioning (ECBI) and on Cognitive outcomes (HAWIK-III). At post hoc analysis significant improvement only for EG 2 on cognitive outcomes and on clinical symptoms.

3.5.2 Intervention on working memory

Seven of the studies (Beck et al., 2010; Bigorra, Garolera, Guijarro, & Hervas, 2016; Bigorra, Garolera, Guijarro, & Hervás, 2016; Chacko et al., 2014; de Vries et al., 2015; Egeland et al., 2013; Klingberg et al., 2005) analysed the effects of interventions targeting working memory (Table 2).

Among the six studies that included other executive functions, assessed with neuropsychological measures, as far effects of the intervention in children with ADHD, three found significant effects on response inhibition (Bigorra, Garolera, Guijarro, & Hervás, 2016; Egeland et al., 2013; Klingberg et al., 2005), one on sustained attention (Bigorra, Garolera, Guijarro, & Hervás, 2016), and one on cognitive flexibility (Egeland et al., 2013). On the contrary, Bigorra et al. (2016b) found no significant effects in improving decision making and De Vries et al. (2015) found no significant effects on sustained attention, inhibition, and cognitive flexibility in children with ASD. Some studies assessed far effects on other executive functions by means of parent or teacher report questionnaires (BRIEF), finding significant effects (Beck et al., 2010; Bigorra, Garolera, Guijarro, & Hervás, 2016) indicating an improvement on executive functions in ecological settings. On the other hand, Egeland et al. (2013) and De Vries et al. (2015) reported no significant effect of the intervention in increasing executive functioning in daily life.

Among the six studies that included the reduction of clinical symptoms, measured with teacher or parent-report, as a far effect of working memory interventions, three studies found a significant reduction in ADHD-related symptoms in children with this neurodevelopmental disorder (Beck et al., 2010; Bigorra, Garolera, Guijarro, & Hervás, 2016; Klingberg et al., 2005). In contrast, other studies did not find significant effects in reducing ADHD-clinical symptoms neither in children with ADHD (Chacko et al., 2014; Egeland et al., 2013) nor in children with ASD (de Vries et al., 2015). Furthermore, when ADHD symptomatology was assessed with direct measures, as attention, activity level and impulse control measured by actigraphs (Chacko et al., 2014) and by the number of head movements measured by an infrared camera (Klingberg et al., 2005), no significant far effects were reported.

Among the three studies that evaluated the improvement of learning skills as a far effect of the intervention, only Egeland et al. (2013) found significant effects in improving speed and accuracy of reading. No significant effects were found in improving reading comprehension (Bigorra, Garolera, Guijarro, & Hervás, 2016), math skills (Egeland et al., 2013), word reading, sentence comprehension, spelling, and mathematical computation (Chacko et al., 2014).

Among the four studies that evaluated functioning in daily life (behaviour, social skills, quality of life), only Bigorra et al. (2016) found a significant effect in improving school learning behaviour (i.e. need for an extra help at school, grades that are below potential), assessed through a parent report questionnaire, while no significant effects were found in improving behavioural and emotional skills (Bigorra, Garolera, Guijarro, & Hervás, 2016; Egeland et al., 2013), social skills (de Vries et al., 2015) or quality of life (de Vries et al., 2015). Finally, a direct test assessing of theory of mind skills (Bigorra, Garolera, Guijarro, & Hervas, 2016) did not yield any improvement.

In the two studies that considered an improvement in cognitive processes as a far effect of the intervention, Klingberg et al. (2005) found a significant effect in improving non-verbal reasoning abilities (Raven's Matrices), while Egeland et al. (2013) found no significant effects on auditory long term memory (word recall and recognition).

Table 2. Studies implementing interventions on working memory

Legend: RCT Randomized Controlled Trial; ADHD Attention Deficit Hyperactivity Disorder; ASD Autism Spectrum Disorder; EG Experimental Group; CG Control Gropu; DSM IV Diagnostic and Statistical Manual of mental disorders; WM Working Memory; WMtr Working memory training; TAU Treatment As Usual; WISC IV Wechsler Intelligence Scale for Children-IV; WMS III Wechsler Memory Scale-III; BRIEF Behavior Rating Inventory of Executive Functions; Corsi – BTT Corsi Block Tapping Task; GEWT Gender Emotion Switch Task; NGST Number gnome switch task; BVRT Benton Visual Retention Test; AWMA The Automatic Working Memory Assessment; CCPT-II Conners' Continuous Performance Test-II; TOL Tower of London; WSCT Wisconsin Card Sorting Test; TMT – B Trail Making Test; CBCL Child Behaviour Checklist; TRF Teacher's report Form/4-18; SDQ Strenght and Difficulties Questionnaire; WFIRS Weiss Functional Impairment rating scale for parents; IGT Iowa Gambling Task; SART Sustained attention response task; CSBQ Children's Social Behavior Questionnaire; PedsQL The Pediatric Quality of Life Inventory; DBDRS parent version of the Disruptive Behavior Disorders Rating Scale; CW Color Word; DKEFS Delis-Kaplan Executive Function System; CAVLT-2 Children's Auditory Verbal Learning Tests-2; ARS ADHD Rating Scale; WRAT4-PMV Wide Range Achievement Test 4 Progress Monitoring Version; CPM Colour Progressive Matrices; ChIPS Children's Interview for Psychiatric Syndromes–Parent Form

Authors	**Study design**	**Diagnosis**	**Population**	**Age**	**Intervention**	**Target of intervention**	**Duration**	**Intensity**	**Assessment of near effect**	**Assessment of far effect**	**Near effects**	**Far effects**
Bigorra et al., (2016a)	RCT	combined-type ADHD	EG n=36, CG (non-adaptive CogMed training) n=30	7-12 yrs	CogMed computer training at home	Spatial and verbal WM	5 wks	5 sessions for week	WM: WISC IV (Digit Span Backward, letter-Number Sequencing), WMS-III (Spatial span backward); BRIEF (WM subscale)	Other Executive functions: BRIEF, CPT II, ToL, WCST-64 and TMT B. Clinical symptoms: Conners' rating scales-revised, CBCL/4-18, TRF/4-18 Daily life functioning: SDQ, Learning skills: Canals	Yes, on BRIEF WM subscale and on a WM composite score	Yes, on other executive functions (BRIEF, CPT), clinical symptoms (composite score) and daily life functioning (school learning behavior at WFIRS-P, only at follow-up) No on learning skills
Bigorra et al., (2016b)	RCT	combined-type ADHD	EG n= 36, CG (non-adaptive CogMed training) n=30	7-12 yrs	CogMed computer training at home	Spatial and verbal WM	5 wks	5 sessions for weeks	WM: WISC IV (Digit Span Backward, Letter-Number Sequencing), WMS-III (Spatial span backward)	Daily life functioning: Happè's Strange Stories, Folk Psychology Test Other Executive function: IGT	Yes, the results are reported in the previous article (Bigorra et al., 2016)	No significant treatment effects found.
De Vries et al., (2015)	RCT	ASD	EG1 (WMtr) n=40, EG2 (FLEXtr) n=37, CG (non-adaptive mock training) n=38	8-12 yrs	Braingame Brian: computer training at home	EG1: 5 WM activities with increasing difficulties (remembering, manipulating and updating). EG2: One Cognitive Flexibility activity with increasing difficulty	6 wks (25 sessions)	Not reported	WM: Corsi-BTT (similar to activities' training), N back task (different to activities' training); Cognitive Flexibility: GEWT (similar to activities' training), NGST (different to activities' training)	Other executive functions: Stop task, SART, BRIEF. Daily Life Functioning: CSBQ, PedsQL. Clinical symptoms: DBDRS.	No significant differences between groups for working memory and cognitive flexibility.	No significant treatment effects found.

Egeland et al., (2013)	RCT	ADHD	EG (TAU + Cogmed) n=38, CG (TAU) n=37	10-12 yrs	CogMed computer training at school	Spatial and verbal WM	5-7 wks	Each school day (30-45 minutes)	WM: BVRT	Other executive functions: CW, TMT (D-KEFS), BRIEF, CCPT-II Cognitive outcomes: CAVLT-2 Learning skills: Key Math, LOGOS Clinical symptoms: ARS-IV Daily life functioning: SDQ	No	Yes, on reading learning skills. No on cognitive outcomes (CAVLT-2), maths learning skills, other executive functions (CW, TMT (D-KEFS), BRIEF, CCPT-II), clinical symptoms (ARS-IV) and daily life functioning (SDQ).
Chacko et al., (2014)	RCT	ADHD	EG n=44, CG (Non adaptive training) n=41	7-11 yrs	Cogmed computer training at home	verbal and non-verbal WM	25 sessions	Fine days per week (30–45 minute)	WM: AWMA	Clinical symptoms: DBD, actigraphs Learning skills: WRAT4-PMV	Yes, on WM (non-verbal and verbal storage) but no significant differences between groups on measures of nonverbal or verbal complex working memory (storage plus processing/manipulation)	No significant treatment effects found.
Klingberg et al., (2005)	RCT	ADHD	EG n=26, CG (non adaptive WM training) n=24	7-12 yrs	Cogmed computer training at home	Spatial and verbal WM	5-6 wks (25 sessions)	40 minutes per day every day	Visuo-spatial WM: span-board task. Verbal WM: Digit-span (WISC III)	Clinical symptoms: parent and teacher-report Conners Rating Scale, number of head movements Cognitive outcomes: CPM Other executive functions: Stroop Task	Yes, on visuo-spatial and verbal WM	Yes, on other executive functions (Stroop task), cognitive outcomes (CPM) and on parent ratings clinical symptoms No on teacher rating clinical symptoms
Beck et al., (2010)	NRS	combined type or inattentive type ADHD	EG n= 27, CG (waitlist) n=25	7-17 yrs	Working Memory Training Program: computer training at home	Spatial and verbal WM	5-6 wks (25 sessions)	30-40 minutes per session	WM: BRIEF (WM subscale)	Other executive functions: BRIEF (other subscales) Clinical symptoms: P-ChIPS, Conners' Rating Scale - teacher and parents	Yes, on WM (for parents at post training and at 4-month follow up, for teachers only at follow up)	Yes, on clinical symptoms (ChIPS, Conners' Rating Scale) and on other executive functions (BRIEF)

3.5.3 Intervention on cognitive flexibility

Only one of the studies included in this systematic review analysed the effects of a treatment aimed at improving cognitive flexibility (de Vries et al., 2015) (Table 3). No significant far effects were reported for children with ASD: neither on other executive functions assessed through questionnaires and standardized tests, nor on clinical symptoms, daily life functioning, or on quality of life.

Table 3. Studies implementing intervention on cognitive flexibility.

Legend: RCT Randomized Controlled Trial; ASD Autism Spectrum Disorder; EG Experimental Group; CG Control Group; DSM IV; WM Working Memory; WMtr Working memory training; FLEXtr Flexibility training; Corsi – BTT Corsi Block Tapping Task; GEWT Gender Emotion Switch Task; NGST Number gnome switch task; SART Sustained attention response task; BRIEF Behavior Rating Inventory of Executive Functions – parent; CSBQ Children's Social Behavior Questionnaire; PedsQL The Pediatric Quality of Life Inventory; DBDRS parent version of the Disruptive Behavior Disorders Rating Scale;

Authors	**Study design**	**Diagnosis**	**Population**	**Age**	**Intervention**	**Target of intervention**	**Duration**	**Intensity**	**Assessment of near effect**	**Assessment of far effect**	**Near effects**	**Far effects**
De Vries et al., (2015)	RCT	ASD	EG1 (WMtr) n=40, EG2 (FLEXtr) n=37, CG (non-adaptive mock training) n=38	8-12 yrs	Braingame Brian: computer training at home	EG1: 5 WM activities with increasing difficulties (remembering, manipulating and updating). EG2: One Cognitive Flexibility activity with increasing difficulty	6 wks (25 sessions)	Not reported	WM: Corsi-BTT (similar to activities' training), N back task (different to activities' training); Cognitive Flexibility: GEWT (similar to activities' training), NGST (different to activities' training)	Other executive functions: Stop task, SART, BRIEF. Daily Life Functioning: CSBQ, PedsQL. Clinical symptoms: DBDRS.	No significant differences between groups for working memory and cognitive flexibility.	No significant treatment effects found.

3.5.4. Intervention on hot executive functions

Three studies (Bowling et al., 2017; Strehl et al., 2017; Weiss et al., 2018) investigated the effects of interventions (physical activity through virtual reality, emotional regulations trainings, neurofeedback) aimed at improving the "hot" component of executive functions on clinical symptomatology, daily life functioning and intelligence in children with different neurodevelopmental disorders (Table 4).

Two studies evaluated the improvement of clinical symptoms as a far effect of the intervention. Specifically, Weiss et al., (2018) found significant effects in the improvement of symptomatology related to mood and behavioural disorders through parent report questionnaires and in the global clinical assessment evaluated by clinicians, while Strehl et al. (2017) found significant effects in terms of a decrease of inattention and hyperactivity from the analysis of teacher and parent report questionnaires, while there was no significant effect as expressed by the clinicians Global Clinical Impression (CGI).

All three studies evaluated functioning in daily life as a far effect of the intervention, finding significant effects on classroom functioning (Bowling et al., 2017) and on emotional and behavioural problems perceived by parents (Weiss et al., 2018). Instead, the neurofeedback intervention (Strehl et al., 2017) yielded no significant effects on the reduction of behavioural and emotional impairments assessed by parents and teachers or on the quality of life.

Only Strehl et al. (2017) evaluated cognitive outcomes, finding significant effects in improving non-verbal reasoning (Raven's Matrices) in the neurofeedback group compared to the electromiography feedback group.

Table 4. Studies implementing interventions on hot executive functions

Legend: RCT Randomized Controlled Trial; ASD Autism Spectrum Disorder; ADHD Attention Deficit Hyperactivity Disorder, BHD behavioral health disorders; EG Experimental Group; CG Control Group; EMG Electromiography; VR Virtual Reality; CATRS Conner's abbreviated teacher rating scale; ERSSQ-P Emotion Regulation and Social Skills Questionnaire; ERC Emotion Regulation Checklist; CEM Children's Emotion Management Scales; TOC Time out of class; BASC-2 Behavior Assessment System for Children, Second Edition – Parent Rating Scales; ADIS-P Anxiety Disorders Interview Schedule – Parent Version; CGI Clinical Global Impression; SDQ Strenght and Difficulties Questionnaire; Kid-KINDL German quality of life assessment for kids; CPM Colour progressive matrices.

Authors	**Study design**	**Diagnosis**	**Population**	**Age**	**Intervention**	**Target of intervention**	**Duration**	**Intensity**	**Assessment of near effect**	**Assessment of far effect**	**Near effects**	**Far effects**
Bowling et al., (2017)	RCT	BHD (ASD, ADHD, anxiety disorders, depressive disorders)	EG n=52, CG (waitlist) n=52	7-16 yrs	Manville Moves: VR-cybercycling at school	Self-regulation	7 wks	2 sessions per week (30-40 minute)	Behavioural self-regulation: CATRS-10	Daily life functioning: classroom functioning (TOC per days)	Yes	Yes
Weiss et al., (2018)	RCT	ASD	EG n=31, CG (waitlist) n= 29	8-12 yrs	Secret Agent Society: Operation Regulation at home and school	Emotional regulation	10-14 wks	Not reported	Emotional regulation: ERSSQ-P, ERC, CEM, Dylan, James	Daily life functioning: BASC-2. Clinical symptoms: ADIS-P, CGI-S, BASC-2	Yes, on parent report emotional regulation measures. No significant group differences on any of the child-reported ER measures.	Yes, on daily life functioning (BASC -2) and clinical symptoms (ADIS-P, CGI-S) Gains maintained at follow-up.
Strehl et al., (2017)	RCT	ADHD	EG1 (Neurofeedback) n=76, EG2 (EMG Feedback) n=74	7-9 yrs	Neurofeedback; EMG feedback in clinics	Self-regulation	3 months (25 sessions with a break after 12 sessions of 4–6 weeks.)	2-3 sessions per week	Cortical self-regulation ADHD symptoms: German ADHD rating scale (subscale inattention, hyperactivity and impulsivity)	Clinical symptoms: Parents' ratings of ADHD subdomains, Teachers' ratings of ADHD symptoms,CGI-I Daily life functioning: SDQ, Kid-KINDL Cognitive outcomes: CPM	Yes, EG1 was significantly superior to EMG in reducing ADHD core symptoms	Yes, there are significant differences between EG groups on clinical symptoms (Parents' Ratings of ADHD Subdomains on impulsivity and inattention) and on cognitive outcomes (CPM) No, there are not differences between EG groups on clinical symptoms (Teachers' Ratings of ADHD Core Symptoms and CGI-I) and on daily life functioning (Kid-KINDL,SDQ)

3.5.5 Integrated intervention on different EF components

Four (Dovis et al., 2015; Esmaili et al., 2019; L. Kenworthy et al., 2014; S. D. Smith et al., 2020) of the studies investigated the effects of integrated trainings, that is, interventions simultaneously training different components of executive functions in children with different neurodevelopmental disorders (Table 5).

Dovis et al. (2015) evaluated the improvement in other executive functions than the target ones, in children with ADHD finding no significant effects either in the improvement of verbal working memory evaluated through standardized direct tests, or in executive functioning in the context of daily life evaluated through parent report questionnaires.

Among the three studies that evaluated the reduction of clinical symptoms as a far effect of the intervention, Dovis et al. (2015) found significant effects in ADHD behaviour perceived by teachers, but not by parents, while Smith et al. (2020) found no significant reduction in ADHD symptoms as assessed by clinicians, nor as perceived by parents and teachers in children with ADHD. Finally, Kenworthy et al. (2014) found no significant reduction in ASD symptoms in children with this disorder.

Kenworthy et al. (2014) found significant effects in classroom functioning of children with ASD after the intervention, assessed by an external blind researcher using observational measures. Instead, Esamaili et al. (2019) in children with specific learning disability, found no significant effects in children’s perceived competence in everyday activities, and Dovis et al. (2015) found no significant effects, in children with ADHD in improving children's motivational behaviours, neither in decreasing problematic behaviours at home and in public situations as assessed by parent report questionnaires nor in quality of life.

Only Dovis et al. (2015) evaluated the improvement of cognitive abilities, finding no significant effects in the improvement of non-verbal reasoning skills (Raven’s Matrices).

Table 5. Studies implementing integrated interventions

Legend: RCT Randomized Controlled Trial; ASD Autism Spectrum Disorder; ADHD Attention Deficit Hyperactivity Disorder; SLD Specific Learning Disability; EG Experimental Group; CG Control Group; TAU Treatment As Usual; SS Social Skills intervention; WM Working Memory; BRIEF Behavior Rating Inventory of Executive Functions; BD Block design; CT Challenge Task; CVLT Verbal Learning and Memory; WRAML-2 Wide Range Assessment of Memory and Learning–Second Edition - visuo spatial memory feed foward and backward; CBTT Corsi Block Tapping Task; TMT Trail Making Test; COSA Child Occupational Self-Assessment; SRS Social Responsiveness Scale; CGI-IThe Clinical Global Impression-Improvement; SNAP The Swanson, Nolan and Pelham Teacher and Parent Rating Scale; CPM Colour Progressive Matrices; DBDRS Disruptive Behavior Disorders Rating Scale; PedsQL Pediatric Quality of Life Inventory; SPSRQ-C Sensitivity to Punishment and Sensitivity to Reward Questionnaire for children; HSQ Home Situations Questionnaire

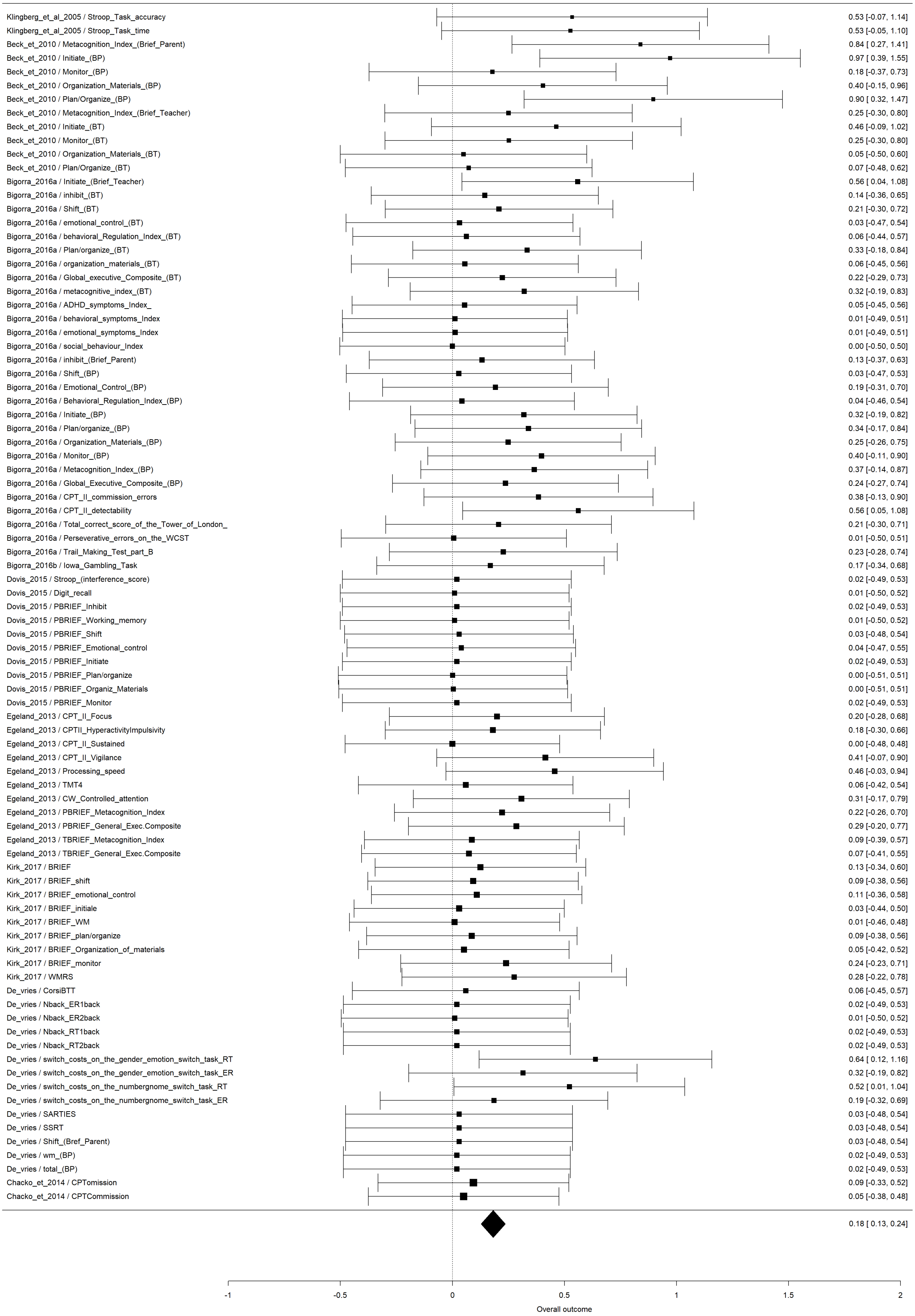
Authors	Study design	Diagnosis	Population	Age	Intervention	Target of intervention	Duration	Intensity	Assessment of near effect	Assessment of far effect	Near effects	Far effects
Esmaili et al., (2019)	RTC	SLD	EG n=28, CG (waitlist) n=28	7-11 yrs	Peer- activities in groups: cooperative and collaborative plays in clinic	Inhibition, shifting, emotional control, working memory, initiation, planning, organization of materials, and monitoring	9 wks	2 sessions per week (3 hr)	Executive functions: BRIEF	Daily life functioning: COSA	Yes	No significant treatment effects found.
Kenworthy et al., (2014)	RCT	ASD	EG n=47, CG (SS intervention) n=20	7-11 yrs	Unstuck and On Target (UOT): curriculum at school	Flexibility, goal-setting, planning, using internalized language to support problem-solving	1 year (28 sessions for children, 1 session for parents and 1 session for teachers)	30-40 minutes	Problem solving: BD. Flexibility and planning: CT. Executive Functions: BRIEF	Clinical symptoms: SRS. Daily life functioning: Classroom functioning (Classroom Observations Coding Form)		Yes on daily life functioning (classroom functioning). No on clinical symptoms.
Smith et al., (2020)	RCT	ADHD	EG n=48, CG (TAU) n=44	5-9 yrs	Integrated Brain, Body and Social intervention (IBBS) at school	EF: Sustained attention, response inhibition, working memory, directed attention, attentional switching, divided attention, visual searching. OTHER: category formation, speed of processing, oppositional behavior, disruptive behavior	15 wks (60 sessions)	In USA: 3-4 days per week (2 hour); In China: 3 days per week (90 minutes)	Memory and Learning: CVLT, WRAML-2. Interference control: Flanker task.	Clinical symptoms: CGI-I, SNAP	Yes on memory and learning (CVLT) No significant treatment effect on memory and learning (WRAML-2) and interference control.	No significant treatment effects found.
Dovis et al., (2015)	RCT	combined-type ADHD	EG1 (full active condition) n=31, EG2 (partially active condition) n=28, CG (placebo non adaptive condition) n=30	8-12 yrs	Braingame Brian: computer training at home	EG1: visuospatial WM, Inhibition and cognitive flexibility EG2: inhibition and cognitive flexibility	5 wks (25 sessions)	Not reported (35-50 minutes per session)	Visuospatial short term memory and WM: CBTT Inhibition: Stop Task Cognitive Flexibility: TMT	Interference control: Stroop Color and Word Test Other executive functions: Digit span, BRIEF Cognitive outcomes: CPM Clinical symptoms: DBDRS Daily life functioning: PedsQL, SPSRQ-C, HSQ	Yes: EG1 improved on visuospatial short term memory, WM and inhibition; EG2 improved on inhibition, but not on visuospatial short term memory and WM	Yes there are significant differences between EG groups on other executive functions (interference control) No, there are not significant differences between EG groups on other executive functions (Digit Span, BRIEF), cognitive outcomes (CPM), clinical symptoms (DBDRS) and daily life functioning (PedsQL, SPSRQ-C, HSQ).

3.6 Metanalysis results

3.6.1 Non-trained executive functions

All of the 9 studies that assessed a non-trained EF as far effect was included in the metanalysis, considering 87 outcome measures. According to the multivariate random-effect model, overall effect size was statistically significant ($p < 0.0001$), estimated as 0.18 (95% CI: [0.13, 0.24]) (Fig. 1). Among the studies with a greater effect size (0.52-0.97), two (Beck et. al 2010, Bigorra et al., 2016a) assessed non trained EF with an indirect (teacher or parent questionnaires) measure of everyday executive functioning, and two with a direct measure of attentional control (Bigorra et al. 2016a) and switching (de Vries et al., 2015) (Figure 2).

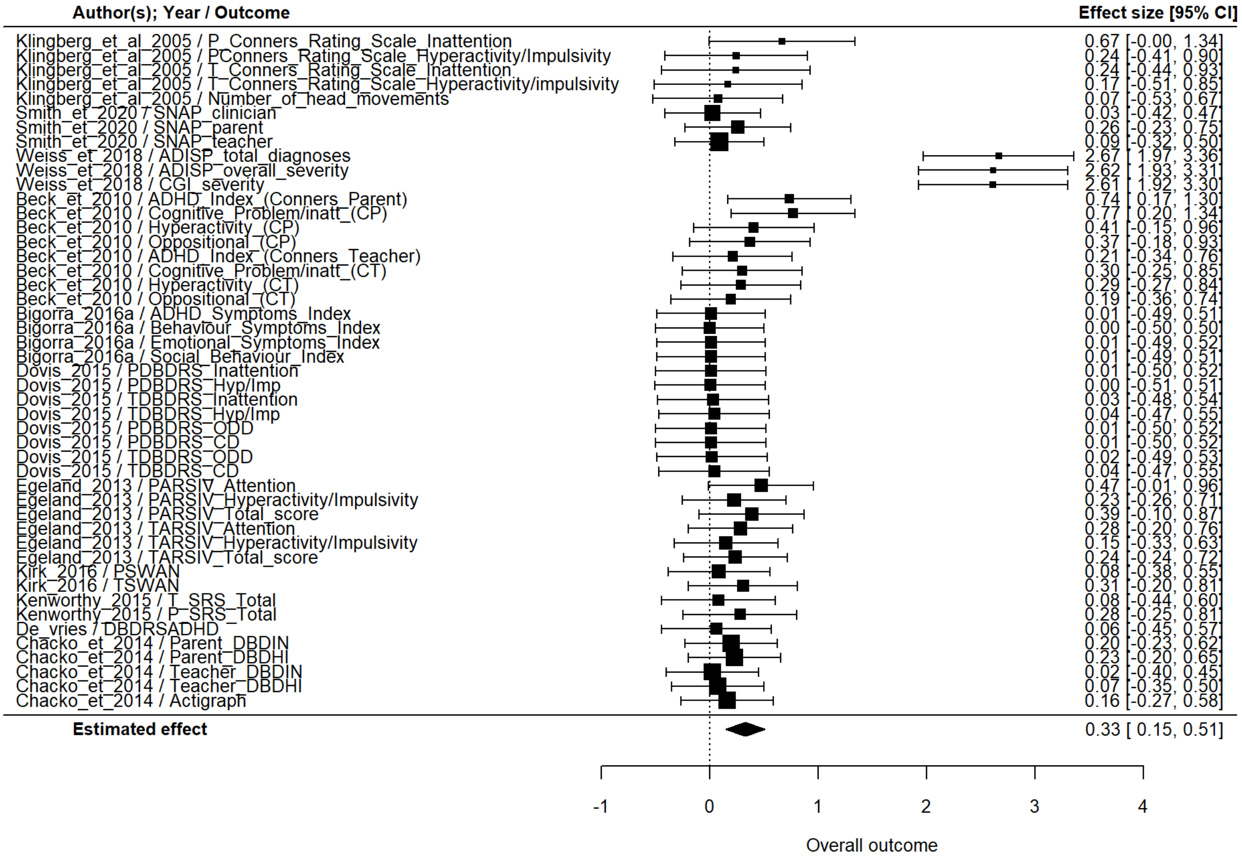
Figure 2. Metanalysis results of far effect on other executive functions.



3.6.2 *Clinical symptoms*

Among the 13 studies that assessed clinical symptoms as the far effect, only those with a control group were included. For this reason, two studies were excluded (Leins et al. 2006, Strehl et al., 2017). Other measures included in some studies (Smith et al., 2020; Weis et al., 2018) have been excluded because of zero sample variance. According to the multivariate random-effect model, overall effect size was statistically significant ($p < 0.001$), estimated as 0.33 (95% CI: [0.15, 0.51]) (Fig. 2). Among the studies with a greater effect size (0.67-2.67), two considered ADHD symptoms (Klingberg et al. 2005, Beck et al. 2010), assessed with standardized questionnaires, while the other one considered ASD symptoms (Weiss et al. 2018) assessed through an interview conducted with parents by clinician and with a blind clinical global impression. (Figure 3)

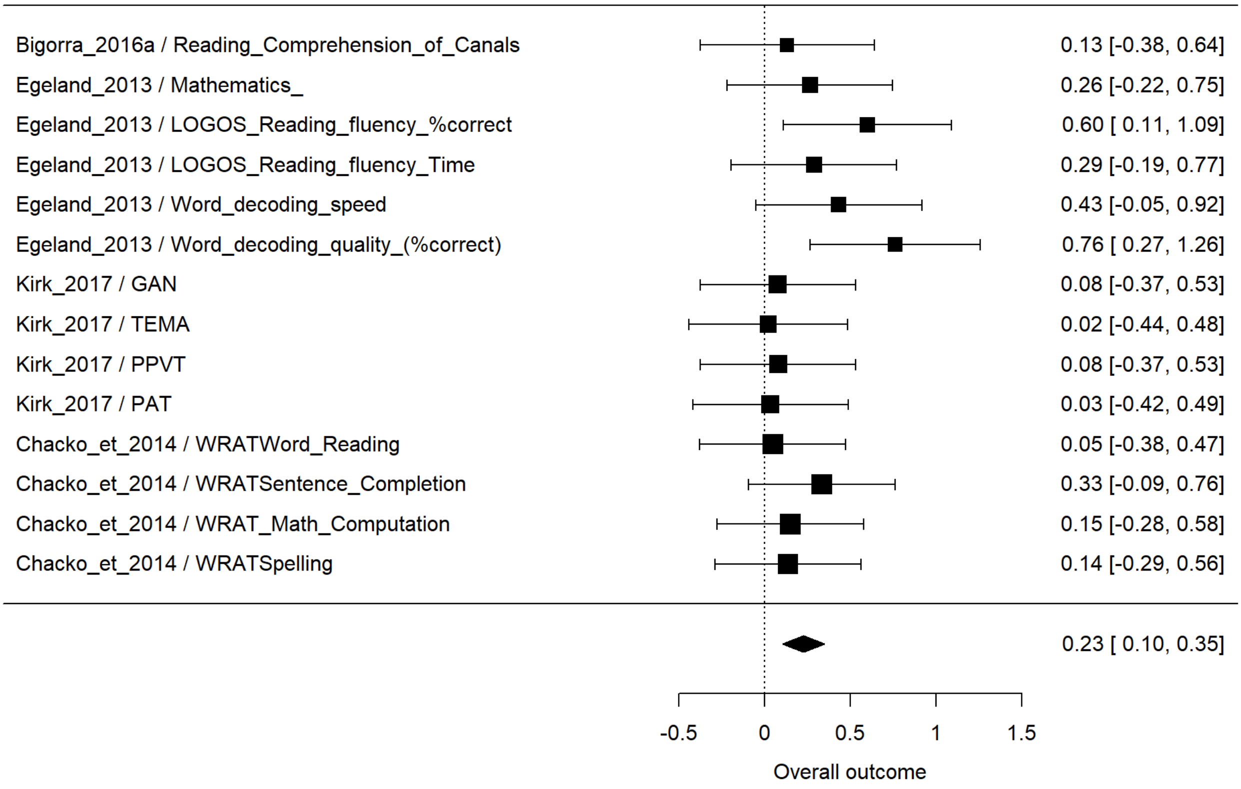
Figure 3. Metanalysis results of far effect on clinical symptoms.



3.6.3 *Learning skills*

All of the 4 studies that assessed learning as a far effect were included in the metanalysis, considering 14 outcome measures. According to the multivariate random-effect model, overall effect size was statistically significant ($p < 0.001$), estimated as 0.23 (95% CI: [0.10, 0.35]) (Figure 4). The only study that found greater effect sizes (0.60-0.76) evaluated reading accuracy (Egeland 2013) in ADHD children. (Figure 4)

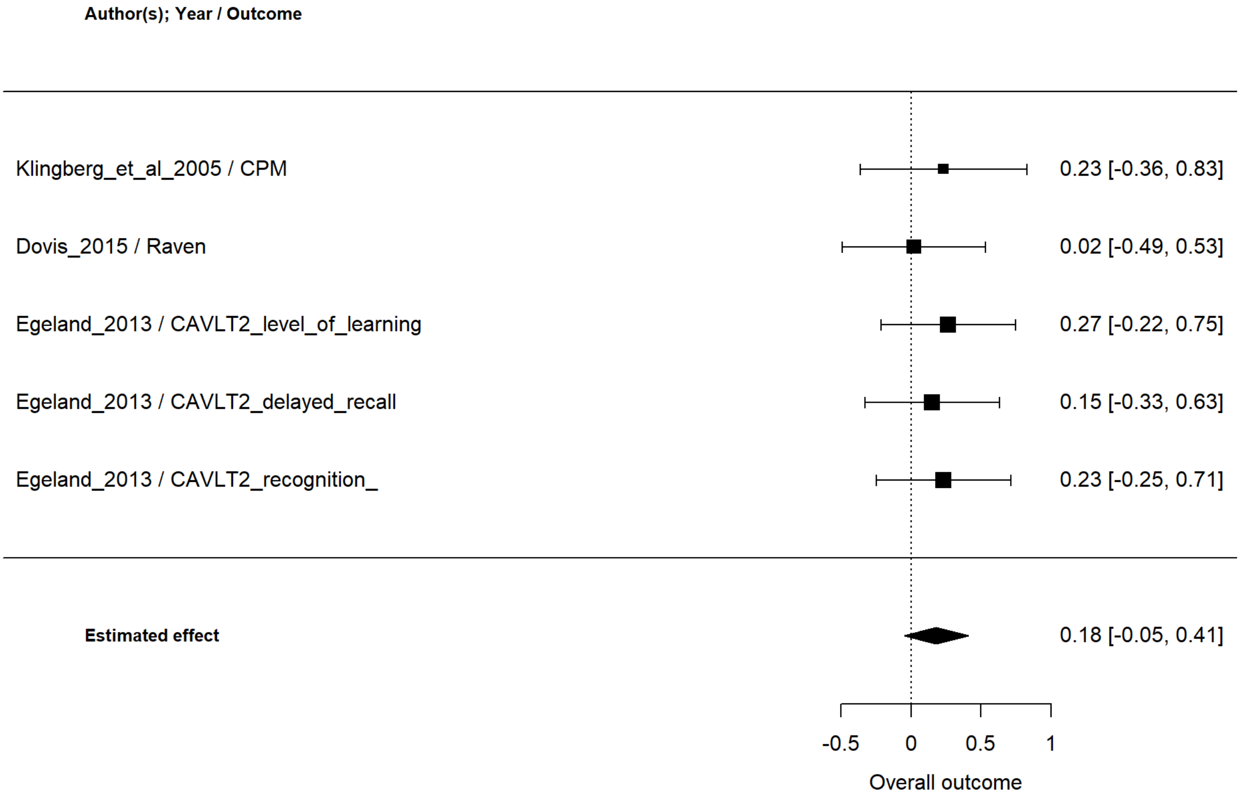
Figure 4. Metanalysis results of far effect on learning skills.



3.6.4 Cognitive outcomes

Among the 5studies that assessed cognitive outcomes as far effects, only those with a control group were included. For this reason, two studies were excluded (Leins et al. 2006, Strehl et al., 2017). According to the multivariate random-effect model, overall effect size was not statistically significant, estimated as 0.18 (95% CI: [-0.05, 0.41]) (Figure 5).

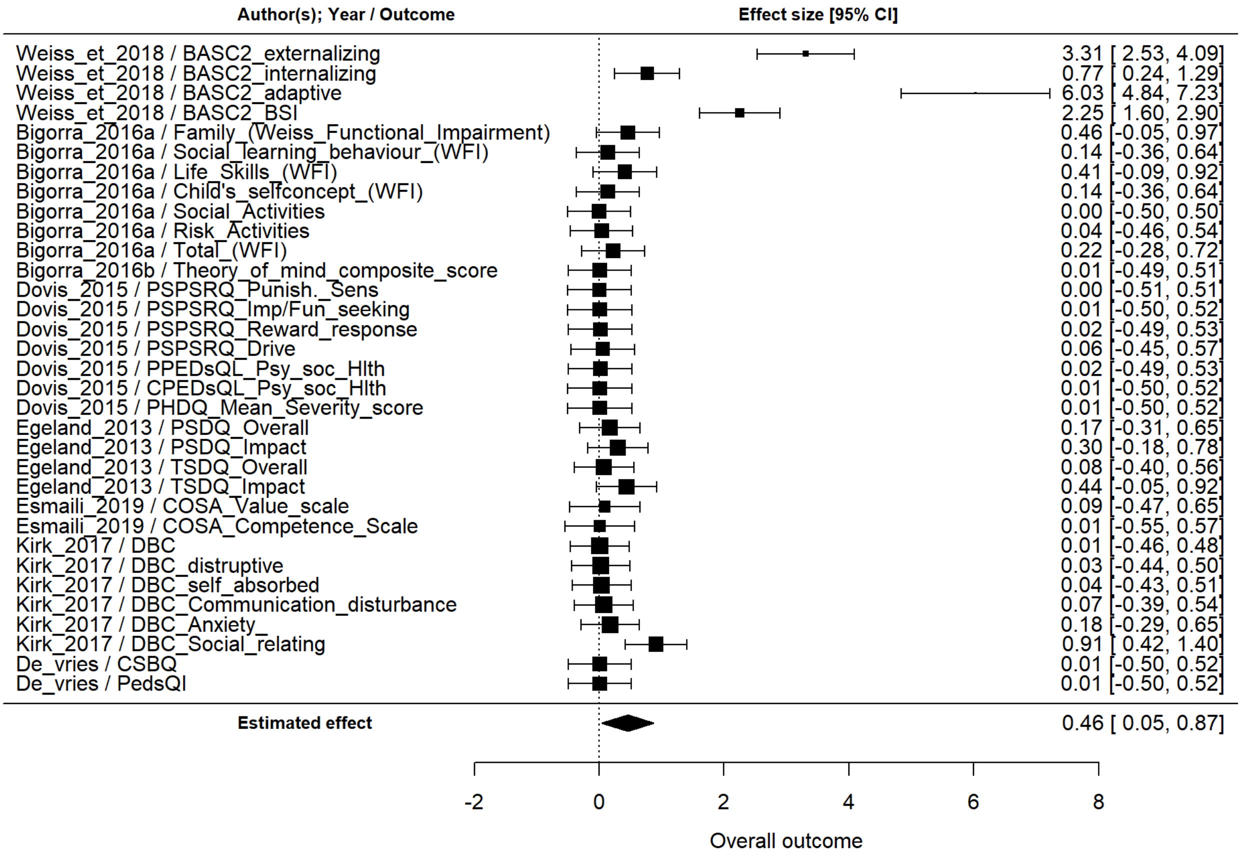
Figure 5. Metanalysis results of far effect on cognitive measures.



3.6.5.1 Daily life functioning

Among the 10 studies that assessed daily life functioning as far effect, only those with a control group were included. For this reason, two studies were excluded (Leins et al. 2006, Strehl et al., 2017). One study had been excluded because of zero sample variance (Bowling et al., 2017). According to the multivariate random-effect model, overall effect size was statistically significant ($p < 0.05$), estimated as 0.46 (95% CI: [0.05, 0.87]) (Figure 6). Among the studies with a greater effect size (0.91-6.03), one (Weiss et al. 2018) investigated behavioural and emotional functioning through a parent report questionnaire in children with ASD, and the other one (Kirk et al. 2017) assessed social functioning in children with intellectual disability.

Figure 6. Metanalysis results of far effect on daily life functioning.



4. Discussion

This systematic review was aimed at investigating the far-transfer effects, that is improvements on any skills or behavior not directly trained, following EF intervention in children with neurodevelopmental disorders. In fact, in neurodevelopmental disorders and in atypical developmental trajectories, EF alterations are a common finding, suggesting that an executive dysfunction is a pervasive and shared outcome among different disorders and a transdiagnostic indicator of atypical development (Zelazo, 2020). Nonetheless, these complex, multi-component functions influence other cognitive abilities and, above all, daily life functioning (Marotta & Varvara, 2013; Marzocchi & Valagussa, 2011; Vicari & Di Vara, 2017) . According to Zelazo's iterative reprocessing model (Zelazo, 2015) which defines a continuous reciprocal relationship between EFs and cognitive development, it is highly probable that a bidirectional relationship is frequently triggered between the specific alterations of a certain disorder and those of EFs. Alternatively (Lahey et al., 2017), EFs could represent either a cognitive factor that contributes to the aetiology of the disorder or a causal factor for the emergence of additional symptoms, making the disorder more complex and severe. Therefore, EF intervention should ultimately improve non trained abilities as well as induce positive cascade effects on development.

Among the different definitions of far transfer (Diamond & Ling, 2016; Klahr & Chen, 2011), for the purpose of this review all the skills not directly involved in the EF intervention and assessed post-intervention have been considered (Melby-Lervåg & Hulme, 2013; Sala & Gobet, 2016, 2017). This conceptualization is in line with the one proposed by Borella and Carretti (Borella & Carretti, 2020), who define as "near transfer" the improvement in the trained skill measured with different tests and "far transfer" the effective generalization of the training effects to tests that detect skills or processes other than those trained. This conceptualization was also used to include articles that did not refer explicitly to "far effect" or "far transfer" in order to provide a more comprehensive overview with respect to the cross-functional effects of interventions on EFs among neurodevelopmental disorders. This approach was used to weigh the impact that improvements in executive functioning have on symptoms or weaknesses characterizing a specific developmental disorder.

According to the Prisma method, out of 1683 studies, only 17 studies met the inclusion criteria. All the studies included, except one (Beck et al., 2010), were randomized control trials, where at least one experimental group and one control group were involved, supporting the quality of the studies according to the National Health and Medical Research Council (NHMRC) Evidence Hierarchy (NHMRC, 2009). Among these, 10 studies reported an improvement right after the intervention in at least one outcome that can be considered as a far effect following an EF treatment.

The results can be summarized by subdividing them according to the main EF components targeted by the interventions.

Among the three studies on *attentional control and inhibition* only one study demonstrated at least one far effect (Kirk et al., 2017). With regard to the interventions on *working memory*, four out of seven studies proved to be effective in producing at least one far effect (Beck et al., 2010; Bigorra, Garolera, Guijarro, & Hervás, 2016; Egeland et al., 2013; Klingberg et al., 2005), while the only study on *cognitive flexibility* intervention did not show any far effect. Thus, interventions on *cold EFs* show high variability on the results: although there is a prevalence of far effects in studies of working memory training, one should note that these prevail in number with respect to those training other EF components. Such a prevalence could be due in part to the exponential increase of interventions on working memory implemented through computerized trainings, that also payed attention to measuring far effects. In contrast, all the three studies on *hot executive* function intervention reported at least one far effect (Bowling et al., 2017; Strehl et al., 2017; Weiss et al., 2018). Finally, among the four studies on *integrated* interventions on different EF components, two reported at least one far effect (Dovis et al., 2015; L. Kenworthy et al., 2014).

Albeit few in number, interventions on “hot” components of EFs seem promising, probably since the target of the intervention, that is emotional-behavioural self-regulation, appears to be more transversal to a wide range of skills and processes.

With regards to the intervention population, the majority of the studies involved children with Attention Deficit/Hyperactivity Disorder (ADHD), followed by children with Autism Spectrum Disorder (ASD), Intellectual Disability (ID) and Specific Learning Disabilities (SLD). One study conducted an intervention on a population with complex diagnosis, called Behavioural Health Disorders, a mixed category that includes Mood Disorder and ADHD. No studies investigating the far-transfer effects following an EF intervention in children with Developmental Coordination Disorder or with Language Disorder were found. The studies that found at least one far effect were found to be six out of ten for ADHD (Beck et al., 2010; Bigorra, Garolera, Guijarro, & Hervás, 2016; Dovis et al., 2015; Egeland et al., 2013; Klingberg et al., 2005; Strehl et al., 2017), two out of three for ASD (Kenworthy et al., 2014; Weiss et al., 2018), one out of two in ID (Kirk et al., 2017), zero out of one in SLD and one out of one in BHD (Bowling et al., 2017). Given the scarce number of studies for each clinical population, conclusive data about the different far effects of EF interventions in different developmental disorders are not obtainable. The preponderance of studies in ADHD might be linked to the hypothesis that EFs are predominantly altered in this neurodevelopmental disorder and extend to different contexts, in part justifying the higher number of far effects respect to other clinical populations.

This review underlines the increasing interest for analysing the impact that intervening on different components of EFs may have on a variety of skills impaired in neurodevelopmental disorders. Thus, such interventions, especially if implemented early on, may indirectly strengthen those functions that become the core deficits or positively shape their developmental trajectories.

As far as the intervention population's age, all studies targeted school-aged children and three of them expanded the sample to include preschool-aged children . Kirk et al., 2017; H. E. Kirk et al., 2016; S. D. Smith et al., 2020). Among the studies on school-age children, 9 out of 14 found at least one far effect (Beck et al., 2010; Bigorra, Garolera, Guijarro, & Hervás, 2016; Bowling et al., 2017; Dovis et al., 2015; Egeland et al., 2013; L. Kenworthy et al., 2014; Klingberg et al., 2005; Strehl et al., 2017; Weiss et al., 2018). In the studies including also preschool children, in line with the developmental trajectories of EFs (Lee et al., 2013; Miller et al., 2012; Usai et al., 2014), the proposed interventions targeted the firsts EF component that develops or adopted an integrated intervention perspective, without differentiation of the components, which occurs in later life (Diamond, 2013; Lee et al., 2013; Lehto et al., 2003; Lunt et al., 2012). Among these, only one demonstrated at least one far effect (H. Kirk et al., 2017).

There was a high variability in frequency, duration and in the EF component target of the intervention. Among the types of EF interventions, computer training activities were the most popular treatments, followed by neurofeedback, interventions embedded in school curricula, individualized manualized Cognitive Behavioural Therapy (CBT) intervention, social activities and physical activities. The following intervention were associated with at least one far effect: computerized training, six out of ten studies (Beck et al., 2010; Bigorra, Garolera, Guijarro, & Hervás, 2016; Dovis et al., 2015; Egeland et al., 2013; H. Kirk et al., 2017; Klingberg et al., 2005), neurofeedback and curriculum interventions one out of two (Strehl et al., 2017) and manualized CBT (Kenworthy et al., 2014), and physical activities (Weiss et al., 2018) one out of one for and (Bowling et al., 2017) interventions, while the study that carried out an intervention including social activities did not find any far effect. The results show high variability in interventions examined and in the number of studies for each type of training, not allowing to define whether it is the type of intervention or other characteristics of it that make it effective in determining far effects.

The duration of the interventions varied from 5 weeks to three months with a minimum frequency of 2 times a week and a maximum of every day. Among the ten studies that reported at least one far effect after EF training, 6 reported an intensive and high frequency weekly intervention plan (5 times a week, from 5 to 7 weeks), with sessions of short duration (20 - 40 minutes) (Beck et al., 2010; Bigorra, Garolera, Guijarro, & Hervás, 2016; Dovis et al., 2015; Egeland et al., 2013; Kirk et al., 2017; Klingberg et al., 2005), while the remaining studies report heterogeneous data on the frequency, intensity and duration of the interventions. These results extend previous literature by suggesting that frequent and intensive intervention have greater efficacy (Diamond & Ling, 2016) also in terms of far effects.

Concerning the definition of far effects, this review underlies the heterogeneity of the meaning of this term. In fact, “far effect” appears to be an umbrella term that includes different degrees of remoteness from the target of the intervention. Extreme variability was found in the far effect-outcome measures chosen by the various studies that ranged from EFs other than those trained, clinical symptoms, child's daily life functioning, learning skills and other cognitive functions. This variability is partly linked to the different scopes of the studies, the different populations involved but also to the absence of a consensus on definition of far-transfer effect in the literature and the lack of data on the effective utility of implementing an EF training to benefit other skills impaired in different neurodevelopmental disorders. For this reason, a metanalysis was conducted, in order to quantify the effect of EF trainings on each outcome measure of far effects. Among the 17 studies included in the systematic review, only those with a control group were considered for the metanalysis. For the cognitive outcome measures none of the studies found significant effect sizes, demonstrating that executive function interventions are unable to actually produce changes in cognitive functioning measures. The results, in general, are difficult to interpret, due to the very large ICs that reveal small and inaccurate overall effects. These issues also occur with respect to far transfer with greater effect sizes, i.e. daily life skills and clinical symptoms. For these reasons is difficult to draw clear conclusions from the metanalysis about which far transfer effect is more significant than others.

This review underlines the importance of considering the specific disorder’s symptomatology or area of functional weakness as a far effect, in order to clarify which interventions on EFs are preferable (as more effective) for specific clinical population and treatment needs. Considering this interpretation, which underlines the importance of the specific difficulties of each disorder within the context of daily life in the choice of a treatment, it is possible to re-examine the results, which have been described above according to the components of EF target intervention. Six studies on ADHD, which is the population most represented in the literature, have shown significant effects on clinical symptoms or areas of weakness detected by questionnaires (Beck et al., 2010; Bigorra, Garolera, Guijarro, & Hervás, 2016; Klingberg et al., 2005; Strehl et al., 2017), and direct assessments (Bigorra, Garolera, Guijarro, & Hervás, 2016; Dovis et al., 2015;

Klingberg et al., 2005). Among the studies that reported an effect on clinical symptoms or areas of weakness assessed directly or indirectly, five utilized computerized intervention programs aimed at enhancing working memory, in school-age groups (7-19 years), for a total duration of 5-6 weeks and with high intensity (from a minimum of 5 times a week to every day).

Among the fewer studies investigating far effects in other neurodevelopmental disorders, only two reported reduction in symptomatology (Kirk et al., 2017; Weiss et al., 2018).

The first used an intensive (20 min per day, 5 times a week for 5 week) computerized treatment targeting various attentive dimensions and learning initiatives in patients with ID. The second involved a 10-14 weeks home/school-based group treatment program on social skills and emotional regulation in patients with ASD.

In an effort to synthetise this results, computer-based treatments are the most studied interventions and seem to be promising for inducing significant far effects in terms of improvement of symptoms and areas of weaknesses. This may be probably due to the characteristics of auto-adaptivity that allows for activities to be always calibrated to one's own performance so as to be challenging for one’s own skills (Klingberg et al., 2005; Thorell et al., 2009), and to the characteristics of enjoyability, which through gamification increases the motivation and fun experienced by the child who performs them (Piqueras et al., 2013; Saine et al., 2011; Torgesen et al., 2010). Furthermore, another feature that could increase the effectiveness of these interventions, also shared by another intervention that has shown significant effects (Weiss et al., 2018), is that it is totally or partially home-based. Although no direct comparisons have been conducted, this feature probably allows for greater intensity of treatment and for embedding the intervention in the context of daily life, actively engaging caregivers.

5. Conclusion

Drawing definitive conclusions from this analysis on far effects after EF treatments in children with neurodevelopmental disorders is still very complex. A conceptualization of far effect across different neurodevelopmental disorders was needed. A broad definition of “far transfer effect”, was adopted to include all the skills not directly involved in the EF intervention and focusing the impact on symptoms or weaknesses characterizing a specific neurodevelopmental disorder.

It is necessary to consider the high disparity in the representation of these disorders in this field of study. A higher number of far transfer effects in ADHD maybe in part due to the predominance of intervention studies in this population, in the face of less availability of data relating to other neurodevelopmental disorders, in which, however, this review documents far effects as well. This heterogeneity is also present with regard to the type of treatment on EFs, with a greater representation of studies that analyse the effects of computerized training, probably in line with the increase in computer-based treatment programs for EFs, which have spread over the last decade and proved highly effective in the treatment of directly treated EF components. Nevertheless, different types of interventions analysed may produce far effects. Beyond the type of intervention, intensity, frequency and the possibility of being embedded in daily life contexts, actively engaging caregivers, seem to be the most influential variables in determining far effects. From a practical standpoint, however, an intervention with these characteristics could be scarcely feasible in the traditional taking in charge, requiring significant resources in terms of time and costs, as well as the involvement of the family system.

The current review has some limitations. First, it is important to take into account that not all the studies included use the terms *far effect* or *far transfer* to refer to effects other than those on target functions. This uncertainty about the terminology prompted the authors of this systematic review to select a definition of far effect on the basis of the available literature that appeared most suitable in the context of the study of neurodevelopmental disorders. Some articles, despite having studied the far effects of EF interventions, could have used different terminologies than those used in this review as keywords may have escaped the search. Another noticeable limitation derives from a characteristic inherent in the construct of EFs, the task impurity, for which we cannot exclude that some tasks used to evaluate the far effects in terms of non-targeted EF actually require the involvement of some transversal executive processes directly treated or indirectly affected by the intervention. Overall, this review pays the cost of heterogeneity at the level of population, type of intervention, far effects analysed. This limit made the meta-analysis work complex, as it was necessary to consider the heterogeneity of all the different aspects investigated. We have tried to account for this in our work, directing readers to multiple possibilities of interpretation, underlining however the need to standardize the scientific language and follow common methods in collecting data and setting up future research. Our meta-analysis managed to take into account some of the prescribed recommendations to increase the reproducibility of meta-analyses (Lakens et al., 2016), such as the involvement and direct support of statistical experts, adherence to the PRISMA paradigm, the most detailed disclosure of meta-analytic data specifying their interpretation. For future meta-analyses in the field to be even more informative, it is important that future studies adhere to a common roadmap in data collection and research designs to facilitate the interpretation and reproducibility of meta-analytic studies.

In spite of the limits mentioned above, a first step in highlighting the need to measure far effects of EF trainings in neurodevelopmental disorders has been accomplished. This review paves the way to future studies about far effects of interventions on EFs in different neurodevelopmental disorders and in different age groups, taking into account the developmental trajectory of EFs and focusing on clinical symptoms and / or areas of weakness specific for each disorder as far effects. This will allow the selection of the most appropriate treatments not only on the basis of the specific EF component targeted by the intervention, but also according to the specific impact on the functional weakness of the disorder. This review may have both clinical and methodological implications. It stimulates greater attention to the far effect induced by the EF treatment on the symptomatology, thus defining more realistic expectations on treatment improvements. The analysis of the features shared by the different types of trainings able to produce far effects also opens the way for a clearer definition of an evidence-based methodology in the EF interventions.

Appendix1:

The complete search string was:

“executive function∗” (searched in Title and Abstract) OR attention* OR “working memory” OR “updating” OR “inhibitory control” OR “self-regulation” OR “self-regulation” OR “cognitive flexibility” OR “mental flexibility” OR “shifting” OR “set shifting” OR “effortful control” OR “cognitive control” OR “problem solving” OR “planning” OR “executive control” OR “metacognition” OR “behavioral control” OR “self-control” OR “response inhibition” OR “interference control” OR “executive attention” OR “focused attention” OR “selective attention” (searched in Full Text)
AND (child OR children OR "0-18 years") searched in Full Text
AND (“neurodevelopmental disorder*” OR “learning disorders” OR “developmental coordination disorder” OR “language disorders” OR “Autism spectrum disorders” OR “attention deficit hyperactivity disorder” OR “intellectual disabilities”) searched in Title and Abstract
AND (training OR education OR treat* OR rehabilitat* OR program OR improv* OR brain training OR curricul* OR empower* OR therapy OR intervention* OR treatment)) searched in Title and Abstract
AND (“Far effects” OR “quality of life” OR “learning skills” OR “academic skills” OR “math ability” OR literacy OR comprehension OR reading OR writing OR numeracy OR “self-regulation” OR “emotional-regulation” OR “far transfer” OR “social cognition” OR “school readiness” OR “self-efficacy” OR behavior OR success OR health OR skills) searched in Full Text
NOT (adult OR adulthood) searched in Title and Abstract

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Conclusion

The present thesis focused on analyzing the neuropsychological profile of children with idiopathic Childhood Apraxia of Speech (CAS), with particular attention to transversal processes such as implicit learning and Executive Functions (EFs). In addition, the thesis aimed to investigate treatment implications through a systematic review and metanalysis.

The first study revealed a deficit in implicit learning in children with CAS, while the second study found multiple alterations in the EF profile of preschool children with CAS. The study also investigated the relationship between EFs, speech severity, and connectivity of the Frontal Aslant Tract (FAT), showing a significant reduction in Fractional Anisotropy (FA) in children with CAS. Furthermore, speech severity was correlated and predicted FA value along FAT, and EF impairment moderated this relationship.

These results suggest that CAS is not only a motor-speech disorder but also involves transversal processes such as implicit learning and EFs in a composite and complex picture. Consequently, a comprehensive multidisciplinary assessment is mandatory to provide a more in-depth characterization of the disorder and define appropriate therapy interventions.

In light of the complex pattern found in the relationship between executive functions and speech and language profile, which is the core deficit of CAS, and the insufficient literature regarding the effect of enhancing executive functions in improving symptoms of children with CAS, the research topic was expanded to all neurodevelopmental disorders. This was done to determine the effects of enhancing executive functions on other far processes and the usefulness of integrating executive function enhancement into specific treatments to achieve better outcomes.

The systematic review and metanalysis conducted emphasized the need to measure the far effects of EF training in neurodevelopmental disorders, selecting treatments not only on directly targeted processes but also according to far impacts on the functional weakness of the disorder. The study found a statistically significant effect size in the majority of far-effect outcome measures considered, suggesting that EF training can produce enhancements of skills not directly trained. This highlights the importance of considering far effects of EF training in neurodevelopmental disorders and selecting treatments that target functional weaknesses in addition to directly targeted processes.

Overall, this thesis contributes to a better understanding of the neuropsychological profile of children with idiopathic CAS and the importance of a comprehensive assessment and appropriate therapy interventions. Additionally, the findings emphasize the potential benefits of EF training for children with neurodevelopmental disorders beyond the directly targeted processes.

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