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DEVELOPMENTAL PATHWAYS OF SUBSTANCE USE DISORDERS AND RELATED CONDITIONS: BEHAVIORAL OUTCOMES AND SPATIOTEMPORAL BRAIN ACTIVITY ORGANIZATION LINKED TO SELF AND SELF-REGULATION

DoS: Prof.ssa Anna Lucia Ogliari

Tesi di DOTTORATO di RICERCA di Marco Cavicchioli

matr. 017373

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Il/la sottoscritto/***I*** Marco Cavicchioli

Matricola / ***registration number*** 017373

nato a/ ***born at*** Terni

Il/***on*** 12/03/1988

autore della tesi di Dottorato di ricerca dal titolo / *author of the PhD Thesis titled*

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Abstract

Problematic substance-use behaviors and substance use disorders (SUDs) that are consistently considered as prototypical for the externalizing spectrum of adult psychopathology. Empirical research has demonstrated multiple developmental trajectories from childhood and adolescence disorders — attention deficit and hyperactivity disorder (ADHD) together with childhood/adolescent oppositional and defiant disorder (ODD) and conduct disorder (CD), adolescent MDD — to the subsequent onset of problematic substance-use behaviors and SUDs. It has been hypothesized that alterations of self-regulation mechanisms might be latent factors that could explain the homotypic and heterotypic continuity of the previous conditions. However, there are no definitive conclusions concerning behavioral outcomes and neural underpinnings of specific self-regulatory mechanisms involved in these developmental trajectories. Furthermore, there are no studies that have clearly conceptualized self-regulation in connection with the development of self and related levels of neural organization. Studies conducted during the 3-year Ph.D. program clarified the most relevant developmental pathways (i.e., ADHD, ODD/CD, MDD) and self-regulation mechanisms (i.e., motor inhibition) for adult SUDs and related problems, This supported a final multi-approach (i.e., multi-level, network, robust voxel-based) meta-analytic study of behavioral outcomes and spatiotemporal brain activity organization in response to behavioral inhibition tasks. Behavioral, neurophysiological and fMRI data collected among children/adolescents with ADHD, MDD and adult with SUDs and related problems (i.e., binge drinking, heavy drinking and positive family history for SUDs) showed that alterations of motor preparation and finalization should be considered as early and stable factors that could be involved in explaining homotypic and heterotypic developmental pathways to adult SUDs and related problems. The hyper-activity of mental self areas suggested that motor disinhibition represents a key challenge for conditions of interest across the life-span. Profiles of neural networks related to self-regulation and self-processing levels also differentiated each condition of interest. Future longitudinal neuroscience research should demonstrate the role of self-processing levels and self-regulatory mechanisms as factors involved in explaining developmental previously discussed. Clinical interventions and prevention programs should be developed focusing on self-regulation and self-organization mechanisms. Ultimately, this work lays the foundations for future conceptualizations of psychopathology based on profiles of self-processing and self-regulation mechanisms in the light of different stages of individual development.

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Acronyms and abbreviations

ADHD = Attention Deficit/Hyperactivity Disorder

AFQY = Avoidance and Fusion Questionnaire for Youth

AMPFC = anteromedial prefrontal cortex

ANT = Attentional Network Test

CBCL = Child Behavior Checklist

CD = Conduct Disorder

CoUD = Cocaine Use Disorder

dACC = dorsal Anterior Cingulate Cortex

DAN = Dorsal Attention Network

DBT-ST = Dialectical Behavior Therapy Skills Training

DERS = Difficulties in Emotion Regulation Scale

DES-A = Adolescent DissociativeExperiences Scale

DLPFC = Dorsolateral Prefrontal Cortex

ECN = Executive Control Network

EROs = Event-Related Brain Oscillations

ERPs = Event-Related Potentials

GAD = Generalized Anxiety Disorder

GNG = Go/No-Go

HEP = Heartbeat Evoked Potential

IGT = Iowa Gambling Task

I-MC = Primary Motor Cortex

IPS = Intraparietal Sulcus

lIFG = left Inferior Frontal Gyrus

LPe = Lack of Perseverance

LPr = Lack of Premeditation

MDD = Major Depressive Disorders

MTG = Middle Temporal Gyrus

NU = Negative Urgency

ODD = Oppositional Defiant Disorder

OFC = Orbitofrontal Cortex

pACC = pregenual Anterior Cingulate Cortex

PCC = Posterior Cingulate Cortex

PPC = Posterior Parietal Cortex

pre-MC = Premotor Cortex

pre-SMA = pre supplementary motor area

PTSD = Post-Traumatic Stress Disorder

PU = Positive Urgency

rIFC = right inferior frontal

ROI = Region-Of-Interest

RRQ = Rumination-Reflection Questionnaire

RT = Reaction Time

SAD = Separation Anxiety Disorder

SPH = Specific Phobia

SS = Sensation Seeking

SSTs = Stop Signal Tasks

STG = Superior Temporal Gyrus

STN = subthalamic nucleus

SUDs = Substance Use Disorders

TPJ = Temporal Parietal Junction

VMPFC = Ventromedial Prefrontal Cortex

VTA = Ventral Tegmental Area

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Introduction

Historically, developmental psychopathology has been conceptualized for the first time by Thomas Achenbach (1974) with the publication of his foundational book entitled "*Developmental Psychopathology*". Largely in contrast to a "static" and categorical approach of the second (APA, 1968) and third (APA, 1980) editions of the DSM published in the same years,the developmental psychopathology framework has laid the foundationson deductive and transactional principles together with a robustempirically-driven lens for the investigation and building of models of clinical conditions (Cicchetti, 1993).

Specifically, Sroufe and Rutter (1984) has operationalized developmental psychopathology as " … *the study of the origins of individual patterns of behavioral maladaptation, whatever the age of onset, whatever the causes, whatever the transformations in behavioral manifestation, and however complex the course of the developmental patterns may be*"(p. 18). Following this comprehensive operationalizion, the main philosophical tenet of developmental psychopathology is the "organicistic world view"(Pepper, 1942). Precisely, living organisms are organized, self-regulating, and actively functioning systems. The self-organization and self-regulation of the living organism is maintained by a balance between its actions on the environment and the transformationsand supports provided by the environment to the development of the living organism.Accordingly, development psychopathology is focused on the study of adaptive pathways of development, the identification of deviations from these trajectories, the articulation of transformations from normal pathways to deviations of them that onset over time, and the exploration of factors and mechanisms that might support both adaptive and maladaptive developmental trajectories (Cicchetti, 1993).

Moreover, the transactional framework at the base of development psychopathology assumes that child's and adult's developmental outcomes, both adaptive and maladaptive, are the result of many proximal and distal determinants (Cicchetti & Lynch,1993; Sroufe, 2009). Consistently, development is considered as repetitive qualitative reorganizations of behavioral, biological and psychological systems. These reorganizations are based on processes of differentiation and hierarchical integration that allow the living organism to differentiate it from an undifferentiated condition, and to persistently increase its level of biological, behavioral and psychological complexity of hierarchical organization (Werner, 1957). Intrinsic/subjective factors and external/environmental factors dynamically interact to each other over time; hence, the transactions between people and their environments produce the individual development throughout the life-span.

Departing from these basic principles of developmental psychopathology, the current work aims at providing evidence of neurobiological underpinnings of self-organization and self-regulation processes linked to substance use disorders (SUDs), which are viewed as a result of different maladaptive developmental trajectories from childhood to adulthood. Accordingly, this manuscript will show empirical findings concerning the hierarchical organization of developmental psychopathology and their dynamics across life-span. Referring to this evidence, empirical findings concerning different developmental trajectories of SUDs will be discussed considering at least two main different pathways, namely homotypic and heterotypic ones. Secondly, it will be provided a discussion of theoretical frameworks and empirical evidence concerning the development of self and its hierarchical organizations together with self-regulatory mechanisms at the base of transactions between individual and environments throughout the life-span. Furthermore, it will be showed how deviations from adaptive development of self and its regulatory mechanisms might play a role in explaining homotypic and heterotypic development pathways from child and adolescent psychopathological conditions to SUDs in adulthood. Third, it will be discussed neurobiological proxies of the self and its hierarchical organization together with self-regulation mechanisms during development, especially considering its implications for SUDs and their developmental pathways. Subesequently, it will be summarized results of empirical studies conducted during the 3-year Ph.D. course supporting the main goal of the current work, namely the application of different meta-analytic procedures in order to highlight behavioral outcomes and neurobiological dimensions linked to the self and self-regulation at the base of developmental pathways from child and adolescent psychopathological conditions to SUDs and related conditions in adulthood. The last chapter of the current manuscript will discuss meta-analytic findings attempting to highlight basic neuro-mental processes that could be involved in clarifying homotypic and heterotypic developmental pathaways to SUDs and related conditions. Specifically, it will be discussed how different levels of self-organization could interact with self-regulation mechanisms as latent dimensions that contribute to the continuity of psychological conditions throughout the development. Ultimately, the limits of the study, future directions together with clinical implications of the current results will be presented.

Developmental psychopathology: basic principles and implications for substance use disorders

Developmental psychopathology and its hierarchical organization

The first evidence concerning a hierarchical organization of psychopathological conditions among children and adolescents comes from pioneering works conducted by Achenbach and colleagues (1966, 1978) based on the application of factor-analytic approach to exploration of several symptoms reported by these populations. Precisely, the first work published by Achenbach (1966) found a higher-order dichotomy, which identified twospectra of symptoms called *Internalizing* and *Externalizing*, respectively. In addition tothese higher-order factors, empirical data suggested that second-order discrete clusters of symptoms within each spectrum. Particularly, aggressive and delinquent behaviors factors had been included the Externalizing domain. Somatic complaints and obsessions, compulsions, and phobias facets had been ascribed to the Internalizing high-order factor. These results were replicated for both males and females. On the one hand, Hyperreactive Behavior factor has been mainly, but not fully, classified by the Externalizing domain. On the contrary, the Schizoid factor seemed to be mainly ascribed to the Internalizing pole, although not fully associated to it. Furthermore, Achenbach interestingly highlighted that Internalizing versus Externalizing dichotomy significantly discriminated biographical information, especially this related to socialization and interpersonal functioning. Specifically, Internalizers lived more frequently with both natural parents. Internalizers, independently of geneder, showed significantly fewer social problems and better school performances. This suggested that the Internalizers had higher social adjustment than the Externalizers.

Taking together these findings, Achebach concluded that Externalizing symptoms represent antisocial behaviors which people might learn through negative sanctions. More precisely, the high frequencies of social problems in connection with a lack of parental support found among Externalizers could suggest that their social learning did not provide an adequate combination of reward contingencies and adaptive models, which are needed to reduce antisocial conducts and to promote cooperative behaviors with others. On the other hand, the better socialization showed by Internalizers indicates that their symptoms might reflect the consequences of a social learning based on a hyper-control of internal states.

Ten years after the publication of the work previously mentioned, Achenbach and Edelbrock (1978) reviewed empirical evidence come from several studies that applied factor-analytic procedures on symptoms reported by children using different assessment instruments, which partially capture the same dimensions found by Achenbach (1966) in his first work. Despite the heterogeneity of assessment tools, it was replicated the hierarchical organization previously presented. Specifically, the high-order dichotomy was labeled as *Undercontrolled* (i.e. Externalizing) and *Overcontrolled* (i.e., Internalizing) spectra. Furthermore, there were replicated the second-order organization which included Aggressive, Delinquent, Hyperactive factors as discrete Undercontrolled/Externalizing syndromes; whereas Schizoid, Anxious, Depressed, Somatic, and Withdrawn factors as Overcontrolled/Internalizingsyndromes.

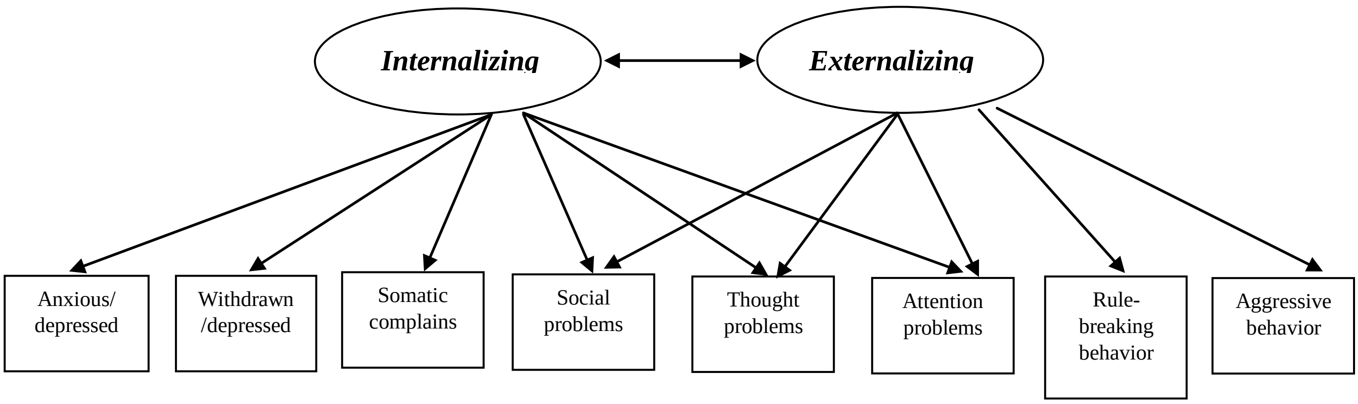
Departing from these attempts to effectively capture psychopathological manifestations, it has been developed the Child Behavior Checklist (CBCL; last version: Achenbach & Rescorla, 2001) that represents the gold standard for evaluating emotional and behavioral difficulities among children and adolescents in both clinical and research settings. Several trans-cultural studies (Achenbach et al., 2008, 2016) has consistently demonstrated the validity and reliability of the instrument, and its hierarchical structure composed of: i) two correlated broad-band internalizing and externalizing domains; ii) second-order narrow-band syndrome scales which are organized as following: a) internalizing — anxious/depressed, withdrawn/depressed, somatic complains — b) externalizing — rule-breaking behavior; aggressive behavior — c) cross-loaded — social problems; thought problems; attention problems. Furthermore, Achenbach and colleagues (2003) developed the CBCL DSM-oriented scales in order to align this dimensional framework with the DSM nosology. Accordingly, six scales were developed: (i) *affective problems*: dysthymic and major depressive disorders (MDD), (ii) *anxiety problems*: generalized anxiety disorder (GAD), separation anxiety disorder (SAD), and specific phobia (SPH)], (iii) *attention deficit/hyperactivity problems*: attention deficit/hyperactivity disorder (ADHD), (iv) *conduct problems*: conduct disorder (CD), (v) *oppositional defiant problems:* oppositional defiant disorder (ODD), and (vi) *somatic problems*: somatization and somatoform disorders.

Therefore, this evidence supports four main considerations:

i) the higher-order domains concerning internalizing vs externalizing might reflect the predominance of underlying processes that sustain a specific self-organization of phenomenological manifestations of symptoms and self-regulation mechanisms needed to response to environmental demands (e.g., Berger & Buttelmann, 2022; Murray & Kochanska, 2002);
ii) the correlation between these high-order domains suggest that internalizing and externalizing self-organization of symptoms and related self-regulation mechanisms recurrently co-occur within the same individual (e.g., Cosgrove et al., 2011), and, in turn, they could reciprocally reinforce each other (Lee & Bukowski, 2012);
iii) considering the second-order level of discrete syndromes in connection with the higher-order level of internalizing and externalizing spectra, it could be possible to hypothesize specific self-organization processes at the base of a different classes of symptoms that tend to covary with each other within the same spectrum in the light of common latent dimensions predominantly related to internalizing and externalizing ones, respectively (Oldehinkel et al., 2004);
iv) according to thesignificant correlations found between high-order domains and evidence concerning the co-occurrence of these problems, there is a class of discrete syndromes that seemed to be characterized by the co-existence of different latent dimensions linked to internalizing and externalizing conditions; alternatively, this class of discrete syndromes might reflect shared mechanisms between the two spectra (Oldehinkel et al., 2004).

Figure 1 highlights a graphical summary of evidence concerning the hierarchical structure of developmental psychopathology.

Figure 1. Hierarchical organization of developmental psychopathology



Dynamics of developmental psychopathology: homotypic and heterotypic continuity

The hallmarks of developmental psychopathology are represented by two concepts concerning the development trajectories, namely *equifinality* and *multifinality* (Cicchetti& Rogosch, 1996). On the one hand, the *equifinality* describes a well-known scenario within research and clinical settings that refers to multiple development pathways for one developmental outcome. On the other hand, the *multifinality* captures another evidence regarding multiple developmental outcomes departing from a same set of initial conditions. Respectively, the emergence of aggressive behaviors might be a consequence of very different starting points, such as, physical and psychological traumatic experiences, maladaptive parenting, parental conflicts, individual difficulties with impulse control (*equifinality*). People who experienced same traumatic experiences (e.g., sex abuse) have very different outcomes throughout the life-span (*multifinality*).

According to the core organismic and transactional theoretical frameworks at the base of developmental psychopathology, several scholars have been attempted to understand this variability of developmental pathways referring to the dynamic systems theory, which includes a set of principles applied to different fields of science (e.g., physics, biology, chemistry, psychology) focusing on different levels of analysis (e.g., cells, behaviors of a large group human being) (Granic & Hollenstein, 2003).

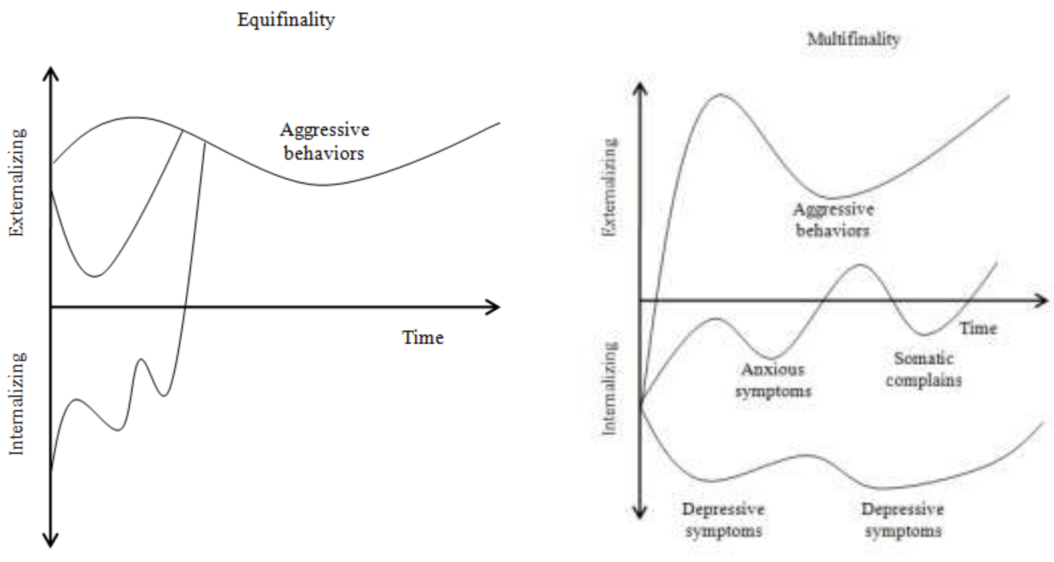
Following dynamics systems theory principles applied to human development, some key properties characterize these dynamic and self-organized systems. The first element refers to *attractors*. On the one hand, a system might theoretically exhibit a wide range of behaviors. On the other hand, systems tend to organize their behaviors in a defined range of possible patterns. Accordingly, an attractor is an absorbing state in which the system moves and regularizes its behaviors with an increasing predictability. Attractors are topographically conceptualized as "valleys on the development landscape". Specifically, a deeper and wider attractor increases the probability that a system evolves toward it, falls into it and remains in this space even in presence of changes in the environment. The complex behavioral repertories of living system are captured by the concept of *multistability* (Kelso, 1995), namely the coexistence of multi attractors, which in present of specific contextual constraints guide the emergence of different patterns of behaviors over time.

The attractors and related mechanisms of change and stability of a system of complex behaviors can be applied in the present (i.e., moment-to-moment scale), and referring to a larger time-scale (e.g., weeks, months, year) (i.e., developmental scale). Accordingly, there is a reciprocal influence between moment-to-moment system dynamics and developmental ones. Specifically, the moment-to-moment self-organization of system affects the developmental scale self-organization, which then guide future self-organization at a specific moment (Granic & Hollenstein, 2003). In other words, the dynamics of the systems guided by an attractor at moment-to-moment scale influence the consolidation or change of long-term attractors that govern behaviors of system in a future moment.

These reciprocal influences among different time-scales capture additional properties of dynamic systems, namely *amplification properties of positive feedback* and *nonlinear changes* in the self-organization of the system. Specifically, the interactions among moment-to-moment self-organizations might induce a *phase transition*, which could precede a radical change of self-organization of the system (*points of bifurcation*). The phase transition represents a threshold of the self-organization of system characterized by an extreme sensitivity to *perturbations*, which might cause disproportionate effects on the system leading to the emerge of new attractors. During the phase transition the behaviors of system are largely variable, and they are easily influenced by perturbations. After the emerge of a new attractor, the system stabilizes its behaviors in more predictable way in the light its reduced variability.

Following these basic principles of dynamic systems theory, equinality and multifinality might be conceptualized in terms of interactions among different attractors, time-scales self-organization processes together with feedback amplification and nonlinear changes system reorganization. On the one hand, the equifinality could be viewed as following: departing from different baseline levels (e.g. levels of internalizing and externalizing psychopathology), each system highlights specific patterns of time-scales self-organization and self-regulation processes that in presence of different kind of perturbations during thephase transition develops a same attractor (e.g., aggressive behaviors). On the other hand, themultifinality might be represented by a same baseline state from which different attractors develop over time through specific interactions among different time-scales self-organization and self-regulation mechanisms of the system. Figure 2 provides a graphical explanation of equifinality and multifinality concepts in the light of dynamic systems theory.

Figure 2. Equifinality and multifinality



Empirical research in developmental psychopathology has largely explored these topics, especially referring to homotypic or within-disorder continuity and heterotypic or across-disorder continuity (Costello et al., 2003). Homotypic continuity describes individuals that at one stage report a class of symptoms (e.g., internalizing: depressive) and at a later stage report the same class of symptoms (e.g., internalizing: depressive or anxious). On the contrary, heterotypic continuity identifies subjects that at one stage highlight a class of symptoms within a spectrum (e.g., internalizing: depressive or anxious) and at later age show another classof symptoms within a different spectrum (e.g., externalizing: aggressive behaviors).

Longitudinal studies on this field of research provides a complex and heterogeneous picture (Speranza et al., 2023). Indeed, Wichstrøm and colleagues (2017) highlighted in a large sample over six years of evaluation (from 4 to 10 years) several homotypic and heterotypic pathways. The strongest homotypic continuity has been found for ADHD and ODD/CD symptoms. Internalizing conditions (i.e., depression and anxiety) also demonstrated a significant, albeit reduced, homotypic continuity. Concerning heterotypic continuity, the authors found a cross-spectrum one for which ADHD represented a significant predictors of anxious symptoms. An additional heterogeneity continuity pathway within the same externalizing spectrum was represented by ODD/CD as predictors of later ADHD. A homotypic continuity among externalizing conditions (i.e., ADHD, ODD/CD symptoms) was replicated by Finsaas and colleagues (2018), who assessed a group of 3-year-old children for nine years. Homotypic continuity was also found for anxiety and depression symptoms. Contrary to previous findings, Finsaas and colleagues (2018) detected a cross-spectrum heterotypic continuity between depressive symptoms and later ODD/CD symptoms together with an additional one composed of ODD/CD symptoms as predictors of later anxious symptoms. Furthermore, Shevlin and colleagues (2017) assessed psychopathological symptoms in a community rapresentative sample (N = 4815 subjects) at age of 7 years old and at 14 years old. The authors confirmed the homotypic continuity among all investigated internalizing (i.e., specific phobias, social phobia, GAD, MDD, post-traumatic stress disorder [PTSD]) and externalizing (i.e., ADHD, ODD, CD) conditions. Heterotypic continuity was demonstrated within both internalizing — MDD > GAD; GAD > MDD; PTSD > GAD — and externalizing spectrum — ADHD > ODD; ADHD > CD; ODD > ADHD; ODD > CD; CD > ADHD; CD > ODD. With exception of PTSD symptoms that predicted later ADHD symptoms, no other cross-spectrum heterogeneity continuities were detected departing from the remaining internalizing conditions. Conversely, ADHD symptoms were significant predictors of later internalizing conditions, especially PTSD, GAD and MDD.

There was also found an additional pathway from CD to later MDD symptoms. Ultimately, a recent study (Picoito et al., 2021) on a large scale population (N = 17216) followed children from 3 years old to adolescence (i.e., 14 years old) identified two groups of subjects characterized by stable internalizing profiles throughout the period of observation. There was also found a high frequency heterotypic transitions from externalizing profiles to internalizing functioning, and vice versa. Nevertheless, it was showed showed that these phenomenological changes were more recurrent between ages 3 and 5 rather than later during development.

Therefore, the dynamics of developmental psychopathology during childhood and adolescence are complex and heterogeneous. However, all scholars have generically interpreted these findings in the light of common genetic and environmental factors that modulate the course of psychopathological manifestations during developmental. Nevertheless, no studies have explored self-organization and regulation mechanisms that could be involved in clarifying the complex pathways previously discussed.

Homotypic and heterotypic developmental trajectories of SUDs

SUDs have been consistently considered as one of the most representative externalizing conditions, especially among adolescents and adults (Kotov et al., 2021). This consideration has been widely sustained by several studies that have suggested and demonstrated a central role of behavioral disinhibition as a core feature of SUDs (i.e., personological, neuropsychological, neurobiological) (e.g., behavioral, emotional) (e.g., for meta-analytic review see: Coskunpinar et al., 2013; Kotov et al., 2010; VanderVeen et al., 2016; Verdejo-García et al., 2008). Behavioral disinhibitionhas been also viewed a latent dimension involved in explaining the co-occurrence with other externalizing disorders across the life-span, including antisocial personality disorder, ADHD, CD and ODD (Kotov et al., 2017).

On the one hand, SUDs has been considered discrete entities that have demonstrated their psychometric validity (e.g., Hasin et al., 2012, 2013; Saha et al., 2012) using both DSM and ICD diagnostic criteria. On the other hand, it has been recognized a dimensional hierarchy of substance-related problems (Saunders, 2017) which ranges from “non-user” and “low risk users” to “hazardous or risky use” (e.g., binge drinkers and heavy drinkers;

National Institute on Alcohol Abuse and Alcoholism, 2004; Hedden, 2015) and SUD clinical conditions.

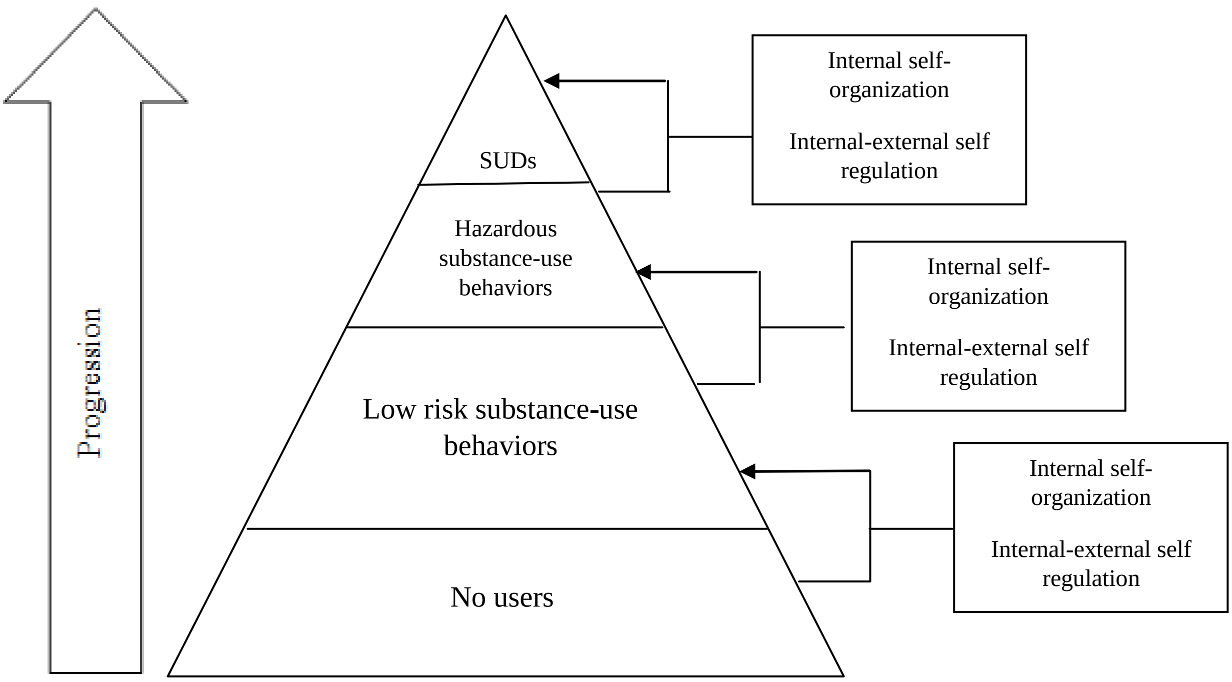
This view of substance-use related problems is consistent with the progressive nature of substance-use behaviors throughout the development. Indeed, a longitudinal study conducted by Richmond-Rakerd and colleagues (2017) that followed a community-based sample of adolescents (mean age: 16 years old; N = 20,745) over 7 years (N = 15,701) has demonstrated an increasing reinforcement of quantity and frequency of substance use across substances (i.e., marijuana, tobacco, alcohol) throughout the period of observation. The authors also showed that these cross-lagged positive correlations were partially moderated by the age of substance use initiation, for which younger substance users had greater reinforcing effects on substance use over time. Moreover, the age of substance initiation represented a significant predictor of transition from substance use to SUDs among different samples followed during the adolescence until early adulthood (e.g., Behrendt et al., 2009; Sung et al., 2004). These reciprocal reinforcing effects across life-span are consistent with well-recognized progressive neuroplastic changes induced by biochemical properties of substances on the brain (Koob & Volkow, 2016), especially among adolescents (Casey & Jones, 2010; Hamidullahet al., 2020; Squeglia et al., 2009).

Nevertheless, the progression of severity of substance-use behaviors over time is a complex phenomenon, which includes several other internal and external factors that interplay in a transactional way during the development. Specifically, in addition to an increasing reinforcing effects of substance-use behaviors from early adolescence to adulthood, Marmorsteinand colleagues (2010) found that anxiety symptoms reported during this period moderated the increasing risk for more severe manifestations of substance-use behaviors. The progression of substance use has also been supported by a community-based (N = 5,632) prospective study that assessed a cohort of subjects from 15 years old to 26 years old (Quinn & Harden, 2013). Interestingly, the authors found that the reinforcing effects of substance-use behaviors were moderated by developmental trajectories of impulsivity levels. Particularly, an increased risk for more invalidating substance-use behaviors was connected to persisting difficulties with behavioral control. Similarly, difficulties with behavioral inhibition and related alterations of neural responses (e.g., reduced activity of bilateral inferior parietal lobules and motor cortices, right inferior frontal gyrus and cingulate gyrus and dorsal and medial frontal areas) represented a factor associated to the transition from non-users to heavy drinking conducts (Norman et al., 2011).

Ultimately, an interesting longitudinal study conducted by Jones and colleagues (2016), whichassumed a developmental cascades model (Masten & Cicchetti, 2010), highlighted complex pathways of SUDs development considering a period of observation that ranged from childhood (10 years) to adulthood (30 years). Indeed, it was found that the progression of adolescent substance use severity until SUDs in adulthood was mediated by relational factors (i.e., family, peer and partner substance use environments), which were more likely among subjects reporting more severe substance-use behaviors from early adolescence.

Taking this evidence together, SUDs and substance-related conditions should be viewed in light of a developmental perspective. Accordingly, several internal self-organization together with internal-external self-regulatory processes should be considered in order to identify pathways involved in the progression from no or low risk substance-use behaviors toriskierones and clinically relevant conditions.

Figure 3. The progression of substance-use related problems



On the one hand SUDs have been viewed as prototypic conditions of the externalizing spectrum on the base of cross-sectional factor-analytic findings (Kotov et al., 2017, 2021). On the other hand, the developmental pathways from childhood psychopathological manifestations to later onset and progression of substance-use behaviors until a clinically relevant condition is complex and widely dynamic.

Accordingly, Kingand colleagues (2004) conducted a community-based longitudinal study that evaluated a cohort of 11-year old subjects for 3 years assessing cross-sectional and prospective associations between externalizing (i.e., ADHD, ODD, CD) and internalizing (i.e., MDD, GAD, separation anxiety disorder) disorders with the initiation and progression different substance-use behaviors (i.e., alcohol, cannabis). The analysis found that all externalizing conditions were associated to an early initiation of substances use, and ODD together with CD were significantly associated to a progression to regular use and/or problematic use at age 14. Interestingly, MDD represented the only internalizing significant predictor of early onset of alcohol-use behaviors, and it was longitudinally associated to a regular use at 14. A robust homotypic externalizing developmental pathway from early adolescent (11-12 years old) deviant behaviors (i.e., rule breaking and aggressive**)** anddifferentsubstance-use behaviors at age 15 has been demonstrated by Colder and colleagues (2013). The authors also showed an additional pathway for adolescent substance-use behaviors that included individuals reporting a co-occurrence of internalizing symptoms (i.e., withdrawn and anxious depressed) and externalizing ones. This group highlighteda slightly weaker, albeit significant, prospective association with substance-use behaviors than the "pure" externalizing pathways. This pattern of interrelations between internalizing and externalizing psychopathology in connection with later substance use was also replicated in a cohort of individuals followed from early (11-12 year-old) to late adolescence (18-19 year-old) (Colder et al., 2018).

Considering a treatment-seeking population of adolescents (16 years old) with SUDs, Wintersand colleagues (2008) highlighted that it was equally composed of subjects with internalizing and externalizing problems. However, subjects with an externalizing profile showed poor treatment outcomes in terms of remission rates of the diagnosis of SUDs over a 5-year observation period. A predominance of an externalizing developmental pathway for substance use and related maladjustment was demonstrated by other longitudinal studies that highlighted how externalizing psychopathological manifestations in childhood and early adolescence were the only significant predictors of subsequent substance-use behaviors (Miettunen et al., 2014; Pedersen et al., 2018), compared to non-significant effects of internalizing symptoms.

Looking at clinical populations, several studies explored prospective associations between childhood ADHD with different diagnoses of SUD in adulthood. Results of a meta-analytic review (Leeet al., 2011) of 27 independent studies consistently showed that ADHD children have a significant increased risk for the development of SUDs, especially alcohol, cannabis and cocaine use disorders. Similarly, an extensive meta-analytic review (Erskine et al., 2016) of 98 independent studies on long-term outcomes of childhood and adolescent CD/ADHD consistently showed significant prospective associations with later SUDs, especially AUDs and cannabis use disorders. The longitudinal associations between adolescent ODD and SUDs in adulthood has been also demonstrated (Nock et al., 2007), especially when ODD was in comorbidity with ADHD (Mustonen et al., 2023).

Despite the externalizing developmental trajectory of substance-use related problems has been consistently supported, Hussongand colleagues (2017) conducted an interesting review of 61 longitudinal studies that test the association between internalizing symptoms, especially depressive and anxious ones, and later substance-use behaviors in adolescence controlling for the effects of externalizing conditions. The authors found a specific correlation between depressive symptoms and later substance use. On the contrary, the other internalizing problems, especially anxious one, showed mixed and non-significant associations with the onset of substance use. This evidence was also corroborated and extended by a longitudinal study (Rothenberg et al., 2020) conducted from childhood (9 years old) to adolescence (14 years) among a sample recruited from 10 different cultural groups. Specifically, the authors found a direct internalizing pathway from childhood and early adolescence depressive symptoms to substance-use behaviors at age 14, and a heterotypic pathway as following: depressive symptoms at age 9 represented a risk factor for externalizing behaviors (e.g., bullying, disobedience) at age 10, which were predictors of substance-use behaviors at age 14. Similarly, a large retrospective community-based (N = 10,123) study among adolescents (13 – 18 years) showed that mood disorders and anxiety disorders were the most representative predictors of alcohol use disorders (AUDs), and they explained the association revealed between externalizing conditions (i.e., CD, ODD) and AUDs (Conway et al., 2016).

According to empirical findings previous discussed, some conclusionscan bedrawn:

i) SUDs should be viewed as developmental conditions that dimensionally progress from non-risky to problematic and clinically relevant ones across life-span, especially departing from adolescence;

ii) the progression from non-risky to clinically relevant conditions might be explained by specific self-organization processes (internal)and self-regulatory mechanisms related to transactions between the individual functioning and effect of environments that dynamically emerge during the development;

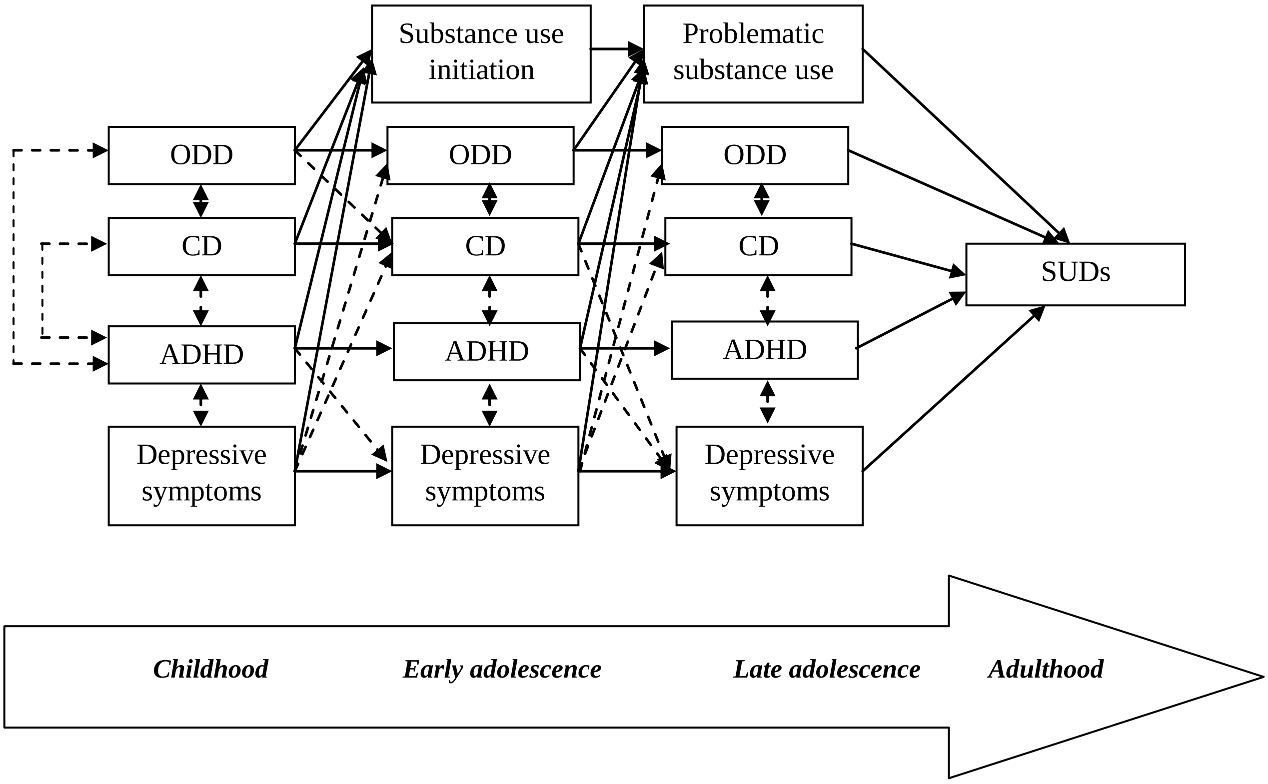
iii) on the one hand SUDs are considered prototypical externalizing disorders. On the other hand, their developmental pathways are complex and include interrelationships among externalizing and internalizing psychopathological conditions from childhood to adulthood;

iv) empirical research has consistently demonstrated “pure” externalizing pathways characterized by an increased risk for substance-use behaviors and related maladjustment across life-span among ADHD children and adolescents, ODD and CD. An additional “pure” internalizing pathway has been found. This highlighted a key role of depressive conditions in childhood and adolescence on an heightened risk for later substance-use related problems. Depressive symptoms in childhood and adolescence was also a relevant risk factor for externalizing problems, which in turn predicted later substance use initiation and progression;

v) therefore, this scenario well fits with principles of developmental psychopathology related to the concept of equifinality together with homotypic and heterotypic continuity of psychopathological manifestations across life-span;

vi) several scholars agree that the previously discussed developmental pathways might be explained by latent dimensions, especially behavioral disinhibition, shared by these conditions. Nevertheless, there are no studies that have explicitly tested this hypothesis referring to robustneurobiological underpinnings of these dimensions.

Figure 4. Developmental pathway to SUDs



Self and its regulatory mechanisms: structures, processes, and implications for developmental pathways of SUDs

The first chapter has provided the principles of developmental psychopathology and related evidence concerning complex pathways from childhood to adulthood across externalizing and internalizing conditions, and their implications of the onset and consolidation of substance-use behaviors and related problems. Referring to application of the dynamic systems theory for a clarification of mechanisms underlying homotypic and heterotypic continuity of psychopathological conditions across life-span, two main processes have been mentioned: i) self-organization proprieties of the system over time in association to external and internal perturbations; ii) self-regulation mechanisms linked to the dynamic transactions between the emerge of specific features of the person-system (i.e., self-organization) and effects of external environments.

According to these notions, the current chapter discusses the topic of the self and its hierarchical organizations departing from different psychological perspectives in order to lay theoretical backgrounds for clarifyingself-organization processes of human mind. Furthermore, it will be provided a comprehensive model of self-regulation mechanisms that are involved in modulating the transactions between the person-system and external contexts. Subsequently, there willdiscuss theoretical models and empirical evidence concerning the development of hierarchical organizations of the self and self-regulation mechanisms across life-span. Ultimately, there will present implications of these processes for substance-use related problems and related developmentalinternalizing and externalizing psychopathological conditions across life-span.

Self: organization and dynamics over time

Historically, the concept of the self is one of the most discussed topics in several fields ofpsychology. However,the concept of the self has beenaddressed in different ways referring to specific theoretical perspectives.

The first definition of the self has been proposed in 1890 by William James, who has separated between "*Me*" — self as an object of experience — and "*I*" —the subjective experience of self. Following James' conceptualization, the "*Me*" might show different levels of organization: i) the *material Me* (e.g., own body); ii) the *social Me* (e.g., ourselves in relation to other human beings); iii) the *spiritual Me* (e.g., own mental processes and contents). Accordingly, the self viewed as "*Me*" can be viwed as a moment-to-moment subgroup of all own experiences that emerges in the field of consciousness. Furthermore, the self viewed as an object of experience provides the basis for the separation between self and non-self, especially referring to the concept of *self-relatedness*. Self-relatedness capturesthe strength of the relation betweenan object emerged in the field of consciousness andthe self (i.e., how one person feels an object in the field consciousness related to the self) (Aron et al., 1992). Therefore, James has conceptualized the self as a stream of objects that arise in the field of consciousness in a given moment (Me) characterized by different degrees of self-relatedness or ownership feelings.

This first conceptualization has laid the backgrounds formore recent phenomenological approaches to the self (for a review see: Woźniak, 2018), which have mainly focused the attention on the exploration of basic elements of self experience. For instance, Metzinger

(2010, 2003) has conceptualized the self as an intermittent process, with a conscious or not conscious feelings of selfhood, which captures the experience of being "*a distinct, holistic entity capable of global self-control and attention, possessing a body and a location in space and time* (Blanke & Metzinger, 2009; p. 7)". This experience has been defined as the "minimal phenomenal selfhood" (Woźniak, 2018). The emergence of the minimal phenomenal selfhood, and in turn self, has been hypothesized to be the consequence of a continuous process of integration between exteroceptive (e.g., motor actions, visual stimuli) and interoceptive (e.g., emotions, body signals) sensory signals (Salomon, 2017; Seth, 2013).

Looking at a clinical psychology perspective, one of the first definitions of the self has been provided by Carl Gustav Jung from a psychodynamic perspective (for reference see: Jung, 2014). Jung described the self as an overarching organizing principle allowing the integration of mind and body. Precisely, Jung describes two different domains of the self in order to highlight its intrinsic relational nature: i) one serves as an interface with the external world, the *persona*. The persona is the results of social interactions and external world; ii) the *shadow* represents the interface with the inner world, and it emerges from the relations between conscious and unconscious aspects of mind.

Carl Rogers (1959) developed a personality theory grounded on the self or self-concept. Accordingly, the self-concept represents a process needed for theindividualactualization, namely all ways in which persons differentiate themselves from others and experience themselves within a group. The sum of these processes and experiences establishes the individual`s self-concept in a given moment. The self-concept is constantly expanding through a basic process of assimilation of experiences into self-concept (Cervone & Pervin, 2008). Furthermore,the self is further organized in two interconnected domains: i) the *real-self* (self-image) is considered the result of feelings, thoughts and actions related to external world, and it also emerges from the relation with real and inner world; ii) the *ideal-self* is represented by personal ambitions and goals that change over time through the effects of external environments (e.g., values absorbed from significant other others or society).

Similar considerations about the self has been proposed by scholars from a socio-cognitive perspective. For instance, Higgins (1987) has proposed an organization of the self based on

3 interconnected domains: (i) the *actual self* includes beliefs about characteristics that someone think to own; (ii) the *ideal self* captures the representations concerning the characteristics that someone expect to own (e.g., wishes, aspirations); (iii) the *ought self* is the set of characteristics that someone believes ones should to possess (e.g., obligations, or responsibilities). According to this organization of the self, Markus and Wurf (1987) have stressed the dynamic nature of moment-to-moment organization of self, which is largely guided by the interactions between the person-system and different contexts, especially considering relationships with other persons (Andersen & Chen, 2002). Specifically, Markus and Wurf (1987) have conceptualized the *working self-concept* as the combination of a specific subset of all possible organizations of self in a given situation. Similar to other authors, Markus and Wurf (1987) viewed self as a dynamic system of representations with different forms (i.e., cognitive, affective, verbal, image, sensorimotor), time-orientation (i.e., past, present, future) and structure (i.e., stable elaborate knowledge and rules for how to behave in specific situations, fluid self-representation for contingent interactions). This here-and-now organization of the self (i.e., working self-concept) has the function to modulate actions of the person-system in order toachievevalue-related goals in a given situation.

Departing from afunctional contextualism perspective and the relation frame theory of human cognition and language (Hayes, 1993; Hayes et al., 2001), the self has been also conceptualized within the Acceptance and Commitment Therapy (ACT) in term of "*self-as-context*" (Hayes, 1995) that is the result of interactions among verbal–social contingencies involved in shaping self-awareness and perspective taking (Zettle, 2016). Furthermore, from the behavioral-analytic perspective of ACT, the self captures an integrated set of behavioral repertories that can be organized in three levels: i) the *conceptualized self* refers to a narrative repertoireabout who weare and how and why we came to be that person. The degree of fusion with this narrative affects self-awareness; ii) the *knowing self* includes individual abilities to notice in a non-judgmental manner all moment-to-moment psychological experiences. This process is involved in the expansion of ongoing awareness and range ofreactions toward to present-moment experiences; iii) the *observing self* might be considered as overarching process reflecting a transcendence sense that "*I am aware that is I who sees whatever is seen and not someone else* (Zettle, 2016; p. 55)".

On the one previously discussed perspectives on the self are characterized by specific features influenced by their theoretical backgrounds. On the other hand, the dynamic system theory might be a meta-theory (Granic & Hollenstein, 2003) thatallows to provide an integration among these approaches to the self. Accordingly, the self should be viewed as a result of moment-to-moment self-organization proprieties of mind and brain activity, which depend on the repetitive transactions between person and environments. Self-organization proprieties are strictly connected to integrative mind-brain processes (Stein & Stanford, 2008) ofinternal and external elements that reciprocally influence each other. The integration processes might be guided by the degree of sense of self-relatedness. Recursive internal-external integrative processes are at the base of the hierarchical nested organization of theself (Scalabrini et al., 2022), which ranges frombasic units to complex high-order patterns.

According to the intrinsic dynamic nature of the self and transactional principles of individual development discussed in the light of dynamic systems theory tenets, different theoretical approaches have discussed models of the self development.

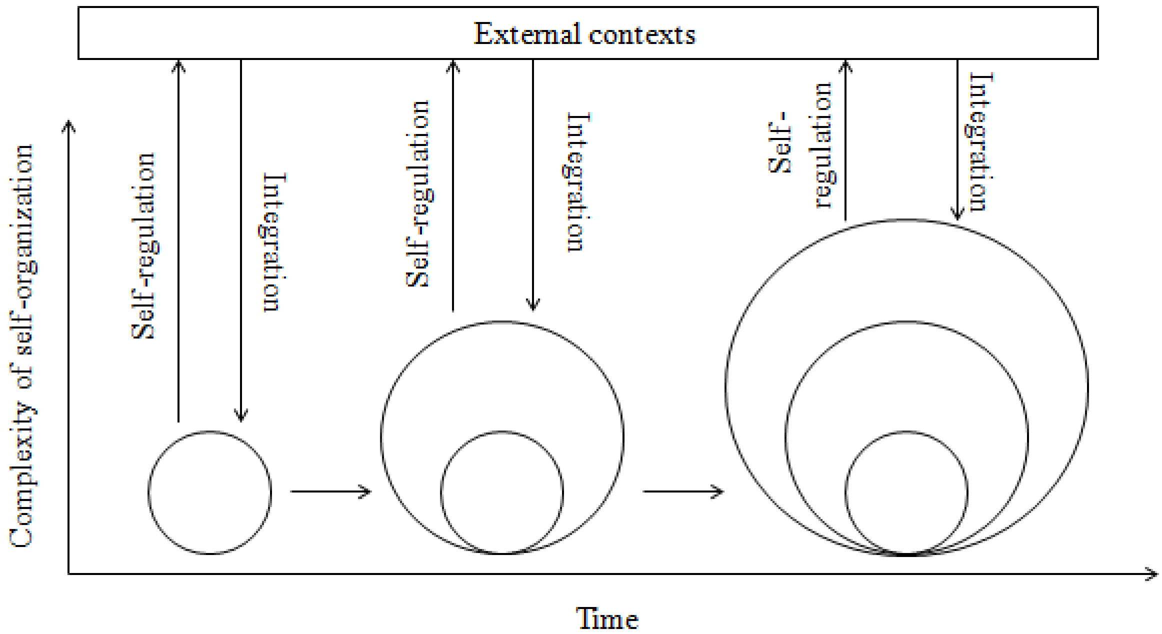
Looking psychodynamic perspectives, Winnicott (1965) has posited that the sense of self emergesfrom the early interactions between the caregiver and infant, which “internalizes” the empathic and mirroring relationship among them. Accordingly, Kohut (1971) affirmed that interactions between an individual and environments, especially relational ones during the infancy and early childhood,might reinforce or fragment the cohesive sense of self including body, mind, self-concept and self-object relationship. Attachment theorists (e.g., Fonagy et al., 2007; Lyons-Ruth, 2015; Schore, 2003) agree that parent–infant dyad represents the first experiences that lay the foundations for the self. Specifically, the mutual exchanges between caregiver and infant support the formation of the growing subject, promote an increasing organization of body-brain-mindinterconnections (i.e., interoceptive), and relations to the other and the world (i.e., exteroception). Overall, several psychodynamic scholars have affirmed that the self has a relational nature, and its basic foundations emerge from the capacity of the caregiver to moment-to-moment synchronize to the emergent self of the infant (Scalabrini et al., 2022). Furthermore, it has been suggested that the early synchronization from the caregiver and infant allows the emergence of the infant’s self-relatedness with internal and external world (Mucci, 2018).

However, the transactional nature of the development posited by the dynamic system theory suggests that the increasing complexity of hierarchical organization of the self should be a continuous process from infancy to adulthood (e.g., Cross & Markus, 1991;Lipka & Brinthaupt, 1992). This notion is in line withtheoretical approaches to the self that have conceptualized it as a dynamic structure or a multifaceted set of processes with different level of organizationin relation to externalcontexts (i.e., culturally, historically, and interpersonally) across life-span. Specifically, the transactions between the person-system and external contexts sustain moment-to-moment changes and re-organization of the self facilitating either integrative mechanisms or self fragmentation (e.g., Fischer& Ayoub, 1994; Hermans et al., 1993; Higgins et al., 1986).

In this regard, Jung (1933) has affirmed that each individual addresses a developmental taskfor the self concerning the confrontation with its contradictory aspects together with their historical reconstruction and integration within a more complex organization during the adulthood. Similarly, Erikson (1982) has posited thatindividuals develop a more complex organization of the self integrating personal successes and failures into a harmonic self-representation across the adulthood. Other scholars (Gutmann, 1987; Labouvie-Vief, 1994) focused the attention on changes in self-organization processes during the life-span. Specifically, it has been hypothesized that children and adolescents are characterized by a predominantly outward self-organization, which is involved in the integration of cultural norms and standardswithin the self. On the contrary, adults are characterized by amainly inward self-organization attuned to own historical, mental and emotional processes. The increasing complexity of self-organization from childhood to adulthood has been also discussed by cognitive-developmental researchers (e.g., Baltes & Staudinger, 1993; Kramer & Woodruff, 1986), who explored the transformation of self-organization processes of thinking quality. Similar to clinical notions mentioned above, empirical studies showed that the thinking of adolescents remains relatively static and non-dialectics, namely the prediction of reality in based on opposed categories (e.g., reason versus emotion, good versus bad). On the contrary, adults address these contradictions using dynamic categories considering contextual differentiation and variability of cognitive-emotional patterns related to specific contexts (e.g., Commons 1984; Kitchener & Brenner, 1990).

Taken these considerations together, some summary remarks might be drawn. According to the dynamic system theory applied to human development, the self and its dynamic organization should be considered across the life-span and in the light of the repetitive transactions between the person-system and environments. During the infancy and early childhood, the transactions between the infant/child and caregiver lay the foundations for the emerge of the basic components of self and sense of internal-external self-relatedness. From childhood to adulthood, the combination of internal integrative mechanisms in connection with contextual characteristics supports the continuous re-organization of the self increasing the levels of its complexity. Departing from these conclusions, the next section addresses the key mechanism involved in supporting the transactions between person-system andenvironments, namely self-regulation. Figure 5 provides a graphical summary of self and in its dynamic organization during the life-span on the base of the transactions with external contexts.

Figure 5. The development of self-organization across life-span



Self-regulation: dynamics, architecture, and development

Self-regulation has been extensively explored in scientific literature from different theoretical perspectives focusing on different features of this umbrella concept (for a compendium see: Vohs & Baumeister, 2016). Nevertheless, I decide to focus the discussion on two models that have conceptualized self-regulation as a system of complex interactions among processes and structures involved in continuous adjustments of goal-oriented behaviors. This was chosen because this operationalization seems to fit with: a) principles of self development and organization across life-span defined in accordance with the dynamic systems theory; b) hypothesized implications of self-regulation mechanisms for transactions between person-system and environments.

Consistently, Caver and Scheier (2016) have provided basic principles for self-regulation mechanisms of behaviors. The first assumption of this self-regulation model is a key role of goals — expected consequences of behaviors — for the modulation of moment-to-moment actions. The key role of goals for self-regulation, and in turn for transactions between the person-system and environments, is supported by the notion that the self can be partially understood in terms of person's goals and their dynamic hierarchical organization (Mischel & Shoda, 1995). Similarly, Carver and Scheier (2016) have posited that goals are hierarchically organized in the light of different levels of abstraction. Therefore, abstract or high-order goals are achieved through the concrete goals needed to define them. Lower-level goals allow to reach high-order goals through briefer and feasible sequences of motor actions.

Furthermore, goals are viewed as the reference value of feedback loops at the base ofaction self-regulation. Specifically, feedback loops, trough recursive and automatic control mechanisms, evaluate the presence of discrepancies between the ongoing action and future goal attainment. The detection of discrepancyis manifested by the onset of a bipolar dimension of affectivity. Particularly, positive affect arises when the person-system is doing better than one needs to; a negative valence reflects that person is doing worse than one needs to. Depending on the specific goal in a given situation and in presence of possiblediscrepancies between it and ongoing action, approach and avoidance behaviors can generate both negative and positive affect. According to affect quality, the feedback loops adjust the ongoing action to achieve the goal set in a specific context.

Ultimately, it has been assumed dynamic interrelationshipsamong goals setting process, feedback loops control mechanisms, and affectivityinduced by discrepancy detection. On the hand, the affect reflects the discrepancy between the ongoing action and the reference value. On the other hand, positive and negative affectivity, which arise from consequences of actions in comparison to theexpected final state, might alsoguidethe reorganization of the goals hierarchy in a given moment (Carver, 2006).

Departing from these principles of self-regulation, it is useful to integrate this model with an additional well-validated approach to self-regulation that allows: i) to clarify neuro-mental functions involved in the adjustment of ongoing actions toward goal attainment; ii) to build a bridge between psychological processes of self-regulation and related neural underpinnings. In this regard, Barkley (2001) has developed an intriguing models of neuropsychological executive functions considered as forms of "*behavior-to-the-self* (Barkley, 2001; p. 1)" that evolve from overt (public) to covert (private) responses with the ultimate goal of adaptation to complex environments (e.g., contingent situations, social groups, here-and-now and future situations), and in turn self-regulate the person-system over time and across contexts. According to this view and principles of self-regulation (Caver & Scheier, 2016), the architecture of executive functions hasamain outcome ofresponse inhibition. Specifically, Barkely (2001) has operationalized response inhibition referring to three domains: i) delaying prepotent responses; ii) interrupting an ongoing ineffective response; iii) resisting to interferences during the engagement in goal- or self-oriented actions. Consistently, executive functions and related response inhibition processes aim at moment-to-moment controlling motor actions. Precisely, Barkley (1997) has extensively defined the motor control as a "*motor control-fluency-syntax* (Barkley, 1997; p. 72)" domain of human functioning. This definition has been chosen in order to emphasize not only the control of motor system, but also the representational abilities to generate novel responses characterized by increasing complexity and related new behavioral sequences needed to achieve goals, which evolve over time. On the one hand, the building of behavioral sequences, or motor syntax, are mainly integrated in and implemented through the motor system. On the contrary, the effective execution of goal-oriented behaviors needs the support of other networks, namely sensory-perceptual, linguistic, memory, and emotional ones.

Departing from developmental psychology and psychopathology evidence, Barkley (1997, 2001) has identified four domains of executive functions involved in motor control, for which have been hypothesized common developmental processes. Specifically, infants and early children show entirely overt forms of these executive functions due to the fact that their targets are others and the external world. With maturation, these executive functions are progressively "internalized" through the reinforcement of inhibition abilities of musculo-skeletal features of the behaviors. According to Barkley's model of self-regulation (2001), the maturation of executive functions involved in motor control seems tobe similar to the internalization of speech (Diaz & Berk, 1992; Vygotsky, 1978).

Looking at the specific domains of executive functions, Barkley (1997, 2001) has operationalized the following constructs: i) *sensing to the self*; ii) *speech to the self;* iii) *emotion/motivation to the self*; iv) *play to the self.*

The *sensing to the self* domain is mainly represented by the executive function of non-verbal working memory. Within Barkley's model, non-verbal working memory overlaps with Baddeley's visual-spatial sketch pad (Baddeley, 1986). Following a developmental approach, non-verbal working emerges from the inclusion of sensory-motor actions, especially referring to two main senses of human experiences, namely vision and audition. Non-verbal working in the context of self-regulation of actions supports different essential processes: i) recalling retrospective sensory-motor sequences that could be useful for the here-and-now situation; ii) supporting prospective representation of sensory-motor sequences for future or imagined situations; iii) holding information/events in mind, and manipulating or acting on them; iv) providing an internal sense of time, and awareness of the self across time; v) allowing cross-temporal organization of behavioral sequences.

The *speech to the self* domain is based on the executive function of verbal working. In this context, verbal working memory reflects the internalization of speech and its implications for behavioral controls. Specifically, the verbal working memory in the context of self-regulation of behaviors includes: i) verbal descriptions and reflections on behavioral sequences needed to adjust ongoing goal-oriented actions, and to reinforce the acquisition of new behavioral sequences; ii) *rule-governed behavior* (Cerutti, 1989; Hayes, 1989; Skinner, 1953). According to behaviorism principles, language might have the function of *rules*, namely a large class of behaviors-specifying stimuli. Following Skinner's (1953) hypotheses, the control of behaviors begins with effects of language of others; subsequently, behaviors are modulated by a self-directed private speech through the progressive internalization of speech. The consolidation of self-directed speech supports the creation of new personal rules, which emerge from self-directed questions and problem-solving reasoning; iii) regulation of behaviors based on moral reasoning, which represents the internalization and creation of general rules from socialization and relationships with others.

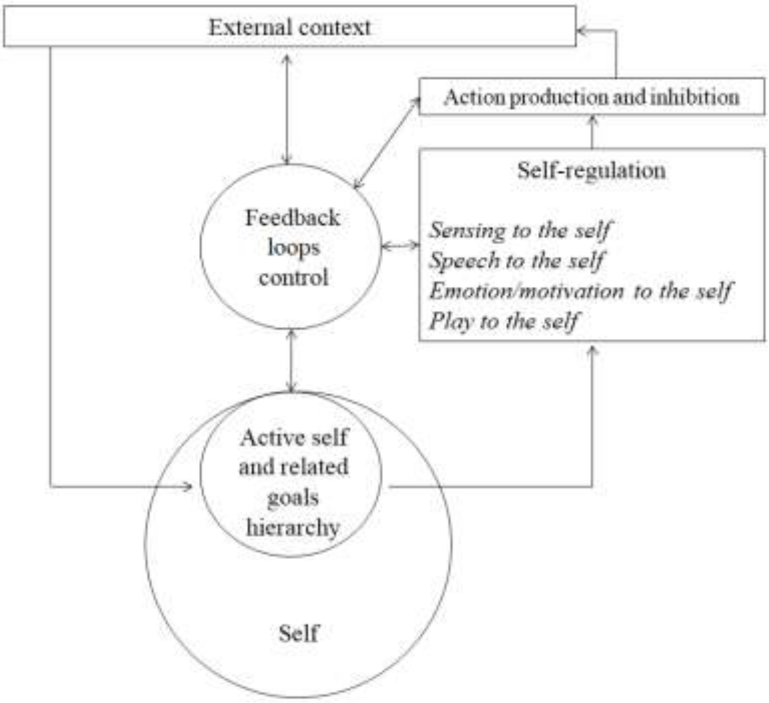
The *emotion/motivation to the self* captures executive functions involved in the integration of sensory-motor and verbal processes with affective and motivational proprieties of them, as conceptualized by Damasio's *somatic marker* (Damasio, 1994). The components of affect (Russell, 2003) — arousal/intensity; valence (positive vs negative)/motivational (reinforcement vs punishment) — are considered key aspects involved in the engagement in a given action, and in ongoing changes of behavioral sequences. Accordingly, the executive functions included in this domain are linked to: i) self-regulation of emotions guided by the achievement of specific goals; ii) self-regulation of emotions in order to assume a perspective taking based on facts, or to facilitate others perspective taking; iii) self-regulation of drives and motivations toward the achievements of different goals; iv) self-regulation (down- and up-regulation) of arousal that allows to engage in goal-oriented behaviors. Similar to the development of other executive functions, infants and early children manifest fully overt forms of these self-regulatory mechanisms (e.g., sucking hands or fist). With maturation, individuals progressively internalize these processes (e.g., shift intentionally the focus of attention, self-reassurance speech, reappraisal of the meaning of a situation) (Kopp, 1982, 1989).

The *play to the self* domainincludes executive functions with the main purpose to generate new combinations of behavioral sequences. According to this aim, the core executive functions of this domain refers to fluency, flexibililty, and generativity. These functions are involved in behavioral analysis (i.e., decomposition of an old behavioral sequence into basic units) and synthesis (i.e., recombination of basic units in a new behavioral sequences). Verbal and behavioral fluency, mental and behavioral creativity, together with abilities of mental simulation represent the key processes addressed by this domain. Children's play and its progressive internalization is considered the developmental pathway linked to the consolidation this domain (Pellegrini & Smith, 1998).

Attempting a synthesis of these models, it could be possible to provide some summary remarks:

i) person’s goals represent the central construct of self-regulation due to the fact that they reflect the organizations of the self in a given moment and situation;
ii) actions allow the self-realization in the external world through goals achievement;
iii) recursive and automatic feedback loops evaluate possible discrepancies between moment-to-moment action and goals or expected self-realization;
iv) in presence of discrepancies, executive functions related to each domain of self-regulation adjust the ongoing action in order to achieve goals or self-realization;
v) consequences of actions might allow to reorganize the goals hierarchy, and in turn might support a new self-organization;
vi) the improvement and consolidation of executive functions relevant for self-regulation should be viewed as continuous processes from infancy to adulthood. Self-regulation mechanisms emerge in infancy and early childhood as pure externalized forms. With maturation, they are progressively internalized as more representational mechanisms characterized by an increasing level of flexibility and complexity

Figure 6. Integrative model of self-regulation



Self-regulation and impulsivity: implications for SUDs

Barkley's (1997, 2001) model of self-regulation could be a solid theoretical background for discussing the implications of these processes for SUDs. Specifically, the relevance of this framework for understanding clinical characteristics of SUDs is represented by the central role of behavioral inhibition, which is viewed as the outcome of self-regulation system (i.e., behavior-to-the-self executive functions). Behavioral disinhibition is also a key facet of the complex construct of impulsivity, which represents a well-validated core feature of SUDs (Verdejo-García et al., 2008).

Historically, impulsivity has been conceptualized from different theoretical framework. Referring to a neuropsychological framework, impulsivity has been generally viewed as an impairment of top-down regulation, or an imbalanced bottom-up modulation offrontal cortices bysubcortical regions (i.e., limbic and striatal) (Bechara 2005). Several neuropsychological models of impulsivity (e.g., Christiansen et al., 2012; Domet al., 2007) have found a hierarchical structure of this construct, showing two high-order domains: a) *impulsive action* that specifically captures difficulties with response inhibition; b) *impulsive choice* that mainly includes reward processing alterations and related decision-making processes (Dalley et al., 2011; Reynolds et al., 2006). Interestingly, Stevens and colleagues (2014) have proposed a second-order classification of the previous domains. Particularly, impulsive action has been divided into: i)*cognitive disinhibition* that refers to inabilities to maintain the focus of attention on the achievement of a given goal in presence of competing or distracting information (i.e., conflict monitoring; Kenemans et al., 2005); ii) *motor disinhibition* or inabilities to restrainthe production of a prepotent orongoing response (Schachar et al., 2007). Furthermore, Verdejo-García and colleagues (2008) have recognized two lower-order factors of impulsive choice dimension, namely: i) *delay discounting* that describes a preference for smallerimmediate rewards compared to larger delayed ones (Richards et al. 1999); ii) *impulsive decision-making* that captures biases toward a selection of riskier options, or choices associated to immediate reward but delayed largerpunishments (Bechara et al. 1994).

Comparing this well-validated neuropsychological model of impulsivity with Barkley's model of self-regulation, some overlaps and differences should be discussed. On the one hand, all neuropsychological factors linked to impulsivity cover all executive functions included in each domain of self-regulation identified by Barkley. On the other hand, the major difference has been found concerning reciprocal and functional relationships existing among domains of self-regulation and neuropsychological impulsivity factors. Indeed, Barkley's model assumes that executive functions and related domains of self-regulationare strictly interconnected to each other, and they are functionally nested within a high-order factor reflecting motor inhibition. On the contrary, empirical neuropsychological data have suggested a different hierarchical organization of functions linked to impulsivity, for which response inhibition abilities and decision-making mechanisms based on altered reward processing are relatively independent to each other.

According to these partial discrepancies between models, it is useful to discuss empirical data concerning neuropsychological performances of individuals with SUDs in order to support which model might better explain the nature of self-regulatory mechanisms of this clinical population. Referring to quantitative findings, Stavro and colleagues (2013) conducted an extensive meta-analysis of 62 independent studies that assessed executive functions relevant for self-regulation (i.e., verbal fluency/language, working memory, attention, problem solving, response inhibition) among adult patients with AUD compared to HCs. Results showed that the most impaired neuropsychological domain among individuals with AUD was response inhibition (d > .70; large effect size), especially consideringfindings of samples with longer period of abstinence maintenance. The other domains were significantly impaired compared to HCs ($.27 \leq d \leq .60$; small to moderate effect size), and significant differences in the extent of pooled effect sizes among functions were not detected. Similar meta-analytic findings (Potvin et al., 2014) were also replicated for adult subjects with cocaine use disorder. Specifically, motor inhibition deficits, verbal and non-verbal working memory, together with verbal fluency represented the more impaired executive functions ($d > .50$; moderate effect size), especially among samples with protracted abstinence maintenance.

Ultimately, Cavicchioli and colleagues (2022a) assessed neuropsychological performances of a sample composed of adult treatment-seeking patients with different SUDs compared to HCs departing from the neuropsychological model of impulsivity previously discussed. Results highlighted that the most impaired domain of impulsivity in this clinical population was motor disinhibition, and in turn difficulties with response inhibition and motor preparation. Impaired motor inhibition was also associated with more severe forms of SUDs. The other neuropsychological domains of impulsivity were also impaired compare to HCs, showing moderate to large effect sizes. Nevertheless, no significant differences in the extent of effect sizes among impulsivity domains were detected.

Taking this evidence together, it could be possible to conclude that: i) the relative independence among neuropsychological domains of impulsivity seems to be not fully corroborate among clinical populations of individuals with SUDs; ii) the most representative dysfunction of these clinical populations refers to motor disinhibition. Therefore, Barkley's model seems to be effective for explaining self-regulatory functioning of individuals with SUDs. Accordingly, alterations of self-regulation processes, which are mainly manifested in deficits with response inhibition, should be considered a core feature of SUDs.

In addition to the current discussion based on a neuropsychological approach to self-regulation and its implication for SUDs, there is large consensus among different theoretical perspectives in considering self-regulation as a core feature of SUDs and related conditions. For instance, Sayette and Creswell (2016) provided an intriguing discussion on self-regulation and its implication for addiction from a social-cognitive perspective. Accordingly, the authors have identified two main maladaptive forms of self-regulation that might represent risk factors for substance use. Specifically, *misregulation* refers to misguided attempts to realize a self-relevant goal. Accordingly, substance use might be considered as a form of misregulation when a person short-term attempts to tolerate distressing affective states with this kind of behavior. Whereas, *underregulation* includes different combinations of difficulties across psychological processes needed to implement effective forms of self-regulation: i) setting properstandards and related goals; ii) monitoring ongoing actions in relation to self-relevant goals; iii) modulating behavioral, cognitive and affective responses to conform to these goals. Consistently, difficulties with a clear representation of actions consequences (monitoring), or inability topersist in long-term goal-oriented behaviors (modulation) increase the probability to engage in automatic short-term rewarding behaviors, such as substance intake.

Departing from a psychodynamic perspective, Khantzian (1997) has developed a robust clinical theory (i.e., self-medication hypothesis) of SUDs which views deficits with self-regulation as the core feature of this condition. According to this approach, deficits with self-regulation have been viewed as inability to regulate self-esteem, relationships, or self-care. Specifically, Khantzian (1997) affirmed thatproblematic substance use should be viewed as a combination of a basic deficit with the tolerance of all the spectrum of affect states, and the inability to self-organize one self within interpersonal contexts together with to actively take care of oneself. This latter impairment has been hypothesized to be a result ofdevelopmental deficiencies to ensure survivability, which do notallow to anticipate harms or dangers.

Hence, self-regulation, independently of theoretical backgrounds and related operationalization, has found robust applications for the study of core mechanisms at the base of clinical features of SUDs. On the one hand, I discussed how self-regulation processes should be connected with the dynamic organization of the self. On the other hand, there are no clinical or experimental studies that have explored the characteristics of the self and their possible altered dynamics among individuals with SUDs.

Self-regulation and developmental pathways of SUDs

The previous section has provided theoretical and empirical backgrounds for considering self-regulation processes in accordance with Barkley's model together with behavioral inhibition/disinhibition as core mechanisms at the base of clinical features of SUDs in adulthood. Furthermore, it has been highlighted that the self-regulation system emerges in infancy and continuously evolves across life-span, increasing its level of complexity and progressively substituting externalized forms with more internalized ones. Consistently, self-regulation could also be considered a key dimension involved in homotypic and heterotypic developmental pathways to SUDs. According to this hypothesis, the current section discusses empirical evidence concerning the implications of Barkleys's model of self-regulation forchildhood and adolescent conditions longitudinally linked to SUDs in adulthood, namely ADHD, CD, ODD and MDD.

Barkley's (1997) model of self-regulation has been specifically developed to clarify mechanisms at the base of clinical manifestations of ADHD. Providing an extensive review of literature, Barkley (2016) discussed how behavioral disinhibition and deficits in related executive functions might explain clinical characteristics of this condition during the development. Departing from the most representative domain of self-regulation, difficulties with behavioral inhibition have been demonstrated across several neuropsychological and experimental studies among ADHD individuals (Wright et al., 2014). According to Barkley (2016), difficulties with behavioral inhibition have secondary detrimental effects on the other domains of self-regulatory executive functions. Specifically, behavioral disinhibition predicts well-supported deficits with nonverbal working memory (Kasper et al., 2012) that could explain several everyday difficulties of children and adolescents with ADHD — different forms of forgetfulness; difficulties with time management; difficulties with representation of long-term consequences of actions. Furthermore, the delayed internalization of speech (e.g., Berk& Potts, 1991; Winsler et al., 2000), which is robustly associated to deficits with verbal working memory (Kasper et al., 2012), is manifested in excessive talking, reduced verbal reflection before acting, disrupted rule-oriented self-speech, and in turn difficulties with modulation of own behaviors through the self-speech. The impairment of internalized processes of self-regulation of emotions (for a meta-analytic review see: Graziano & Garcia, 2016) are functionally linked to other clinical features characterizing ADHD children and adolescents, such as heightened emotional intensity and expressions in response to events, decreased objectivity in appraising emotional-eliciting events, reduced access to internal motivationsneeded to persist in long-term goal-oriented behaviors. Ultimately, deficits with verbal fluency, cognitive flexibility and planning (Frazier et al., 2004) represent the basis for difficulties reported by ADHD children and adolescents with analysis and synthesis of own verbal and non-verbal responses to events.

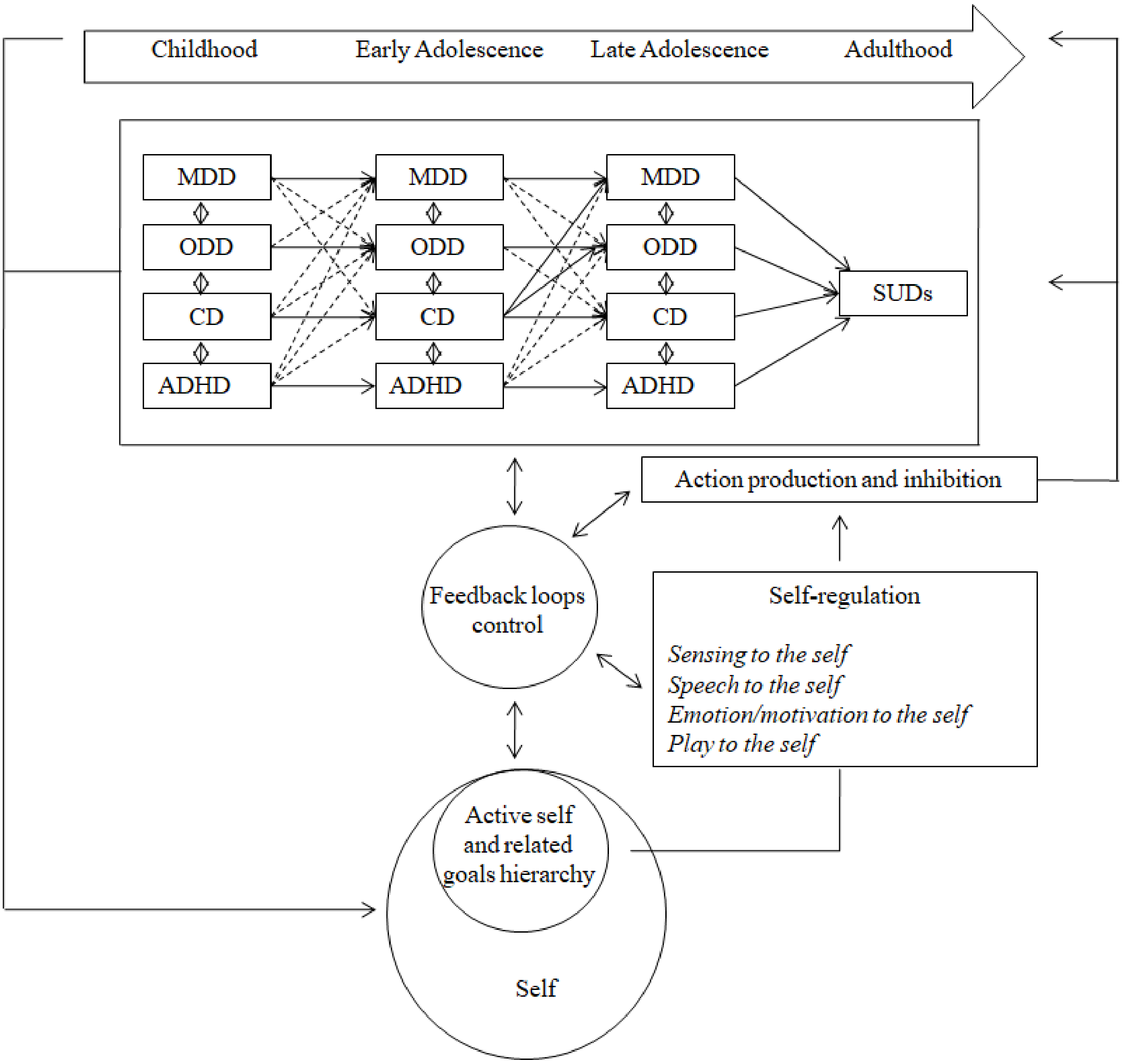
Remaining within the externalizing spectrum, behavioral disinhibition has been also theorized as a core latent dimension of CD and ODD (Krueger et al., 2021). On the one hand, empirical evidence has widely supported this conclusion through self-report investigations (for a review see: Krueger et al., 2021). On the contrary, neuropsychological research among children and adolescents with CDD and ODD appears more limited. However, an experimental study administering a go/no-go task showed a significant and positive association between difficulties with behavioral inhibition and CDsymptoms, especially among adolescent males. Similarly, Lueger and Gill (1990) demonstrated poor performances of adolescents with CD compared to HCs on different motor control tasks. Romer and colleagues (2011) showed that impairments in working memory predicted CD behaviors during adolescence. Furthermore, deficits in verbal abilities were predictors of aggressive behaviors among a sample of adolescents (Lansing et al., 2019). Only one study (Manfei et al., 2017) assessed the neuropsychological functioning of adolescents with ODD, and there were showed impairments of response inhibition, working memory-related and cognitive flexibility skills.

The implications of executive functions relevant for self-regulation as defined by Barkley's models a topic of debate among MDD children and adolescents, and empirical findings are mixed. Specifically, Vilgis and colleagues (2015) conducted a qualitative review of 33 studies assessing several executive functions within this clinical population. The qualitative evaluation of findings led the authors to conclude that only few studies supported poor performances in response inhibition, verbal working memory and verbal fluency among MDD children and adolescents compared to HCs. Nevertheless, the authors suggested that impairments in the previous self-regulatory functions might be more pronounced when stimuli with a negative affective valence were administered. On the contrary, results seemed to be more consistent in showing impairments in planning, spatial working memory together with decision-making and related reward processing mechanisms.

Hence, neuropsychological research consistently supports the notion concerning the centrality of deficits in self-regulation among children and adolescents with ADHD.

Provisional findings, albeit consistent, suggest that impairments in self-regulation as conceptualized by the Barkley's model might be considered key dimensions in explaining clinical features of CD and ODD. Altered self-regulation processes might have implications for MDD in childhood and adolescence, especially when considering specific situations characterized by negative affect valence. Nevertheless, no studies have evaluated whether responses inhibition and related executive functions constituting the system of self-regulation processes might be involved in homotypic and heterotypic developmental trajectories between these conditions SUDs in adulthood. Furthermore, no studies have provided information concerning the organization of the self among these childhood and adolescence conditions, especially in the context of self-relevant goal-oriented actions.

Figure 7. Integrative model of self-regulation for developmental pathways of SUDs



Self and its regulation: spatial and temporal organization of neural activity

The previous chapterhas discussed different theoretical frameworks concerning the self and its dynamic hierarchical organization over time and across situations. Furthermore, it has been proposed an integrative model of self-regulation based on a synthesis between basic principles hypothesized by Caver and Scheier (2016) and functional relationships among different neuropsychological domains as postulated by Barkley (1997, 2001). Looking at self-regulation, it has been also suggested that these processes and related alterations should be considered core features of SUDs in adulthood, and they might represent a developmental dimension involved in clarifying homotypic and heterotypic developmental pathways from childhood and adolescence psychopathological conditions (i.e., ADHD, CD, ODD, MDD) to adult SUDs.

Departing from these considerations, the current chapter will discuss neuroscience evidence that might support the dynamic hierarchical approach to the self and its regulatory mechanisms in order to provide an empirical background supporting the main investigation of the current work. Accordingly, neuroscience findings concerning the hierarchical organization of the self and its regulatory mechanisms will be discussed. Specifically, the presentation of results is inspired by the spatiotemporal theory of brain and mind (Northoff et al., 2020a,b), and its implications for understanding psychopathological phenomena (Northoff, 2018).

The spatiotemporal neuroscience approach attempts to go beyond the classic cognitive neuroscience framework that has conceptualized the brain as input(stimuli)-cognitive processes-output(overt or covert responses) information processing device. Specifically, spatiotemporal neuroscience posits four main tenetsthat distinguish it from a classical cognitive neuroscience paradigm:

i) classical cognitive neuroscience assumes a one-to-one relationship between changes in brain activity after the presentation of a given stimuli and changes in brain function (cognitive processes and overt/covert responses). Accordingly, this approach is focused on the study of input-cognition-output relationships. On the contrary, the spatiotemporal neuroscience is interested in studying spatiotemporal relationships (e.g., entropy, scale-free activity) of brain activity at the base of relationships at aninput-cognition-output level;

ii) the focus on information processing which characterized classical cognitive neuroscience is replaced by a shift toward the study how the intrinsic capacity of brain integrates and organizes at different levels of complexity the temporal spatial activity of mind-brain-body in connection with the environment;

iii) on the one hand classical cognitive neuroscience paradigm focuses on how the processing of stimuli, contents of cognitive processes and outputs (both internal and external) are reflected in brain's neural activitywithin a single network. On the other hand, spationtemporal neuroscience investigates the spatiotemporal organization of brain activity or the structure of neural activity in the light of relationships among several networks;

iv) the spatiotemporal approach provides a theoretical and empirical framework to study the brain/person-world relationship in terms of degrees of temporal-spatial alignment between brain/person and external world.

On the one hand a detailed discussion of these spatiotemporal neuroscience tenets and their implication for experimentalinvestigation of brain activity goes beyond the scopes of this chapter and the possibility to test them within the current meta-analytic work. On the other hand, this new neuroscience approach justifies the focus of the current work on different levels of brain activity organization with different spatiotemporal scales (i.e., fMRI and EEG). This approach is also consistent with the dynamic system theory, which has been used to conceptualized homotypic and heterotypic developmental pathways of SUDs from childhood to adulthood and related self-organization and self-regulation processes involved in these trajectories across the life-span.

Hence, next sessions will explore fMRI and EEG results supporting a hierarchical neural organization of the self. Furthermore, it will show findings that highlight structural and temporal organizations of brain activity involved in self-regulation, especially referring to behavioral inhibition tasks. This choice is supported by the evidence that has demonstrated a key role of behavioral inhibition capabilities as a core outcome of the self-regulation system (Barkley, 1997, 2001),together with their implications for conditions of interest throughout the development.

Spatial neural architecture of hierarchical organization of self

Several scholars have proposed different modelsin order to capture the hierarchical organization of the self and related neural architecture.Looking at neuroimaging evidence, Damasio (2010) has theorized three levels of self organization. Specifically, the "proto self" emerges fromthe interactions among multiple neural structures at different levels — from the brainstem, hypothalamus, hippocampus and cerebullum to the cerebral cortex (i.e., sensory cortices, inferotemporal cortices, prefrontal cortices). The "proto self" and related brain structures have the main function of regulating and representing the state of the organism. In other words, the "protoself" is a coherent integration of moment-to-moment patterns of neural activity that represent the basic physical states of the organism in a given moment (Parvizi & Damasio, 2001).The "proto self" lays the foundations for the other two high-level organization of the self, which Damasio called "core self" and "autobiographical self". The "core self" captures a moment-to-moment sense of self, which emerges from the continuous integration of body states (i.e., interoception) and exteroceptive changes due to the interactions between the body and external world. The "core self" is organized around the activity of regions linked to body experiences (e.g., somatosensory cortices, and extrastriate body area), superior posteromedial cortex, and posterior insular cortices (Araujo et al., 2015). On the contrary, the "autobiographical self" emerges during memoryretrievalof biographical information, such as facts of one's identity, personality traits and relevant life events. The "autobiographical self" has been associated to the activity of a brain network composed of: regions involved in mnestic processes (e.g., hippocampus), medial prefrontal cortex, superior posteromedial cortex, and anterior insula cortices.

Looking at these empirical findings supporting the Damasio's (2010) conceptualization of the self and its neural underpinnings, it seems of interest to focus the attention on experimental paradigms that were used to evaluate the neural activity linked to the different hierarchical levels of self. On the one hand, the conceptualization of the "proto self" has been developed departing from neuroscience evidence concerning neural activity associated to states of consciousness (Damasio & Meyer, 2009). On the other hand, the neural organization of "core and autobiographical self" were experimentally investigated administering stimuli characterized by different levels of self-relatedness (e.g., own sensations vs other states) and contents (e.g., personal traits, biographical events, own internal sensations [e.g., stomach], external [e.g., sensation of dryness]) (Northoff et al., 2006). Therefore, it could be possible to suggest that this spatial organization of neural activity induced by these experimental paradigms captures how the brain organize the degree of self-relatedness of a given internal or external stimulus, and which layer of the self is involved for the integration internal-external stimuli in the field of consciousness.

The hierarchical organization of the self and related brain activity has been alsowell discussed by Northoff and colleagues (2011). Particularly, it has been hypothesized a three-layer model of the self characterized by multiple interactions between a basic unconscious pre-reflective self and high-order levels identified by minimal self experiences and a complex idiographic narrative self(i.e., interpersonal and sociocultural experiences). Consistently, it has been proposed anintegrated subcortical–cortical midline system with different organizations linked to the self. According to Nieuwenhuys (1996), subcortical regions can be distinguished into three concentricdomains (Feinberg, 2009): i) core — peri-aqueductal gray, pontine central gray, hypothalamus and septum together with the dorsal vagal complex; ii) median — striatal terminalis, hypothalamus and raphe nuclei; iii) lateral paracore — ventral tegmental area (VTA), the locus coeruleus, the substantia nigra, the nucleus reticularis. These subcortical regions are mainly involved in interoception and homeostasis. This concentric organization also extents to the hypothalamus, amygdala, hippocampus, and parahippocampal gyrus, constituting what has been called as '*greater, distributed or extended limbic system*'(Morgane et al., 2005; Morgane & Mokler, 2006).

Therefore, the neural organization of these subcortical regions and their interactions should provide the neural underpinnings for the most basic form of a pre-reflexive self (Northoff et al., 2011). Extending the concentric organization of neural structure linked to thepre-reflective self, Feinberg (2009) suggested that a similar neural hierarchy among paralimbic areas, which refers to the orbitofrontal cortex, the perigenual, supragenual and posterior cingulate cortex, the temporal pole and the insula. Moreover, Feinberg (2009) has suggested that this kind of neural organization is preserved at a cortex level. Specifically, it has been supported the existence of a medial ring between the inner one related to interoceptive substrates of the self and the more external one concerning extero-sensorimotor systems (internal and sociocultural aspects of the self). This medial ring includes cortical midline structures (Northoff & Bermpohl, 2004) (i.e., medial orbitofrontal cortex, ventromedial and dorsomedial prefrontal cortex, medial parietal cortex) that have an integrative function of intero-exteroceptive dynamics of the self, allowing the experience of a moment-to-moment sense of self.

Departing from previous considerations concerning the interpretation of neuroimaging results ofself organization in relation to specific experimental paradigms built for these scopes, Northoff and colleagues (2011) have proposed two self conceptualizations, namely content-based and/or process-based ones. Focusing on the empirical evaluation of a process-based conceptualization of the self, experimental paradigms administrateinternal (e.g., body) of external stimuli (e.g., an object). These stimuli interact with spontaneous brain or resting-state activity. Resting-state or rest-stimulus brain activities represent predictors (i.e., independent variables) of stimulus-induced activity or the extent of sense of self-relatedness (i.e., dependent variables).

A recent meta-analysis of fMRI studies (Qin et al., 2020) has further corroborated a three-level organization of the self. Accordingly, the authors have identified three domains of self processing:

i) *interoceptive self processing* refers to a moment-to-moment representation of internal body signals. This level of self processing is involved in the integration of body signals and outer world information, which are linked to a basic sense of self. Considering experimental contexts, interoceptive self processing is mainly evaluated through heartbeat detection/differentiation tasks, hunger (e.g., differentiation between eatable and non-eatable stimuli after period of fasting) and thirsty (e.g., injection of hypertonic saline and subsequent discrimination between beverage/non-beverage stimuli) studies. Meta-analytic results showed three significant clusters of activity located at the insula (i.e., left anterior insula and right insula), the dorsal anterior cingulate cortex (dACC), thalamus and bilateral parahippocampus gyrus;

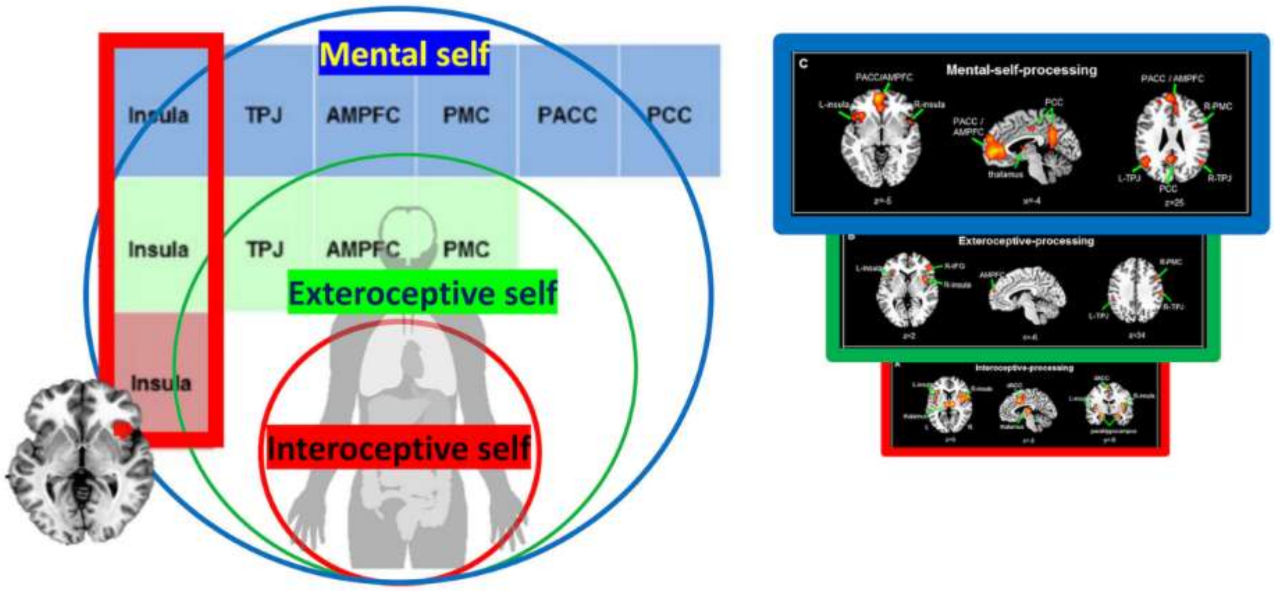
ii) *exteroceptive self processing* incorporates exteroceptive (e.g.,vision, touch, multisensory signals) and proprioceptive (e.g., sense of agency) signals relevant for the self. The exteroceptive self processing also integrates internal body signals and exteroceptive ones with external information, which is directly related to own body. This represents a key functions for the development of self-other boundaries, and in turn social relationships. According to this operationalization,the most widely used tasks are: own face and body recognition, self-agency (e.g., distinction between bodily signals and active actions), and body ownership (e.g., rubber hand illusion task). Meta-analytic findings highlighted an involvement of the following network composed of: left anterior insula, right middle insula, anteromedial prefrontal cortex (AMPFC), premotor cortex (pre-MC) and bilateral temporal parietal junction (TPJ);

iii) *mental processing self* is related to all external self-relevant stimuli without a direct implication of own body. Accordingly, this level of self processing refers to a wide class of more abstract stimuli, such asself-related traits, one's own name, memories of personal life events (i.e., self-related non-bodily signals). In other words, it captures the mental representation of the connection of external information with the self or the degree of self-relatedness of external stimuli. It also incorporates the intero-and extetoceptive self levels finalizing the process of integration of external information relevant for the self. Experimentally, the mental processing self is investigated through the judgment of self-other trait words, own name recognition, autobiographical memory tasks, object assignment and first/third person perspective judgement tasks.The aggregation of neuroimaging findings showed an involvement of bilateral insula, pregenual anterior cingulate cortex (pACC) / AMPFC, posterior cingulate cortex (PCC), pre-MC, and bilateral TPJ.

According to the evidence-based models mentioned above, different theoretical approaches to the self and related neural organization converge in identifying nested hierarchical patterns of neural activity (Scalabrini et al., 2022) that have specific, albeit complementary, integrative functions of different kind of self-relevant information, namely interoceptive, exteroceptive and self-related external abstract ones. According to the nested organization of self brain networks, each high-order level incorporates lower-order ones. However, each level of self processing ismainly organized around the functioning of specific brain areas. Specifically, interoceptive self processing is based on a key role of the insula. Exteroceptive self is mainly characterized by the activity of inferior frontal gyrus, temporal parietal junction and premotor cortex.

Ultimately, the mental self processing is linked to a predominant activity of AMPFC, pACC and PCC**.** Figure 8 depicts a graphical summary of spatial neural architecturereflecting the nested hierarchical organization of the self.

Figure 8. Neural architecture of the nested hierarchy of the self



Note: The figure was reproduced with permission of authors (Scalabrini et al., 2022)

Temporal organization of brain activity and hierarchical levels of self

The previous paragraph has summarized empirical evidence that supports a spatial definition of brain regions involved in eachlayer of internal-external selfprocessing. According to the spatiotemporal neuroscience approach, the discussion of neural underpinnings of self organization should be extended including data from techniques characterized by a high temporal resolution, namely EEG findings. Nevertheless, it seems to be useful to provide a brief discussion of temporal organization of brain activity, especially taking into account experimental paradigms developed to explore intero-extero-mental self processing.

Departing from these considerations, the first index of temporal organization of stimulus-induced neural activity refers to event-related potentials (ERPs), namely potentials elicited by the brain in response to internal or external events. Generally speaking, the ERPs are divided into three domains on the base on their temporal components (Luck &

Kappenman, 2011). The *exogenous* sensory components are obligatorily elicited by the presence of a stimulus, and they capture the neural processing of stimulus quality itself. However, they could be also partially modulated by top-down processes. Overall, the peak of these ERPs occurs between 50ms and 100ms after the stimulus. The *endogenous* components reflect full task-dependent neural processes. They include a large class of waves that occur 200 ms after the stimulus. For instance, the N2 classes of ERPs describethe ongoing process of stimulus categorization (e.g., larger waves for infrequent stimulus) together with implicit expectancies on stimuli onset. Whereas, the P3 classes are associated to processes that follow the stimuli categorization (e.g., probability evaluation of a given stimulus). They are mainly localized at frontal and central sites with the peak that occurs 300-600ms after the stimuli. It is well-established that these two classes of ERPs play a role in complex stimuli processing, such as emotion-eliciting ones. For instance, early N2 is linked to valence processing (e.g., larger for affective stimuli than neutral); whereas late P300 is associated to subjective experience of emotions (e.g., arousal rating ranging: 300- 600ms) (Hajcak et al., 2012). Late ERP components (400-800ms), both negative and positive ones, have been also consistently associated to task-evoked neural activity based on an intentionalverbal processing (e.g., language- and memory-related components) (Luck & Kappenman, 2011). The *motor* components are associated to the preparation and execution of motor responses. Deecke and Kornhuber (1978) distinguished 4 components of motor ERPs: (a) Bereitschafts potential, (b) Reafferent potential, (c) Pre-motion positivity and (d) Motor potential.

Focusing on the quality of exogenous and endogenous ERPs, their temporal components suggest a hierarchical organization of neural processing, which ranges from an implicit sensory processing of stimuli qualities (50-100ms) to a progressive non-verbal implicit self-centered processing of trigger stimuli (200-300ms), followed by an intentional verbal processing of stimuli and related voluntary mental operations on them (400-800 ms).

Interestingly, ERPs evoked by cognitive and sensory stimuli can be also capture by event-related brain oscillations (EROs), referring to time–frequency domain of brain activity (Herrmann et al., 2014). According to this approach, ERPs can be convert into a specific frequency or a superposition of different frequencies (Başar et al., 2001). For instance, a P100 component shows its peak at 100 ms with a typical temporal width of 50ms. Looking at this ERP as one half cycle of an oscillation, the 50 ms corresponds to an oscillation with a period of 100 ms (i.e. 10 Hz). According to the historical classification of EEG frequency band (Berger, 1930; Jasper & Andrews, 1936), 10Hz corresponds to the alpha power band (8–12 Hz). Using the same principles, the P300 could be captured by delta (0–4 Hz). and theta (4–8 Hz) frequencies (Başar-Eroglu et al., 1992). Therefore, the complex temporal organization of stimuli processing reflected by a combination of different ERPs components can be transformed into a superposition of EROs in all frequencies bands that constitute the temporal structure of ERPs amplitude(Karakas¸ et al. 2000). Differently to the ERPs, each power band linked to EROs might suggest information concerning the involvement different brain networks and related ongoing processes (for a review see: Karakaş, 2020). For instance, theta EROs capture the hippocampal activity and cortico-hippocampal interplays, which has been involved in different memory processes and functions (e.g., working memory, retrieval, consolidation), attention (e.g., selective attention, focused attention, sustained attention), sensory processing, motor preparation and voluntary movements. Furthermore, experimental research has demonstrated a whole theta system that acts in concert with hippocampal activity promoting multimodal stimuli integration. Furthermore, different power bands might interplay with each other in supporting different mental phenomena and functions (e.g., theta/delta: cognitive load; theta/alpha: working memory; theta/gamma: sensory/perceptual processing).

Departing from interoceptive self processing, one of the most studied indexes refers to Heartbeat Evoked Potential (HEP). The HEPs is a scalp-recorded ERP time-locked to participants' R-wave seen in the ECG. Differently to other well-validated ERPs (e.g., N200, P300), time interval between the R-wave peak (i.e., trigger stimulus) and the onset of the HEP is largely heterogeneous. It has been suggested that the HEP reflects the cortical processing of cardiac activity during time, and in turn is considered a marker of interoception (Park & Blanke, 2019). According to the wide use of the HEP, Coll and colleagues (2021) conducted a systematic review and meta-analysis of 45 independent studies that administered different interoceptive experimental paradigms, especially heartbeat detection tasks (i.e., deploy the attention on heart beat sensations; accuracy of heart beat evaluation), together with studies that recorded HEPs associated to presentation of arousal-eliciting stimuli. Studies that evaluated the effect of attention of internal signals of body showed thatthe strongest effects emerged at approximately 350 ms and peaked at 400 ms in central and fronto-central electrodes (Cz, C3,C4, Fz, F3, F4, FC3, FCz, FC4).

The intentional focus of attention on heartbeat induced a moderate increase of HEPs. Considering accuracy-based interoception tasks, it was highlighted that the strongest effects peaked at 250 ms in centraland fronto-central electrodes (Cz, C1, C2, C3, C4, FCz, FC1, FC2, FC3, FC4, FC5, FC6). Nevertheless, the time-window of peaks across studies was widespread, ranging from 200ms to 500ms. Furthermore, the analysis found that subjects who highlighted better performances in interoceptive evaluation tasks showed moderate increased responses considering both early (i.e., 200-300ms) and later (i.e., 400-500ms) components of HEPs. Accordingly, interoceptive self processing is represented by endogenous components of ERPs with a wide range of peak onset (200-500ms).This might suggest that interoceptive self processing is related to both non-verbal implicit and more intentional and verbally-mediated mechanisms. These findings might also corroborate the notion concerning a functional continuity from non-verbal implicit interoceptive processing to more reflexive and verbally-oriented mental self processing of internal stimuli.

Coll and colleagues (2021) also meta-analyzed results concerning the effects of arousal (i.e., presentation of external affective-eliciting stimuli) on HEPs. According to Qin and colleagues (2020) categorization of experimental paradigms developed for the evaluation of each layer of self processing, these meta-analytic results should capture a possible integration between the interoceptive layer (i.e., heat beat processing) and extero-mental layers (e.g., external self-relevant stimuli, such as emotional pictures or pain stimuli). The analyses found that the strongest effects peaked at 250 ms in centraland fronto-central electrodes(Cz, C1, C2, C3, C4, FCz, FC1, FC2, FC3, FC4, FC5, FC6and AFz). Furthermore, there was found a large effect of arousal on HEPs amplitude. According to this temporal organization of internal-external self processing and functional continuity among layers of self processing, it could be possible to suggest that integrative mechanisms between external self-relevant information and related internal body sensations might mainly action at a non-verbal implicit level.

Considering temporal organization of brain activity linked to exteroceptive self processing, studies on phasic pain perception provide empirical bases for a discussion of this topic. Consistently, Ploner and colleagues (2017) conducted an extensive review of studies that evaluated EROs linked to the administration of different type pain stimuli. Consistently, noxious stimuli inducedcomplex spectral–temporal–spatial patterns of neural activity, which have allowed to identify 3 different domains of responses.

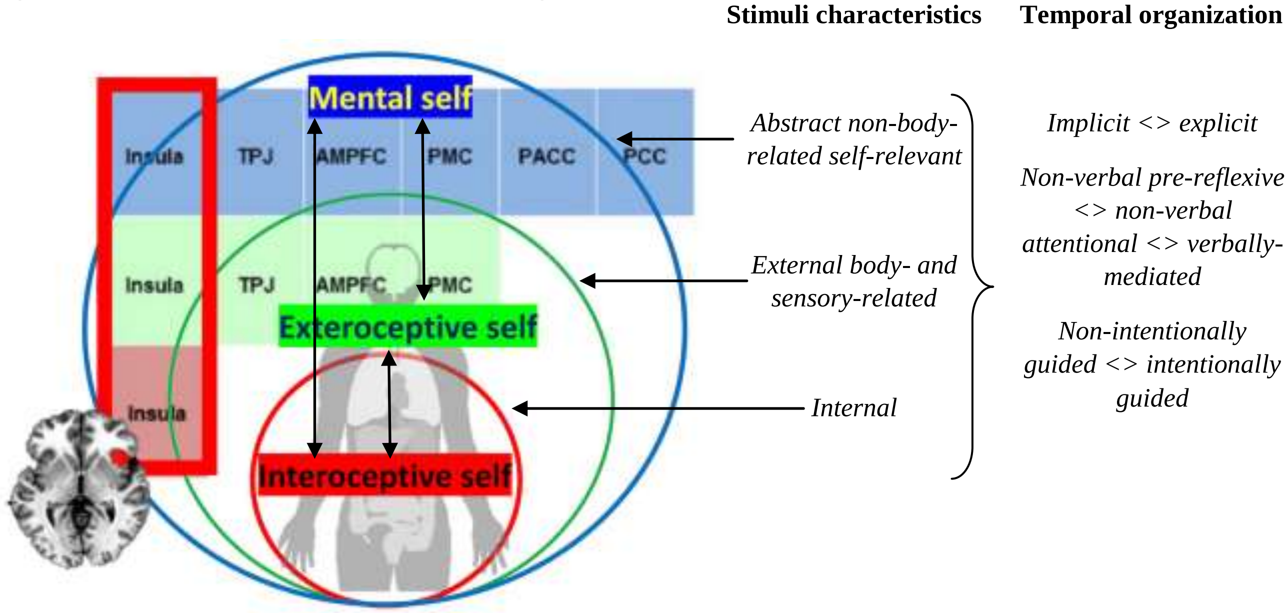
Fist, noxious stimuli evoke increased neural activity between 150 and 400 ms after their applicationsat frequencies below 10 Hz (i.e., alpha and theta activity). They are associated to pain-related ERPs, which include N2-P2-P3 components involved in endogenous evoked attentional mechanisms for pain stimuli processing. This activity has been located in an extended brain network composed of sensorimotor cortex and the frontoparietal operculum (i.e.,insula and somatosensory cortex, mid-/anterior cingulate cortex). Second, phasic pain stimuli reduced alpha and beta waves within a time window that ranges from 300 and 1000 ms, referring to sensorimotor and occipital areas. This has been interpreted as an effect of the alerting function on the noxious stimulus and subsequentpreparation of complex reactions to this self-relevant stimulus. Third, pain stimuli induce oscillations between 150 and 350 ms after stimuli presentation at gamma frequencies over the sensorimotor cortex. These findings suggest that gamma oscillations linked to pain administration capture early stages ofendogenousnociception and related subjective experience (Li et al., 2023).

Taking together this evidence, the temporal organization of exteroceptive self processing seem to overlaps with the interoceptive layer. Similarly, the integration of external stimuli directly connected to the body are integrated within the self departing from non-verbal implicit mechanisms and, subsequently might be the object of an intentional non-verbalattentional processing until a verbally-mediated conscious experience.

Ultimately, the temporal organization of mental self processing has been study within self-referential processing paradigms, namely through the administration of external self-related stimuli not directly connected to the body (e.g., picture of own face vs other; scripts of own name vs other; hearing own voice vs. other). In this context, Knyazev (2013) qualitatively summarized EEG results, referring to both ERPs and EROs. On the one hand, ERP studies highlighted that increased early (170 ms) and late (300-450 ms) negative and positive waves were involved in endogenous self-referential stimuli processing. The most recurrent findings referred to heightened P300 components, especially for discriminating self- from non-self-related stimuli. Looking at the EROs, empirical findings suggested an involvement during later stages (500-1000ms) frequencies below 10 Hz (i.e., alpha and theta activity) for self-referential stimuli processing. Gamma responses were also found across all stages of processing of self-referential stimuli, departing from early exogenous (40 ms) to later endogenous (> 400 ms) ones.

Therefore, evidence concerning the temporal organization of brain activity linked to the three interconnected layers of self processing might support the following considerations. According to substantial overlaps among layers, temporal organization of neural activity might suggest that internal-external-mental stimuli are processed with different: degrees of conscious availability (i.e., implicit vs explicit), qualities of mental processes (i.e., non-verbal pre-reflexive; non-verbal attentional; verbally-mediated) and related levels of intentionality (i.e., non-intentionally guided vs intentionally modulated), independently of their body-relatedness (i.e., internal; external directly connected to the body; external abstract self-related). Furthermore, the shared temporal organization of stimuli processing across layers might support the concentric view of self organization, that assumes a dynamic interplay among levels of self processing. For instance, interoceptive self stimuli (e.g., heart beat) could be early processed at an implicit non-verbal and non-intentional level, and subsequently they might be progressively processed using intentional non-verbal (e.g. attentional) and verbally-mediated (e.g., evaluation of subjective experiences) mechanisms at a mental self processing layer. Similarly, the external self-relevant and non-body-connected stimuli (mental self processing) (e.g., own face) might be processed with different time-windows (e.g., early implicit interoceptive level vs later explicit and intentional mental level). Figure 9 graphically summaries the hypothesized spatio-temporal model of self organization.

Figure 9. The spatio-temporal model of self-organization



Developmental pathways of self processing layers

The previous paragraph has provided a discussion of spatio-temporal neural activity of different self processing layers mainly based on results of empirical research on adult subjects. Nevertheless, clinical and theoretical frameworks discussed in the second chapter have supported a continuous development of the self across the life span. According to this notion, it could be useful to discuss available neuroscience evidence regarding spatiotemporal organization of brain activity linked to the administration of intero-extero-mental self paradigms among children and adolescents using different neuroscience techniques.

Departing from interoceptive self processing, some studies investigated neural activity during interoceptive tasks among children and adolescents. For instance, Klabunde and colleagues (2019) found that children and adolescents recruited an increased activity of the insula during intentional interoceptive self processing of heart beat, compared to exteroceptive non-self related stimuli (e.g., external sound). Interestingly, they also highlighted a positive association between age and activity of the anterior cingulate cortex, medial and mid-frontal gyrus, which represent areas involved in mental self processing. This suggests a progressive integration of interoceptive stimuli at different levels of complexity, from pure body sensation to more abstract mental experiences. A key role of insula for interoceptive self processing among adolescents has been shown by Li and colleagues (2017). Specifically, they found an increased activity of insula when subjects intentionally focused the attention on breath. Furthermore, the authors also found a positive linear association between activity of dorsal insula and age duringthis interoceptive task. This evidence has been linked to a maturation of interoceptive mechanisms during the adolescents, especially including a progressive recruitment of insula portions with a strict connection with the mental self processing layer (e.g., middle frontal cortex and precuneus) (Fichtenholtz & LaBar, 2012). Looking at temporal organization of interoceptive self processing, empirical results among children and adolescents seem to overlap with those collected among adults. Specifically, Mai and colleagues (2018) found that adolescents who showed better performances duringa heart-beat accuracy detection task highlighted significant increased HEPs and peaked between 360ms and 500ms. Accordingly, adolescent interoceptive self processing seem to be characterized by late components of HEP, suggesting a main implication of explicit and verbally-mediated mechanisms.

A few number of empirical studies has been conducted among children and adolescents regarding exteroceptive self processing of external body-connected stimuli (e.g., noxious stimuli). Particularly, only one study (Hohmeister et al., 2010) invested the neurobiological proxies of painful heat processing among children and adolescents. Results showed increased brain responses within posterior parietal cortex, anterior insula, pre-supplementary motor areas and premotor cortex, and a portion of inferior frontal gyrus. Accordingly, these provisional findings support that spatial organization of neural activity involved in exteropective self processing among children and adolescents substantially overlaps with adult subjects. Furthermore, these results corroborated the hierarchical nested organization of self and related brain activity, as shown by the co-occurrence of core interoceptive brain area (i.e., insula) with exteroceptive ones (i.e., inferior frontal gyrus and motor cortices).

The mental self processing layer has been widely investigated among adolescents, especially referring to the self-referential processing tasks. As shown for adults, the administration of self-referential stimuli induced an increased activity of structures included in the cortical midline— medial prefrontal cortex, ACC, PCC, and the precuneus — across several studies among adolescent individuals (for a review see: Pfeifer & Peake, 2012). Nevertheless, results of mental self processing dynamics from childhood to adulthood are mixed (for a review see: Butterfield& Silk, 2023). For instance, some studies showed that children and adolescents highlighted a greater responsiveness of cortical midline regions to the administration abstract self-relevant stimuli (e.g., self-descriptive trait words, self-related affective states) compared to adult individuals. Other evidence showed that adolescents were significantly more responsive than children and adult to self-referential stimuli with respect to cortical midline areas activity. However, the most consistent findings suggested that dynamics of the well-recognized brain network involved in mental self processing layer seemed to relatively stable from childhood to adulthood. Looking at temporal organization of neural activity linked to mental self processing, the empirical research focusing on typical developmental populations is limited compared to the huge amount of data collected from case-controlstudies. According to the purpose concerning the identification of an adaptive organization of neural activity, the discuss will focused on the few available evidence among healthy adolescent populations. Accordingly, data from a healthy adolescent population (Auerbach et al., 2016) confirmed that self-referential information was processed from early exogenous components (P100) from late positive potentials (> 400ms), and this temporal organization of brain activity linked to mental self processing remained stable over time considering different follow-up evaluation. This might confirm the notions discussed for adults concerning different levels of processing of external self-relevant information, which range from implicit pre-reflexive mechanisms (i.e., early components) to intentional and verbally-mediated ones referring late ERP components.

Taking these findings together, it could be possible to conclude that the hierarchical nested organization of the self and related neural underpinnings considering different spatiotemporal scales emerges from childhood and, its dynamic structure remains relatively stable until adulthood. Nevertheless, these considerations should be considered provisional, according to the limited empirical research on this topic among healthy populations of children and adolescents. Furthermore, future longitudinal studies are needed to effectively outline developmental pathways of self organization across life-span.

Brain networks of self-regulation

Departing from the integrative neuro-psychological model of self-regulation proposed in the previous paragraphs, neuroscience evidence will be discussed in order to highlight key neural networks involved in the self-regulation system. According to this framework, the main focus will be on empirical results regarding brain networks involved in behavioral inhibition tasks, considered as the key outcome of Barkley's self-regulation model. Furthermore, there will be explored neuroscience findings concerning the secondary domains of self-regulation, with a special attention to their implications for motor control: i) *sensing to the self* – nonverbal working memory; ii) *speech to the self*– verbal working memory and internalized speech; iii) *emotion/motivation to the self*– down and up regulation of emotions linked to goal-oriented actions; iv) *play with self* – cognitive flexibility, problem solving and creativity linked to the achievement of self-relevant goals.

Looking at behavioral inhibition, it could be useful to briefly describe the main experimental paradigms developed for evaluating this dimension. On the one hand, there are several tasks (e.g., Eriksen flanker, Stroop, Simon, Wisconsin card sort, continuous performance, reversal learning) that request to control different response tedencies. On the other hand, the most representative paradigms for studying behavioral inhibition are stop signal tasks (SSTs) and Go/No-Go (GNG) paradigm (for review see: Aron, 2011).

The SSTs ask subjects to refrain an already initiated response (Logan & Cowan, 1984). Specifically, a "Go" signal (e.g., press the left button for a leftward pointing arrow) is presented in each trial. A "Stop" signal (e.g., a sound) is presented after the "Go" signal in a small portion of trials. The task requires to respondas fast as possible on Go trials, and subjects have to dothe best to stop the response when the Stop signal occurs. The shorter the delay between Go and Stop signals is, the higher is the probability to stop; whereas the longer the delay is, the subject is less likely to stop. Classical GNG paradigms are a stream of "Go" stimuli (e.g., a letter: A), and subjects are required to respond to all"Go" stimulus except the "No-Go" stimulus(e.g., a no-go letter: X), which arepresented less likely than "Go" ones. On the one hand, SSTs and GNG paradigms assess the similar abilities ofmotor actioncontrol. On the other hand, these experimental tasks show specific features (Aron, 2011). Particularly, the SSTs allow to precisely identify the moment when motor inhibition processes begin. On the contrary, the GNG paradigms do not provide information for estimating when a subject begins to refrain a motor response. Furthermore, successful stopping within GNG paradigms is significantly influenced by the ratio between "Go" and "No-Go" stimuli. On the contrary,the performances concerning action inhibition are independent of the ratio between frequencies of “Go” stimuli and“stop signals”; whereas, they are exclusively influenced by the onset of the “stop signal” stimuli.

According to common and specific features of these tasks, neuroscience evidence highlighted an extended motor network involved in different aspects of motor inhibition. Reviewing empirical data among human samples (Aron; 2011; Isoda & Hikosaka, 2011), it has identified a role of the following areas:

i) *right inferior frontal* (rIFC) *cortex* includes pars triangularis, pars opercularis, pars orbitalis (i.e., Broadmann areas 44, 45, 47). Several fMRI, lesion and TMS studies confirmed its crucial role in inhibitory control referring to both SSTs and GNG paradigms;

ii) *pre supplementary motor area* (pre-SMA) isfunctionally linked to rIFC. The functional association of these areas is supported by input from basal ganglia, especially subthalamic nucleus and striatum. The pre-SMA is associated to preparation of motor inhibition together with the selection of superordinate sets of possible actions and related rules, conflict resolution and monitoring, and modulation of response thresholds;

iii) *subthalamic nucleus* (STN) is a structure of basal ganglia. It was associated to successful motor inhibition, especially referring to no-go commission errors;

iv) *striatum* was linked to the processing ofsuccessful outcomes of behaviors considering both correct responses and inhibition, and it was involved in preparation of stop responses;

v) *primary motor cortex* (I-MC) is considered the last cortical site before the movement production through commands descend the corticospinal tract.

vi) *cerebellum* plays also a role in action execution (Smith et al., 2009), and it has been included within the brain network that play a role on motor control and inhibition (Manto et al., 2012)

Therefore, there is a consistent evidence that highlights a brain network involved in motor inhibition and related processes, namely preparation of a stop response and monitoring of action outcomes. However, the current comprehensive model of self-regulation postulates the role of other relevant systems at the base of self-regulatory mechanisms. Accordingly, it will be showed neuroscience evidence that could define the neural underpinnings of each self-regulation subsystem relevant for response inhibition.

It has been affirmed that the *sensing to the self* domain is mainly represented by the non-verbal working memory. It has the function to hold in mind here-and-now relevant information for moment-to-moment actions, and it allows to represent future situations and related actions. Accordingly, several fMRI studies have identified a brain network which is called "*executive control network*" (ECN) at the base of these processes. The ECN is mainly composed of dorsolateral prefrontal cortex (DLPFC) and ventrolater prefrontal cortex (VLPFC), which has been consistently associated to non-verbal working processes and their implications for guidance of goal-oriented behaviors (Segal & Elkana, 2023). However, it has been also recognized anindependent network that sustain working memory processes, especially in relation to motor preparation, namely the "*dorsal attention network*" (DAN) (Ptaket al., 2017). The DAN includes intraparietal sulcus areas (IPS) and posterior parietal cortex (PPC) (Silver& Kastner, 2009).

The *speech to the self* domain is based on verbal working, and it has been considered a result of the internalization of speech. Neuroscience of inner speech have consistently demonstrated a relevant role of the left inferior frontal gyrus (lIFG) together with superior (STG) and middle (MTG) temporal gyrus (for a review see: Langland-Hassan, 2021).

The *emotion/motivation to the self* has been conceptualized in line with Damasio's *somatic marker* and its implications for decision-making (Damasio, 1994).Consistently, a huge amount of empirical data has highlighted a somatic maker's brain network composed of ventromedial prefrontal cortex (VMPFC) (i.e., including the mesial orbitofrontal; OFC), which represents the central node of this network, together with the amygdala and insula functionally connected to the VMPFC (for a review see: Poppa & Bechara, 2018).As discussed in the previous paragraphs, these areas fully overlap with two layers of self processing, namely the interoceptive and mental ones. Furthermore,a recent meta-analysis of fMRI findings (Tan et al., 2022) supported a hierarchical nested organization of interoception, decision-making and emotion regulation mechanism, which is organized around the central role of the insula. Taking together these considerations, the neural underpinnings of the emotion/motivation to the self domaincould be ascribed to interoceptive and mental self processing layers. Accordingly, affective states and related regulatory mechanismslinked to goal-oriented behaviors should be considered as a bridge between internal self-organization of neural-mental activity and self-regulation processes at the base of self-relevant goals realization.

The *play to the self* includes high-order functions concerningflexibility and generativity needed to generate new motor sequences. On the one hand, this subsystem of self-regulation phenomenologically different from the other cognitive-based domains. On the other hand, empirical data have been consistently showed a significant association with ECN (Dajani, & Uddin, 2015), similarly to the sensing to the self domain.

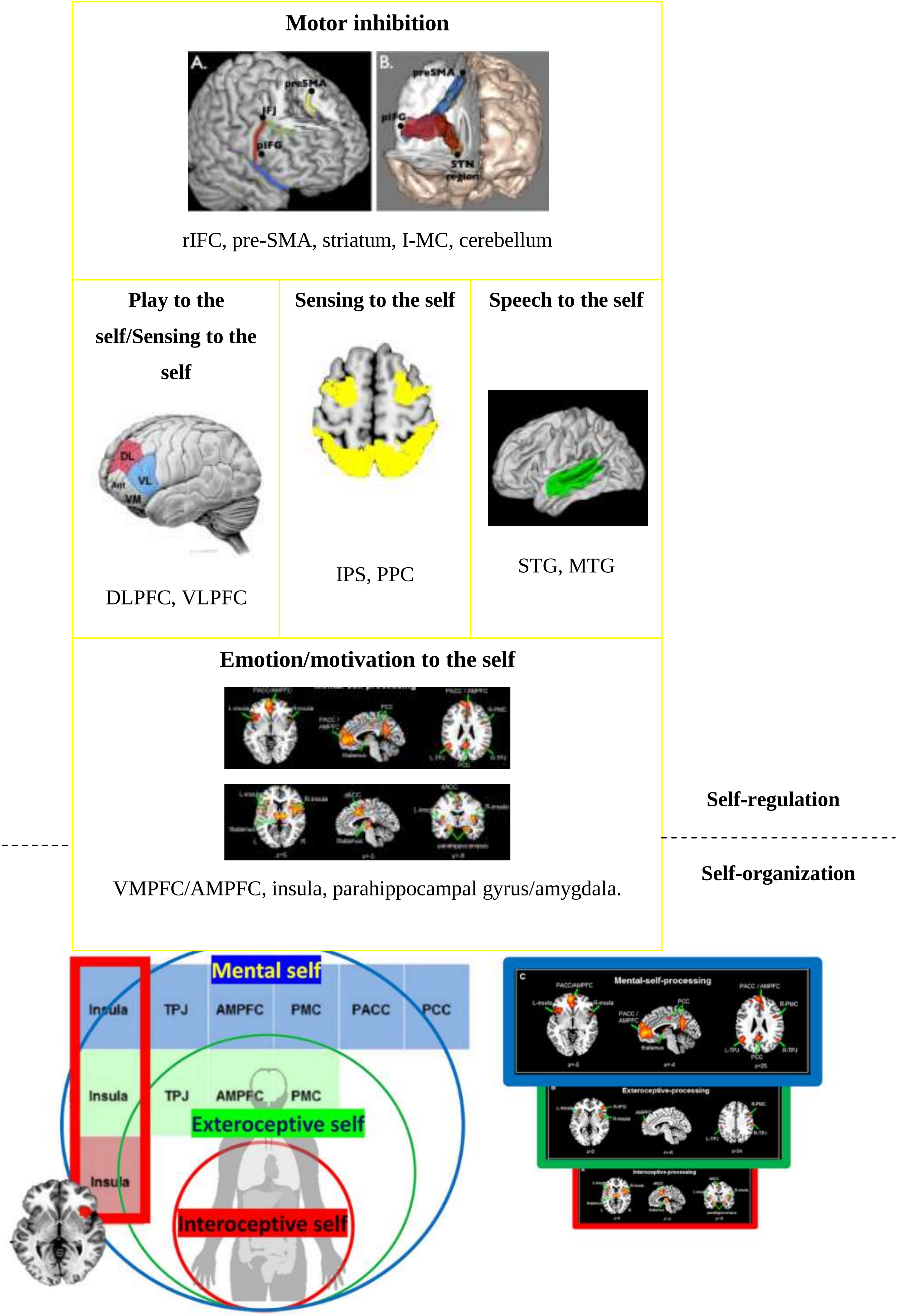
Therefore, it could be possible to conclude that specific brain networks underpin the neuro-mental subsystems of self-regulatory processes. Looking at a neural level, the main self-regulation outcome concerning motor inhibition is represented by a distinct network involved in motor control. The other self-regulatory domains functionally linked to motor inhibition are supported by common and distinct brain networks, namely the ECN (i.e, sensing to the self, play to the self), DAN (i.e., sensing to the self) and the inner speech processing network (i.e., speech to the self). On the contrary, the emotion/motivation to the self domain should be mainly considered as a bridge betweeninternal layers of the self, especially mentaland interoceptive levels, and self-regulation of behaviors linked to the realization of self relevant values in the external world. Table 1 summaries neuroscience evidence concerning self-regulation subsystems and related brain networks associated to specific areas. Figure 10 depicts the integration between the neural architecture of self-organization levels and self-regulation system.

Table 1. Neural underpinnings of self-regulation

Domain of self-regulation	Brain network	Areas
Motor inhibition	Motor Network	rIFC, pre-SMA, striatum, I-MC, cerebellum
Play to the self Sensing to the self	ECN	DLPFC, VLPFC
Sensing to the self	DAN	IPS, PPC
Speech to the self	Inner speech processing network	STG, MTG
Emotion/motivation to the self	Mental and interoceptive self	VMPFC/AMPFC,insula, parahippocampal gyrus/amygdala.

AMPFC= Anteromedial Prefrontal Cortex; I-MC = Primary Motor Cortex; IPS = intraparietal sulcus; DAN = Dorsal Attention Network; DLPFC = Dorsolater Prefrontal Cortex; MTG = Middle Temporal Gyrus; pACC = pregenual Anterior Cingulate Cortex; PCC = Posterior Cingulate Cortex PPC = posterior parietal cortex; pre-SMA = Pre supplementaty Motor Area; rIFC = Right Inferior Frontal Cortex; STG = Superior Temporal Gyrus; VLPFC = Ventrolateral Prefrontal Cortex;

Figure 10. Neural correlates of the integrative model of self-organization and self-regulation



Developmental pathways of neural architecture of self-regulation system

The study of neural underpinnings of response inhibition across the life-span might help to outlinedevelopmental pathways of self-regulation subsystems with a main outcome of motor control. According to this purpose, some studies compared neural responses of children and adolescents during behavioral inhibition tasks with adult individuals. A pioneristic study on this topic was proposed by Casey and colleagues (1997), who compared the neural activity of prefrontal cortex between a group of children (ages 7–12) compared to young adults (ages 21–24) during a GNG paradigm. The authors highlighted two main findings. On the one hand, children and adults recruited the same prefrontal regions (i.e., inferior frontal, middle frontal, orbital frontal, superior frontal, and anterior cingulate cortices) during within No-Go conditions. On the contrary, children highlighted a significant great activation of dorsal and lateral prefrontal cortices than adults, which was interpreted as an index of an increased cognitive load to inhibit a motor response. Conversely, Rubia and colleagues (2000) compared a group of adolescents (ages 12–19) with an adult one (ages 22–40), focusing on neural responses to a SST. Interestingly, results highlighted that adults showed greater activations than adolescents in the left middle and inferior frontal gyri, which linearly increased with age. Whereas, adolescents showed greater activations than adults in the right caudate nucleus and right inferior frontal gyrus, although no significant associations were found between age and extent of neural activations.

Tamm and colleagues (2002) recruited a group of typically developing subjects with ages ranging from 8 to 20 year-old, and they collected neuroimaging data during the administration of a GNG task. The authors showed different forms of maturation of response inhibition. Looking at behavioral outcomes, it was found a negative relationships between reaction times and age. Referring to neural activations, the analysis highlighted a positive association between age and the left inferior frontal gyrus/insula/orbitofrontal gyrus, and a negative correlation considering the left middle/superior frontal gyri. Accordingly, it was suggested that younger subjects highlight more enhanced prefrontal activity than older ones due to increased cognitive demands linked to inefficient executive functioning, especially working memory. On the contrary, older individuals seemed to show a maturation of brain areas involved in the ability to reflect on one’s performance and integrate internal and external information to engage in effective behaviors.

Constantinidis and Luna, (2019) conducted a review focusing on brain maturation during the adolescence, especially focusing of brain networks involved in behavioral inhibition.The authors showed different patterns of age-related increase and decrease of prefrontal regions recruitment. One of the most replicated findings referred to a linear decrease of recruitment of DLPFC from childhood to late adolescence, which should capture a progressive decrease of cognitive demands to module behavioral responses. On the contrary, it has been shown a linear increase of dACC recruitment, which has been correlated to better response inhibition performances. This seemed to suggest that the maturation of response inhibition should be supported by an improvement of attentional functioning and conflict monitoring. Taken together this evidence, it could be possible to conclude that response inhibition during childhood and early adolescence is mainly guided by intentional high-cognitive demanding working memory processes. The maturation across the adolescence supports a form of response inhibition based on more implicit and less-cognitive demanding attentional mechanisms.

Interestingly, Constantinidis and Luna (2019) also discussed that the maturation of neural functioning linked to response inhibition from childhood to late adolescence could be captured by an increased integration among prefrontal, oculomotor and subcortical systems. Indeed, empirical data showed that younger individuals were characterized by a local prefrontal recruitment during inhibition tasks. Whereas, late adolescents and adults seemed to highlight a more extended processing of response inhibition task, which involved different neural subsystems of self-regulation.

Hence, the maturation of brain areas involved in motor inhibition, and in turn self-regulation, across life-span mainly includes brain areas associated to the sensing to the self, play to the self and emotion/motivation to the selfsubsystems. Specifically, empirical findings suggest that maturation of behavioral inhibition departs from intentional high-cognitive load working memory mechanisms (i.e., sensing and play to the self) to more implicit self-related attentional mechanisms (i.e., salience network and interoceptive self-processing layer) (Peters et al., 2016) characterized by a less cognitive demand. Furthermore, the maturation of response inhibition should be viewed in the light of an increased integration among neural networks, which changes from a limited prefrontal working memory related organization to a more extended one including all cortical and subcortical subsystems of self-regulation. Therefore, self-regulation subsystems and related brain networks involved in response inhibition emerge and are recognizable from childhood. However, functional relationships among them and their implications for response inhibition change over time reflecting a progressive decrease of cognitive loads and an increased complexity of neural activityorganization.

Temporal organization of neural activity linked to self-regulation and its developmental pathways

The most investigated indexes of temporal organization of brain activity associated toself-regulation, especially consideringmotor responses inhibition, refer to the endogenous N2 and P3 classes of ERPs. Departing from this main outcome of the self-regulation system, several empirical data have found that larger N2 responses witha fronto-central localization are involved in successful inhibition during GNG paradigms (e.g., Brydges et al., 2012; Falkenstein et al., 1999; Jodo & Kayama, 1992; Kopp et al., 1996). Specifically, results were consistent in showing an increased N2 response to No-Go conditions (Kopp et al., 1996; Jodo & Kayama, 1992), which was replicated among samples composed of adolescents and adults (Vuillier et al., 2016). Consistently, many scholars suggested that the N2 should be considered a core neurophysiological maker of response inhibition. Nevertheless, there were found more complex patterns of neural activity during motor inhibition tasks reflecting interaction between the N2 and P3 components. For instance, Albert and colleagues (2013) highlighted that the N2 was associated to No-Go responses, when infrequent No-Go trials were compared to frequent Go trials (i.e., classical GNG paradigm). On the contrary, the N2did not show different amplitudes comparing No-Go and Go trials characterized by the same rates of occurrence. Whereas, an increased P3 amplitude was specifically associated to No-Go conditions comparing them with both frequent and infrequent Go trials. According to these findings, Albert and colleagues (2013)suggested that the N2 captures processes that occurs prior to the moment of response onset, independently of its quality (i.e., response inhibition or response production). Hence, the N2 might have a main function of conflict monitoring and/ordetection of novelty or mismatch. Contrary to provisional findings (Kopp et al., 1996; Jodo& Kayama, 1992), these results seemed to support that fronto-central P3 activity played a key role on the finalization of motor inhibition. This hypothesis was experimentally corroborated by Groom and Cragg (2015), who differentiated the implications of N2 and P3 for conflict monitoring and response inhibition within a hybrid

GNG flanker task. Accordingly, it was found that the N2 was enhanced for incongruent stimuli compared to congruent ones, independently of their quality (i.e., Go or No-Go). Conversely, a heightened P3, but not the N2, was associated to response inhibition trials. An additional study (Albert et al., 2010) highlighted that both N2 and P3 were involved in responses inhibition. However, their implications for motor self-regulation were different considering the quality of No-Go stimuli. Specifically, the N2 was the key marker of motor inhibition considering neutral No-Go conditions. On the contrary, the P3 was specifically associated to response inhibition withinNo-Go conditions characterized by a positive affective valence.

Looking at complex interactions between the N2 and P3 waves involved in behavioral inhibition, data from children and adolescent might enrich the scenario previously described. Specifically, Johnstone and colleagues (2007) found that heightened N2 and P3 responses were associated to No-Go conditions within a GNG paradigm among individuals between 7 and 12 years old. Interestingly, the amplitude of N2 for response inhibition linearly decreased with age. On the contrary, the association between response inhibition and P3 linearly increased with age, especially considering parietal sites.

Taking these findings together, it could be possible to conclude that both N2 and P3 play a key role for response inhibition, and therefore for self-regulation. Departing from childhood, the N2 and P3 are commonly involved in inhibition of behavioral responses. From adolescence to adulthood, the implications of N2 and P3 for the main outcome of self-regulation progressively differentiate each other. Specifically, the N2 assumes a main function of conflict monitoring and mismatch detection. On the other hand, the P3should be mainly involved in finalizing the inhibition of motor responses itself.

Interestingly, Kirmizi-Alsan and colleagues (2006) provided a comprehensive view of temporal dynamics of brain activity during a GNG paradigm compared to a sustained attention task. Specifically, they explored both the time domain focusing on the N2 and P3 together with the time-frequency spectrum of neural responses to pure behavioral response inhibition and attentional tasks. Specifically, the analysis confirmed that enhanced amplitudes of N2 and P3 were associated to response inhibition within the GNG paradigm. The GNG and sustained attention differed from each other considering the P3 and its prolongation over time, which was reduced for the GNG paradigm. Furthermore, responses inhibition was also associated to early (first 167 ms) and late (334–500 ms) poststimulus theta activity, which has been hypothesize to capture motor preparation mechanisms. Delta activity was also found considering a larger time window (167–833 ms), and it was higher for the sustained attention task compared to the GNG paradigm. This was associated to ahigher cognitive load of the sustained attention task compared to the GNG paradigm, and it might support significant differences in later P3 amplitudes found between these tasks.

Referring to the time-frequency domain of neural activity, Huster and colleagues (2013) published a qualitative review of studies based on the application of time frequency analysis of neural oscillations during responses inhibition tasks. Specifically, the most replicated findingswere an increased theta activity in frontal-midline localization for no-go and stop conditions compared to go trials,with respect to a poststimulus time window ranging from 200 and 600 ms (time window of N2/P3responses). Some studies also reported augmented delta activity in the same time window. Providing a discussion of empirical results, the authors suggested that theta activity should mainly capture N2 responses. On the contrary, delta frequency mainly reflected later neural activity associated to P3 responses. According to these findings, theta activity associated to N2 has beeninterpreted as a generic marker of cognitive control involved in responses inhibition, especially reflecting the activity of conflict monitoring system located in the cingulate cortex (Nigbur et al., 2011). With respect to task-dependent delta activity, the available data seemed to suggested that it might reflect endogenous processing of the motivational salience of internal and external stimuli, and therefore could be in line with theories of P3 as an index of motivated attention (Hajcak et al., 2010).

Therefore, the N2/P3 complex should be considered as the key temporal domain of brain activity involved in response inhibition (Ramautar et la., 2004, 2006). These ERPs capture basic processes that interact with each other forsustaining motor inhibition, namely conflict monitoring, mismatch detection, motivated attention, motor preparation and finalization. The N2 seems to mainly capture processes of conflict monitoring and mismatch detection. Whereas, the P3 is mainly associated to attentional deployment and motor finalization. On the one hand, the N2 and P3 are commonly involved in response inhibition from childhood. During the development, the N2 and P3 progressively differentiate their implications for motor control. Furthermore, this functional differentiation is corroborated by related time-frequency oscillations associated to No-Go conditions, namely theta (N2) and delta (P3) waves, which support mental mechanisms ascribed to different subsystems of self-regulation functionally linked to motor control.

Limitations of existing literature for clarifying neural underpinnings of self-regulation for developmental pathways of SUDs

The previous paragraphs have discussed the spatiotemporal organization of brain activity linked to the self and related regulatory mechanisms with a special attention to their developmental features. Specifically, it has been demonstrated a hierarchical nested neural organization of the self — interocepetive, exteroceptive, mental — in relation to the processing of different types of self-related stimuli (i.e., internal body signals, external body and sensory related stimuli, internal- external abstract self-related stimuli). The available empirical data have suggested that this hierarchical nested structure of the self is recognizable from childhood and remains relatively stable until adulthood. The temporal organization of neural activity linked to these layers of the self supports the notion that different kinds of mechanisms involved in internal-external-abstract self-related stimuli processing are shared among them and range from implicit non-verbal (early negative and positive waves) to more intentional attention- (i.e., N2 and P3 ERPs) or verbal-based (e.g., late positive waves) ones. Similar to the spatial organization of neural activity, this temporal organization of neural self-processing is relatively stable from childhood to adulthood. Looking at the neural underpinnings of self-regulation, it has been proposed an integrative model that identifies specific and common brain networks linked to each subsystems of regulatory mechanisms involved in response inhibition. On the one hand, these brain networks play a role in response inhibition from early childhood. On the other hand, it has been demonstrated a maturation over time of functional relationships among these networks. Specifically, children and early adolescents recruit local working memory and related networks for response inhibition tasks, which represent high cognitive demands for these populations. Progressively, response inhibition is mainly guided by attentional/conflict monitoring processes characterized by a reduced cognitive load compared to working memory (verbal and non-verbal) ones, together with a more extended involvement of different self-regulation networks that sustains better performances during the development. The temporal organization of neural activity associated to response inhibition is mainly captured by the complex N2/P3. These waves are indifferently involved in response inhibition during the early stages of development. With the maturation, the N2 and P3 capture specific mechanisms needed to support an effective motor inhibition. On the one hand, the N2 is mainly linked to conflict monitoring and mismatch detection. On the other hand, the P3 is associated to intentional deployment of attention and motor finalization.

The neural spatiotemporal correlates of response inhibition previously discussed were explored among clinical conditions constituting developmental pathways to SUDs. Particularly, Qiu and Wang (2021) meta-analyzed fMRI data during the administration of different types of response inhibition tasks (i.e., GNG, SST, Stroop tasks) among adult individuals with SUDs compared to HCs. Their voxel-based meta-analysis conduted using the Seed-based *d* Mapping (SDM) Permutation of Subject Images (Albajes-Eizagirre et al., 2019) showed a reduced activity in areas ascirbed to fronto-pariental and vental attention networks (i.e., IFG, MTG, insula) together with a heightened response of cerebellum among SUDs considering response inhibition conditions. Despite the robusteness of findings, this study showed some limitations in order to clarify spatial organization of neural activity linked to response inhibition departing from the current self-regulation theoretical framework. Additional limitations have been found in order to identify possible underpinnings of developmental trajectories to SUDs taking into account the dynamic progression from problematic substance-use to SUDs. First, there were included a huge amount of studies that administered different versions of the Stroop task, which mainly capture attentional components of executive functioning rather than action inhibition ones (MacLeod, 1992; Rueda et al., 2016; Tian et al., 2014). Second, the authors excluded studies that recruited samples with problematic substance-use. This did not allow to highlight possible shared neural mechanisms involved in the progression from subclinical to more severe forms of substance use. Ultimately, this study meta-analyzed data from adults samples not considering findings from adolescent and young adult populations. Again, this did not allow to support possible implications of these findings for clarifying neural developmental dimensions at the base of SUDs onset. Zhang and colleagues (2021) summarized results of neurophysiological reactitivy to response inhibition tasks showing reduced a N2 amplitude for no-go conditions among adult individuals with SUDs compared to HCs. On the one hand, this meta-analysis showed consistent findings across studies that administered GNG tasks. On the contrary, this work included a limited number of studies conducted among samples with problematic substance-use, and no studies among adolescents and young adults were considered. Accordingly, this did not allow to support whether alterations of N2/P3 complex could be considered developmental markers of SUDs.

Neural underpinnings of self-regulation, with a special attention to motor inhibition, have been investigated among samples of individuals with ADHD across the life-span. A meta-analysis based on the SDM algorithm (Hart et al., 2013) investigated spatial neural activation of ADHD samples from childhood to adulthood compared to HCs during inhibition tasks (GNG, SST, Stroop and Simon task). On the one hand, the analysis found significant deactivations of IFC, SMA, ACC, and striato-thalamic areas among ADHD individuals relative to HCs. On the other hand, the meta-regression found that SMA and basal ganglia were significantly deactiveded solely in children with ADHD compared to HCs; whereas, IFC and thalamus responses were reduced soly for adults with ADHD. Despite these interesting findings, some limitations were detected. First, these meta-analytic results were outdated. Second, the results might be affected by the inclusion of Stroop and Simon tasks, which mainly assess attentional processes (Hübne & Mishra, 2013; Proctor, 2011). Third, this meta-analytic study did not provide evidence for sustaining whether these brain networks might be involved in explaining comorbities between childhood and adolescent ADHD with other internalizing/externalizing developmental disorders and later problematic substance-use/SUDs. Looking at the temporal organization of brain responses to motor inhibition tasks, a recent meta-analysis (Kaiser et al., 2020) of ERPs among individuals with ADHD across the life-span highlighted that the most representative alteration was a moderate reduction of P3 amplitude relative to HCs for no-go conditions. On the contrary, no significant differences between ADHD and HC groups were found with respect to the N2 considering the same experimental conditions. Results of Go conditions showed no significant differences between groups. The age of participants was a significant moderator of effect sizes. Accordingly, a larger reduction of P3 linked to no-go conditions was found in children relative to adolescents or adults. Nevertheless, this extensive work seemed to show some limitations, especially considering the aggregation of results from GNG and stop signal tasks with conflict monitoring ones. Moreover, the authors did not explore whether ERPs alterations could be detected at a specific localization (i.e., frontal, fronto-central, central, parietal, occipital). Ultimately, this meta-analysis did not compare the extent of pooled effect sizes reflecting ERPs alterations within response inhibition of individuals with other clinical conditions of interest constituting developmental pathways of adult SUDs.

Referring to adult MDD, Piani and colleagues (2022) qualitatively summarized fMRI data of GNG and sustained attention studies discussing that this clinical population highlighted increased brain responses within areas ascribed to the default mode network (i.e., inferior parietal lobule, ACC, and precuneus), ventral attention network (i.e., ventral PFC and STG) and executive attention network (i.e., insula, and ACC), which well-overlap with different layers of self-processing and self-regulation subsystems. However, the qualitative nature of this work did not allow to robustly evaluate the implicatons of each brain network for response inhibition among this clinical population. Futhermore, the discussion of findings referred to a general overview that combined studies administering GNG paradigms and sustained attention tasks, without differentiating implications for motor inhibition and attention regulation. This could affect conclusions concerning brain network involved in self-regulation among adults with MDD. Moreover, results from adolescent MDD were not included. Accordingly, there is a lack of information regarding developmental dynamics of these networks involved in response modulation among individuals with MDD, and it is not clear which brain areas might be shared with other externalizing conditions during the development, such as ADHD or CD/ODD relevant for later SUDs. Referring to temporal organization of brain activity, Greco and colleagues (2021) attempted to qualitatively summarized results of empirical reaserch on ERPs among patients with MDD compared to HCs. On the one hand, it was detected a limitation concerning the inclusion of mixed tasks for evaluating alterations of neurophysiological responses. On the other hand, results seemed to be consistent in showing a reduced amplitudes of N2 and P3, especially when affective no-go stimuli were compared to neutral ones. Limitations concerning temporal organization of brain activity linked to self-regulation among individuals with MDD are exactly the same discussed for high spatial resolution findings.

Looking at neuroscientific evidence concerning executive functioning of children and adolescents with ODD and CD, Noordermeer and colleagues (2016) attempted to summarize fMRI data referring to two models postulating deficits of cold (i.e., inhibition, working memory, planning, flexibility, creativity) and hot (i.e., sensitivity to reward and punishment and their processing) executive functions as core features of these disorders.

Interenstigly, this work discussed neuroimaging results taking into account samples composed of individuals who were affected by comorbid externalinzing conditions, such as ODD/ADHD, CD/ADHD. Referring to cold executive functions, the authors qualitatively summarized results of mixed tasks concerning attentional control and problem solving, but not inhibitory control. On the one hand, they suggested common structural and functional abnormatilies of precuneus, which represents a core region of mental self layer. On the other hand, this qualitative conclusion cannot be considered robust enough in order to support implications of self brain networks for these conditions. Moreover, no data were available considering brain responses within response inhibition tasks. Therefore, this lack of empirical evidence did not allow to draw conclusions concerning neural underpinnings of self-regulation among these externalinzing developmental conditions. The temporal organization of brain activity among children and adolescents with ODD and CD, especially in response to inhibition tasks, is a topic rarely investigated within empirical research and, it mainly refers to samples composed of children and adolescents with a primary diagnosis of ADHD in comorbidity with ODD/CD. Furthermore, research on temporal organization of brain activity among these populations was focused on resting-state EEG signals, rather than response inhibition task-dependent ERPs. For instance, Clarke and colleagues (2002) compared resting-state EEG activity between ADHD children with (ADHD-ODD) and without ODD. The analysis found a laterazation of absolute theta activity that was more pronounced among ADHD children than ADHD-ODD in the left hemisphere, but reduced than ADHD-ODD in the right hemisphere. Furthermore, the theta/alpha ratio was greater among ADHD compared to ADHD-ODD, especially referring to posterior localization. Another study (Tor et al., 2021) explored non-linear organization of resting-state EEG among three groups including ADHD, ADHD-CD and CD children. Results showed that the CD group exhibited the highest level of disorganization of brain activity compared to the other groups, which was reflected in a higher resting-state EEG variability over time. Taking these provisional findings together, both children and adolescent with ODD and CD might be characterized by higher self-disorganization of brain activity than ADHD. Nevertheless, these results did not allow to draw conclusions regarding which layer of self could be impaired among these populations. Looking at empirical evidence concerning ERPs among adolescents with CD, there two studies that neurophysiological responses during two different attentional tasks, namely the Stroop task and continous performance test. Specifically, Bauer and

Hesselbrock (1999) showed that individuals with CD were characterized by a reduced P3 in responses to incongruent conditions during the administration of the Stroop test. Whereas, Overtoom and colleagues (1998) found in a small subgroup of ADHD-ODD a reduced N2 in response to target stimuli compared to a clinical group of children with ADHD and HCs. On the one hand, these alterations of P3 and N2 are fully in line with the well-demonstrated role of such waves in explaining self-regulation conceptualized as motor inhibition capabilities. On the other hand, the previously discussed results only referred to the attentional domain of self-segulation system. Therefore, there is a lack of empirical evidence that could support the implications of P3 and N2 as a key marker of altered temporal organization of brain acitivity linked motor inhibition, and in turn the core domain of self-regulation, among children and adolescents with ODD and CD.

Conclusive remarks

The previous paragraphs have discussed neuroscience evidence supporting a spatiotemporal organization of brain activity at the base of the dynamics related to different levels of self-processing of internal and external self-relevant stimuli. Specifically, three levels of self-processing has been robustly demonstrated, namely interoceptive, exteroceptive and mental ones. Temporal organization of brain activity in response to the presentation of different types of self-relevant stimuli has suggested that they are processed in a continuum from a pre-reflexive implicit level to intentional non-verbal-attentional and verbally-based ones. This spatiotemporal organization of brain activity linked to the self emerges from childhood and seems to remain stable until the adulthood. A neural spatiotemporal model of self-regulation has also been proposed. Accordingly, specific brain networks has been discussed for each domain of self-regulation originally proposed by Barkley (1997, 2001), namely emotion/motivation to the self, sensing to the self, speech to the self and play. All these domains are functionally connected to motor inhibition, which represents the main outcome of self-regulation system. The organization of self brain networks is strickly connected with self-regulation ones, and the bridge between them is represented by the mental self layer that shared with the emotion/motivation to the self domain the same cerebral structures. Temporal organization of brain activity linked to motor inhibition has been consistently associated to the N2 and P3 waves, which capture key mechanisms involved in this dimension, namely conflict monitoring/mismacht detection (i.e., N2) together with intentional deployment of attention and finalization of motor actions (i.e., P3). The spatiotemporal organization of brain activity at the base of motor inhibition, and in turn self-regulation, changes across the life-span. Specifically, motor inhibition recruits limited working-memory related brain networks charactized by a high cognitive load during the childhood. Children also show an undifferentiated involvement of N2 and P3 responses during motor inhibition. This spatiotemporal organization of brain activity evolves across the life-span. Particularly, adolescents and adults highlight an extended recruitment of different brain networks sustaining at the base of non verbally-mediated mechanisms involved in self-regulation with low cognitive load. Furthemore, the temporal organization of brain activity progressively differentiates its implications for motor control from childhood to adulthood — N2: conflict monitoring and mismatch detection; P3: intentional attentional deployment and motor finalization. On the one hand, different spatiotemporal neurobiological markers of self-regulation mechanisms among individuals with problematic substance-use behaviors and SUDs and related developmental psychopathology conditions have been exstensively explored. On the other hand, the existing literature shows some limitations in providing a comprehensive view of spatiotemporal brain mechanisms involved in self-regulation processes at the base of problematic substance-use behaviors and SUDs, especially taking into account different developmental pathways to these conditions. This evidence supports the current meta-analytic works exploring spatiotemporal neural markers of motor inhibition, which represents the main outcome of the self-regulation system among these conditions across the life-span.

Studies supporting the current meta-analysis

Departing from theoretical backgrounds discussed in the Introduction section, there were also conducted several published and unpublished works in order to empirically provide a robust support concerning:

i) the identification of homotypic and heterotypic development trajectories of SUDs;

ii) the key role of behavioral self-regulation or motor inhibition as a core feature of SUDs and clinical conditions developmentally linked to them;

iii) methodological procedures for combining a ROI-based approach with a coordinate-based one in order to meta-analyze fMRI data.

Developmental trajectories of SUDs

Looking at an empirical support for homotypic and heterotypic developmental trajectories of SUDs from adolescence, it was recruited from different high schools located in south and north Italy a sample composed of 434 students (i.e., age ranges from 12 to 18 years old; 54% males; 46% females). It was administered a self-report assessment battery composed of: i) the Child Behavior Checklist (CBCL) - Youth Self Report (Achenbach& Rescorla, 2001); ii) the Difficulties in Emotion Regulation Scale (DERS) (Gratz & Roemer, 2004); iii) the Adolescent DissociativeExperiences Scale (DES-A) (Armstrong et al., 1997); iv) the Rumination-Reflection Questionnaire (RRQ) – rumination subscale (Trapnell & Campbell, 1999); v) the Avoidance and Fusion Questionnaire for Youth (AFQY) (Greco et al., 2008). The CBCL was used in order to test specific associations among DSM-oriented externalizing (ADHD, ODD, CD) and internalizing (MDD, anxiety problems, somatic problems) conditions with recurrent alcohol and other drugs use during the adolescence (i.e., rating = 2: CBCL items investingating the frequency of alcohol and other substance use). The other questionnaires capture a comprehensive network of emotion regulation strategies that plays a role in explaining homotypic and heterotypic continuity of developmental psychopathology (Cavicchioli et al., 2023d). Sixty-five subjects (15.0%) self-reported a recurrent alcohol/other drugs use. This kind of substance use behaviors was more recurrent among older adolescents (i.e., 16-18 years old: N = 45; 10.4% of total subjects; 21.2% of late adolescents) than younger adolescents (i.e., 12 – 15 years old: N = 20; 4.6% of total subjects; 9.0% of early adolescents) ($\chi^2_{(1)} = 12.71$, $p < .001$; *Phi*= .17, $p< .001$). Younger adolescents who reported a recurrent substance use also reported significant higher scores of DSM-oriented externalizing conditions — ADHD problems: Z = 3.20, $p < .01$; ODD problems: Z = 3.70, $p < .001$; CD problems: Z = 4.79 $p < .001$. However, the partial correlations between substance use and these conditions, controlling for interrelationships existing within the externalizing spectrum, showed that only CD problems were significantly correlated with a recurrent substance use ($\rho = .21$; p < .01). Similarly, older adolescents who recurrently use alcohol and other drugs reported higher levels of DSM-oriented externalizing scales — ADHD problems: Z = 4.20, $p < .001$; ODD problems: Z = 4.90, $p< .001$; CD problems: Z = 4.76 $p< .001$. Moreover, there were found significant higher levels of MDD problems (Z = 3.01; p < .01) and somatic problems (Z = 2.69; p < .01). Partial correlations among externalizing conditions showed that CD problems (ρ = .14; p < .05) and ODD problems (ρ = .16; p < .01) highlighted significant associations with substance use. On the contrary, partial correlations among internalizing conditions showed a tendency toward significance for the association between MDD problems and substance use (ρ = .13; p = .06). Considering the entire sample of adolescents, both externalizing — ADHD problems: Z = 4.74, *p* < .001; ODD problems: Z = 6.61, *p*< .001; CD problems: Z = 6.64. *p* < .001 — and internalizing — MDD problems: Z = 4.14; p < .001; somatic problems Z = 3.32; p < .01 — conditions were associated to substance use. Partial correlations within the externalizing spectrum confirmed that CD problems (ρ = .17; p < .001) and ODD problems (ρ = .12; p < .05) were significantly associated with substance use. On the contrary, MDD problems (ρ = .13; p < .01) was the only internalizing condition significantly associated to substance use among adolescents, when controlling for the interrelationships within this spectrum. Ultimatelly, considering results of partial correlations controlling for the interrelationships among both externalizing and internalizing domains, the ODD problems (ρ = .11; p < .05) and CD problems (ρ = .16; p < .01) were the most representative psychopathological developmental conditions associated to recurrent substance-use behaviors.

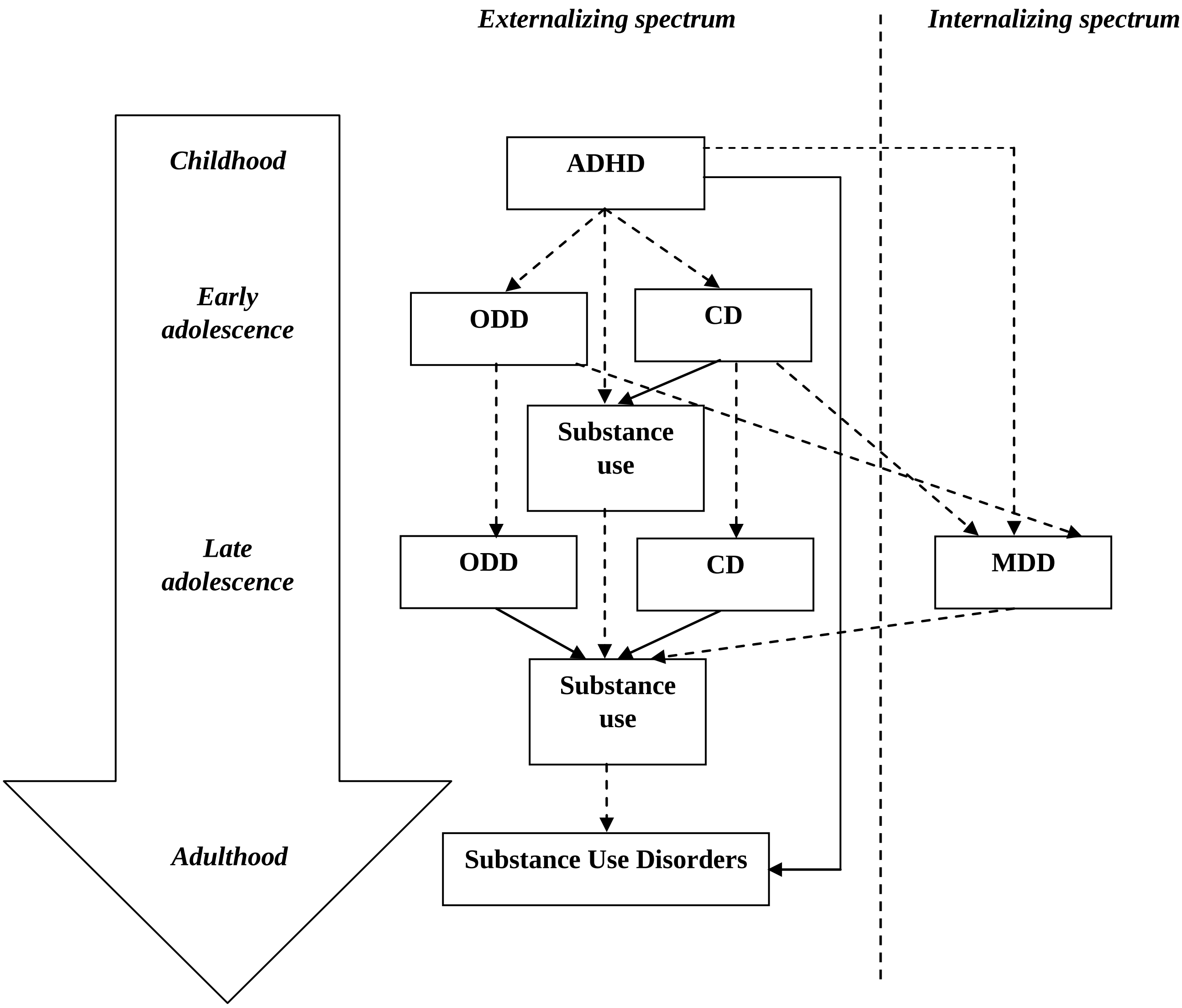
Therefore, these data provided a provisional support for the hypothesis different developmental trajectories of problematic substance use during the adolescence. On the one hand, it could be possible to recognize a main homotypic externalizing trajectory identified by ODD and CD. On the other hand, it might be possible to suggest a heterotypic trajectory including both externalzing and internalizing conditions, especially adolescent MDD, that are associated to clinically relevant substance-use behaviors.

However, it was also specifically explored the role of childhood ADHD for addiction psychopathology. Specifically, Cavicchioli and colleagues (2022b) self-report assessed the severity of childhood ADHD symptoms (i.e., Wender Utah Rating Scale [WURS]; Ward et al., 1993) among 204 treatment-seeking patients with SUDs. Results showed that 11.2% of sample met criteria for a probable diagnosis of childhood ADHD. Furthermore, the analysis highlighted a positive and significant relationships between the severity of childhood ADHD symptoms and the severity of SUDs in adulthood (R^2 = .08).

Taken previous findings together, it might be possible to suggest that childhood ADHD represents a neurodevelopmental disorder related to the onset of SUDs in adulthood.

However, it might be possible to suggest an indirect developmental association. Specifically, childhood ADHD might present a risk factor for subsequent ODD and CD problems, which represent the main psychopathological developmental conditions linked to adolescent problematic substance-use. These childhood and adolescent psychopathological problems mght also be risk factors for adolescent internalizing problems, especially MDD, which should be considered an additional risk factor for clinically relevant substance-use behaviors. Figure 11 provided a graphical summary of these results.

Figure 11. Developmental trajectories of SUDs



Behavioral self-regulation: a core feature of SUDs and implications for their developmental trajectories

According to no definitive conclusions concerning core alterations of self-regulatory mechanisms characterizing individuals with SUDs, Cavicchioli and colleagues (2022a) conducted a case-control study comparing neuropsychological performances and self-report measures of different domains linked to the construct of impulsivity between 59 abstinent treatment-seeking individuals with SUDs (41 outpatient; 18 from a therapeutic community) and 54 age-matched HCs. In line with a comprehensive neuropsychological model of impulsivity (Stevens et al., 2014; Verdejo-García et al., 2008), it was administered a computerized battery composed of: i) cognitive disinhibition: Attentional Network Test – Conflict Monitoring index (ANT) (Fan et al., 2002); ii) motor disinhibition: GNG task (Bezdjian et al., 2009); iii) impulsive choice: Bechara's "Iowa" Gambling Task (IGT) (Bechara et al., 1994). These dimensions were also chosen due to their overlaps with Barkley's domains of self-regulation. Indeed, the cognitive disihinibition domain and related attentional mechanisms could be ascribed to the sensiting to the self domain of Barkley's model. The impulsive choice factor and performances within the IGT capture the emotion/motivation to the self. Motor disinhibition and performances during the GNG task represent the main outcome of self-regulation system, namely motor inhibition. Impulsive personality traits were assessed using the UPPS-P Impulsive Behavior Scale (Lynam et al., 2007), which captures five dimensions related to this construct, namely: negative (NU) and positive urgency (PU) (i.e., behavioral disnhibition linked to intense negative abd positive emotions), lack of perseverance (LPe) (i.e., tendency to show difficulties with finishing tasks), lack of premeditation (LPr) (i.e., acting without thinking), sensation seeking (SS) (i.e., tendencies of trying new sensations). Specifically, LPr together with NU and PU could be ascribed to motor inhibition and emotion/motivation to the self subsystems of self-regultaion. Whereas, the LPe facet might capture the sensiting to the self domain according to key implications of attentional functioning for this dimension.

Neuropsychological results showed that the motor disinhibition was the most impaired domain (i.e., large effect sizes) of individuals with SUDs compared to HCs. Specifically, alterations of motor preparation processes (i.e., slower RTs) seemed to be a key mechanism characterizing individuals with SUDs. Poor response inhibition abilities (i.e., higher error rates) could be considered a marker that characterized more severe forms of SUDs. Looking at personality traits, NU and PU (i.e., behavioral dysregulation in response to emotional states) were the core (i.e., large effect size) impulsive personality dimensions of individuals with SUDs. This might further support that motor inhibition represents a core feature of adult SUDs, especially when the impact of affective states is considered (i.e.. emotion/motivation to the self domain).

The key role of motor disinhibition for addiction psychopathology was also supported by results of a clinical study that evaluated therapeutic effects of a well-validated adaptation of Dialectical Behavior Therapy Skills Training (DBT-ST) as an outpatient intervention for SUDs (Cavicchioli et al., 2019, 2020, 2021). Particularly, SUD patients treated with the DBT-ST program showed significant improvements from the beginning to the end of intervention in neuropsychological (i.e., cognitive disinhibition, impulsive choice) and personality dimensions (i.e., NU and PU) linked to impulsivity, with the exception of motor disinhibition performances (i.e., Go/No-Go: RTs and error rates) that remained unaltered during the treatment and were worst compared to a HC group both at the beginning and the end of intervention (Cavicchioli et al., 2023b).

Behavioral disinhibition also represented a key dimension that might explain the homotypic continuity between childhood ADHD and SUDs in adulthood. Indeed, Cavicchioli and colleagues (2022b) highlighted that a self-report measure of behavioral disinhibition (i.e., Barratt Impulsiveness Scale ; Patton et al., 1995) was a full mediator of the relationship found between the severity of ADHD symptoms in childhood and the severity of addiction psychopathology in large sample of treatment-seeking individuals with SUDs.

Ultimately, Carli, Cavicchioli and colleagues (2023) conducted a ^{18}F-FDG PET study that compared the resting-state brain metabolism among adult treatment-seeking patients with ADHD and cocaine use disorder (CoUD) (N = 19), CoUD patients without ADHD (N = 16) and HCs (N = 30). The study focused on specific ROIs relevant for ADHD and addiction psychopathology. Referring to the neural underpinnings of self layers and Barkely's models, the mental self and motor network capture the ROIs used for evaluating alterations of resting-state metabolism among these clinical conditions. Results of this study highlighted a significant hypometabolism in the frontopolar cortex among CoUD patients with and without ADHD. Interestingly, some studies showed a role of frontopolar cortex on contingent motor control (Koechlin et al., 2000) and motor inhibition (Rubia et al., 2003), suggesting how a resting-state hypometabolism could provide a vulnerability factor for task dependent neuro-behavioral activity. Futhermore, the resting-state hypometabolism of frontopolar activity, which represent a key regions of the default mode network (Raichle, 2015), supported a key role of alterations of mental self organization (Qin et al., 2020) among individuals with SUDs and ADHD.

Taken these findings together, motor inhibition and related mechanisms should be considered the core features of SUDs. Furthermore, motor disnhibition seems to represent a latent dimension involved in explaining a developmental pathway from childhood ADHD to SUDs in adulthood. Considering this developmental pathway, neuroscience data also suggested that alterations of mental self layer might represent a common feature shared between these conditions. Nevertheless, no studies have explored the role of neural underpinnings of motor inhibition reflecting the main outcome of self-regulatory system and layers of self-processing as relevant dimensions for understaning developmental trajectories from adolescent externalizing (e.g., ODD, CD) and internalizing (i.e., MDD) psychopathological conditions to SUDs in adulthood.

Meta-analysis of fMRI data: the integration of ROI- and coordinate-based approaches

According to the aims concerning the identificatio of neural underpinnings related to self-processing layers, motor inhibition processes and their implications for developmental trajectories of SUDs, the current study referred a mixed approach to meta-analyze fMRI data. Specifically, an apriori ROI-based approach referred to the application of network meta-analytic procedures. The choice to conduct a network meta-analysis using a Bayesian method focusing on specific ROIs was supported by the fact this method allows to simultaneously estimate multiple pooled effect sizes of more than two conditions (Salanti et al., 2008). Specifically, this method uses both direct and indirect evidence for estimating the pooled effect sizes of comparisons; it also allows a computation of the rank of probabilities of a set of conditions of interest. This supports the identification of the most representative ROIs involved in motor inhibition tasks for each condition of interest — childhood and adolescent ADHD, ODD, CD, adolescent MDD and individuals with substance-use-related condition.

Whereas, robust coordinate-based approaches (e.g., ALE meta-analysis, SDM) (Albajes-Eizagirre et al., 2019; Eickhoff et al., 2009; Laird et al., 2005; Turkeltaub et al., 2002) allow to find common brain responses shared across studies toward a specific task adminstered during fMRI acquisition. Accordingly, robust coordinate-based methods might support the identification of common neural network among different conditions constituing the homotypic and heterotypic developemental trajectories of SUDs.

This methodological meta-analytic approach was previously used in a work focused on the identification of common and specific mechanisms linked to emotion regulation among several conditions (i.e., borderline personality disorder, conversion and somatoform disorders, post-traumatic stress disorders, dissociative disorders) ascribed to the dissociative spectrum (Cavicchioli et al., 2023c). Similarly, Scalabrini, Cavicchioli and colleagues (*under revision*) adopted the same approach in order to demonstrated distinct patterns of self-processing neural activity (Scalabrini et al., 2022) among individuals with post-traumatic stress disorder (PTSD) linked to non-relational traumatic events and those with PTSD associated to intepersonal traumatic experiences.

Aim of the work

Departing from theoretical and empirical backgrounds concerning the implications of the self-organization and self-regulation mechanisms for homotypic and heterotypic developmental pathways of SUDs and related conditions together with limitations of existing neuroscientific literature on this topic, the current study aims at conducting a comprehensive meta-analytic review of behavioral outcomes and spatiotemporal neural responses to the administration of motor inhibition tasks among conditions constituting well-supported developmental trajectories from childhood and adolescence psychopathological conditions to subsequent problematic substance-use behaviors and SUDs. According to Barkley's model (1997, 2001), which has posited response inhibition as the main outcome of self-regulation system, this meta-analytic review was focused on the inclusion of studies that administered GNG and SST paradigms during the acquisition of EEG and fMRI signals. This was chosen in line with a large consensus in viewing these tasks as the gold standard for the assessment of motor inhibition capabilities (Aron, 2011). Looking at developmental psychopathogy conditions relevant for the current work, there were considered child and adolescent ADHD, ODD and CD together with adolescent MDD. According to the huge amount of empirical data discussed in the Introduction section, it was assumed a dimensional approach to substance-related problems, whic range from problematic substance-use behaviors (e.g., binge drinking: National Institute on Alcohol Abuse and Alcoholism, 2004; heavy drinking: Hedden, 2015) to SUDs. The current comprehensive meta-analytic work adopted a data driven approach in order to clarify which and to what extent specific domains of behavioral performances and temporal organization of brain activity might represent the most relevant features of self-regulation mechanisms at the base of homotypic and heterotypic developmental of SUDs and related problematic behaviors. On the contrary, the investigation of spatial organization of brain activity linked to self-processing layers (Qin et al., 2020) and self-regulation domains (Barkley, 1997, 2001) for developmental trajectories of SUDs and related conditions was based on both an *a priori* region-of-interest (ROI) approach and a robust data driven voxel-based one.

Results

Descriptive statistics

Figure 12 graphically summarizes the inclusion processes of studies used for meta-analytic procedures. Sixty-eight independent studies (see table 2 for a detailed description of characteristics of studies) were included for a total of 3,546 subjects — SUDs and related across the life span: 954; children and adolescents with ADHD: 796; adolescents with MDD: 102.

Figure 12. CONSORT flow chart of studies inclusion process

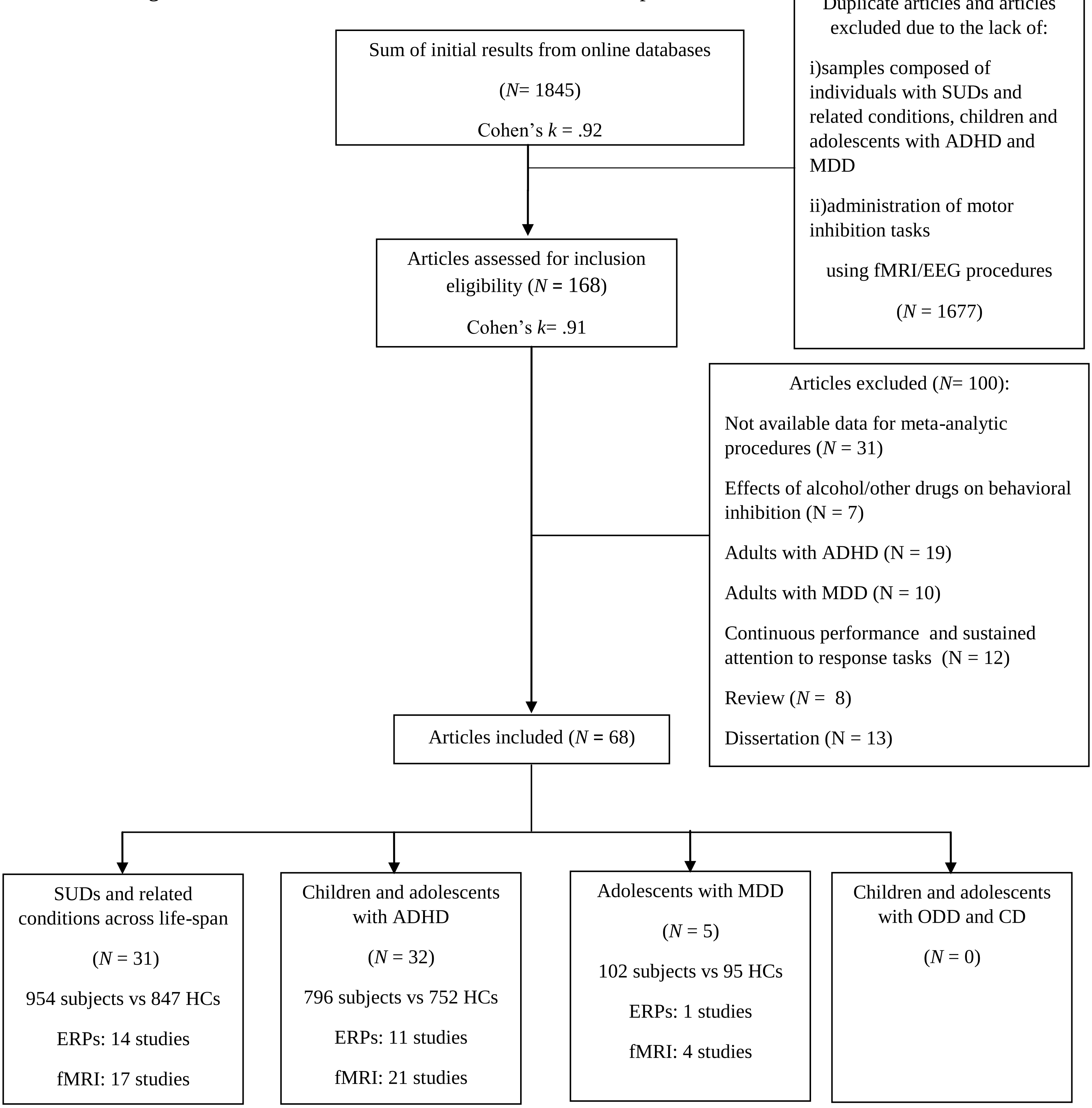


Table 2. Characteristics of studies included

Study	Research design	*N*	Gender	Age	Sample Characteristics	Task	Behavioral measures	Main findings Behavioral data	Main findings Neural data
Acheson et al., 2014	fMRI	104	M + W	12.90	FH^+ SUDs (N = 72) Vs FH^- SUDs (N = 32)	Go No-Go Go: 50% No Go: 50% 1500ms interstimulus presentetion 500ms stimulus presentation	RTs Commission and Omission errors	FH^+ showed slower RTs (small effect sizes) Trivial differences for errors rates	FH^+ showed increased activity than FH^- for Go and No-Go conditions: ↑ Mental Self ↑ Motor Network ↑ Speech processing network
Ahmadi et al., 2013	fMRI	91	M + W	18.90	Heavy Drinkers (HD) (N = 56) Vs Light Drinkers (LD) (N = 35)	Go No-Go Go: 85% No Go: 15% 1750ms interstimulus presentetion 50ms stimulus presentation	RTs Hit rates and Errors rates	HD showed slower RTs (medium effect sizes) Small differences for hit and errors rates between groups	HD showed decreased responses than controls for No Go condition: ↓ Mental Self ↑ Motor Network ↑ Speech processing network
Alperin et al., 2017	ERP	109	M + W	13.75	ADHD (N = 49) Vs	Go No-Go Go: 70%	RTs Hit rates	Significant differences were not detected between groups	Significant differences were not detected between groups

					HC (N = 60)	No Go: 30% 1000ms interstimulus presentetion 500ms stimulus presentation			
Barrós-Loscertales et al., 2020	fMRI	58	M + W	32.39	Cocaine Use Disorder (N = 30) Vs HC (N = 28)	Stop Signal Task Go: 70% No Go: 30% 2000/3000/4000 ms interstimulus presentetion 1000 ms stimulus presentation	RTs Hit rates and Errors rates	No differences between groups	Neural responses of individuals with CoUD was modulated by reward within Go condition
Baytunca et al., 2021	fMRI	37	M + W	10.95	ADHD (N = 20) Vs HC (N = 17)	Go No Go Go: 80% No Go: 20% 1500 ms interstimulus presentetion 500 ms stimulus presentation	Not Reported	Not Reported	ADHD showed increased brain responses than HCs within Go and No Go conditions ↑ Mental Self ↑ Motor Network ↑ Executive control network ↑ Speech processing network
Beerten-Duijkers et	ERP	50	M + W	41.38	Mixed SUDs	Stop Signal Task	RTs	Patients with	Patients showed an

al., 2021					(N = 25) Vs HC (N = 25)	Go: % not reported No Go: % not reported Not reported characteristics of stimuli presentation	Errors rates	SUDs showed a higher rate of error, but not significant differences concerning RTs	increased N200 for Go and No-Go conditions, together with a reduced P300 for Go and No-Go conditions
Bell et al., 2014	fMRI	72	M + W	38.00	CoUD (N = 27) Vs HC (N = 45)	Go No Go Go: 88% No Go: 12% 800ms stimuli presentation 200ms interstimulus presentation	RTs Hit rates and Errors rates	Behavioral results did not showed significant differences between groups	Patients showed increased neural responses than controls considering No Go condition: ↑ Interoceptive Self ↑ Motor Network ↑ Executive control network ↑ Speech processing network
Booth et al., 2005	fMRI	24	M + W	11.00	ADHD (N = 12) Vs HC (N = 12)	Go No Go Go: 50% No Go: 50% 1400ms stimuli presentation 2000 ms interstimulus presentation	RTs Error rates	ADHD showed slower RTs and higher error rates	ADHD showed increased brain reponses: ↑ Interoceptive Self ↑ Motor Network ↑ Dorsal Attention Network ↑ Speech processing network

									On the contrary, HCs highlighted increased brain responses activity: ↓ Executive Control Network
Campanella et al., 2017	fMRI	37	M + W	25.00	HD (N = 19) Vs LD (N = 17)	Go No Go Go: 70% No Go: 30% 200ms stimuli presentation 1300ms interstimulus presentation	RTs Hit rates and Errors rates	No significant differences between groups were detected for RTs, accuracy (small effect sizes) and commission error (small effect size) rates	HD highlighted significant increased and decreased brain responses for No Go condition: ↑ Interoceptive Self ↑ Motor Network ↑ Dorsal Attention Network ↓ Exteroceptive Self ↓ Speech processing network
Cha et al., 2021	fMRI	70	M + W	24.95	MDD (N = 41) Vs HC (N = 29)	Go No Go Go: 50% No Go: 50% 500ms stimuli presentation 1000 ms interstimulus presentation	Not reported	Not reported	MDD showed decreased brain responses within No Go conditions than HCs: ↓ Mental Self ↓ Dorsal Attention Network ↓ Speech processing network

Cohen et al., 1997	ERP	77	M	30.45	AUD (N = 47) Vs HC (N = 30)	Go No Go Go: 25% No Go: 75% 100ms stimuli presentation 4000 – 6000 ms interstimulus presentation	RTs	AUD patients showed slower RTs for both Go and No Go condition	AUD showed significant reduced P300 for both Go and No Go conditions
Czapla et al.,	fMRI	40	M + W	46.58	AUD (N = 19) Vs HC (N = 21)	Go No Go Go: 80% No Go: 20% 490ms stimuli presentation 1000ms interstimulus presentation	Commission Error	AUD patient showed higher commission errors than HC (moderate effect size)	AUD highlighted increased and activity within No-Go conditions: ↑ Mental Self ↑ Dorsal Attention Network ↑ Speech Processing Network ↓ Executive control Network ↓ Motor Network
Diler et al., 2010	fMRI	20	M + W	15.6	MDD (N = 10) Vs HC (N = 10)	Go No Go Go: 66.0% No 33.0% 500ms stimuli presentation 1000ms	RTs Commission error	No significant differences were detected between groups	MDD showed increased brain responses within No Go condition: ↑ Speech Processing Network

						interstimulus presentation			
Diler et al., 2014	fMRI	24	M + W	15.9	MDD (N = 12) Vs HC (N = 12)	Go No Go Go: 66.0% No 33.0% 500ms stimuli presentation 1000ms interstimulus presentation	RTs Commission error	No significant differences were detected between groups	MDD showed increased and dcreased brain responses within No-Go conditions: ↑ Dorsal Attention Network ↑ Motor Network ↓ Speech processing Network
Durston et al., 2007	fMRI	44	M + W	13.35	ADHD (N = 22) Vs HC (N = 22)	Go No Go Go: 76% No Go: 24% 500ms stimuli presentation 2500 ms interstimulus presentation	Error rates	ADHD individuals showed higher errors than HCs	ADHD showed decreased brain responses compared to HCs considering both Go and No Go conditions: ↓ Mental Self ↓ Executive control Network ↓ Motor Network ↓ Dorsal Attention Network
Durston et al., 2003	fMRI	14	M + W	8.60	ADHD (N = 7) Vs HC (N = 7)	Go No Go Go: 75% No Go: 25% 500ms stimuli	Commission error	ADHD individuals showed higher commission errors than HCs	ADHD patients showed increased brain activity within Go conditions: ↑ Mental Self

						presentation 3500 ms interstimulus presentation			↑ Executive Control Network ↑ Dorsal Attention Network ↑ Speech Processing Network
Epstein et al., 2007	fMRI	18	M + W	17.30	ADHD (N = 9) Vs HC (N = 9)	Go No Go Go: 80% No Go: 20% 500ms stimuli presentation 2000 ms interstimulus presentation	RT Commission and omission erors	ADHD showed slower RTs than HCs	ADHD highlighted decreased brain responses within No Go condition compared to HCs ↓ Mental Self ↓ Exteroceptive Self ↓ Interoceptive Self ↓ Motor Network ↓ Dorsal Attention Network
Franken et al., 2017	ERP	97	M + W	23.15	HD (N = 48) Vs LD (N= 49)	Go No Go Go: 25% No Go: 75% 700ms stimuli presentation 300 ms interstimulus presentation	RTs Commission error rates	No differences between groups considering RTs and commission error rates	HD showed a reduced N200 localized at Pz compared to LD
Groom et al., 2010	ERP	42	M + W	17.50	ADHD (N = 23) Vs HC	Go No Go Go: 80% No Go: 20%	RTs Error rates	ADHD group higher error rates than HCs	ADHD highlighted a P200 compared to HCs in relation to No Go conditions

					(N = 19)	450ms stimuli presentation 900 ms interstimulus presentation			
Groom et al., 2010	ERP	51	M + W	12.50	ADHD (N = 23) Vs HC (N = 28)	Go No Go Go: 75% No Go: 25% 100ms stimuli presentation 3300 ms interstimulus presentation	RTs and commission error	No differences between groups considering RTs and commission error rates	ADHD patients showed reduced N200 and P300 waves compared to HCs considering both Go and No Go conditions
Häger et al., 2021	ERP	130	M + W	10.50	ADHD (N = 61) Vs HC (N = 69)	Go No Go Go: not reported No Go: not reported 1000ms stimuli presentation 3000 ms interstimulus presentation	Omission and commission error	ADHD individuals showed higher error rates than HCs	ADHD showed reduced N200 and P300 waves within Go and No-Go conditions compared to HCs.
Hardee et al., 2014	fMRI	198	M + W	12.20	FH+ (N = 113) Vs FH- (N = 85)	Go No Go Go: 75.6% No Go: 24.4% 500ms stimuli presentation 3500 ms interstimulus presentation	Not Reported	Not Reported	FH+ showed increased and decreased brain responses for No Go conditions ↑ Speech Processing Network ↓ Mental Self ↓ Motor Network

									↓ Executive Control Network ↓ Dorsal Attention Network
Hart et al., 2014	fMRI	60	M	14.00	ADHD (N = 30) Vs HC (N = 30)	Stop Signal Task Go: 80.0% No Go: 20.0% 1000ms stimuli presentation 1800 ms interstimulus presentation	RT Commission Error	ADHD showed higher error rates than HCs	ADHD highlighted decreased brain responses within No Go condition: ↓ Mental Self ↓ Interoceptive Self ↓ Motor Network ↓ Executive Control Network ↓ Speech processing Network
Heitzeg et al., 2010	fMRI	41	M + W	19.00	FH^+ + AUD (N = 21) Vs FH^- - HC	Go No Go Go: 75.6% No Go: 24.4% 500ms stimuli presentation 3500 ms interstimulus presentation	RTs Commission error rates	No significant differences between groups	FH^+ + AUD showed increased neural responses for No Go condition: ↑ Mental Self
Janssen et al., 2015	fMRI	38	M + W	10.40	ADHD (N = 21) Vs HC (N = 17)	Stop Signal Task Go: 83.3% No Go: 16.7% 1500ms stimuli	RTs Hit Error rates	ADHD showed slower RTs, lower RTs and higher error rates	ADHD highlighted increased and decreased brain responses within No Go condition ↑ Mental Self

						presentation 3000 ms interstimulus presentation			↑ Motor Network ↑ Exectuive Control Network ↓ Interoceptive Self ↓ Speech processing Network
Janssen et al., 2018	ERP	97	M + W	9.80	ADHD (N = 46) Vs HC (N = 51)	Stop Signal Task Go: not reported No Go: not reported 1250ms stimuli presentation 100 ms interstimulus presentation	RTs Omission error	ADHD showed slower RTs and higher omission errors than HCs	ADHD highlighted reduced N200 and P300 compared to HCs
Johnstone et al., 2007	ERP	37	M + W	11.80	ADHD (N = 24) Vs HC (N = 13)	Stop Signal Task Go: 50% No Go: 50% 500ms stimuli presentation 1500 ms interstimulus presentation	RTs Error rates	ADHD group showed slower RTs and higher error rates than control	ADHD showed an increased N100 response within Go and No-Go conditions compared to HCs.
Kamarajan et al., 2004	ERP	87	M + W	28.16	AUD (N = 58) Vs HC (N = 29)	Go No Go Go: 50% No Go: 50% 100ms stimuli presentation	RTs Error rates	AUD showed higher error rates (small effect size) than HCs	AUD showed decreased delta activity for Go and No-Go condition

Kamarajan et al., 2005	ERP	60	M + W	29.02	AUD (N = 30) Vs HC (N = 30)	700 ms interstimulus presentation Go No Go Go: 50% No Go: 50% 100ms stimuli presentation	RTs Error rates	AUD showed higher error rates (small effect size) than HCs	AUD showed decreased P300 for Go and No-Go conditions
Karch et al., 2007	ERP	32	M	40.45	AUD (N = 16) Vs HC (N = 16)	700 ms interstimulus presentation Go No Go Go: % not reported No Go: % not reported 400ms stimuli presentation	RTs	AUD slower RTs than HC	No significant differences were detected considering the amplitude of P300
Kreusch et al., 2014	ERP	30	M + W	21.50	Heavy Drinkers (HD) (N = 15) Vs Light Drinkers (LD) (N = 15)	1000 ms interstimulus presentation Go No Go Go: 50% No Go: 50% 500ms stimuli presentation	RTs Errors rates	HD showed higher error rates than LD. There were not detected significant differences between groups	HD showed alterations of N200 and P300 for Go and No Go conditions
Lannoy et al., 2020	ERP	50	M + W	21.28	Heavy Drinkers (HD)	1200 ms interstimulus presentation Go No Go	RTs	No significant difference were	Small alterations of P100, N200 and

					(N = 25) Vs Light Drinkers (LD) (N = 25)	Go: 75% No Go: 25% 500ms stimuli presentation 900 ms interstimulus presentation	Hit and Errors rates	detected between groups considering RT and Hit rates. BD showed slightly higher error rates	P300 were found among BD compared to LD for Go and No Go conditions
Li et al., 2008	fMRI	30	M	37.15	CoUD (N = 15) Vs HC (N = 15)	Go No Go Go: 75% No Go: 25% Not reported characteristics of stimuli presentation	RTs Hit rates	No significant difference were detected between groups considering RT and Hit rates	CoUD patients highlighted reduced brain responses for No Go condition: ↓ Mental Self ↓ Executive Control Network ↓ Dorsal Attention Network
Li et al., 2009	fMRI	48	M + W	37.10	AUD (N = 24) Vs HC (N = 24)	Go No Go Go: 75% No Go: 25% The time of stimuli presentation was not reported. The interstimuli interval ranged from 1000 and 5000ms	RTs Hit rates	AUD patients showed slower RTs than HC. No significant differences were observed concerning Hit rates	AUD highlighted increased and reduced activation for No Go conditions: ↑ Mental Self ↑ Motor Network ↑ Speech Processing Network ↑ Dorsal Attention Network ↓ Executive Control Network
Li & Xu, 2019	ERP	32	M	34.12	CoUD	Go No Go	RTs	HUD showed	HUD highlighted a

					(N = 15) Vs HC (N = 17)	Go: 75% No Go: 25% 200ms stimuli presentation 200 - 400 ms interstimulus presentation	Hit rates	slower RTs than HC. No significant differences were detected for Hit rates	reduced theta activity for No Go conditions
Liotti et al., 2010	ERP	38	M + W	12.30	ADHD (N = 16) Vs HC (N = 22)	Go No Go Go: 73.4% No Go: 26.6% 200ms stimuli presentation 200 - 400 ms interstimulus presentation	RTs Hit rates	ADHD showed faster RTs than HCs. No significant differences were detected in Hit rates	ADHD showed reduced N200 and P300 waves within No Go conditions
López-Martín et al., 2015	ERP	48	M + W	10.50	ADHD (N = 24) Vs HC (N = 24)	Go No Go Go: 60.0% No Go: 40.0% 300ms stimuli presentation 1300 ms interstimulus presentation	RTs Omission errors Commission errors	ADHD showed higher commission errors than HCs	ADHD highlighted an increased P300 for No Go conditions compared to HCs
Ma et al., 2012	fMRI	30	M + W	9.85	ADHD (N = 15) Vs HC	Go No Go Go: 50.00% No Go: 50.0%	RTs Hit rates Error rates	No significant differences were detected between groups	ADHD highlighted increased brain responses within No-Go condition: ↑ Mental Self

					(N = 15)	1000ms stimuli presentation 1000 ms interstimulus presentation			↑ Interoceptive Self ↑ Motor Network ↑ Executive control Network ↑ Speech Processing Network ↑ Dorsal Attention Network
Mahmood et al., 2013	fMRI	80	M + W	17.5	High Substance Users (HSU) (N = 39) Low Substance Users (LSU) (N = 39)	Go No Go Go: 68.4% No Go: 31.6% 200ms stimuli presentation 1300 ms interstimulus presentation	Not Reported	-	HSUs showed increased and decreased activity for No Go conditions
Massat et al., 2018	fMRI	38	M + W	12.50	ADHD (N = 19) Vs HC (N = 19)	Stop Signal Task Go: 80.0% No Go: 20.0% 500ms stimuli presentation 3125 ms interstimulus presentation	RTs Hit	No significant differences between groups were detected	ADHD showed increased brain responses than within No Go condition: ↑ Mental Self ↑ Interoceptive Self ↑ Motor Network ↑ Executive
Matheus-Roth et al., 2016	ERP	61	M + W	43.80	AUD (N = 30) HC (N = 31)	Go No Go Go: 25% No Go: 75%	Error Rates	AUD higher error rates than HCs, albeit differences were smal	AUD showed a significant reduced N170 waves at occipital sites

Morein-Zamir et al., 2013	fMRI	73	M + W	33.07	Stimulant Use Disorder (N = 32) HC (N = 41)	500ms stimuli presentation 2500 ms interstimulus presentation Go: 83.3% No Go: 16.7%	RTs Error rates	Patient with SUDs showed no significant differences in RTs and significant higher error rates compared to HC	SUDs showed reduced activation of within No-Go conditions: ↓ Mental Self ↓ Interoceptive Self
Myers et al., 2021	fMRI	37	M + W	24.55	Heavy Drinkers (HD) (N = 19) Vs Light Drinkers (LD) (N = 18)	1000ms stimuli presentation 250 ms interstimulus presentation Go No-Go Go: 83% No Go: 17% 230ms stimuli presentation 1300 ms interstimulus presentation	RTs Errors rates	HD showed slower RTs (small effect size) HD highlighted higher error rates (medium effect sizes) than LD	HD showed increased neural responses for No Go condition: ↑ Mental Self
Norman et al., 2011	fMRI	38	M + W	13.07	Substance users (N = 17) Vs HC (N = 21)	Go No-Go Go: not reported No Go: not reported 1000ms stimuli presentation	Hit rates Correct inhibition False alarm	Substance users showed better behavioral performances	Substance users highlighted significant decreased neural responses within No-Go condition: ↓ Mental Self ↓ Executive

						250 ms interstimulus presentation			Central Network ↓ Dorsal Attention Network ↓ Speech Processing Network
Pan et al., 2011	fMRI	29	M + W	15.87	MDD (N = 15) Vs HC (N= 14)	Go No-Go Go: 66% No Go: 34% 500ms stimuli presentation 1000 ms interstimulus presentation	Hit Omission and Commission errors	No significant differences were detected between groups	MDD showed increased response within No Go conditions: ↑ Mental Self ↑ Interoceptive Self
Paraskevopoulou et al., 2022	fMRI	64	M + W	17.78	ADHD (N = 33) Vs HC (N = 31)	Stop Signal Task Go: 75% No 25% ms stimuli presentation not reported ms interstimulus presentation not reported	RTs Error rates	ADHD showed slower RTs than HCs. No significant differences were detected in error rates	ADHD showed reduced brain responses within both Go and No Go trails: ↓ Mental Self ↓ Exteroceptive Self
Passarotti et al.., 2010	fMRI	26	M + W	13.50	ADHD (N = 11) Vs HC (N = 15)	Go No-Go Go: 70% No 30% 800ms stimuli presentation	RTs Hit rates	ADHD individuals showed faster RTs and lower hits rates than HCs	ADHD showed increased and decreased brain responses within No Go condition: ↑ Motor Network ↓ Executive

						850 ms interstimulus presentation			Central Network
Petit et al., 2014	ERP	54	M + W	45.00	AUD (N = 27) Vs HC (N = 27)	Go: 70% No 30% 200ms stimuli presentation 1300 ms interstimulus presentation	RTs Commission Error Omission Error	AUD did not show significant differences in Go RTs. On the contrary, significant and large differences were detected in Error rates. AUD patients highlighted higher error rates than HCs	AUD showed an increased P300 within No Go condition
Pliszka et al., 2006	fMRI	32	M + W	13.20	ADHD (N = 17) Vs HC (N = 15)	Stop signal Task Go: 75% No 25% 150ms stimuli presentation ms interstimulus presentation not reported	RTs Hit rates	ADHD showed faster RTs and lower hit rates than HCs	ADHD highlighted increased responses within No Go condition: ↑ Mental Self ↑ Interoceptive Self ↑ Executive Central Network
Rubia et al., 2011	fMRI	25	M	13.00	ADHD (N = 12) Vs HC (N = 13)	Stop signal Task Go: 80% No 20% 500ms stimuli presentation 1800 ms	RTs	No significant differences were detected between groups	ADHD showed decreased brain responses within No Go conditions: ↓ Mental Self ↓ Interoceptive Self ↓ Executive Central Network

						interstimulus presentation			↓ Dorsal Attention Network ↓ Motor Network ↓ Speech processing
Rubia et al., 2005	fMRI	37	M	13.50	ADHD (N = 16) Vs HC (N = 21)	Stop signal Task Go: 80% No 20% 500ms stimuli presentation 1800 ms interstimulus presentation	RTs Omission Error	ADHD showed higher commission errors than HCs	ADHD highlighted decreased neural responses within No Go condition: ↓ Mental Self ↓ Interoceptive Self ↓ Speech processing
Rubia et al., 1999	fMRI	16	M	15.71	ADHD (N = 7) Vs HC (N = 9)	Stop signal Task Go: 50% No 50% 1000ms stimuli presentation 650 ms interstimulus presentation	RTs Hit rates	ADHD showed faster RTs and lower Hit rates than HCs	ADHD highlighted reduced neural responses within No Go condition: ↓ Executive Central Network ↓ Motor Network ↓ Speech processing
Schulz et al., 2004	fMRI	16	M	17.70	ADHD (N = 7) Vs HC (N = 9)	Go: 83% No:17% 500ms stimuli presentation 1000 ms interstimulus	RTs Error rates	ADHD showed higher commission error than HCs	ADHD highlighted increased and decreased responses No Go condition: ↑ Mental Self ↓ Interoceptive Self

						presentation			↑ Motor Network ↓ Speech processing
Schulz et al., 2005	fMRI	20	M	8.80	ADHD (N = 10) Vs HC (N = 10)	Go: 83% No:17% 500ms stimuli presentation 1000 ms interstimulus presentation	Error rates	ADHD individuals showed higher error rates	ADHD showed increased and decreased responses for No-Go conditions: ↑ Exteroceptive Self ↓ Dorsal Attention Network
Senderecka et al., 2012	ERP	40	M + W	9.30	ADHD (N = 20) Vs HC (N = 20)	Stop Signal Task Go: 75% No 25% ms stimuli presentation not reported ms interstimulus presentation not reported	RTs Error rates	ADHD individuals showed slower RTs and higher error rates than HCs	ADHD individuals showed decreased N200, P200 and P300 within No-Go conditions compared to HCs
Shen et al., 2011	ERP	28	M	8.00	ADHD (N = 14) Vs HC (N = 14)	Stop Signal Task Go: 75% No 25% 150ms stimuli presentation 850 ms interstimulus presentation	RTs Hit rates Error rates	ADHD showed faster RTs and lower Hit rates.	ADHD showed reduced P100, N100 and LPW within No Go conditions compared to HCs

Siniatchkin	fMRI	31	M + W	9.20	ADHD (N = 17) Vs HC (N = 14)	Go No-Go Go: 87% No 13% 300ms stimuli presentation 1500 ms interstimulus presentation	Not reported	Not reported	ADHD showed significant decreasaed activity for No-Go condition: ↓ Mental Self ↓ Executive Central network ↓ Motor network
Sjoerds et al., 2014	fMRI	47	M + W	46.70	AUD (N = 31) Vs HC (N = 17)	Go No-Go Go: 80% No 20% 500ms stimuli presentation 1000 ms interstimulus presentation	RTs Hit Correct Rejection	AUD and HCs did not significantly differ to each other in behavioral performances	AUD patients showed a increased and activity within No Go conditions: ↑ Motor network
Smit & Mattick, 2013	ERP	30	W	20.00	HD (N = 13) Vs HC (N=17)	Go: 75% No 25% 1000ms stimuli presentation 1500 ms interstimulus presentation	RTs Hit	HD and HC did not significantly differ to each other in behavioral performances	HD showed a slight reduction of P300 for No Go commission error.
Smith et al., 2016	ERP	41	M	20.00	HD (N = 20) Vs	Go: 75% No 25%	RT Hit	No significant differences were detected between groups	No significant differences were detected concerning N100

					HC (N=21)	1000ms stimuli presentation 1500 ms interstimulus presentation			and P300 between groups
Spinelli et al., 2011	fMRI	30	M + W	10.50	ADHD (N = 13) Vs HC (N = 17)	Go: 74.8% No 25.2% 300ms stimuli presentation 1500 ms interstimulus presentation	RTs Commission and omission error	ADHD slower RTs and higher error rates than HCs	ADHD highlighted increased brain responses within No Go conditions: ↑ Mental Self ↑ Exteroceptive Self ↑ Executive Central Network ↑ Motor Network
Stein et al., 2021	fMRI	27	M + W	41.66	AUD (N = 13) Vs HC (N = 14)	Go: 88.8% No 11.2% 900ms stimuli presentation 100 ms interstimulus presentation	RTs Commission and omission error	AUD showed slower RTs and higher error rates	AUD highlighted increased brain responses for No-Go condition: ↑ Mental Self ↑ Interoceptive Self ↑ Motor Network ↑ Dorsal Attention Network ↑ Speech Processing
Suskauer et al., 2008	fMRI	50	M + W	10.80	ADHD (N = 25) Vs HC (N= 25)	Go: 75.0% No 25.0% 900ms stimuli presentation 100 ms interstimulus presentation	RTs Commission and omission errors	There were no significant differences between groups	ADHD showed increased and decreased activity within No Go conditions: ↓ Exteroceptive Self ↑ Executive

									Central Network ↓ Dorsal Attention Network ↓ Motor Network
Tamm et al., 2004	fMRI	20	M	15.7	ADHD (N = 10) Vs HC (N=10)	Go:66% No 34% 200ms stimuli presentation 2000 ms interstimulus presentation	RTs Commission and omission error	ADHD showed faster RTs and higher error rates than HCs	ADHD showed increased and reduced responses within No-Go conditions: ↓ Mental Self ↑ Speech processing network
Trinkl et al., 2015	ERP	54	M + W	14.70	MDD (N = 24) Vs HC (N = 30)	Go: 75.0 % No Go: 25% 300ms stimuli presentation 1200 ms interstimulus presentation	Hit Commission Error	No significant difference were detected between groups	MDD showed reduced N200 waves for positive stimuli
van Rooij	fMRI	309	M + W	16.90	ADHD (N = 185) Vs HC (N= 124)	Not reported	RTs Commission errors	ADHD showed higher commission error rates	ADHD showed decreased activity for No-Go conditions: ↓ Mental Self ↓ Exteroceptive Self ↓ Frontal Executive ↓ Speech processing ↓ Motor Network

Watson et al., 2016	ERP	31	M + W	20.40	BD (N = 13) Vs HC (N= 18)	Go: 70.00% No 30% 500ms stimuli presentation 1300 ms interstimulus presentation	Error rates	No significant differences were detected between BD and HC	BD showed larger N100 waves for No Go conditions compared to HCs
Wiersema et al., 2006	ERP	37	M + W	10.25	ADHD (N = 22) Vs HC (N= 15)	Go:75% No 25% 300ms stimuli presentation 2000 ms interstimulus presentation	RTs Commission error	ADHD showed more commission error than HCs	ADHD showed a significant reduced P300 for Go condition and an increased P200 for the same condition

Table 3 reports a summary of descriptive statistics concerning characteristics of samples, procedures of brain activity acquisition (i.e., ERPs, fMRI) and behavioral tasks administered (i.e., GNG, SST). Briefly, thirty-one studies assessed samples composed of individuals with SUDs (*N* = 20; 29.4%; mean age: 33.74) and related conditions (subclinical: 9 studies [13.4%], mean age: 21.70; FH^+ for SUDs: 2 studies [2.9%], mean age: 12.55) recording ERPs (*N* = 14; 20.6%) and fMRI (*N* = 17; 25%) data. Thirty-two studies (47.1%) included children and adolescents (mean age: 12.49) with primary diagnosis of ADHD reporting ERPs (N = 11; 16.2%) and fMRI (N = 21; 30.9%) results. The remaining studies evaluated adolescents with MDD (mean age: 17.40) through EEG (*N* = 1; 1.5%) and fMRI (N = 4; 5.9%) procedures. No studies evaluating the brain activity of children and adolescents with a primary diagnosis of ODD and CD during the administration of behavioral inhibition tasks were found. Fifty-four studies (79.4%) administered the GNG task and, 14 studies (20.6%) used SST for assessing behavioral inhibition performances.

Table 3. Descriptive statistics of studies included (*N* = 68)

	% (*N*)	M (SD)
SUDs and related conditions	45.6% (31)	Total sample: 954 Mean sample size: 30.77 (21.11)
HCs – SUDs and related conditions		Total sample: 847 Mean sample size: 27.32 (14.08)
Age – SUDs and related conditions		28.88 (11.12)
SUD clinical samples	29.4% (20)	Total subjects: 518 Mean sample size: 25.90 (11.17)
HCs – SUD clinical samples		Total subjects: 493 Mean sample size: 24.65 (8.34)
Age – SUD clinical samples		33.74 (10.14)
SUD subclinical samples	13.2% (9)	Total subjects: 251 Mean sample size: 27.89 (15.77)
HCs – SUD subclinical samples		Total subjects: 237 Mean sample size: 26.33 (11.90)
Age – SUD subclinical samples		21.70 (6.01)
FH^+ for SUDs	2.9% (2)	Total subjects: 185 Mean sample size: 92.50 (28.99)
HCs – FH^+ for SUDs		Total subjects: 117 Mean sample size: 58.50 (37.48)
Age - FH^+ for SUDs		12.55 (.49)
ADHD	47.1% (32)	Total subjects: 796 Mean sample size: 25.47 (31.62)
HCs – ADHD		Total subjects: 752 Mean sample size: 24.09 (23.17)
Age – ADHD		Age: 12.49 (2.91)
MDD	7.4% (5)	Total subjects: 102 Mean sample size: 20.40 (12.70)
HCs – MDD		Total subjects: 95 Mean sample size: 19.00 (9.96)
Age – MDD		17.40 (4.25)
fMRI studies	61.8% (42)	
SUDs and related conditions	25% (17)	

SUD clinical samples	14.7% (10)	
SUD clinical samples	7.3% (5)	
FH+ for SUDs	2.9% (2)	
ADHD	30.9% (21)	
MDD	5.9% (4)	
ERP studies	38.2% (26)	
SUDs and related conditions	20.6% (14)	
SUD clinical samples	14.7% (10)	
SUD clinical samples	5.9% (4)	
FH+ for SUDs	-	
ADHD	16.2% (11)	
MDD	1.5% (1)	
Go No-Go Task	79.4% (54)	
% Go trails		69.02 (15.25)
Stimuli presentation (ms)		516.73 (332.13)
Inter-stimulus interval (ms)		1423.58 (1026.69)
SUDs and related conditions	42.6% (29)	
SUD clinical samples	24.5% (18)	
SUD clinical samples	12.3% (9)	
FH+ for SUDs	2.9% (2)	
ADHD	29.4% (20)	
MDD	7.3% (5)	
Stop Signal Task	20.6% (14)	
% Go trails		72.57 (11.74)
Stimuli presentation (ms)		790.00 (420.85)
Inter-stimulus interval (ms)		1830.56 (1061.82)
SUDs and related conditions	2.9% (2)	
SUD clinical samples	2.9% (2)	
SUD clinical samples	-	
FH+ for SUDs	-	
ADHD	17.6% (12)	
MDD	-	

Referring to behavioral data, 53 studies (77.9%) measured RTs, 37 studies (54.4%) reported error rates (i.e., commission and omission errors) and, 21 studies (30.9%) provided correct response rates (i.e., hits and correct rejections).

Tables 4 and 5 shows distributions of the estimated ESs for negative and positive waves recorded within No-Go and Go conditions. On the one hand, the N200 was the most recurrent negative wave assessed within No-Go (62.2%) and Go (72.4%) conditions and, it was mainly localized at frontal and central sites considering No-Go and Go conditions. On the other hand, the P300 was the most investigated positive wave within No-Go (69.1%) and Go (72.7%) conditions and, it was equally localized at frontal, central and parietal sites with respect to both experimental conditions.

Table 4. Neurophysiogical responses within No-Go conditions

Negative Waves (total ESs = 90)

Distribution by condition

Waves	Overall	SUDs and related conditions	ADHD	MDD
N 100	31.1% (28)	18.9 (17)	12.2% (11)	-
N 170	6.7% (6)	6.7% (6)	-	-
N 200	62.2% (59)	35.6% (32)	22.2% (20)	4.4% (4)

Distribution by localization

Waves	Frontal	Frontal – Central	Central	Parietal	Temporal	Occipital
N 100	6.7% (6)	6.7% (6)	15.6% (14)	2.2% (2)	-	-
N 170	-	-	-	-	-	6.7% (6)
N 200	20.0% (18)	12.2% (11)	21.1% (19)	8.9% (8)	-	

Positive waves (total effect sizes = 94)

Distribution by condition

Waves	Overall	SUDs and related conditions	ADHD	MDD
P 100	10.6% (10)	9.6% (9)	1.1% (1)	-
P 200	19.1% (18)	-	19.1% (18)	-
P 300	69.1% (65)	48.9% (46)	20.2% (19)	-
Late positive waves	1.1% (1)	-	1.1% (1)	-

Distribution by localization

Waves	Frontal	Frontal – Central	Central	Parietal	Temporal	Occipital
P 100	-	-	-	-	-	10.6% (10)
P 200	6.4% (6)	1.1% (1)	6.4% (6)	5.3% (5)	-	-
P 300	16.0% (15)	9.6% (9)	26.6% (25)	11.7% (11)	3.2% (3)	2.1% (2)
Late positive waves	-	-	-	1.1% (1)	-	-

Table 5. Neurophysiogical responses within Go conditions

Negative Waves (total effect sizes = 29)

Distribution by condition

Waves	Overall	SUDs and related conditions	ADHD	MDD
N 100	3.4% (1)	-	3.4% (1)	-
N 170	24.1% (7)	20.7% (6)	3.4% (1)	-
N 200	72.4% (21)	55.2% (16)	3.4% (1)	13.8% (4)

Distribution by localization

Waves	Frontal	Frontal – Central	Central	Parietal	Temporal	Occipital
N 100	-	-	3.4% (1)	-	-	-
N 170	-	-	-	3.4% (1)	-	20.7% (6)
N 200	31.0% (9)	13.8% (4)	24.1% (7)	3.4% (1)	-	-

Positive waves (total effect sizes = 44)

Distribution by condition

Waves	Overall	SUDs and related	ADHD	MDD

		conditions		
P 100	22.7% (10)	20.5% (9)	2.3% (1)	-
P 200	2.3% (1)	-	2.3% (1)	-
P 300	72.7% (32)	63.3% (28)	9.1% (4)	-
Late positive waves	2.3% (1)	-	2.3% (1)	-

Distribution by localization

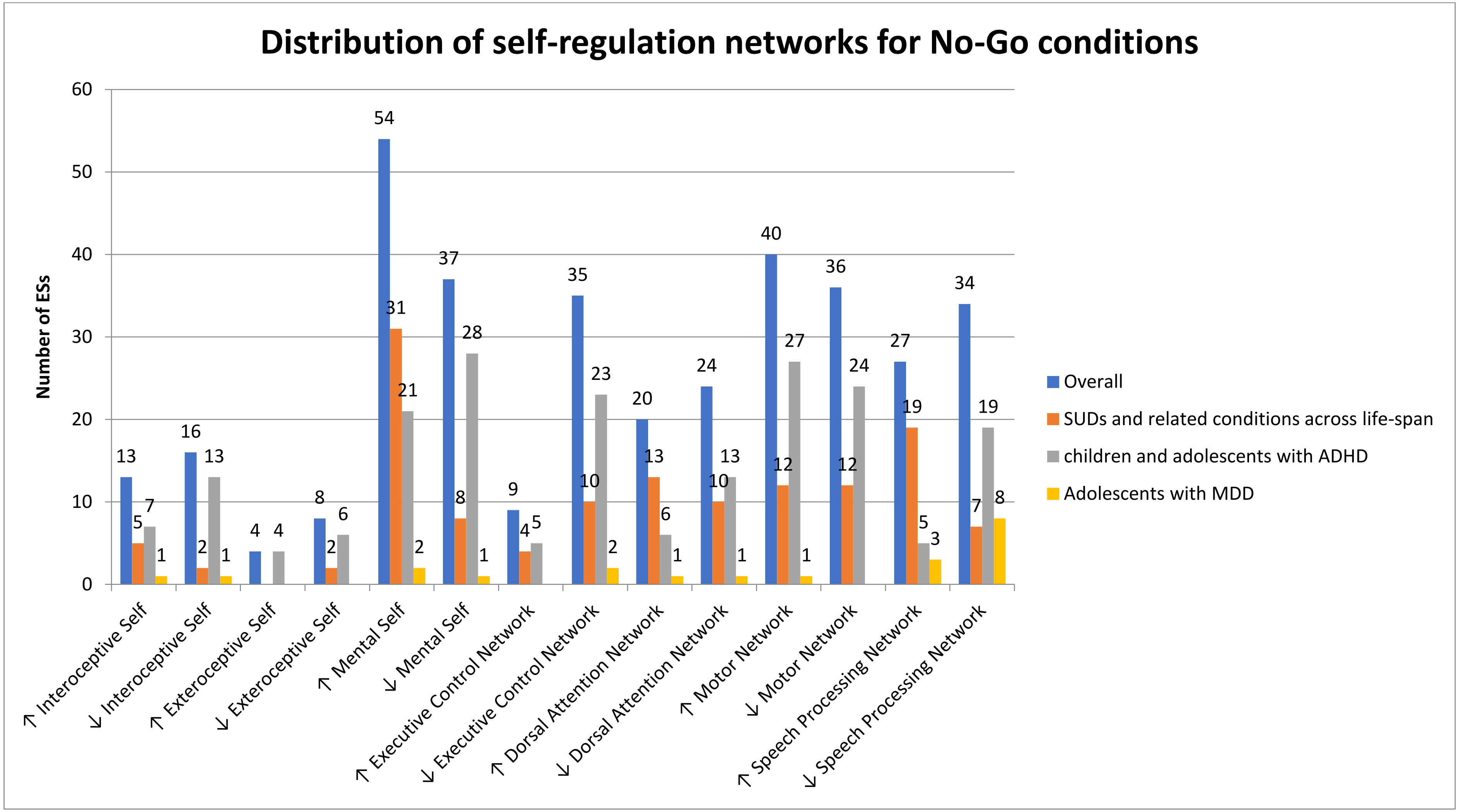
Waves	Frontal	Frontal – Central	Central	Parietal	Temporal	Occipital
P 100	-	-	-	-	-	20.5% (9)
P 200	2.3% (1)	-	-	-	-	-
P 300	18.2% (8)	2.3% (1)	20.5% (9)	20.5% (9)	6.8% (3)	4.5% (2)
Late positive waves	-	-	-	2.3% (1)	-	-

Looking at fMRI data for No-Go conditions, an increased activity of the Mental Self Network among groups of interest compared to HCs was the most recurrent evidence (15.6%) found across studies, followed by an increased activity of Motor Network (11.2%) and decreased responses of Speech Processing Network (9.5%). Considering results of each group of interest, some differences were detected. Indeed, SUDs and related conditions showed that the most recurrent findings were increased activities of the Mental Self Network (8.7%), Dorsal Attention Network (3.6%) and Speech Processing Network (5.3%). Children and adolescents with ADHD highlighted an equal distribution of increased (5.9%) and decreased (7.8%) responses of the Mental Self Network together with Motor Network (increased: 7.6%; decreased: 6.7%). However, findings also showed reduced responses of Executive Control (6.4%), Dorsal Attention (3.6%) and Speech Processing (5.3%) networks. Ultimately, studies that evaluated adolescents with MDD found recurrent increased activity of the Mental Self Network (.60%) and decreased responses of Speech Processing Network (2.2%). Table 6 and figure 13 provide a detailed a description of distribution of ESs estimated for each brain network considered in the current work.

Table 6. Distribution of brain networks activity within No-Go conditions (Conditions of interest vs HCs)

Total effect sizes estimated = 357				
Self Networks				
	Overall	SUDs and related conditions	ADHD	MDD
↑ Interoceptive Self	3.6% (13)	1.4% (5)	2.0% (7)	.3 % (1)
↓ Interoceptive Self	4.5% (16)	.6% (2)	3.6% (13)	.3 % (1)
↑ Exteroceptive Self	1.1% (4)	-	1.1% (4)	-
↓ Exteroceptive Self	2.2% (8)	.6% (2)	1.7% (6)	-
↑ Mental Self	15.1% (54)	8.7% (31)	5.9% (21)	.6% (2)
↓ Mental Self	10.4% (37)	2.2% (8)	7.8% (28)	.3 % (1)
Executive Networks				
↑ Executive Control	2.5% (9)	1.1% (4)	1.4% (5)	-
↓ Executive Control	9.8% (35)	2.8% (10)	6.4% (23)	.6% (2)
↑ Dorsal Attention	5.6% (20)	3.6% (13)	1.7% (6)	.3 % (1)
↓ Dorsal Attention	6.7% (24)	2.8% (10)	3.6% (13)	.3 % (1)
Motor Network				
↑ Motor	11.2% (40)	3.4% (12)	7.6% (27)	.3 % (1)
↓ Motor	10.1% (36)	3.4% (12)	6.7% (24)	-
Speech Processing Network				
↑ Speech Processing	7.6% (27)	5.3% (19)	1.4% (5)	.8% (3)
↓ Speech Processing	9.5% (34)	2.0% (7)	5.3% (19)	2.2% (8)

Figure 13. Distribution of self-regulation networks for No-Go conditions

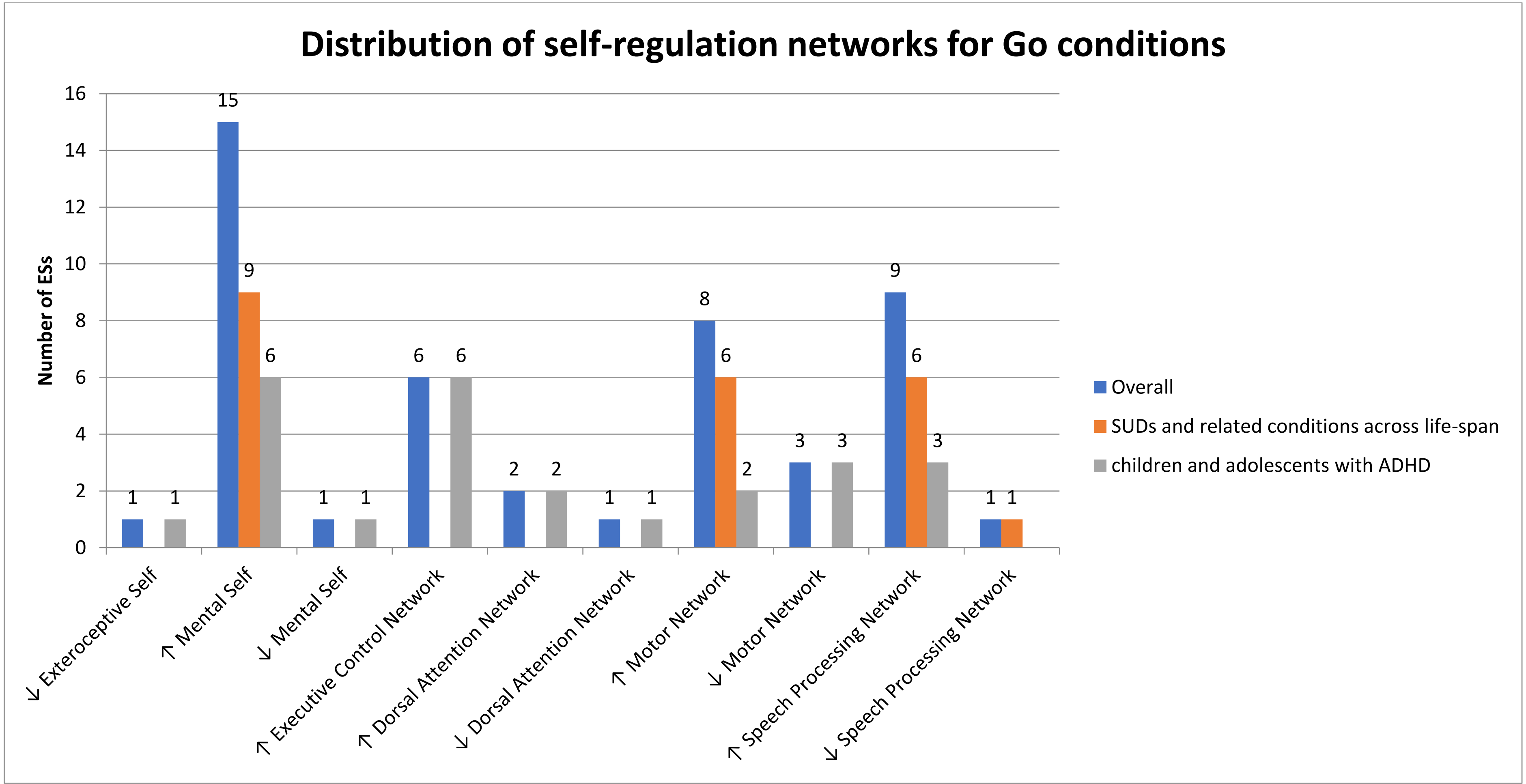


With respect to fMRI results of Go conditions, the analysis detected that the increased activity of the Mental Self Network was the most recurrent findings (31.9%) among individuals with SUDs and related conditions (19.1%) together with children/adolescents with ADHD (12.8%). The recruitment of Executive Control Network was exclusively found among ADHD children and adolescents. The increased activity of Motor and Speech Processing Networks was mainly detected among the SUDs and related conditions group. Table 7 and figure 14 reports a detailed description of descriptive statistics.

Table 7. Distribution of brain networks activity within Go conditions (Conditions of interest vs HCs)

Total effect sizes estimated = 47			
	Self Networks		
	Overall	SUDs and related conditions	ADHD
↓ Exteroceptive Self	2.1% (1)	-	2.1% (1)
↑ Mental Self	31.9% (15)	19.1% (9)	12.8% (6)
↓ Mental Self	2.1% (1)	-	2.1% (1)
	Executive Networks		
↑ Executive Control	12.8% (6)	-	12.8% (6)
↑ Dorsal Attention	4.3% (2)	-	4.3% (2)
↓ Dorsal Attention	2.1% (1)	-	2.1% (1)
	Motor Network		
↑ Motor	17.0% (8)	12.8% (6)	4.3% (2)
↓ Motor	6.4% (3)	6.4% (3)	-
	Speech Processing Network		
↑ Speech Processing	19.1% (9)	12.8% (6)	6.4% (3)
↓ Speech Processing	2.1% (1)	2.1% (1)	-

Figure 14. Distribution of self-regulation networks for Go conditions



Multi-level meta-analysis: behavioral performances

Table 8 provides a detailed description of results of multi-level meta-analytic procedures for behavioral data. Looking at RTs, the best fit model (AICc = 78.61; BIC = 85.22) was a 3-level one ($\chi^2_{(1)}$ = 10.85; p < .01). The analysis highlighted a small, albeit significant, difference between conditions of interest and HCs (d_{pooled} = .13 [.02 – .24]; p< .05). Specifically, conditions of interest showed slightly slower RTs than HCs for both Go and No-Go conditions. On the one hand, findings were heterogeneous ($Q_{(75)}$ = 127.54; p< .001) across studies ($I^2_{\text{Level 2}}$ = .00%; $I^2_{\text{Level 3}}$ = 48.99%). On the other hand, no significant moderators of ESs were detected. Furthermore, no bias of publication were found.

Overall, a 3-level model (AICc = 68.42; BIC = 72.61) fitted better than a 2-level (AICc = 73.01; BIC = 77.20) one for meta-analyzing findings of error rates ($\chi^2_{(1)}$ = 6.79; p < .01). Results showed a small to moderate difference between conditions of interest and HCs (d_{pooled} = .41 [.29 – .53]; p < .001). Accordingly, conditions of interest highlighted higher error rates than HCs. Nevertheless, results were heterogeneous ($Q_{(66)}$ = 105.01; p < .001) across studies ($I^2_{\text{Level 2}}$ = .00%; $I^2_{\text{Level 3}}$ = 42.09%). The analysis of moderators showed 2 significant models. The first model ($F_{(2,64)}$ = 6.03, p< .01; AICc = 61.64; BIC = 71.40), which explained the variability of results previously reported ($Q_{(63)}$ = 81.64; *ns*;$I^2_{\text{Level 2}}$ = .00%; $I^2_{\text{Level 3}}$ = 31.22%), showed a significant effect of specific conditions of interest. Particularly, children and adolescents with ADHD showed significant and moderate higher error rates than HCs (d_{pooled} = .59 [.44 – .74]; p< .001). The SUDs and related conditions group highlighted small, albeit significant, higher errors rates than HCs (d_{pooled} = .23 [.02– .44]; p < .05). On the contrary, a non-significant pooled ES was found for the comparison between adolescents with MDD and HCs.

The second model ($F_{(2,64)}$ = 5.73, p< .01; AICc = 61.26; BIC = 71.02) detected a significant moderator effect of error type. Specifically, studies that reported a combined measure of error rates (i.e., commission error + omission error) highlighted large differences between conditions of interests and HCs (d_{pooled} = .97 [.33 – 1.60]; p< .001). Conversely, studies that provided data for specific type of errors showed non-significant pooled ESs for commission and omission errors. Furthermore, this model did not explain the variability of results across studies ($Q_{(63)}$ = 97.78; p <.05). Overall, the analysis did not find bias of publication for error rates results.

Ultimately, results concerning correct response rates (i.e., hits + correct rejection) highlighted no significant differences between conditions of interest and HCs (d_{pooled} = -.14 [-.51 – .23]; *ns*). There was detected a significant heterogeneity of findings across studies ($Q_{(30)}$ = 104.84; p< .001; $I^2_{\text{Level 2}}$

= .00%; $I^2_{\text{Level 3}}$ = 86.41%). Nevertheless, no significant moderating effects were detected. Bias of publication were not found. Figure 15 graphically summarizes results previously discussed.

Table 8. Multi-level meta-analysis results of behavioral performances

Level 2 *N* of effect sizes	Level 3 *N* of studies	Moderators	*F* (df $_{1,}$ df $_{2}$)	*b*	d_w (95% CI)	*Q* *(df)*	τ^2 Level 2 I^2 Level 2	τ^2 Level 3 I^2 Level 3	AIC_c	BIC	$\chi^2_{(1)}$	Egger's coefficient 95% Bootstrap CI
					Reaction Times							
76	**53**				**.13 (.02 –.24)***	127.54*** (75)	**.00 .00%**	**.08 48.99%**	**78.61**	**85.22**	10.85**	.57 (-1.71 – .37)
76	-				.14 (.05 - .23)**		.05 38.86%	-	87.30	91.76		
					Data collection procedures							
76	53	EEG	.02 (1, 74)		.12 (-.05 –.16)	126.89*** (74)	.00	.08	80.51	89.15		
		fMRI			.13 (-.08 –.34)							
					Year of publication							
76	53		.29 (1, 74)	.005 (-.01 – 0.02)		127.47*** (74)	.00	.08	80.03	88.67		
					Sample size							
76	53		.74 (1, 74)	.001 (-.001 – 0.003)		126.95*** (74)	.00	.08	80.28	89.91		
					Gender							
76	53	M	.93 (2, 73)		-.02 (-.28 –.23)	126.84*** (73)	.00	.09	80.59	91.14		
		M + W			.17 (-.10 – .44)							
		W			.04 (-.92 – 1.00)							
					Age							
76	53		.05 (1, 74)	.001 (-.001 – 0.01)		127.42*** (74)	.00	.08	80.33	88.97		
					Sample characteristics							
76	53	SUD and related	.78 (2, 73)		.16 (-.05 –.39)	124.05*** (73)	.00	.08	80.71	91.27		

		conditions										
		ADHD			.12 (-.04 – .28)							
		MDD			-.29 (-1.01 – .43)							
Task												
76	53	Go No-Go SST	.08 (1, 74)		.12 (-.01 – .25) 15 (-.08 – .38)	127.21*** (74)	.00	.08	80.42	86.06		
% Go trails												
75	52		.09 (1, 73)	-.001 (-.001 – 0.01)		126.88*** (73)	.00	.09	80.76	89.33		
Length of stimuli presentation (ms)												
74	51		1.48 (1, 72)	.0002 (-.0001 – 0.0005)		121.06*** (72)	.00	.08	77.73	86.24		
Length of interstimulus interval (ms)												
72	50		.23 (1, 70)	.000 (-.0001 – 0.0001)		114.87*** (70)	.00	.08	74.02	82.40		
Error rates												
67	37				.41 (.29 – .53)***	105.01*** (66)	.00 .00%	.06 42.09%	68.42	72.61	6.79**	.74 (-.39 – 2.36)
67	-				.41 (.32 – .51)***	105.01*** (66)	.06 38.86%	-	73.01	77.20		
Experimental context												
67	37	ERP fMRI	2.08 (1,65)		.52 (.33 – .71)*** .35 (.12 – .58)***	96.17*** (65)	.00	.06	68.43	76.46		
Year of publication												
67	37		2.99 (1, 65)	-.02 (-.04 – .003)		103.09** (65)	.00	.06	67.17	75.20		
Sample size												
67	37		.08 (1, 65)	-.0003 (-.002 – .002)		104.72** (65)	.00	.07	70.96	78.99		

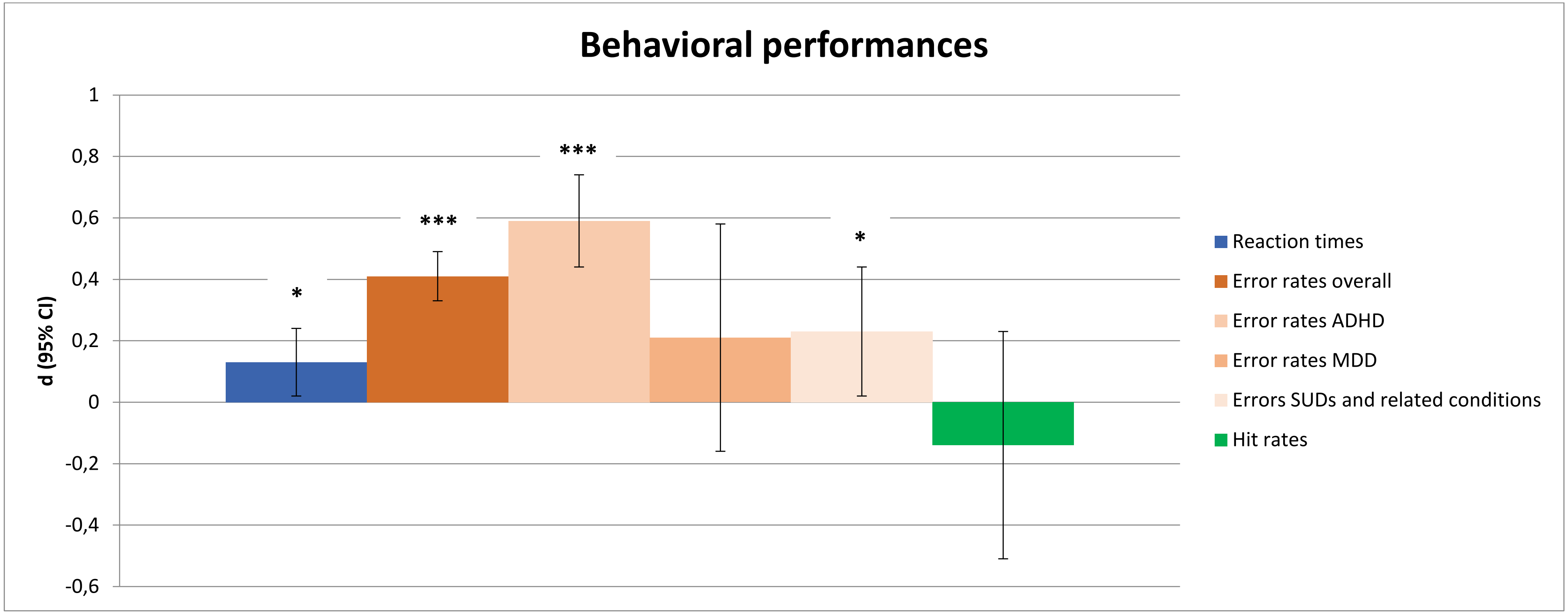
					Gender					
67	37	M	5.45* (1, 65)		.82 (.45 – 1.19)***	97.36** (65)	.00	.06 38.82%	64.83	72.87
		M + W			.37 (.01 – .73)*					
					Age					
67	37		.27 (1, 65)	-.003 (-.01 – .008)		104.58** (65)	.00	.07	69.91	77.95
					Sample characteristics					
67	**37**	**ADHD**	**6.03 (2, 64)****		**.59 (.44 – .74)*****	**81.64 (63)**	**.00**	**.04 31.22%**	**61.64**	**71.40**
		SUD and related conditions			**.23 (.02 – .44)***					
		MDD			**.21 (-.16 – .58)**					
					Task					
67	37	Go No-Go	.79 (1, 65)		.38 (.24 – .52)***	102.70*** (65)	.00	.07	69.61	69.75
		SST			.50 (.25 – .75)***					
					% Go trails					
63	34		.12 (1, 65)	-.002 (-.01 – .009)		90.22** (65)	.00	.07	65.62	73.25
					Length of stimuli presentation (ms)					
65	35		.06 (1, 63)	-.00 (-.0004 – .0003)		102.07*** (63)	.00	.07	69.33	77.21
					Length of interstimulus interval (ms)					
65	35		2.91 (1, 63)	.0001 (-.0001 – .0003)		91.33* (63)	.00	.06	66.78	74.66
					Error type					
67	37	Combined error	5.73 (2, 64)**		.97 (.33 – 1.60)***	97.68* (63)	.00	.06	61.26	71.02
		Commission errors			.33 (-.30 – .99)					
		Omission			.61					

		errors			(-.03 – 1.25)							
Correct response rates												
31	**21**				**-.14** **(-.51 – .23)**	**104.84*** (30)**	**.00** **.00%**	**.58** **86.41%**	**68.05**	**71.33**	8.42**	.48 (-2.90 – 4.01)
31	-				-.15 (-.39 – .10)		.58	-	73.99	76.35		
Experimental context												
31	21	ERP fMRI	1.57 (1, 29)		-.42 (-1.01 – .17) .04 (-.29 – 1.21)	93.22*** (29)	.00	.57	67.42	71.23		
Year of publication												
31	21		.58 (1,29)	.03 (-.05 – .11)		104.10*** (29)	.00	.60	68.53	72.15		
Sample size												
31	21		.37 (1,29)	.005 (-.01 – .02)		104.93*** (29)	.00	.62	68.33	72.14		
Gender												
31	21	M M + W W	1.91 (2,28)		-.77 (-1.51 – -.01)* .05 (-.77 – .87) -.29 (-2.05 –1.47)	96.82*** (28)	.00	.53	67.05	70.89		
Age												
31	21		.12 (1,29)	.006 (-.03 – .04)		101.35*** (29)	.00	.62	68.82	72.62		
Sample characteristics												
31	21	ADHD SUD and related conditions MDD	2.91 (2,28)		-.70* (-1.29 – -.11) .17 (-.53 – .87) -.08 (-1.22 – 1.06)	78.45*** (28)	.00	.46	64.74	68.67		
Task												
31	21	Go No-Go SST	3.20 (1,29)		.05 (-.36 – .46) -.63 (-1.37 – .11)	104.04*** (29)	.00	.52	65.85	69.65		

% Go trails								
30	20	.58 (1,28)	.008 (-.01 – .03)	51.90** (28)	.00	.08	40.46	44.05
Length of stimuli presentation (ms)								
30	20	.04 (1,28)	-.0001 (-.0006 – .0005)	53.52** (28)	.00	.08	40.94	44.53
Length of interstimulus interval (ms)								
28	19	.46 (1,26)	-.0001 (-.0004 – .0002)	49.75** (26)	.00	.08	37.94	41.07

Bold: The best fit model; *p< .05; **p< .01; ***p< .001

Figure 15. Main findings of multi-level meta-analysis for behavioral performances



Comparisons among pooled effect sizes

Contrasting the absolute values of pooled ESs of behavioral performances, the analyses found a significant difference between RTs and errors rates. Specifically, error rates highlighted a significant larger pooled ES than RTs (Z = 3.58; $p < .001$). This finding suggested that behavioral inhibition (i.e., commission errors) and sustained attention (i.e., omission errors) could be more impaired than motor preparation processes (i.e., RTs). On the contrary, no significant differences were found when pooled ESs of correct response rates was compared to RTs (Z = .05; *ns*) and error rates (Z = 1.44; *ns*).

Considering the moderating effect of specific conditions of interest on error rates, children and adolescents with ADHD highlighted the worst behavioral performances compared to individuals with SUDs and related conditions (Z = 2.76; $p < .01$) and adolescents with MDD (Z = 1.88; $p < .05$). On the contrary, individuals with SUDs and related conditions and MDD adolescents did not show significant differences in pooled ESs of error rates (Z = .09; *ns*).

Multi-level meta-analysis: neurophysiological results

Table 9 provides detailed results of multi-level meta-analytic procedures for negative waves recorded within No-Go and Go conditions. The 3-level model highlighted the best fit (AICc = 137.73; BIC = 143.83) compared to a 2-level one (AICc = 221.94; BIC = 227.31; $\chi^2_{(1)} = 86.36$; $p < .001$). Overall, no significant differences between conditions of interest and HCs were found ($d_{pooled} = .05$ [-.21 – .31]; *ns*). However, the analyses detected a significant heterogeneity ($Q_{(118)} = 462.73$; $p < .001$) of results within ($I^2_{\text{Level 2}} = 10.54\%$) and between studies ($I^2_{\text{Level 3}} = 66.36\%$). The moderator analysis showed a significant effect ($F_{(2,116)} = 18.97$, $p < .001$; AICc = 112.36; BIC = 125.85) of specific ERPs for both No-Go and Go experimental conditions. Specifically, the N200 showed a significant and small amplitude reduction ($d_{pooled} = .27$ [.11 – .43]; $p < .001$) among conditions of interest compared to HCs. On the contrary, the N100 ($d_{pooled} = -.24$ [-.54 – .06]; *ns*) and the N170 highlighted non-significant and small amplitude enhancements among conditions of interest compared to HCs. This model explained the within study variability ($I^2_{\text{Level 2}} = .00\%$), but not the between studies heterogeneity ($Q_{(115)} = 365.15$; $p < .001$; $I^2_{\text{Level 3}} = 75.88\%$). Although the localization of negative waves was not a significant moderator of ES, frontal electrodes recorded significant amplitude reductions ($d_{pooled} = .24$ [.04 – .44]; $p < .01$) among conditions of interest compared to HCs. This result might reflect the significant association found between frontal activity and the N200 ($\chi^2_{(2)} = 8.34$, $p < .05$; N200: 81.8%, N170: .00%, N100: 18.2%). Consistently, it was conducted a subgroup analysis on the N200 including the brain activity localization as moderators.

On the one hand, the analysis did not detect a significant moderating effect ($F_{(3,73)}$ = 1.63, *ns*; AICc = 89.53; BIC = 102.00). On the other hand, it was found a significant amplitude reduction of the N200 at a frontal localization (d_{pooled} = .29 [.06 – .52]; p <.01). The other pooled ESs were not significant — frontal-central: d_{pooled} = .01 [-.36 – .38], *ns*; central: d_{pooled}= .09 [-.24 – .42], *ns*; parietal: d_{pooled} = .07 [-.24 – .38], *ns*.Ultimately, the analysis detected a bias of publication.

Looking at positive waves, a 3-level model (AICc = 122.08; BIC = 130.67) showed a better fit than a 2-level one (AICc = 258.77; BIC = 264.52; $\chi^2_{(1)}$ = 138.77; p< .001). This model detected a non-significant reduction of positive waves amplitudes (d_{pooled} = -.23 [-.48 – .02]; *ns*) among conditions of interest compared to HCs. The heterogeneity of findings was significant ($Q_{(137)}$ = 498.65; p< .001) and large between studies (I^2 $_{\text{Level 3}}$ = 75.55%).The evaluation of moderators highlighted a significant effect ($F_{(5,132)}$ = 5.25, p< .001; AICc = 105.65; BIC = 129.54) of localization of ERPs. Specifically, central (d_{pooled} = -.31 [-.58 – -.04]; p <.05) and parietal (d_{pooled} = -.37 [-.53 – -.21]; p <.001) electrodes recorded significant amplitude reductions of positive waves among conditions of interest compared to HCs. Nevertheless, the heterogeneity of results remained significant ($Q_{(132)}$ = 464.27; p< .001) and large (I^2 $_{\text{Level 3}}$ = 79.14%). On the one hand, specific positive ERPs represented significant moderators of ESs ($F_{(3,134)}$ = 5.36, p < .01; AICc = 112.61; BIC = 129.34). On the other hand, the estimation of pooled ESs for each ERPs did not show significant differences between conditions of interest and HCs — P100: (d_{pooled} = -.22 [-.67 – .21]; *ns*); P200: (d_{pooled}= .08 [-.39 – .55]; *ns*); P300: (d_{pooled} = -.28 [-.71 – .15]; *ns*); late positive waves: (d_{pooled} = -.33 [-.82 – .17]; *ns*). Furthermore, this model did not explain the variability of results ($Q_{(134)}$ = 464.54; p < .001). However, additional analyses supported a significant association between the P300 with central ($\chi^2_{(3)}$ = 13.23, p < .01; P300: 82.9%, P200: 17.1%, P100: .00%; late positive waves: .00%) and parietal ($\chi^2_{(3)}$ = 9.11, p < .05; P300: 71.4%, P200: 17.9%, P100: 3.6%; late positive waves: 7.1%) localization. Accordingly, it was conducted a subgroup analysis focusing on the P300 considering the moderating effect of brain activity localization. Results showed a significant moderating effect of brain activity localization ($F_{(5,91)}$ = 5.44, p < .001; AICc = 95.24; BIC = 113.57). Specifically, there was detected a significant amplitude reduction of the P300 at central (d_{pooled}= -.33 [-.64 – -.03]; p <.05) and parietal (d_{pooled} = -.37 [-.57 – -.17]; p <.001) sites. On the contrary, no significant alterations of the P300 were found in the other localizations — frontal: d_{pooled} = .07 [-.11 – .25], *ns*; frontal-central: d_{pooled}= -.20 [-.55 – .15], *ns*;temporal: d_{pooled}= -.21 [-.48 – .06], *ns*; occipital: d_{pooled} = -.12 [-.33 – .09], *ns*.

Interestingly, the analyses found an additional moderator effect of tasks administered ($F_{(1,136)}$ = 5.36, p < .05; AICc = 116.69; BIC = 128.04). Particularly, studies that used the SST showed large reductions of positive waves (d_{pooled} = -.76 [-1.32–-.20]; p <.001) among conditions of interest compared to HCs. On the contrary, no significant differences were detected for studies that administered the GNG task (d_{pooled} = -.10 [-.36 – .16]; *ns*). Nevertheless, the heterogeneity of findings remained unexplained ($Q_{(136)}$ = 469.96; p < .001). Moreover, the goodness of fit indexes were worst than the previous models that considered as moderators specific ERPs and localization of brain activity. Ultimately, the analysis did not detect bias of publication. Figures 16 graphically summaries results discussed above.

Table 9. Multi-level meta-analysis results of EEG studies

Level 2 *N* of effect sizes	Level 3 *N* of studies	Moderators	*F* (df $_{1,}$ df $_{2}$)	*b*	d_w (95% CI)	*Q* *(df)*	τ^2 Level 2 I^2 Level 2	τ^2 Level 3 I^2 Level 3	AIC_c	BIC	$\chi^2_{(1)}$	Egger's coefficient 95% Bootstrap CI
					Negative waves							
119	18				.05 (-.21 –.31)	462.73*** (118)	.04 10.54%	.24 66.36%	137.73	143.83	86.36***	-2.34* (-3.74 – -.90)
119	-				-.07 (-.18 - .03)		.26 75.45%	-	221.94	227.31		
					Year of publication							
119	18		1.92 (1, 117)	.05 (-.02 – .11)		359.17*** (117)	.04	.22	136.05	146.74		
					Sample size							
119	18		.65 (1, 117)	.003 (-.005 – .01)		408.74*** (117)	.04	.22	137.12	147.81		
					Gender							
		M			.28 (-.70 – 1.27)							
119	18	M + W	.84 (2, 116)		.00 (-1.02 – 1.02)	457.62*** (116)	.04	.25	138.16	151.38		
		W			.80 (-.80 – 1.60)							
					Age							
119	18		.001 (1, 117)	-.0004 (-.03 – .02)		461.93*** (117)	.04	.22	137.08	147.78		
					Sample characteristics							
		ADHD			.13 (-.28 – .54)							
119	18	SUD and related conditions	.19 (3, 115)		.00 (-.75 – .75)	423.23*** (115)	.04	.30	135.51	151.20		
		MDD			.10 (-1.01 – 1.24)							
					Task							

119	18	Go No-Go SST	.90 (1, 117)		-.01 (-.31 – .28) .28 (-.47 – .89)	375.55*** (117)	.04	.25	136.23	146.92
					Condition					
119	18	Go No-Go	.05 (1, 117)		.04 (-.26 – .33) .06 (-.12 – .24)	462.20*** (117)	.04	.25	139.61	150.30
					ERPs					
119	**18**	**N100** **N170** **N200**	**18.97*** (2, 116)**		**-.24 (-.54 – .06) -.26 (-1.06 – .66) .27*** (.11 – .43)**	**365.15*** (115)**	**.00 .00%**	**.27 75.88%**	**112.63**	**125.85**
					Localization					
119	18	F FC C P O	2.32 (4, 114)		.24** (.04 – .44) .04 (-.21 – .29) -.01 (-.29 – .26) -.03 (-.30 – .24) -.56 (-1.48 – .36)	335.15*** (114)	.04	.19	134.14	152.22
					% Go trails					
104	16		3.72 (1, 102)	.02 (-.005 – .03)		293.38*** (114)	.04	.19	110.08	120.17
					Length of stimuli presentation (ms)					
98	16		.89 (1, 96)	.0004 (-.0004 – .001)		218.48*** (96)	.03	.17	103.05	112.86
					Length of interstimulus interval (ms)					
98	16		.15 (1, 96)	-.0001 (-.0004 –		230.65*** (96)	.03	.20	103.87	113.69

				.0003)								
Positive waves												
138	21				-.23 (-.48 – .02)	498.65*** (137)	.00 .00%	.30 75.55%	122.08	130.67	138.77***	-.28 (-1.92 – 1.18)
138	-				-.29*** (-.39 – -.19)		.26	-	258.77	264.52		
Year of publication												
138	21		.08 (1, 136)	.006 (-.04 – .05)		485.25*** (136)	.00	.33	121.30	132.64		
Sample size												
138	21		.01 (1, 136)	-.0006 (-.009 – .008)		498.33*** (136)	.00	.33	121.68	133.03		
Gender												
138	21	M M + W W	.05 (2, 135)		-.28 (-.98 – .38) -.22 (-.94 – .50) -.37 (-.94 – .50)	434.33*** (135)	.00	.37	121.75	138.48		
Age												
138	21		.01 (1, 136)	-.0006 (-.009 – .008)		469.54*** (136)	.00	.37	121.54	132.88		
Sample characteristics												
138	21	ADHD SUD and related conditions	.17 (1, 136)		-.28 (-.67 – .09) -.18 (-.69 – .33)	497.81*** (136)	.00	.37	121.47	132.82		
Task												
138	21	Go No-Go SST	5.04* (1, 136)		-.10 (-.36 – .16) -.76*** (-1.32 – -.20)	469.96*** (136)	.00	.25 76.00%	116.69	128.04		
Condition												
138	21	Go	.16		-.24	493.09***	.00	.30	124.37	135.71		

			(1, 136)		(-.51 – .02)	(136)				
		No-Go			-.22*** (-.32 – -.10)					
ERPs										
138	21	P100	5.36** (3, 134)		-.22 (-.67 – .21)	464.54*** (134)	.00	.30	112.61	129.34
		P200			.08 (-.39 – .55)					
		P300			-.28 (-.71 – .15)					
		LPW			-.33 (-.82 – .17)					
Localization										
138	**21**	**F**	**5.25*** (5, 132)**		**.01 (-.13 – .15)**	**464.27*** (132)**	**.00 .00%**	**.30 79.14%**	**107.65**	**129.54**
		FC			**-.20 (-.51 – .11)**					
		C			**-.31* (-.58 – -.04)**					
		P			**-.37*** (-.53 – -.21)**					
		T			**-.25 (-.51 – .01)**					
		O			**-.23 (-.47– .00)**					
% Go trails										
122	18		.06 (1, 120)	-.002 (-.02 – .02)		488.25*** (120)	.00	.36	113.50	124.30
Length of stimuli presentation (ms)										
108	19		.06 (1, 106)	.0002 (-.0005 – .001)		263.52*** (106)	.00	.36	53.31	63.57
Length of interstimulus interval (ms)										
108	19		.05 (1, 106)	.000 (-.0002 – .0002)		248.53*** (106)	.00	.25	53.18	63.44

Bold: The best fit model; *p< .05; **p< .01; ***p< .001

Summary of main findings concerning neurophysiological responses

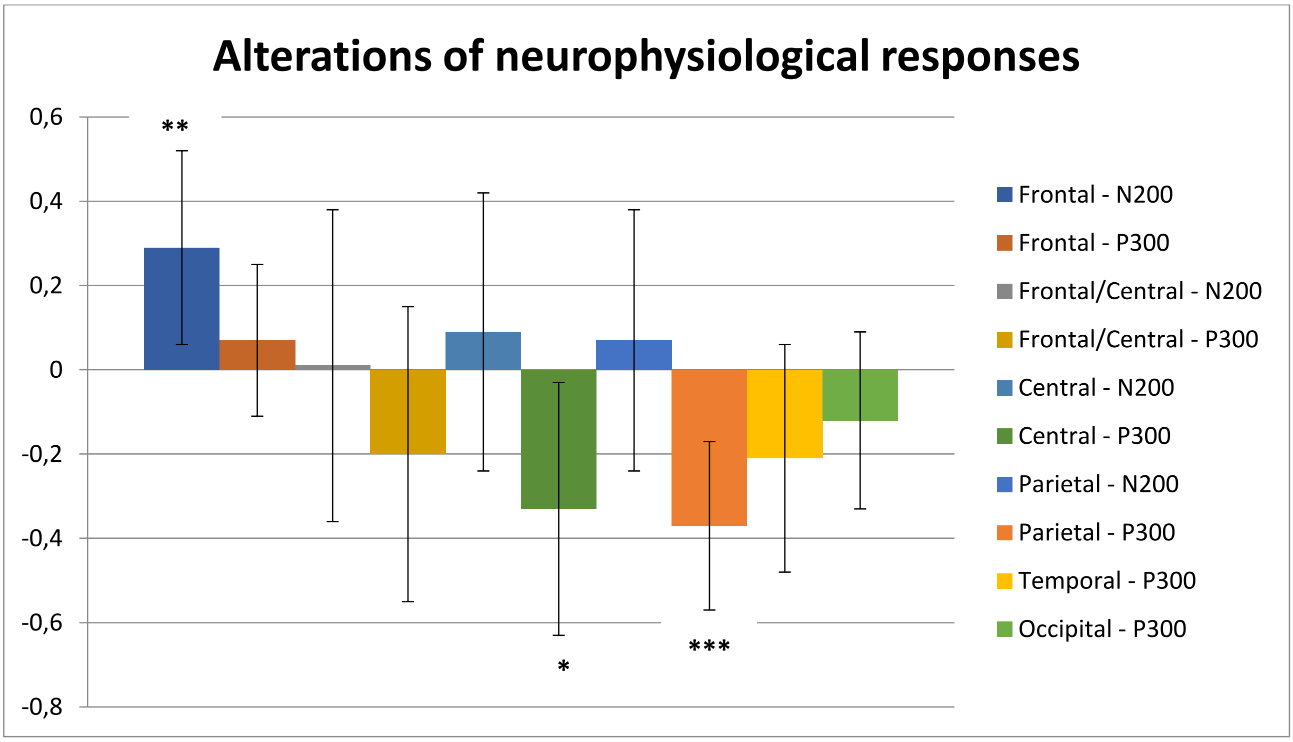
The meta-analytic results of neurophyisiological activity within behavioral inhibition tasks highlighted 3 main findings:

i) a reduction of N200 amplitude, especially with a frontal localization, might be considered a neurophysiological maker of altered self-regulation of behaviors among conditions of interest, considering both motor inhibition and production;

ii) reduction of positive waves amplitudes with a central and parietal localization, especially referring to the P300, could be considered an additional neurophysiological indexes of altered mechanisms of behavioral self-regulation;

iii) these alterations were shared by conditions of interest and, they could be stable across different stages of development. This might support the notion that neuro-mental alterations of behavioral self-regulatory mechanisms represent common features of SUDs and related conditions across the life-span, child and adolescent ADHD and adolescent MDD and, they could be latent processes at the base of homotypic and heterotypic continuity among these conditions during the development.

Figure 16. Alterations of neurophysiological responses



Meta-analysis of brain networks related to self and its regulation

No-Go conditions

Table 10 reports a detailed description of results of network meta-analysis conducted on the base of ROIs linked to self-processing layesr and domains of self-regulation referring to No-Go conditions. Considering the overall network composed of all conditions of interest compared to HCs, the analysis found that the most representative brain responses in terms of extent of altered activity were an increased recruitment of the Exteroceptive Self Network (d_{pooled} = 1.50; 95% CrI: [.94 – -2.50]; SUCRA: .93) and a large deactivation of Dorsal Attention Network (d_{pooled} = -1.40; 95% CrI: [-1.60– -1.10]; SUCRA: .94). However, the nodesplit analysis revealed a significant inconsistency within this network. Therefore, there were conducted separate network meta-analysese for each condition of interest.

Referring to SUDs and related conditions across the life-span, the nodesplit analysis demonstrated the consistency of this spectrum. Results showed that the most representative brain responses during No-Go experimental paradigms were a large deactivation of the Exteroceptive Self Network (d_{pooled} = -2.10; 95% CrI: [-3.00 – -1.10]; SUCRA: .99) and a heightened activity of Dorsal Attention Network (d_{pooled} = 1.30; 95% CrI: [.87 – 1.70]; SUCRA: .87).

The network meta-analysis regarding the functioning of ADHD children and adolescents highlighted a consistency within this group through the nodesplit findings. Interestingly, the analysis showed that the most representative brain activities during No-Go conditions were a deactivation of Dorsal Attention Network (d_{pooled} = -1.80; 95% CrI: [-2.40 – -1.30]; SUCRA: .99) and, a large increased activity of Speech Processing Network (d_{pooled} = 2.50; 95% CrI: [1.50 – 3.40]; SUCRA: .98).

Moreover, the consistency was demonstrated for the adolescents with MDD group using the nodesplit analysis. The network meta-analysis showed that the most representative responses toward No-Go paradigms were a large, albeit not significant, deactivation of Executive Control Network (d_{pooled} = -.77; 95% CrI: [-2.60 – 1.10]; SUCRA: .79) and, a significant heightened activity of Speech Processing Network (d_{pooled} = 1.60; 95% CrI: [.14 – 3.10]; SUCRA: .86).

Table 10. Results of network meta-analysis for No-Go trails

Brain Network	All conditions		SUDs and related conditions across life span		Children and adolescents with ADHD		Adolescents with MDD	
	d (95% CrI) ↑ vs HCs [SUCRA]	*d* (95% CrI) ↓ vs HCs [SUCRA]	*d* (95% CrI) ↑ vs HCs [SUCRA]	*d* (95% CrI) ↓ vs HCs [SUCRA]	*d* (95% CrI) ↑ vs HCs [SUCRA]	*d* (95% CrI) ↓ vs HCs [SUCRA]	*d* (95% CrI) ↑ vs HCs [SUCRA]	*d* (95% CrI) ↓ vs HCs [SUCRA]
Interoceptive Self	1.20 (.86 – 1.50) [.68]	-1.00 (-1.30 – -.72) [.67]	1.30 (.94 – 1.60) [.85]	-1.00 (-1.60 – -.49) [.71]	1.10 (.44 – 1.70) [.66]	-1.10 (-1.50 – -.66) [.79]	.93 (-1.00 – 2.90) [.70]	-.65 (-2.50 – 1.20) [.72]
Exteroceptive Self	**1.70 (.94 – 2.50) [.93]**	-1.20 (-1.60 – -.82) [.79]	-	**-2.10 (-3.00 – -1.10) [.99]**	1.60 (.81 – 2.40) [.84]	-1.10 (-1.60 – -.64) [.71]	-	-
Mental Self	1.30 (1.00 – 1.60) [.78]	-1.20 (-1.40 – -.96) [.79]	1.10 (.77 – 1.30) [.70]	-1.10 (-1.40 – -.84) [.76]	1.60 (1.20 – 2.00) [.85]	-1.20 (-1.60 – -.88) [.78]	.90 (-1.00 – 2.80) [.69]	-.73 (-2.60 – 1.20) [.76]
Executive Control	1.20 (.82 – 1.60) [.70]	-1.20 (-1.40 – -.96) [.77]	1.30 (.80 – 1.80) [.85]	-1.10 (-1.40 – -.84) [.75]	1.10 (.57 – 1.60) [.67]	-1.20 (-1.60 – -.85) [.77]	-	**-.77 (-2.60 – 1.10) [.79]**
Dorsal Attention	1.30 (.90 – 1.70) [.78]	**-1.40 (-1.60 – -1.10) [.94]**	**1.30 (.87 – 1.70) [.87]**	-1.10 (-1.40 – -.80) [.74]	1.30 (.20 – 2.40) [.75]	**-1.80 (-2.40 – -1.30) [.99]**	1.10 (-.81 – 3.00) [.73]	-.71 (-2.50 – 1.20) [.75]
Motor	1.30 (1.00 – 1.60) [.79]	-1.20 (-1.40 – -.91) [.77]	1.20 (.90 – 1.60) [.84]	-1.00 (-1.40 – -.74) [.70]	1.30 (.80 – 1.80) [.74]	-1.20 (-1.60 – -.86) [.79]	1.60 (-.38 – 3.50) [.84]	-
Speech Processing	1.40 (1.10 – 1.70) [.84]	-1.20 (-1.40 – -.94) [.78]	1.10 (.80 – 1.40) [.73]	-1.10 (-1.50 – -.80) [.73]	**2.50 (1.50 – 3.40) [.98]**	-1.20 (-1.50 – -.84) [.76]	**1.60 (.14 – 3.10) [.86]**	-.80 (-2.70 – 1.11) [.78]

Bold: The most representative brain responses from SUCRA values

Looking at ALE meta-analysis of increased brain responses among conditions of interest compared to HCs for No-Go conditions, the cluster-based FWE correction (p < .05) identified a cluster of activation, which is ascribed to the Mental Self Network, composed of: i) the anterior cingulate (74.3%); ii) the medial frontal gyrus (20.4%); iii) cingulate gyrus (4.3%). Table 11 reports detailed coordinates of ALE meta-analysis.

Table 11. Results of cluster-based meta-analysis across samples — No-Go trails

Cluster	Brain Region	*x*	*y*	*z*	Brodmann area	Z	% of cluster composition	Volume (mm^3)
SUDs and related conditions; children and adolescents with ADHD; adolescents with MDD >controls								
1	Anterior Cingulate	12	50	-2	10	3.60	74.3%	10168
1	Anterior Cingulate	4	48	-6	32	3.39		
1	Anterior Cingulate	-4	48	0	32	3.14		
1	Anterior Cingulate	-8	40	-4	24	3.02		
1	Anterior Cingulate	12	44	-4	32	2.99		
1	Anterior Cingulate	4	44	6	32	2.83		
1	Medial Frontal Gyrus	-2	48	-16	10	2.94	20.4%	
1	Medial Frontal Gyrus	24	50	2	10	2.80		
1	Medial Frontal Gyrus	-8	48	16	9	2.77		
1	Superior Frontal Gyrus	30	58	6	10	2.41		
1	Cingulate Gyrus	2	38	20	32	3.40	4.3%	
1	Cingulate Gyrus	-12	36	20	32	3.03		

The ALE meta-analysis was also separately conducted for each group of interest. Considering the SUDs and related conditions group, the cluster-based FWE correction (p< .05) found a cluster composed of: i) the anterior cingulate (55.2%); ii) the medial (24.4%) and superior (2.2%) frontal gyrus; iii) the caudate (13.9%) and lentiform nucleus (2.2%). This cluster is mainly ascribed to the Mental Self Network and, it also partially captures the Motor Network. Table 12 provides a detailed description of ALE coordinates among individuals with SUDs and related conditions.

Table 12. Results of cluster-based meta-analysis among SUDs and related conditions — No-Go trails

Cluster	Brain Region	*x*	*y*	*z*	Brodmann area	*Z*	% of cluster composition	Volume (mm^3)
SUDs and related conditions > controls								
1	Anterior Cingulate	12	50	-2	10	3.94	55.2%	13832
1	Anterior Cingulate	-4	48	0	32	3.44		
1	Anterior Cingulate	6	48	-4	32	3.41		
1	Anterior Cingulate	-8	40	-4	24	3.34		
1	Anterior Cingulate	4	44	6	32	3.15		
1	Superior Frontal Gyrus	-8	62	-12	10	3.20	Medial Frontal Gyrus: 24.4% Superior Frontal Gyrus: 2.2%	
1	Medial Frontal Gyrus	-18	52	-12	10	3.11		
1	Medial Frontal Gyrus	-4	48	-16	10	3.10		
1	Caudate	-14	22	-10	Caudate Head	3.61	Caudate: 13.9% Lentiform nucleus: 2.2%	
1	Caudate	-6	26	-4	Caudate Head	3.27		

Referring to children and adolescents with ADHD, cluster-based FEW correction ($p < .05$) ALE meta-analysis highlighted a cluster composed of: i) the cingulate gyrus (56.0%) and the anterior cingulate (11.2%); ii) the medial (20.4%) and superior (3.5%) frontal gyrus; iii) the caudate (8.9%). As previously mentioned, this regions are mainly ascribed to the Mental Self Network and partially to the Motor Network. Table 13 summarizes coordinates of ALE meta-analysis.

Table 13. Results of cluster-based meta-analysis among children and adolescent with ADHD — No-Go trails

Cluster	Brain Region	*x*	*y*	*z*	Brodmann area	*Z*	% of cluster composition	Volume (mm^3)
Children and adolescents with ADHD > controls								
1	Cingulate Gyrus	2	38	20	32	3.92	Cingulate Gyrus: 56% Anterior Cingulate: 11.2%	13832
1	Cingulate Gyrus	10	30	32	32	3.44		
1	Cingulate Gyrus	2	24	30	32	3.30		
1	Cingulate Gyrus	8	6	40	24	3.34		
1	Cingulate Gyrus	12	6	48	24	3.18		
1	Cingulate Gyrus	0	4	26	24	2.78		
1	Medial Frontal Gyrus	8	18	44	6	3.66	Medial Frontal Gyrus: 20.4% Superior Frontal Gyrus: 3.5%	
1	Medial Frontal Gyrus	2	6	50	6	3.12		
1	Caudate	-10	12	18	Caudate body	4.22	8.9%	

Ultimately, the ALE meta-analysis applying the cluster-based FWE correction ($p < .05$) among adolescents with MDD highlighted 4 independent clusters: i) the cingulate gyrus (62.5%); ii) the middle occipital gyrus (22.2%); iii) the right inferior frontal gyrus (57.2%); iv) the left inferior frontal gyrus (64.9%). These clusters are mainly ascribed to the Mental Self Network, and partially to the Dorsal Attention Network, and the Exteroceptive Self Network. Table 14 reports detailed coordinates of these clusters.

Table 14. Results of cluster-based meta-analysis among adolescents with MDD — No-Go trials

Cluster	Brain Region	*x*	*y*	*z*	Brodmann area	*Z*	% of cluster composition	Volume (mm^3)
Adolescents with MDD> controls								
1	Cingulate Gyrus	15	15	42	32	3.77	Cingulate Gyrus: 62.5% Medial Frontal Gyrus: 22.9%	9824
2	Middle Occipital Gyrus	-39	-66	12	19	4.07	Middle Temporal Gyrus: 64.3% Middle Occipital Gyrus: 22.2%	9776
3	Inferior Frontal Gyrus	51	24	0	45	3.74	Inferior Frontal Gyrus: 57.2% Insula: 30.1%	8472
4	Inferior Frontal Gyrus	-48	24	-6	47	4.03	Inferior Frontal Gyrus: 64.9% Insula: 23%	8152

The ALE meta-analysis using a cluster-based FWE correction ($p < .05$) was also conducted aggregating results of studies that reported increased brain responses of HCs compared to conditions of interest for No-Go paradigms. However, the algorithm did not reveal significant brain deactivation shared by conditions of interest. Furthermore, this analysis was separately estimated for each group. Nevertheless, no significant results were found. Therefore, it could be possible to conclude that the deactivation of brain regions assuming no a priori ROIs during No-Go condition is heterogeneous across studies and conditions of interest.

Summary of main findings concerning brain networks of self-processing layers and domains of self-regulation for No-Go trails

The ROI-based network meta-analysis together with robust cluster-based ALE meta-analysis suggest the following conclusions:

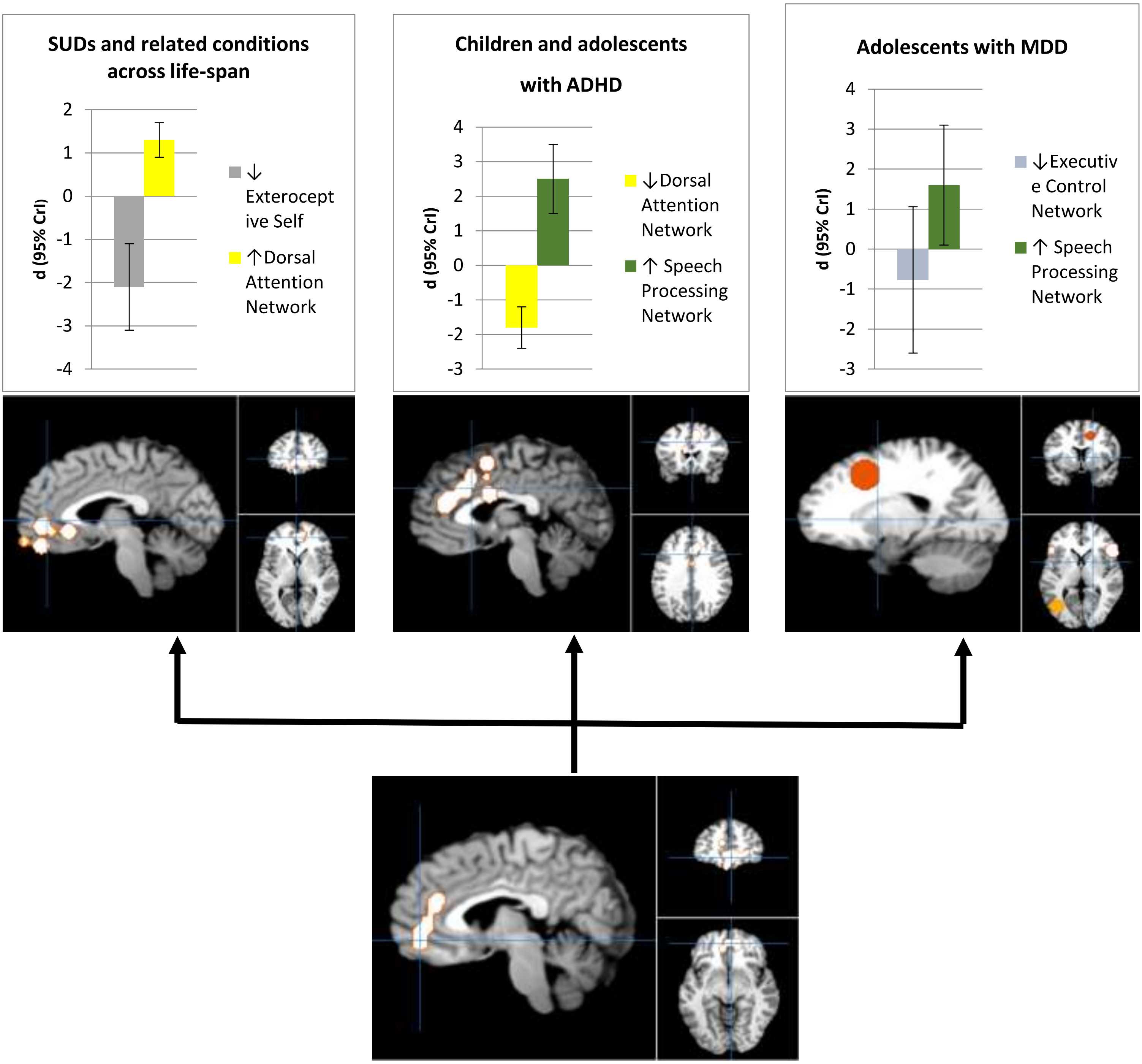
i) conditions of interest compared to HCs shared an increased activity of brain areas ascribed to the Mental Self Network during behavioral inhibition paradigm;

ii) considering each group of interest, some differences were detected. On the one hand, the Mental Self areas of individuals with SUDs and related conditions are mainly located at anterior regions, especially the ventromedial frontal areas. On the other hand, the Mental Self areas characterizing children and adolescent with ADHD were mainly captured by the anterior cingulate cortex (ACC) (Brodmann area 24). Similarly, the recruitment of the Mental Self Network for adolescents with MDD was mainly located in the ACC;

iii) interestingly, individuals with SUDs/related conditions and children/adolescents with ADHD shared an additional recruitment, albeit modest, of areas ascribed to the Motor Network. On the contrary, adolescent with MDD highlighted additional involvements of brain regions ascribed to the Exteroceptive Self Network (Broadmann area 47) and Dorsal Attention Network (Broadmann area 19);

iv) network meta-analysis showed that each group should be differentiated to each other on the base specific patterns of brain activity toward No-Go conditions linked to specific domains of self-regulation of the self-processing layers. Specifically, SUDs and related conditions across life-span are characterized by an increased recruitment of non-verbal attentional self-regulation processes in connection with a reduced activity of Exteroceptive Self Network involved in the integration of proprioceptive inputs from body with external demands and goals achievement. Children and adolescent with ADHD addressed behavioral inhibition tasks through an increased recruitment of verbal self-regulation processes (e.g., self-speech to control motor behaviors) in presence of a reduced activity of non-verbal attentional self-regulation mechanisms. Similarly, adolescents with MDD highlighted an increased involvement of the verbal domain of self-regulation in presence of a slight deactivation of the Executive Control Network.

Figure 17. Cluster-based ALE meta-analysis and ROI-based network meta-analysis for No-Go conditions



Common increased activity among conditions of interest compared to HCs

Go conditions

Table 15 reports findings of network meta-analysis conducted for Go paradigms. The nodeplist analysis demonstrated the consistency of the network composed of data from individuals with a FH^+ for SUDs and children/adolescents with ADHD. The analysis showed that the most representative brain responses for motor production among these conditions of interest were a heightened, albeit not significant, activation of the Executive Control Network (d_{pooled} = 1.40; 95% CrI: [-.19 – 2.40]; SUCRA: .81) and, a large deactivation of Dorsal Attention Network (d_{pooled} = -2.90; 95% CrI: [-4.20 – -1.50]; SUCRA: .96).

Table 15. Results of Network Meta-analysis for Go trails

Brain Network	All conditions	
	d (95% CrI) ↑ vs HCs [SUCR]	*d* (95% CrI) ↓ vs HCs (SUCRA)
Interoceptive Self	-	-
Exteroceptive Self	-	-.69 (-1.80 – .37) [.61]
Mental Self	1.10 (.53 – 2.00) [.76]	-1.40 (-2.50 – -.22) [.71]
Executive Control	**1.40 (-.19 – 2.90) [.81]**	-
Dorsal Attention	2.00 (.21 – 3.80) [.92]	**-2.90 (-4.20 – -1.50) [.96]**
Motor	1.00 (.41 – 1.90) [.74]	-1.90 (-2.90 – -.97) [.81]
Speech	1.10 (.47 – 1.90) [.75]	-2.40 (-3.70 – -1.10) [.89]

Bold: The most representative brain responses

Considering studies that reported increased activity among conditions of interest compared to HCs, the ALE meta-analysis using a cluster-based FWE correction ($p < .05$) showed a significant cluster composed of: i) precuneus (74.8%); ii) cingulate gryus (16.1%); iii) cuneus (8.4%). This brain regions are mainly ascribed to the Broadmann area 7, which plays a key role in visuo-motor coordination. Accordingly, the conditions of interest shared an increased recruitment of Motor Network within motor production experimental condition. Table 16 provides a detailed description of ALE coordinates.

Table 16. Results of cluster-based meta-analysis across samples — Go trails

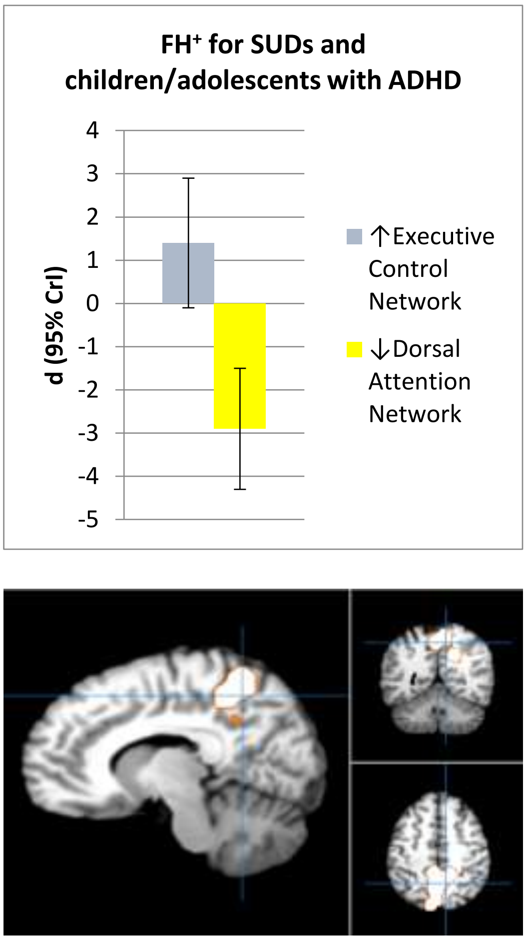
Cluster	Brain Region	*x*	*y*	*z*	Brodmann area	*Z*	% of cluster composition	Volume (mm^3)
SUDs and related conditions; children and adolescent with ADHD > controls								
1	Precuneus	-2	-58	48	7	4.26	74.8%	23184
1	Precuneus	18	-48	34	31	4.11		
1	Precuneus	-2	-70	50	7	3.66		
1	Precuneus	7	-51	54	7	2.83		
1	Cingulate Gyrus	-4	-40	48	31	3.97	16.1%	
1	Cingulate Gyrus	14	-42	46	31	3.96		
1	Cingulate Gyrus	30	-42	26	31	2.82		
1	Cuneus	-8	76	42	19	3.66	8.4%	

On the contrary, the analysis did not find significant brain regions when there were considered studies that reported increased brain responses among HCs compared to control conditions.

Summary of main findings concerning brain networks of self-processing layers and domain of self-regulation for Go trails

The ALE meta-analysis in connection with ROI-based network meta-analysis suggested that an increased activation of the Motor Network is a common feature shared by individuals with a FH^+ for SUDs and children/adolescents with ADHD for motor production tasks. Furthermore, self-regulatory mechanisms linked to motor production are associated to a decreased activity of non-verbal attentional processes. Despite these significant findings, it is needed to consider that these conclusions were based only on 3 independent studies.

Figure 18. Cluster-based ALE meta-analysis and ROI-based network meta-analysis for Go conditions



Discussion

The current study sought to investigate behavioral outcomes and spatiotemporal brain activity organization linked to self-regulation domains (Barkley, 1997, 2001) and self-processing layers (Qin et al., 2020) as key dimensions involved in clarifying developmental pathways of SUDs and related condition (i.e. binge drinking, heavy drinking) . Departing from limitations of existing quantitative meta-analysis and qualitative reviews on these topics, this work provided an existensive meta-analysis using different approaches in order to identify common a specific behavioral and neurobiological makers of altered self-regulation mechanisms across SUDs and related conditions together with the most representative psychopathological disorders during the development associated to them, namely childhood/adolescent ADHD and adolescent MDD. Referring to a well-validated neuro-psychological model of self-regulation (Barkley, 1997, 2001), the current meta-analytic work focused the attention on neuroscience studies that administered GNG tasks and SSTs that have been considered as the gold standard for the assessment of motor inhibition capabilities (Aron, 2011), and in turn the main oucome of self-regulation system (Barkley, 1997, 2001). Furthermore, it has been proposed an integration between neuro-mental self-regulatory domains with neural self-processing levels (Qin et al., 2020) in order to provide a comprehensive framework that assumes at the base of developmental pathways of SUDs and related conditions alterations of self organization across the life-span and its manifestations through impaired self-regulatory processes.

The current extensive meta-analytic work highlighted 3 main findings:

i) looking at behavioral outcomes, conditions (i.e., child/adolescent ADHD, adolescent MDD) constituting developmental pathways of SUDs and related conditions showed slower reaction times within No-Go and Go trails compared to HCs. Error rates and related mechanisms were significantly more impaired than alterations linked to reaction times, and they were associated to specific stages of development and psychopathological domains. Particularly, it was identified a continuum where children and adolescents with ADHD showed the worst performances followed by adult individuals with SUDs and relaed conditions (externalizing spectrum). Adolescents with MDD did not highlight significant impairments (internalizing spectrum);

ii) referring to a temporal organization of brain activity, all conditions of interest shared a decreased of frontal N2 response together with reduced central and parietal P3 waves for both No-Go and Go trials;

iii) considering fMRI results, increased responses to motor inhibition conditions (i.e., No-Go trials) of VMPFC and the rostral part of dorsal ACC ascribed to the mental-self layer (Qin et al., 2020) represented the common neural markers of developmental psychopathology conditions linked to SUDs and related conditions. Nevertheless, results highlighted that self-regulation subsystems involved in response inhibition differentiated these psychopathological conditions from each other. This differentiation among conditions of interest was also replicated referring to specific portions of mental self layer.

The current meta-analytic results showed that slower reaction times during No-Go and Go trials were consistent among conditions contistituing developmental pathways of SUDs. Slower reaction times during motor inhibition tasks has been viewed as alterations of motor preparation mechanisms (Wright et al., 2014) and, several studies consistently found these features among individuals with ADHD (e.g., Gorman Bozorgpour et al., 2013; McLoughlin et al., 2010), MDD (e.g., Aker et al., 2016; Gerber et al., 2023; Sommerfeldt et al., 2016), SUDs (e.g., Cavicchioli et al., 2022a) and related conditions (Paz et al., 2018) across the life-span. Taken together this evidence with the relevance of motor behaviors development for adaptive evolutions of perceptual, cognitive and social abilities during the life-span, especially during the infancy (Adolph & Franchak, 2017), it could be possible to conclude that an alterated organization of motor preparation should be viewed as an early and stable marker of alterated self-regulatory mechanisms associated to homotypic and heterotypic developmental pathways of SUDs and related conditions. Nevertheless, future longitudinal studies should empirically test the predictive value of early (e.g., infancy) alterations of motor organization mechanisms for subsequent externalizing and internalizing psychopathological manifestations across the childhood and the adolescence, and their implications for the onset of problematic-use behaviors and SUDs throughout the adulthood.

The analyses demonstrated that error rates (i.e., commission and omission rates) highlighted significantly larger effect sizes than reaction times and related alterations of motor preparation mechanisms. Accordingly, it could be possible to sustain that alterations of motor execution (Lee et al., 1999; Theios, 1975) should be considered as the most representative behavioral marker among conditions constituting developmental pathways of SUDs and related conditions. This different degree of impairment concerning to two distinct, albeit interrelated, self-regulatory mechanisms is not fully surprising. Indeed, the meta-analytic review conducted by Wright and colleagues (2014) showed larger effect sizes for error rates than reaction times across different psychopathological conditions, especially considering externalizing psychopathology. These results are fully in line with the significant moderating effect of specific conditions of interest found in the current meta-analysis. Particularly, children and adolescent with ADHD highlighted the worst performances compared to adult individuals with SUDs and related conditions. On the contrary, no significant differences were found between performances of adolescents with MDD and HCs. Taken together current meta-analytic results concerning reaction times and error rates, it could be possible to further sustain that alterations of motor preparation represent a common, albeit modest, factor associated to homotypic and heterotypic developmental trajectories of SUDs and related conditions. Accordingly, it might represent an aspecific vulnerability dimension for the onset of different psychopathological conditions (Gale et al., 2016). On the contrary, impairments of motor finalization due to inabilities to refrain prepotent responses (i.e., commission errors) and to maintain the focus of attention on goal-oriented behaviors (i.e., omission errors) might be the core latent mechanism at the base of homotypic continuity from childhood and adolescent ADHD to SUDs and other problematic substance-use behaviors during the adulthood. Nevertheless, the current results also supported the hypothesis that deficits in motor finalization might improve from childhood to middle adulthood, as demonstrated by the significant lower pooled effect size of adults with SUDs and related conditions compared to children and adolescent with ADHD. This could reflect well-supported development trajectories of inhibitory control capabilities that linearly increase from infancy to early adulthood, and subsequently decline with senescence (Motes et al., 2018).

The behavioral results suggesting differential alterations of self-regulation mechanisms (i.e., motor preparation and finalization) associated to homotypic and heterotypic developmental pathways of SUDs and related conditions were supported by meta-analytic findings concerning temporal organization of brain responses toward behavioral inhibition tasks. Specifically, conditions of interest shared significant decreased frontal N2 and centro-parietal P3 responses compared to HCs, considering both motor inhibition (No-Go trials) and execution (Go trials) experimental demands. It has been extensively discussed that the N2 among adult individuals mainly reflects a basic process of brain and mind during behavioral inhibition tasks, namely conflict monitoring and mismatch detection (Albert et al., 2013, 2010; Groom & Cragg, 2015). On the contrary, the N2 also plays a relevant role in motor inhibition, especially during the childhood (Johnstone et al., 2007). Precisely, the frontal N2 was specifically associated to error detection, processing of stimuli probability, intentional cognitive control and premotor organization processes (Hajihosseini & Holroyd, 2013; Huster et al., 2013; Sutton & Barto, 1998). Taken the current meta-analytic results with the previous well-supported evidence concerning the role of N2 within motor inhibition tasks, it could be possible to sustain that early neurophysiological frontal responses, referring to the time-domain of brain activity organization, should be considered a stable dimension linked to homotypic and heterotypic developmental pathways to adult SUDs and related conditions. Therefore, early alterations of neurophysilogical responses linked to error detection and action program organization might be considered as relevant risk factors for the onset of externalizing and internalizing developmental psychopathology, and their maintenance from childhood to adolescence. These neuro-mental mechanisms might also represent significant factors that increase the probability to develop problematic substance-use behaviors and SUDs during the adulthood. Looking at the P3, several empirical studies highlighted distinct functions of this ERP compared to the N2 within response inhibition tasks. Specifically, it has been demonstrated that the P3 reflects two basic neuro-mental mechanisms involved in self-regulation of behaviors, namely the intentional deployment of attention on task (Kirmizi-Alsan et al., 2006) and motor finalization (Albert et al., 2010, 2013). Specifically, the current findings highlighted reduced amplitudes of P3 with central and parietal localizations. Referring to this evidence, Polich (2007) suggested an interesting distinction of the P3 implications for self-regulatory mechanisms taking into account its topographical localizations. Particularly, frontal-central P3 activity mainly captures attentional mechanisms on stimuli, especially related to detection of target stimuli from distracters. Whereas, parietal P3 activity seems to be related to memory storage, and it promotes memory operations on target stimuli. The P3 and related mechanisms have been associated to a basic function of brain and mind, namely the inhibition of non-pertinent brain activation (e.g., spontaneous and/or distracter-related) during task execution (Polich, 2007). Therefore, the reduced P3 waves found in the current meta-analysis for both No-Go and Go trials, which are shared among all conditions of interest throughout different stages of development, might suggest basic deficits with inhibitory processes that are manifested as alterations of the ability to intentionally maintain the attention on target stimuli due to ineffective inhibition of internal and external distracters. This could further affect memory operations and storage of target stimuli, and in turn induce detrimental effects on update of contextual information needed to effectively respond to environmental demands. Hence, these patterns of altered self-regulatory mechanisms might represent common latent dimensions associated to homotypic and heterotypic developmental pathways to SUDs and related conditions across the life-span.

Taken together behavioral outcomes and N2/P3 complex findings, it could be possible to conclude that:

i) homotypic and heterotypic developmental pathways to SUDs and related conditions are sustained by altered basic processes of brain and mind involved in self-regulation of motor actions: a) conflict monitoring and mismatch detection (i.e., reduced frontal N2) together with motor preparation (i.e., reduced frontal N2, behavioral outcomes: slower RTs); b) inhibition of internal and external non-pertinent sources with task demands, which are reflected in difficulties with continuous attention on task due to altered discrimination of target from non-target stimuli (i.e., reduced central P3) and update of contextual information for the implementation of effective motor responses (i.e., reduced parietal P3);

ii) the homotypic externalizing pathway characterized by child/adolescent ADHD and subsequent SUDs and/or related conditions might be mainly related to problems with motor finalization (i.e., higher error rates for these groups relative to adolescent MDD).

Departing from robust voxel-based findings of ALE meta-analysis, the results showed an increased activity of the VMPFC and the rostral part of dorsal ACC during motor inhibition trails among children/adolescent with ADHD, adolescent with MDD together with individuals with SUDs and related conditions across the life-span compared to HCs. According to Qin and colleagues (2020), the regions found by the ALE algorithm fully overlaps with the mental self layer that capture areas involved in processing the degree of self-relatedness at a cognitive level of abstract external stimuli. Referring to the concept of self-relatedness, an increased activity of VMPFC has been consistently associated to the processing of personal value or relevance of a given stimuli (e.g., D'Argembeau, 2013; Moore III et al., 2014; Yin et al., 2021). Consistently, the current meta-analytic findings concerning the implication of VMPFC during motor inhibition tasks might suggest two main conclusions:

a) motor inhibition has a high personal value or relevance across the life-span for all conditions constituting developmental pathways of SUDs and related conditions. Therefore, motor disinhibition, and in turn self-regulation, might be considered a key feature of different developmental trajectories to SUDs and related conditions;
b) the increased response of VMPFC toward No-Go trails might also indicate that motor inhibition represents an intense subjective effort (Hogan et al., 2019; Pardini et al., 2010) across different stages of development for all conditions of interest constituting homotypic and heterotypic pathways to SUDs and related conditions compared to HCs. This should be in line with theoretical frameworks that view behavioral dysregulation as a result of *ego depletion* (Baumeister, 2002; Baumeister & Vohs, 2007). Specifically, the high subjective effort to intentionally inhibit prepotent motor actions dramatically reduces the limited cognitive and affective resources of self-regulation, and in turn increasing the probability to engage in automatic, non-voluntary conditioned behaviors (Baumeister, 2003; Hofmann, et al., 2012).

The ACC has been associated to several cognitive and affective processes (for a reviews see: Botvinick et al., 2004; Bush et al., 2000; Devinsky et al., 1995). Referring to the ventral AAC and the rostral part of dorsal AAC, several empirical findings have demonstrated that these portions of AAC are involved in the processing of emotional salience of stimuli together with the regulation of emotional responses (Bush et al., 2000). This evidence provides an additional support for considerations concerning the high self-relevance of motor inhibition demands across the life-span for individuals affected from conditions constituting the different development pathways to SUDs. Furthermore, the recruitment of the affective division of ACC during motor inhibition tasks might suggest that these kinds of demands are mainly processed as emotional information rather than pure cognitive one by individuals included in the developmental trajectories of SUDs and related conditions. On the contrary, a huge amount of fMRI studies has demonstrated that healthy populations specifically recruit cognitive-motor networks, rather than emotional ones, during motor inhibition trials (for meta-analytic reviews see: Criaud, & Boulinguez, 2013; Simmonds et al., 2008). Therefore, the current meta-analytic results might further suggest that individuals constituting developmental pathways to SUDs and related conditions share an imbalanced *hot* executive functioning linked to cognitions guided by emotional, motivational and rewarding features (Salehinejad et al., 2021), which is particularly manifested when subjects must address pure cognitive motor inhibition tasks, which should mainly recruit *cold* executive systems based on attentional control, inhibition, error detection, and working memory.

However, the results of the current meta-analysis highlighted a more complex scenario. Indeed, the ALE meta-analysis separately conducted for each subgroup associated to specific stages of development (i.e., SUDs and related conditions: mainly adulthood; ADHD: childhood and adolescence; MDD: adolescence) showed that they were differentiated by specific brain responses toward motor inhibition trails. Precisely, adults with SUDs and related conditions showed an increased responsiveness of VMPFC/orbitofrontal cortex (OFC) and subgenual ACC. Children and adolescents with ADHD highlighted a heightened activity of dorsal ACC and supplementary motor areas during motor inhibition tasks. Adolescents with MDD were characterized a hyper-reactivity of a smaller portion of dorsal ACC compared to ADHD individuals and supplementary motor areas together with a recruitment of bilateral inferior frontal gyrus.

Referring to the previous robust voxel-based findings, some considerations might be discussed concerning developmental trajectories of brain networks involved in self-regulation among conditions of interest. Specifically, Constantinidis and Luna (2019) have been supported a typical maturation of neural networks involved in motor inhibition, which is characterized by a linear decrease of DLPFC activity from childhood/adolescence to adulthood. This might reflect that motor inhibition demands are supported by high-cognitive-load verbally-based control mechanisms during the first stages of development, which progressively decrease with the maturation. Whereas, the authors have sustained a positive linear recruitment from adolescence to adulthood of the dorsal ACC (i.e., non-verbal attentional control) together with an extended network associated to self-regulation (e.g., frontal eye field, inferior frontal gyrus, insula), which facilitates the effective integration between internal signals and external demands, for the inhibition of motor actions. Looking at the current data, it could be possible to suggest an atypical developmental trajectories of brain networks involved in self-regulation among conditions of interest constituting homotypic and heterotypic pathways to adult SUDs and related problems. Specifically, children and adolescent affected from externalizing and internalizing problems, compared to age-matched HCs, might be characterized by an altered brain organization for addressing motor inhibition tasks, which is laid on an immature functioning of the dorsal ACC. With the maturation and the development of substance-related externalizing problems during the adulthood, there is a progressive change of brain organization for modulating behaviors that is mainly guided by a hyper-reactivity of affective/mental self areas (i.e., VMPFC and subgenual ACC), rather than an extended brain network linked to *cold* self-regulation processes. This might support the altered and worst behavioral performances found among conditions of interest across the life-span.

Nevertheless, the differential recruitment of brain networks identified for each subgroup might also reflect specific clinical features characterizing these conditions. Indeed, some fMRI studies highlighted that inattention and hyperactivity symptoms among children and adolescence with ADHD were associated to altered functioning of the dorsal ACC and supplementary motos areas (e.g., Fassbender et al., 2015; Damiani et al., 2021). Similarly, empirical research has also highlighted relevant implications of insula (for a review see: Sliz & Hayley, 2012), inferior frontal gyrus (e.g., Rolls et al., 2020; Su et al., 2018) and dorsal ACC (Dedovic et al., 2016; Ho et al., 2017) for MDD psychopathological manifestations. Referring to adult individuals with SUDs and related conditions, the role of subgenual ACC has been consistently associations with a core psychopathological feature of these clinical problems, namely craving for substance use (Kobo & Volker, 2016). Moreover, neuroscience research has consistently demonstrated a key role of VMPFC and OFC for addiction pathology. Indeed, activity of VMPFC/OFC has been associated to craving, especially referring to the processing of rewarding values of a given stimulus directly or indirectly associated to substance use (George & Koob, 2013; Sinha,2013), and relapse in addictive behaviors (Seo et al., 2013; Moeller & Paulus, 2018). The central role of VMPFC/OFC for addiction has been also discussed by authors who have proposed a *somatic maker* model of this clinical condition (Olsen et al., 2015; Verdejo-García, A., & Bechara, 2009; Verdejo-Garcia et al., 2006). Accordingly, the VMPFC and OFC are involved in explaining deficits in decision-making, which represent a key dimension characterzing the maladaptive functioning of individuals with SUDs (Schoenbaum et al., 2006; Verdejo-Garcia et al., 2018) and related problems (e.g., binge drinking; Lees et al., 2019).

Distinct profiles of neural underpinnings of self-regulation among conditions of interest were also supported by results of network meta-analysis. Specifically, the analyses found that the most representative brain responses to motor inhibition trials in terms of the extent of pooled effect size among children and adolescents with ADHD were a large increased activation of areas ascribed to the *speech to the self* domain of self-regulation (i.e., superior and middle temporal gyrus) together with a large reduced activation of areas included in the dorsal attention network (i.e., intraparietal sulcus and posterior parietal cortex) associated to the *sensing to the self* self-regulation subsystem. Adolescents with MDD were also characterized by large increased responses of the brain network associated to the *speech to the self*. On the contrary, adult individuals with SUDs and related conditions were characterized by a large activation of dorsal attention network, and in turn a recruitment of the *sensing to the self* domain, during motor inhibition trials together with a reduced activity of areas ascribed to the exteroceptive self layer (i.e., right inferior frontal gyrus, temporo-parietal junction, fusiform gyrus).

These findings could further corroborate considerations previously provided concerning an atypical development of brain networks involved in self-regulation among conditions identifying homotypic and heterotypic developmental pathways to SUDs and related problems. Contrary to a typical recruitment of working memory-related brain networks for motor inhibition during the childhood and adolescence, children and adolescents with externalizing and internalizing problems attempt to refrain their motor responses organizing their brain acitivity around networks involved in inner speech (Langland-Hassan, 2021) and sematic processing (Hickok & Poeppel, 2007). On the one hand, theoretical frameworks (Cerutti, 1989; Hayes, 1989; Skinner, 1953) have been discussed the adaptive implications of internalization of speech for regulating behaviors during the development, especially considering the childhood. On the other hand, it has been also demonstrated that verbally-based cognitive processes represent the mental activity characterized by the highest effort (Carruthers, 2002; Ellis, 2019). Accordingly, the fact that children and adolescent with externalizing and internalizing problems seem to process motor tasks at a verbal high-cognitive-load level might further support the hypothesis that behavioral inhibition represents a critical demand for these populations compared to typically developing controls. This could increase the probability of ego depletion states and related difficulties with effective behavioral regulation (e.g., motor inhibition and organization). Moreover, the significant reduced activation of dorsal attention network found among children and adolescents with ADHD is consistent with empirical studies that showed the implications of this network for core clinical features of this condition (e.g., inattention symptoms due to failures to ignore extraneous stimuli)

(Castellanos & Proal, 2012). Indeed, the dorsal attention network is involved in self-regulation of spatial attention by selecting sensory stimuli based on self-relevant goals, expectations and related motor programs needed to achieve them (Fox et al., 2006). This finding might provide a neurobiological support for behavioral outcomes highlighted in the current meta-analysis that showed how children and adolescents with ADHD were characterized by the worst behavioral performances (i.e., error rates) compared to the other conditions. Looking at results of adults with SUDs and related problems, it could be possible to suggest a progressive reorganization of brain networks involved in self-regulation. Specifically, motor inhibition demands seemed to elicit heightened responses of the dorsal attention network in presence of a reduced activity areas of exteroceptive network (e.g., inferior frontal gyrus), which show some overlaps with the motor network. Accordingly, it could be possible to suggest that individuals with an atypical development progressively change their self-regulation of behaviors from verbally-based mechanisms during childhood and adolescence to attentional-based ones without a support of networks regulating the relationships between the individual and external environments (i.e., exteropective self layers; inferior frontal gyrus). This might affect the effectiveness of dorsal attention network involved in the implementation of motor programs (e.g., Papadelis et al., 2016; Verbruggen et al., 2010) and/or inhibition of response tendencies (for a review see: Aron et al., 2014). On the contrary, it has been consistently demonstrated that adults characterized by a typical development of self-regulatory mechanisms of behaviors show positive functional relationships among attentional and motor networks, which support effective performances within several inhibition tasks (Dambacher et al., 2014; Duann et al., 2009; Hirose et al., 2012). These considerations might also provide a support for the current meta-analytic results of behavioral outcomes that showed higher error rates within response inhibition tasks among individuals with SUDs and related problems compared to HCs. Ultimately, a hyper-reactivity of areas ascribed to the dorsal attention network play a role in supporting attentional biases toward substance-use (for a meta-analysis see: Hanlon et al., 2014), which represent an additional key clinical feature of SUDs (Field et al., 2014). Similarly, a hypo-activation of inferior frontal gyrus, which is included in the exteroceptive self layer, has been associated to the loss of control on substance-use behaviors and relapse in addictive behaviors (for a review see: Goldstein et al., 2011) representing the most relevant clinical feature of SUDs.

In conclusion, the current meta-analytic results concerning behavioral outcomes and spatiotemporal brain activity linked to self-processing layers and self-regulation mechanisms suggested 3 main considerations:

i) the developmental continuity from childhood/adolescent externalizing (i.e., ADHD) and internalizing (i.e., MDD) conditions to subsequent SUDs and related problems might be viewed in the light of stable alterations of motor preparation (i.e., slow RTs) and finalization (i.e., higher error rates) linked to early brain responses (i.e, reduced N2 and P3) involved in the inhibition of internal (i.e., increased activity default mode network/mental self layer) and external not-pertinent information with the resolution of pure cognitive-motor demands;

ii) the maladaptive homotypic and heterotypic developmental trajectories of psychopathological manifestations studied in the current work might reflect atypical development pathways of brain networks (mental self layer, exteroceptive layer, inner speech processing network, dorsal attention network), which sustain self-regulatory mechanisms characterized by high-cognitive load and effort. This might increase the probability of ego depletion states linked to behavioral dyscontrol and poor adjustment;

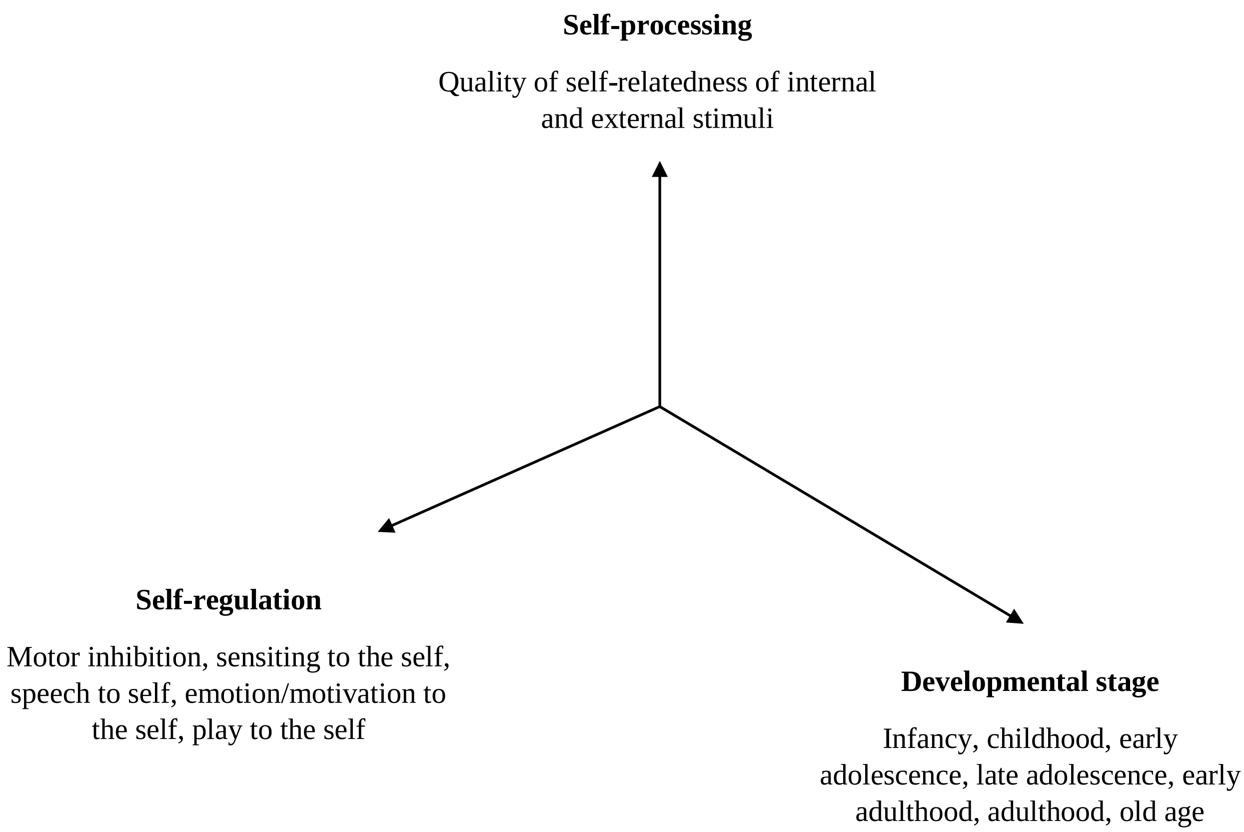
iii) clinical manifestations of each disorder could be captured by specific patterns of neural activity linked to self-processing and self-regulation subsystems.

Despite these findings, some limitations must be discussed. The first limitation refers to the cross-sectional nature of data meta-analyzed. On the one hand, the current meta-analytic results found common neuro-behavioral markers of altered self-regulatory mechanisms among different externalizing and internalizing conditions across the life-span suggesting how these dimensions might be involved in their developmental continuity well-demonstrated in several longitudinal studies. On the other hand, the case-control quality of studies included for meta-analytic procedures did not allow to definitely conclude that self-regulation mechanisms and related neuro-mental processes could explain the transactions from childhood and adolescent clinical conditions to subsequent SUDs and related problems. Therefore, future longitudinal neuroscience studies should be carried to empirically demonstrate the considerations sustained in the current meta-analytic work. The lack of longitudinal data represented an additional limitation in order to support the hypotheses previously discussed concerning an altered maturation and organization of brain networks linked to self-processing and self-regulation among individuals with a psychopathological development compared to age-matched controls. The few number of studies (i.e., 4 fMRI studies; 1 EEG study) that evaluated adolescents with MDD was a further limitation of generalization of the current result to this population, especially considering conclusion regarding behavioral outcome and related neurophysiological responses. Hence, future neuroscience research should be conducted in order to clarify self-regulation mechanisms of this growing clinical population (Shorey et al., 2022), and how they could predict the progression to subsequent externalizing conditions including SUDs (e.g., McCarty et al., 2013; Sihvola et al., 2008). Limitations concerning the generalization of the current results to all conditions constituting developmental pathways to SUDs were also related to the absence of neuroscience studies that evaluated self-regulation mechanisms among children and adolescents with ODD and CD administering motor inhibition tasks. This aspect is particularly relevant taking into account the fact that these externalizing conditions are the most robust developmental psychopathology predictors of SUDs and problematic substance-use during the late adolescence and adulthood (e.g., Colder et al., 2018; Scalco et al., 2014). Accordingly, future neuroscience research is needed in order to replicate the alterations of self and self-regulation neuro-mental mechanisms found in the current work among children and adolescents with ODD and CD. Moreover, longitudinal neuroscience studies should demonstrate how neural markers of self and self-regulation could predict the onset and progression of substance use behaviors among this externalizing population. It was not also possible to systematically control the effects of ODD/CD diagnoses among studies including children and adolescents with ADHD, even though several studies have well demonstrated high rates of comorbity among these developmental clinical conditions (Frick & Nigg, 2012). Specifically, it was detected a large inconsistency within studies considered for the current meta-analysis regarding a systematic assessment of this clinical aspect. Additional limitations referred to no significant findings of voxel-based ALE meta-analysis regarding increased brain responses of HC subjects compared to psychopathological conditions of interest in response to No-Go trials. On the one hand, this result might suggest that the hypothesis of hypoactivation of brain areas involved in self-regulation at the base of behavioral disinhibition of condition of interests is not consistent enough across studies. On the other hand, this inconsistency could be linked to the large clinical heterogeneity of children and adolescent ADHD (Luo et al., 2019), adolescent MDD (Chahal et al., 2020), SUDs (Carroll, 2021) and related conditions (e.g., binge drinking: Lannoy et al., 2017;

Lightowlers, 2017), which was not possible to systematically and precisely control within meta-analytic procedures. Consistently, future neuroscience research on motor inhibition should systematically take into account this clinical heterogeneity in order to effectively test for which subgroups of patients the hypothesis of hypoactivation could be verified. An additional source of possible heterogeneity could be the experimental control conditions for the evaluation of brain responses related to motor inhibition/disinhibition (e.g., No-Go vs baseline; No-Go vs Go; error No-Go vs correct No-Go). According to the few number of studies for each experimental design used for the assessment of neural underpinnings associated to self-regulation of behaviors, this aspect significantly affected the power of analysis, and in turn it was not possible to control in the voxel-based ALE meta-analysis. Therefore, it is possible to hypothesize that hypoactivation of brain regions involved in self-regulation of conditions constituting the developmental pathways of SUDs and related problems compared to HCs might be associated to specific methodological issues, which could reflect different mechanisms linked to motor inhibition. Ultimately, another limitation referred to the few number of studies (N = 3) that provided results of brain activity among children and adolescents with ADHD together with young subjects with a FH^+ for SUDs in response to Go trial, and in turn neural mechanisms involved in motor execution. Specifically, the current provisional findings showed that the previous groups compared to HCs highlighted an increased activity of a portion of the precenus associated to visuo-motor coordination (Li et al., 2021). The precuneus is also key region of mental self-processing layer (Qin et al., 2020). Accordingly, these findings might be in line with behavioral and neurophysiological results highlighted in the current work that supported alterations of self-regulatory processes also in experimental conditions requiring motor execution. Furthermore, the hyper-reactivity of precuneus might suggest the high self-relevance and personal/mental effort for these developmental conditions the implementation of actions to achieve a given goal. On the one hand, this considerantion might be fully in line with the conclusion reported for more robust data linked to motor inhibition. On the other hand, future neuroscience on self-regulation and its implications for different conditions developmentally associated to SUDs and related problems should systematically focus on both inhibition and execution of goal-oriented behaviors in order to comprehensively clarify specific alterations such mechanisms and their relation with self-processing layers.

Nevertheless, this is the first study that highlights specific neuro-behavioral alterations linked to self-processing and self-regulation mechanism associated to homotypic and heterotypic developmental pathways to SUDs and related problems. Accordingly, these neuro-behavioral markers should be considered early risk factors for the development of externalizing and internalizing problems during the childhood and adolescence, and subsequently for substance-use related problems during the adulthood. Furthemore, mechanisms linked to self-processing and specific self-regulation processes identified for each condition shoud be considered as key targets of clinical interventions, independently of theoretical approach. Furthermore, prevention programs for SUDs should be developed focusing on the improvement of self-processing and self-regulation mechanisms in order to reduce the probability of the onset of substance-use behaviors during the late adolescent and early adulthood. Ultimately, the current work lays the foundations for future conceptualizations of externalinzing and internalizing psychopathology on the base of different profiles reflecting the interactions between self-processig layers and self-regulation subsystems, also taking into account specific stages of individual development (see figure 19 for a graphical summary).

Figure 19. A proposal for a new conceptualization of psychopathology



Materials and Methods

Criteria for selecting studies

This meta-analysis was conducted referring to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Moher et al., 2009; Page et al., 2020). Figure 12 shows the flow chart for the inclusion of studies. The analysis considered studies published in scientific journals in order to support their quality. Scopus, PubMed, PsychINFo, ISI Web of Knowledge, and online databases were used for the research.

According to theoretical backgrounds discussed in the Introduction section together with results of ancillary studies conducted during the 3-year Ph.D. program, the online research included the following keywords reported in tables 17 and 18.

Table 17. Keywords of online research for SUDs and related conditions

Condition of interests		Tasks		Data collection procedures
"substance use disorder", "alcohol use disorder", "cannabis use disorder", "cocaine use disorder", "heroin use disorder", "amphetamine use disorder", "stimulant use disorder", "hallucinogen use disorder"	AND	"go/no-go task" , "go/no-go", "go/no go", "gnat"	AND	"fmri", "functional magnetic resonance imaging", "brain imaging", "neuroimaging"
		"stop signal task", "stop signal", "sst"		"electroencephalography or electroencephalogram or eeg", "event related potential"

Table 18. Keywords of online research for child and adolescent conditions

Condition of interests		Age		Tasks		Data collection procedures
"adhd","attention deficit hyperactivity disorder", "attention deficit-hyperactivity disorder"	AND	"child*"	AND	"go/no-go task" , "go/no-go", "go/no go", "gnat"	AND	"fmri", "functional magnetic resonance imaging", "brain imaging", "neuroimaging"
		"adolesc*"				
"major depressive disorder", "mdd", "major depression"	AND	"child*"				
		"adolesc*"				

“oppositional defiant disorder”,“oppositional defiance disorder”, “oppositional disorder”, “odd”	AND	“child*”	“stop signal task”, “stop signal”, “sst”	“electroencephalography or electroencephalogram or eeg”, “event related potential”
		“adolesc*”		
“conduct disorder”,“conduct problem”, “cd”	AND	“child*”		
		“adolesc*”		

The key words were included within each database. Marco Cavicchioli (M.C.) and Professor Anna Ogliari (A.O.) conducted the online research. A reliable initial sample of articles was guaranteed through a double-checked screening process. M.C. and A.O. focused the screening process departing from articles that showed, within the abstract section, at least the administration of a behavioral inhibition task among conditions of interest collecting fMRI or EEG data. Cohen *k* inter-rater reliability index (Cohen, 1960) was calculated for the studies selected.

In order to be included in the current work, the studies met the following inclusion criteria to support the validity and reliability of findings:

1) all studies should assess clinical conditions (i.e., SUDs, ADHD, ODD, CD, MDD) referring to valid and reliable diagnostic criteria (i.e., *Diagnostic and Statistical Manual of Mental Disorders*, *International Classification of Diseases*);
2) different SUDs have been included according to common neurobiological mechanisms of addiction that are shared by all substance-related and addictive disorders (Koob & Volkow; 2016).
3) problematic alcohol use should be evaluated through the administration of valid and reliable assessment instruments or by the application of well-recognized criteria (i.e., binge drinking: National Institute on Alcohol Abuse and Alcoholism, 2004; heavy drinking: Hedden, 2015). The inclusion of individuals with a problematic alcohol use was supported by the dimensional nature of AUD and related conditions considering phenomenological (e.g.,Borges et al., 2010;Kerridge et al., 2013; Watts et al., 2021) and neurobiological (e.g., Dager et al., 2014; King et al., 2016; Lejuez et al., 2010) evidence;
4) the FH^+ for SUDs should be assessed with valid and reliable assessment procedures. This was chosen according to empirical findings that highlighted

overlapping alterations of brain activity between patients with SUDs and individuals with a FH^+ for SUDs (Cavicchioli et al., 2023a)

5) individuals with ADHD, MDD, ODD and CD should be 18-year old or younger;
6) all studies should administer GNG or SST paradigm, according to the consensus in considering them as the gold standard for a valid and reliable assessment of motor inhibition capabilities (Aron, 2011), and in turn self-regulation processes.On the one hand, continuous performance and sustained attention to response tasks have been ascribed to the umbrella of "Go/No-Go" experimental paradigms (Wright et al., 2014). These tasks were not included due to the fact that they mainly capture self-regulation of attention abilities rather than motor inhibition mechanisms (Clark et al., 2023; Testa et al., 2012)

Studies that evaluated the *in vivo* effects of substance use on behavioral performances were excluded. On the contrary, gender was not considered as an exclusion criterion of the current meta-analysis.

Data analysis

The Cohen's *d* (Cohen, 1988) and its standard error (SE) was used as an effect size (ES) index. Cohen's *d* greater than or equal to 0.20, 0.50, and 0.80 were interpreted as small, moderate, and large ESs, respectively (Cohen, 1988). Descriptive statistics reported in the Results section were used to estimat ESs. Moreover, procedures incaduted by Borenstein, and colleagues (2011) and Wolf (1986) were used to convert *t* and *z* values together with the *r* coefficient into *d* index when descriptive statistics were not available. The toolbox included in the SDM (https://www.sdmproject.com/) (Albajes-Eizagirre et al., 2019) was also adopted to convert the previous indexes to *d*. This work was based on the application of three different meta-analytic procedures, namely: i) multi-level meta-analysis; ii) network meta-analysis using a Bayesian hierarchical framework; iii) robust coordinates-based meta-analysis (ALE meta-analysis).

Multi-level meta-analysis

According to the data structure, the multi-level approach was adopted to analyze findings related to behavioral performances and neurophysiological responses. The multilevel meta-analytic procedures were supported by the {metafor} *R* package. This allowed to to estimate pooled ESs (d_{pooled}) controlling for interrelationships among multiple ESs calculated within the same study (Viechtbauer, 2010). The estimation of model parameters was based on the restricted maximum likelihood method (Harrer et al., 2021). The 3-level meta-analysis posited that ESs (level 2) were aggregated within clusters composed of each study (level 3).

The *Q* statistic (Hedges & Olkin, 1985) and multi-level I^2 index (Cheung, 2014) were estimatated in order to evaluate the heterogeneity in ESs. According to the multi-level version of I^2 index, the total heterogeneity was splitted into a within- (i.e. level 2) and between-study (level 3) variability. Following a multi-level approach, the Akaike (AIC) and Bayesian Information Criterion (BIC) indexes were used to compare the fit to data of the 2-level with the 3-level model through the application of a likelihood ratio test (LRT).

Three level mixed-effect meta-regressions were computed in order to test the impact of several variables on ESs. Referring to behavioral data (i.e., RTs, error rates, correct response rates), there were evaluated moderating effects of the following variables: i) data collection procedures (i.e., EEG vs fMRI); ii) year of publication; iii) sample size; iv) gender (i.e., males + females vs females vs males); v) age; vi) sample characteristics (i.e., SUDs and related conditions across the life-span; children and adolescents with ADHD, adolescents with MDD); vii) task (i.e., GNG vs SST); viii) % Go trials; ix) length of stimuli presentation (ms); x) length of interstimulus interval (ms). With respect to error rates, it was also evaluated the impact of error type (i.e., commission + omission errors vs commission errors vs omission errors).

Looking at neurophysiological data, in addition to the previously mentioned moderating variables excluding the data collection procedures factor, it was evaluated the effects of specific ERPs for both negative (i.e., N100 vs N170 vs N200) and positive (i.e., P100 vs P200 vs P300 vs late positive waves) waves together with possible impacts of experimental conditions (i.e., Go vs No-Go) on ESs.

Publication bias was tested using Egger’s regression (Egger et al., 1997). Bootstrap procedures (Davison & Hinkley, 1997) were applied for the estimation of the significance Egger’s regression parameters.

According to the fact that behavioral indexes reflect different self-regulatory mechanisms of behaviors (i.e., RTs: motor preparation; error rates: motor inhibition; correct response rates: motor production) (Wright et al., 2014), Z-test procedures (Borenstein et al., 2011) were applied to constrast the extent of pooled ESs of these domains to each other. These procedures were applied in order to assess which of these domains of behavioral self-regulation could be considered as a core feature of conditions of interest. Bonferroni correction was applied in presence of multiple comparisons.

Bayesian network meta-analysis

A Bayesian hierarchical network meta-analysis was applied for the ROI-based approach related to fMRI data. The {gemtc} *R* package (Valkenhoef et al., 2012) was used to estimate the pooled ES for each brain network associated to the self layers and domain of self-regulation. The choice of prior distributions, which represents core aspect of Bayesian inference, is automated by the The {gemtc} R package (Valkenhoef et al., 2012). The posterior distributions of estimated parameters were calcuted through Markov Chain Monte Carlo simulation. This allowed to estimate the d_{pooled} and its 95% credible interval (CrI). A random-effect model was applied. The {gemtc} *R* package used *d* and related SE to estimate the network meta-analysis. The Cohen *d* reflects the extent of difference of neural response between conditions of interest (i.e., SUDs and related conditions, children and adolescents with ADHD, adolescents with MDD) and HCs within No-Go and Go trails.

The nodesplit method (Dias et al., 2010) was adopted in order to assess the inconsistency of results within the network, which is represented by one or more significant differences between estimates based on direct and indirect evidence. In presence of inconsistency, separate network meta-analyses for each condition of interest were conducted.

The Surface Under the Cumulative Ranking (SUCRA) score (Salanti et al., 2014) was calculated to highlight which brain brain network of self layers and domains of self-regulation could be the most representative for all conditions and for each specific population. The SUCRA score reflects the cumulative probability of a ROI within the distribution of probabilities of analyzed ROIs to be the most representative considering the extent of brain responses differences between conditions of interest and HCs. The SUCRA score was computed considering both directions of ESs. Accordingly, positive ESs indicates that conditions of interest showed a heightened response compared to HCs within No-Go/Go trails. On the contrary, negative ESs suggested that conditions of interest respond to the administration of No-Go/Go trails with a reduced brain activity than HCs.

ALE meta-analysis

The voxe-based meta-analysis was conducted using the Ginger ALE 3.0.2 software (http://www.brainmap.org/). This program allows to perform meta-analysis on the base of coordinates of fMRI data (Eickhoff et al., 2009; Laird et al., 2005; Turkeltaub et al., 2002). Differently to the ROI-based network meta-analysis, the ALE meta-analysis aims at estimating brain responses to experimental paradigms that could be shared between conditions and within the same population without *a priori* hypotheses. According to the purposes of the current study, this approach allows to robustly test the existence of common neurobiological underpinnings across conditions of interests, which could provide a support for homotypic and heterotypic developmental trajectories of SUDs in adulthood.

The algorithm of ALE uses the reported activation coordinates from studies. The foci are centers of three-dimensional Gaussian probability distribution used to evaluate the spatial uncertainty associated with them (Caspers et al., 2010). Considering a single study, all distribution of probabilities were merged to create a modeled activation map (MAMap). With respect to the single analysis, the MAMaps of each study are combined, and they yield voxel-wise ALE scores, which describe the overlaps among experiments at each particular coordinates.

According to aims of study, there were performed several single analyses. First, there were analyzed all studies that reported increased brain responses of conditions of interest compared to HCs for No-Go trails. Subsequently, this approach was separately replicated for each population (i.e., SUDs and related conditions, children and adolescents with ADHD, adolescents with MDD). Considering No-go trials, there were also analyzed studies that reported heightened brain responses of HCs compared to conditions of interest. The same approach was also adopted for studies that reported neuroimaging data for Go trails.

Studies that showed results in Talairach coordinates were converted to Montreal Neurological Institute (MNI) space using the algorithm provided by the GingerALE 3.0.2 (Laird et al., 2011). The cluster threshold was set at a voxel-level $p < .05$ (1000 permutations, minimum volume 200 mm^3). Clustering level family-wise error (FWE) correction was performed to compute the significance of results with a $p < .05$ (Eklund et al., 2016).

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