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Pathophysiology of Negative Symptom Dimensions of Schizophrenia – Current Developments and Implications for Treatment

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Highlights

- Negative symptoms map on at least two dimensions: apathy and diminished expression
- Growing evidence points to dimension-specific cognitive and neural mechanisms
- For apathy: dysfunction of goal-directed behavior and fronto-striatal circuits.
- For diminished expression: comprehensive pathophysiological model yet to be established
- Multi-level models of distinct negative symptoms to identify targets for treatment

Abstract

Negative symptoms of schizophrenia comprise a group of severe symptoms contributing to high disease burden and poor long-term prognosis. Conceptual work has shown that these symptoms can be mapped onto, at least, two distinct dimensions: apathy including the domains avolition, asociality and anhedonia, and diminished expression including the domains blunted affect and alogia. Growing evidence suggest that these dimensions have partly distinct behavioral, cognitive and neural correlates. Nonetheless, modulation and treatment of specific processes and brain correlates related to these negative symptom dimensions through behavioral, pharmacological, and brain stimulation interventions remains poorly understood. Here, we address this question by employing an integrative approach and comprehensively synthesizing the current literature on neuroimaging, behavior and clinical studies of both negative symptom dimensions. While considerable progress has been made, it remains an open challenge to develop integrative mechanistic pathophysiological models for apathy and diminished expression. We conclude that such multi-level frameworks are key for the development of new biological and psychosocial treatments and may advance progress towards an individualized treatment of negative symptoms.

Key words: Schizophrenia, Negative Symptoms, Apathy, Avolition, Diminished Expression, Pathophysiology, Behavioral, Neuroimaging

1. Introduction

1.1. Current concepts of negative symptoms

Negative symptoms in schizophrenia consist of a range of often debilitating symptoms including blunted affect, alogia, asociality, anhedonia, and avolition (Box 1) (Kirkpatrick et al., 2006). Negative symptoms have a negative impact on everyday functioning, long-term outcome and quality of life (Faerden et al., 2013; Fervaha et al., 2014; Galderisi et al., 2013; Rabinowitz et al., 2012; Strauss et al., 2013). Despite recent efforts for developing biological and psychological interventions, treatment options for negative symptoms remain limited (Fusar-Poli et al., 2015). Thus, treatment development for the improvement of negative symptoms for patients with schizophrenia and other psychotic disorders remains one of the most important challenges in psychiatry.

Traditionally, negative symptoms have been grouped together and homogeneously reported as one symptomatology domain, but growing evidence from factorial analyses of different psychometric scales shows that negative symptoms map onto at least two distinct dimensions (Figure 1) - apathy and diminished expression (Blanchard and Cohen, 2006; Galderisi et al., 2018; Kirkpatrick, 2014).

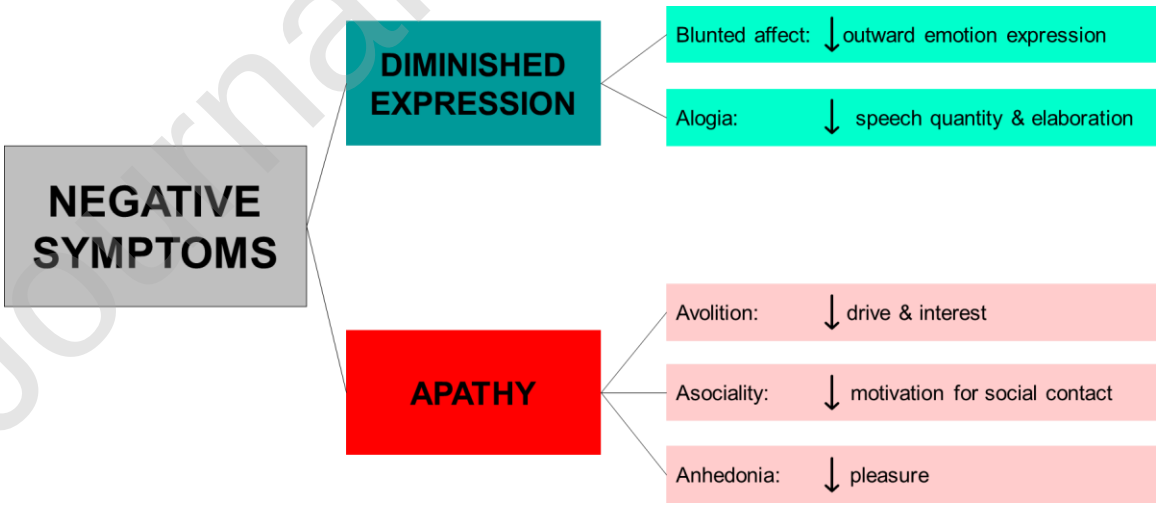

Figure 1. Schematic representation of negative symptom dimensions and individual negative symptom domains.

The apathy dimension includes asociality, anhedonia, and avolition symptom domains, while the diminished expression dimension comprises blunted affect and alogia domains. According to this classification, the apathy dimension can, thus, be defined as a reduction in parameters pertaining to the motivation and goal-directed behavior and/or to the experience of pleasant emotions. By contrast, the diminished expression dimension can be defined as a reduction in the outward expression of emotion and/or speech. More recently, it has been suggested that a further differentiation of negative symptoms into five factors may provide a more appropriate fit to the psychometric data (Ahmed et al., 2018; Strauss et al., 2019b; Strauss et al., 2018), see for a perspective (Strauss et al., 2019a). For the purpose of this review, we focus on the consensual two-dimensions model, which has been mostly widely employed in recent pathophysiological research (Marder and Galderisi, 2017). However, where applicable evidence for specific mechanisms for each of the five domains will be reported.

Further, it is important to mention the distinction between primary and secondary symptoms with the former being inherent to schizophrenia *per se* and the latter being secondary to positive symptoms, comorbid depression, substance abuse, medication side-effects or social deprivation (Carpenter et al., 1985; Kirkpatrick, 2014; Kirschner et al., 2017). Of note, recent studies reviewed in this article have frequently attempted to exclude patients with obvious sources of secondary negative symptoms. Nevertheless, the lack of the primary-secondary negative symptom distinction remains a source of considerable heterogeneity and has to be systematically accounted for in research on negative symptoms.

Another factor contributing to the heterogeneity in negative symptom research are their diverse trajectories across the lifespan (Lyne et al., 2018). Differential baseline levels of negative symptoms, premorbid functioning and the duration of untreated psychosis have been suggested to predict the course of negative symptoms, in particular apathy (Lyngstad et al., 2020). During the course of the illness negative symptoms seem to fluctuate more over time than originally thought and show complex interactions with other symptoms (Savill et al., 2015). This represents an important source of heterogeneity for research on the pathophysiology of negative symptoms, given that mostly cross-sectional

design has been employed so far. The concept of the deficit syndrome is an important attempt to reduce heterogeneity and requires the presence of primary negative symptoms for at least 12 months duration (Kirkpatrick et al., 2017). Persistent negative symptoms have a broader definition that requires 6 months duration and is less strict concerning the primary nature of the symptoms (Buchanan, 2007). Overall, the longitudinal evolution of negative symptoms is an important research field that will need to be linked to the pathophysiological approach taken in this paper.

Here, we focus on the distinction between apathy and diminished expression to reduce heterogeneity in negative symptom research. In accordance with clinical and psychometric distinctions between the two dimensions, a growing body of literature also suggest distinct underlying pathophysiological mechanisms (Galderisi et al., 2018; Marder and Galderisi, 2017; Messinger et al., 2011). Here, we aim to provide an integrative overview of these recent advances in domain-specific mechanisms. To this end, we review research on negative symptoms across multiple levels of analysis: behavioral, psychological, pharmacological, cognitive and computational mechanisms. Correspondingly, we review the literature on structural and functional brain correlates of negative symptoms. To bridge the gap between basic science and clinic, we describe potential ways through which dimension-specific behavioral mechanisms and brain correlates may be modulated by psychosocial and biological treatments. Finally, we discuss putative approaches combining different treatment modalities (e.g. biological and psychosocial) to modulate underlying pathological processes of both negative symptom dimensions and thereby improve treatment outcome.

This integrative review provides a narrative overview across various lines of research in order to inform experts and non-experts alike. In this regard, an in-depth systematic report of specific research fields is beyond the scope of this work. However, for further reading, we refer throughout this review to systematic or more in-depth work respectively.

1.2. Assessment of negative symptoms

Traditionally, negative symptoms were assessed by scales such as the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987) and the Scale for the

Assessment of Negative Symptoms (SANS) (Andreasen, 1984). These instruments included neurocognitive and other items, unrelated to the consensual constructs of negative symptoms (Figure 1) (Kirkpatrick et al., 2006). For example, PANSS included items such as difficulty in abstract and stereotyped thinking, while SANS included items such as inattentiveness, increased latency of response, blocking, and inappropriate affect. While some of these issues have been addressed in adaptations of the scales or their interpretation, other problems like the insufficient differentiation of anhedonia and asociality as well as the lack of assessment of the subjective aspects of negative symptoms have remained.

To overcome these limitations, two new negative symptom instruments have been developed: the Clinical Assessment Interview for Negative Symptoms (CAINS) (Horan et al., 2011) and Brief Negative Symptom Scale (BNSS) (Kirkpatrick et al., 2011). These interview-based observer-rated scales allow a more fine-grained assessment of all five negative symptom domains as well as the dimensions apathy and diminished expression (Strauss et al., 2018). In addition, both scales also focus on the internal experience of anhedonia, avolition and asociality. Please note, that for the apathy dimension, scales developed for patients with neurologic and other disorders like the Apathy Evaluation Scale have also been successfully employed in patients with schizophrenia (Faerden et al., 2008; Marin et al., 1991).

With respect to self-reports, two scales have been developed after the NIMH consensus statement: The Motivation and Pleasure Scale—Self Report (MAP-SR) (Llerena et al., 2013), and the Self-evaluation of Negative Symptoms (SNS) (Dollfus et al., 2016). The MAP-SR comprises a self-rating of the CAINS motivation and pleasure subscale but does not cover the expressive domain (blunted affect and alogia). In contrast, the SNS covers the subjective experience of all five negative symptom dimensions measured with the CAINS and BNSS, although the self-assessment of expressive deficits might diverge from observer ratings.

While the instruments described here illustrate recent developments in assessing negative symptoms (see for comprehensive review (Lincoln et al., 2017), distinction between primary and secondary negative symptoms remains a major challenge and source to heterogeneity. In addition, assessments of negative symptoms that have been

validated in patients with schizophrenia may not be sufficiently sensitive in other clinical and non-clinical populations. It would be useful for transdiagnostic research of negative symptoms to develop instruments that allow a dimensional evaluation of subclinical and clinical symptoms across all stages of the schizophrenia spectrum and other psychiatric disorders (e.g. bipolar disorder, depression).

2. The pathophysiology of apathy

2.1. Mechanisms related to apathy

Current theories across different neuropsychiatric disorders widely conceptualize apathy as impairments in several aspects of goal-directed behavior and decision-making (Husain and Roiser, 2018; Le Heron et al., 2018). These deficits implicate motivational mechanisms including reward anticipation and reward learning as well as effort-based decision-making (Barch et al., 2017; Culbreth et al., 2018; Hartmann-Riemer et al., 2018; Kring and Barch, 2014; Strauss et al., 2014). A second line of research has focused on the association between apathy and neurocognitive abnormalities (e.g. a set of competences underlying working memory, perception etc.) including deficient option generation and planning (Faerden et al., 2009; Hartmann et al., 2015b). Further, recent studies provide evidence for an interaction between apathy and impaired social cognition (e.g. a range of cognitive processes underlying social interactions) even though results are heterogeneous (Johnston et al., 2010; Rassovsky et al., 2011; Shean and Meyer, 2009; Ventura et al., 2013). Finally, research has focused on dysfunctional beliefs, e.g. negative expectations, beliefs and self-stigma about future rewards with respect to social interactions) (Beck et al., 2018; Grant and Beck, 2009; Staring et al., 2013). All of these mechanisms potentially work in concert and ultimately decrease engagement in goal-directed behavior (see Figure 2, red box).

2.1.1. Motivational mechanisms

Although motivational and reward-related processes have been proposed as a general factor for all negative symptoms, growing evidence suggests that these mechanisms may preferentially underpin the apathy dimension (Kring and Barch, 2014; Strauss et al., 2014). Reinforcement learning, the ability to predict and learn from positive rewards, is a key component of goal-directed behavior. Several studies found that patients with schizophrenia display selective impairments in successfully generalizing from repeated exposure to positive but not negative outcomes (Gold et al., 2012; Waltz et al., 2007; Yilmaz et al., 2012). Thus, learning from positive outcomes (positive prediction error) is impaired, while learning from negative outcomes (negative prediction error,

punishment) is relatively intact (Maia and Frank, 2017a). Evidence points to a specific link between impaired learning from positive outcomes and apathy (Dowd et al., 2016; Gold et al., 2012; Waltz et al., 2007), although not all studies found this association (Hartmann-Riemer et al., 2017). Together, these studies emphasized the role of reduced prediction error coding i.e. computation of differences between predicted vs. obtained outcomes. However, the fact that learning from negative feedback is spared suggests that additional mechanisms may contribute to impaired reward learning, such as a deficient representation of choice value. Using an elegant computational model, Gold and colleagues (Gold et al., 2012) showed that learning deficits cannot be fully explained by deficient prediction error coding alone, but also derive from impaired representation of expected values. In particular, this study demonstrated that patients with more severe negative symptoms fail to distinguish between rewarding and loss-avoiding stimuli. Such a dysfunction in positive expected value representation putatively impairs decision making for actions with positive outcome (for detailed review see (Waltz and Gold, 2016)). Adding to this, recent work from the same authors showed that patients with schizophrenia rely more on “valueless” stimulus-response learning rather than learning from positive expected values to guide decisions (Hernaus et al., 2018). These findings were confirmed in a second independent study demonstrating that impaired expected value-based learning (and overutilization of stimulus-response learning) was directly associated with severity of apathy (Hernaus et al., 2019). *In toto*, considerable evidence points to dysfunctional reward-based learning including impaired decision making and action-selection for actions related to positive outcomes. Ultimately, these impairments can lead to reduced goal-directed behavior and the clinical expression of apathy. Although this mechanistic framework has some explanatory power, future studies are needed to draw conclusion about precise learning deficits as cause for apathy and amotivated behavior in schizophrenia.

Another line of research has focused on impairments in effort-based decision-making and has received increased attention in recent years (Culbreth et al., 2018; Hartmann-Riemer et al., 2018). Decision-making requires the computation of the cost/benefit value of options, as a function of the rewards available and the amount of effort required to attain them. An overestimation of effort in relation to reward value may thus reduce goal-directed behavior. Several studies suggest that patients with negative symptoms – in particular, apathy - fail to make high-effort choices in order to obtain higher

rewards during cognitive and physical effort tasks (Culbreth et al., 2016a; Fervaha et al., 2013; Gold et al., 2013; Hartmann et al., 2015a). However, results from other studies are only partially consistent (for in-depth reviews see (Culbreth et al., 2018; Gold et al., 2015; Hartmann-Riemer et al., 2018). Further research is needed considering the high heterogeneity between studies including variability in type of required effort (physical vs. cognitive), task design and type of clinical assessment.

Overall, despite some heterogeneity in the literature, there is increasing evidence suggesting that motivational mechanisms underlying apathy encompass abnormalities in reward learning and effort-based decision-making. These constructs are of particular interest for development of biological treatments, because they can be employed in translational studies using pharmacological manipulations in rodents. The current advances in animal models are beyond the scope of this review and we recommend recent reviews in this field (Der-Avakian and Pizzagalli, 2018; Ward, 2016).

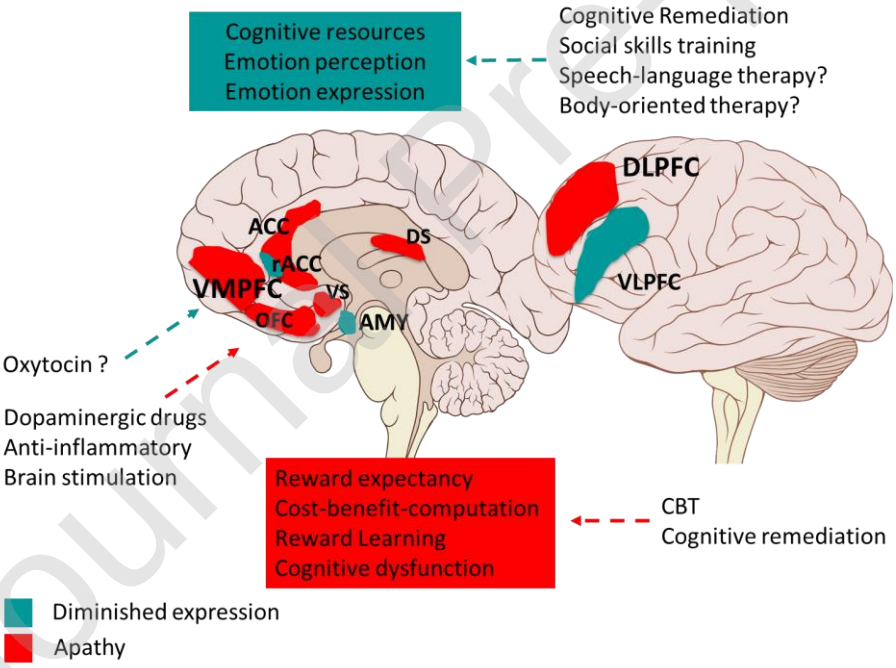

Figure 2: Schematic summary of pathophysiological processes and brain regions implicated with apathy (red) and diminished expression (green) and potential targets for treatment. Abbreviations: ACC, anterior cingulate cortex; AMY, amygdala; CBT, cognitive-behavioral therapy; DS, dorsal striatum; OFC, orbito-frontal cortex; rACC, rostral ACC; DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; VS, ventral striatum.

2.1.2. Neurocognitive mechanisms

Overall, current evidence does not support a specific association between apathy and general neurocognitive impairment in patients with schizophrenia (Galderisi et al., 2014; Hartmann-Riemer et al., 2015), even though specific aspects of neurocognition may be particularly relevant to impairments of goal-directed behavior. Executive functions and planning are essential for implementing actions and there is some evidence for an association with apathy (Faerden et al., 2009), although the findings are not fully consistent. More recently, a deficit in option generation – the capacity to generate options for action in ill-structured situations – has been shown to be associated with apathy (Hartmann et al., 2015b).

In addition to a potential role for reward learning (see section 2.1.1. above), working memory deficits have been suggested to play a role in apathy (Raffard et al., 2016), but the evidence is only partially consistent (Cella et al., 2017b). This influence on apathy has been suggested to occur via the contribution of working memory to the inability to maintain emotional experiences over time (Burbridge and Barch, 2007; Raffard et al., 2016). Another potential pathway is through a contribution of working memory impairment to deficits in instrumental learning (Collins et al., 2017), but a specific association with apathy has so far not been elucidated. Nevertheless, this is an important observation providing a potential link between deficits in reward learning and cognitive dysfunction.

It has been also proposed that negative symptoms may arise from disturbances of basic core selfhood stemming from a disrupted intermodal perceptual integration due to neurocognitive deficits. According to the model put forward by Sass and Borda (Borda and Sass, 2015; Sass et al., 2018), a *diminished self-presence* — defined as "a decline in the (passively or automatically) experienced sense of existing as a subject of awareness or agent of action" – may relate to negative symptoms. This may, in particular, reflect the subjective experience of apathy, but behavioral apathy as well as diminished affective expression might also be impaired. Future work should further explore the link between neurocognition, self-disturbances and specific negative symptoms dimensions.

In sum, cognitive impairment including deficient action planning, option generation and working memory may contribute to apathy symptoms, but at present, the specific contribution of each mechanism needs to be determined.

2.1.3. Social cognition

Social cognition comprises several distinct capacities of social interactions that involve understanding, interpreting and generating behavioral response to affects, intentions, thoughts and feelings of others (Gallagher and Varga, 2015). These capacities include processes like affect sharing, mentalizing, emotion experience, and emotion regulation (Green et al., 2015).

Although aspects related to emotion perception and expressions are included in social cognition, research has shown that these processes predominantly relate to the diminished expression dimension, rather than the apathy dimension (Gur et al., 2006; Lepage et al., 2011). Therefore, emotion perception and expression will be discussed in the diminished expression section (see section 3.1.2.).

Social cognition impairments have been directly linked to poor outcome (see for a meta-analysis (Fett et al., 2011)). Theoretically, social cognition impairments manifest with decreased participation in social activities, which, in turn, will exert deleterious effects on the capacity to elicit positive reward from social interactions resulting in a vicious circle, ultimately diminishing social cognition even more. Numerous studies have examined the relationship between social cognition and global negative symptoms. However, evidence from the current literature is mixed. Although some studies found significant associations between social cognition and negative symptoms (Johnston et al., 2010; Shean and Meyer, 2009; Ventura et al., 2013), others did not (Mancuso et al., 2011; Rassovsky et al., 2011). To the best of our knowledge, no study specifically looked at the relationship between apathy and impairment of social cognition. Thus, more research is warranted to elucidate the causal relationship between specific social cognitive deficits and motivational deficits in schizophrenia

2.1.4. Dysfunctional beliefs

Psychological concepts have suggested a role for dysfunctional beliefs in the pathophysiology of apathy (Grant and Beck, 2009; Staring et al., 2013). These models conceptualize negative symptoms as resulting from negative beliefs about the self and the future, particularly, about the potential results of behavior. Negative self-beliefs have been conceptualized as “defeatist beliefs”, for example “If I try this, I will surely fail”. Negative beliefs about the future concern a low expectancy of prospective activity-related pleasure. Such “defeatist beliefs”, coupled with internalized stigma, may further discourage goal-directed behavior and perpetuate diminished interactions with the outside world. This, in turn, can lead to a clinical presentation of apathy symptoms (Campellone et al., 2014; Couture et al., 2011; Quinlan et al., 2014), although not all studies are fully consistent with this model (Pillny and Lincoln, 2016).

In sum, these studies demonstrate that multiple mechanisms including motivational, neurocognitive, social cognitive, and psychological impairments, contribute to the complex clinical syndrome of apathy. It is important to note, that it remains an open question how neurocognitive, social cognitive and motivational deficits interact over time, and how they are linked to dysfunctional beliefs. In this regard, a recent study suggests a complex interaction between these different dimensions (Reddy et al., 2017) highlighting the need for further systematic research.

2.2. Neural substrates of apathy

Neuroimaging studies of the apathy dimension may be clustered in a) task-based functional magnetic resonance imaging (fMRI) using reward- and cognition-related tasks, b) resting-state fMRI (rs-fMRI) and c) structural magnetic resonance imaging (sMRI) assessing gray and white matter changes in patients with schizophrenia (see Figure 2, regions in red).

2.2.1. Task-based functional neuroimaging

FMRI studies employing reward processing tasks have consistently shown a negative association between ventral striatal (VS) activation and negative symptoms in

patients with schizophrenia (see for a meta-analysis (Radua et al., 2015)). Increasing evidence corroborates that blunted ventral striatal reward anticipation signal is a specific neural correlate of apathy and is not related to diminished expression (Kirschner et al., 2015; Moran et al., 2019; Simon et al., 2010; Stepien et al., 2018; Waltz et al., 2010; Waltz et al., 2018; Wolf et al., 2014). This association has also extended across a continuum with subclinical apathy in the general population (Simon et al., 2015) Additionally, recent studies have reported an association between reduced dorsal striatum activation during reward anticipation and apathy (Morris et al., 2015; Mucci et al., 2015; Stepien et al., 2018). Some studies proposed that this blunted dorsal striatal activity might be specifically related to avolition (motivation) and not anhedonia (pleasure) and could be a neural correlate of impaired action-selection (Morris et al., 2015; Mucci et al., 2015). Other studies reported a direct relationship between anhedonia and reduced ventral striatal activation during reward anticipation (Arrondo et al., 2015; Dowd and Barch, 2012). Few studies also showed that apathy is associated with extra-striatal hypoactivation of the inferior frontal gyrus (Dowd and Barch, 2012; Kluge et al., 2018), the ventromedial prefrontal cortex (Dowd and Barch, 2012; Waltz et al., 2018), anterior cingulate cortex and insula (Moran et al., 2019). In sum, these results provide strong evidence for an association between apathy and striatal activation during reward anticipation – in particular, for the ventral striatum. Future work should determine whether ventral and dorsal striatum function are differentially related to motivational (avolition) and hedonic (anhedonia) aspects of apathy.

While there is a rapidly growing literature on the neural correlates of abnormal reward learning in schizophrenia, relatively few studies have specifically addressed the associations with distinct negative symptoms domains. Interestingly, most recent studies observed intact neural prediction error coding in patients with schizophrenia (Culbreth et al., 2016b; Dowd et al., 2016; Waltz et al., 2018), but findings are not fully consistent (Reinen et al., 2016). Similarly, only few studies directly linked impaired prediction error coding engaging the medial prefrontal cortex and the inferior frontal gyrus to negative symptoms and apathy (Waltz et al., 2010). In contrast to these inconclusive findings, other processes involved in reward learning have been associated with apathy. For example, impaired striatal signal in response to reward values has been reported in one earlier study reporting a negative correlation between striatal response to natural reinforcer (juice) and

avolition scores (Waltz et al., 2009). Adding to this, Dowd and colleagues (Dowd et al., 2016) showed that dorsolateral PFC and caudate activity in response to reward feedback is negatively correlated with anhedonia and avolition. With respect to impaired learning from positive expected values, Waltz and colleagues (2018) found that severity of apathy was associated with impaired neural differentiation between gain and loss-avoidance outcome in the ventral striatum. Together, these studies support the view that the association between impaired reinforcement learning and apathy in schizophrenia cannot be explained by a simple general blunted prediction error signaling. Motivational deficits in schizophrenia rather appear to be related to imprecise differentiation, update and representation of reward values.

In addition to the plethora of fMRI work dealing with various aspects of reward processing, some studies have focused on the relationship between negative symptoms and neural correlates of neurocognitive processes. Several studies examined prefrontal cortex activation during working memory performance, but results have been heterogeneous, showing a complex pattern of prefrontal hypo- and hyperactivation in relation to negative symptoms (Menon et al., 2001; Sanz et al., 2009; Vogel et al., 2016). In addition, one large study reported negative symptoms to be associated with reduced dorsal striatal activation during a working memory task (Ehrlich et al., 2012). Few studies have addressed the association of negative symptoms with the neural correlates of more complex processes underlying goal-directed behavior such as planning (Liemburg et al., 2015). However, almost all studies relied on global negative symptom measures and did not address specific relationships to the two negative symptom dimensions of apathy and diminished expression separately. To clarify the contribution of high-order processes and their neural correlates to apathy more research is clearly needed.

In sum, evidence from task-related fMRI studies points to a key role of the VS, ventromedial PFC/OFC in addition to caudate nucleus and dorsolateral PFC in the pathophysiology of apathy. In line with distinct cortico-basal ganglia circuits (Haber, 2016), two distinct striatal pathways may contribute to the apathy dimension: one “reward” circuit including VS and ventromedial PFC and one “cognitive” circuit including caudate nucleus and dorsolateral PFC. A critical open question for future research is whether motivational (avolition) and hedonic (anhedonia) aspects of apathy can be consistently mapped onto distinct functional cortico-striatal pathway. Two possible mechanisms have been recently

proposed: a) a dysfunctional motivational value circuit related to (anticipatory) anhedonia b) a dysfunctional motivational salience circuit related to avolition (lack of motivation) (Galderisi et al., 2018). Regarding a transdiagnostic understanding of these distinct mechanisms, it is also instrumental to study the overlap and differentiation between apathy, anhedonia and depression. Apathy and depression occur transdiagnostically in neurological and psychiatric disorders, but they are also dissociable (Kirschner et al., 2020). Anhedonia is a symptom of apathy in schizophrenia, but also a core symptom of depression (Husain and Roiser, 2018). It has been suggested that the overlap between anhedonia and apathy in schizophrenia can be explained by specific deficits in anticipatory anhedonia, while consummatory hedonic experiences are relatively intact (Gard et al., 2007; Horan et al., 2006; Juckel et al., 2006; Mote et al., 2014). Here, transdiagnostic multi-component frameworks of apathy and anhedonia might help to identify shared and distinct behavioral, computational and neuroimaging parameters of both conditions (Husain and Roiser, 2018).

2.2.2. Resting state functional neuroimaging

Emerging findings from studies assessing functional connectivity during resting-state converge on a key role of fronto-striatal network abnormalities for general negative symptoms (Fornito et al., 2013; Shukla et al., 2019; Tu et al., 2012). More specifically, one study has found that resting-state functional connectivity (RS-FC) of the ventro-tegmental area (VTA) with the bilateral insular cortex, the right ventrolateral prefrontal cortex and right lateral complex were significantly negatively correlated with avolition scores (Giordano et al., 2018). In conjunction with findings from other modalities, these results suggest that avolition may result from a disconnection of core reward processing regions (VTA) from other key areas coding value information and guiding action selection (Amodio et al., 2018). In addition, work from Abram and colleagues (Abram et al., 2017) identified fronto-temporal connectivity abnormalities related to apathy and cognitive empathy, suggesting a shared neural basis for social cognition deficits and apathy. With respect to anhedonia, Wang and colleagues (Wang et al., 2016) observed an association between social anhedonia and altered corticostriatal functional connectivity in healthy individuals with high schizotypal traits. These latter findings point towards dimensional mechanisms of cortico-striatal dysconnectivity within the schizophrenia-spectrum. Taken together,

future work should try to disentangle distinct fronto-striatal network abnormalities related to avolition and anhedonia across the entire schizophrenia-spectrum. In addition, although we have strong evidence for large-scale cortical network dysfunction in schizophrenia (Dong et al., 2018; Li et al., 2019), the question of how cortico-cortical network abnormalities contribute to the development of apathy still remains unanswered.

2.2.3. Structural neuroimaging

Most sMRI studies have addressed the association with overall negative symptoms, but there is an increasing number of studies on apathy. At a structural level, more severe apathy has been associated with reduced gray matter (GM) volume in the right VS (Roth et al., 2016). This finding has been confirmed in a recent study in older patients with schizophrenia (Caravaggio et al., 2018). Regarding cortical GM changes, apathy has been associated with reductions in gray matter volume in different prefrontal areas, including the frontal inferior operculum and the dorsal anterior ACC (Caravaggio et al., 2017). Patients with persistent apathy have shown decreased cortical thickness of limbic motivational areas including the left OFC and ACC (Morch-Johnsen et al., 2015). This is in line with a recent ENIGMA meta-analysis showing orbitofrontal cortical thinning in association with total negative symptoms (Walton et al., 2018).

White matter integrity (quantified by fractional anisotropy values) was more reduced in the tracts linking medial OFC and rostral ACC in patients with more severe avolition-apathy and anhedonia-asociality scores quantified by the SANS (Ohtani et al., 2014). Severity of anhedonia-asociality correlated with lower fractional anisotropy (FA) values in the right cingulum tract (Hovington et al., 2015) and FA values in anterior part of the corpus callosum were negatively correlated with anhedonia–asociality (Asami et al., 2014). In addition, Amodio and colleagues (2018) showed that reduced FA values observed in the white matter tracts connecting the left amygdala to the ventro-anterior insular cortex were negatively correlated with apathy but not with diminished expression.

2.2.4. Transdiagnostic perspectives on apathy

In summary, studies across different functional and structural modalities indicate a major role of prefrontal-striatal networks in the pathophysiology of apathy in patients with schizophrenia. Within this network, key structures include the ventral and dorsal striatum, ventromedial PFC/OFC, DLPFC and ACC. Taking a transdiagnostic view it is worth mentioning that similar regions have been described for apathy in patients with lesions affecting these regions and in patients with neurodegenerative disorders (Kos et al., 2016; Le Heron et al., 2018; Levy and Dubois, 2005). In this regard, a seminal work by Levy and Dubois proposed three subtypes of apathy mapping onto distinct neuroanatomical localizations (Levy and Dubois, 2005). According to this neuroanatomical account, lesions of the OFC/VMPFC or ventral striatum/pallidum would cause an 'emotional–affective' apathy (e.g. inability to effectively decode the emotional–affective signals in service of goal-directed behavior), lesions in the DLPFC and basal ganglia (dorsal caudate) may be responsible for a 'cognitive' apathy (e.g. difficulties in action planning, maintenance and finalization in ongoing or anticipated behavior). Lastly, bilateral damage to associative and limbic territories of the internal portion of the globus pallidus may cause an 'auto-activation' deficit, defined as the inability to internally generate thoughts and actions, despite a relatively preserved capacity to comply with externally driven behavior (Levy and Dubois, 2005). These distinctions may also be useful for investigating apathy in patients with schizophrenia, but the framework has only infrequently been applied (Bortolon et al., 2018). More recently, a dysfunction of the dACC and VS and their connected brain areas has been proposed as a unifying feature of apathy across neurological disorders (Le Heron et al., 2018). Considering the significant overlap between brain networks of apathy in neurological disorders and schizophrenia, additional integrative efforts are warranted to better dissect the transdiagnostic neuroanatomy of apathy (Guessoum et al., 2020).

2.2.5 Pharmacology of apathy

Tonic and phasic dopamine signaling within the mesocorticolimbic system are key for motivated behavior, decision making and reward learning (Bromberg-Martin et al., 2010; Haber and Knutson, 2010; Salamone and Correa, 2012) The evidence from behavioral and neuroimaging studies for motivational deficits, reward learning, and

disrupted fronto-striatal pathways emphasize the pivotal role of disturbed dopamine transmission in the pathophysiology of apathy.

However, an important, albeit less explored, role in the pathophysiology of apathy has been attributed to other neurotransmitters. These neurotransmitters operate in segregated cortico-subcortical circuits and/or in open-loops of afferent and efferent projections constituting the frontal-subcortical connectivity network. Indeed, pro-apathetic effects of selective serotonin reuptake inhibitors (e.g. escitalopram) have been observed and suggest a role for serotonin in the pathophysiology of apathy (Cassano and Fava, 2004; Morelli et al., 2011; Price et al., 2009).This may be, at least partly, through modulation of dopaminergic transmission via 5-HT2C receptors in the substantia nigra pars reticulata and GABAergic neurons in the ventral tegmental area (Demireva et al., 2018). Other neurotransmitters potentially involved in negative symptoms include glutamate (McCutcheon et al., 2020), GABA (de Jonge et al., 2017) and acetylcholine (Foster et al., 2012). It remains to be clarified how they may contribute to distinct dimensions of negative symptoms and future efforts should be dedicated to shed light on the pharmacological mechanisms (Husain and Roiser, 2018).

2.3. Treatment of apathy, related mechanisms and neural substrates

A review of all treatment trials targeting total negative symptoms is beyond the scope of this review. Here, we focus on treatments that may have some specificity for apathy. Studies were selected when they either showed ameliorations in apathy scores on a clinical scale or targeted one of the processes/neural changes underlying apathy (Figure 2). This approach was applied to all potential treatments for apathy and, similarly, for diminished expression (see paragraph below). The ultimate goal of this approach is to understand the effects of treatment on all three levels of description – symptom, process, neural, but this type of integrated model is still in its infancy as outlined below.

2.3.1. Psychosocial interventions

Regarding psychosocial interventions, several studies have employed cognitive-behavioral therapy (CBT)-based approaches for defeatist beliefs to treat overall negative symptoms with promising results (Grant et al., 2012; Klingberg et al., 2011). In a multicenter study, Klingberg and colleagues observed a positive effect of CBT on total negative symptoms, while Grant and colleagues found a specific effect of CBT on avolition-apathy in a smaller single-site study (Grant et al., 2012; Klingberg et al., 2011). Thus, overall, the specificity of CBT for the apathy domain remains to be established. More recent studies have found an effect of therapeutic interventions specifically targeting anticipatory pleasure (Favrod et al., 2015; Velligan et al., 2015). Favrod and colleagues (2015) developed a short group-based CBT approach to increase anticipation and maintenance of positive emotions and to reduce defeatist thinking. In a recent randomized control trial in 80 patients with schizophrenia, they showed a significant advantage of their positive emotions program in comparison to treatment as usual (TAU) with respect to apathy scores (avolition-apathy and anhedonia-asociality on the SANS) (Favrod et al., 2019). Thus, in sum, promising initial results suggest that apathy is amenable to CBT-based interventions (Grant et al., 2012; Velligan et al., 2015). However, these findings warrant further investigation with standardized protocols in larger cohorts.

From a theoretical perspective, cognitive remediation therapy (CRT) approaches hold a potential for ameliorating both dimensions of negative symptoms. A recent meta-analysis (n=309) has provided evidence for an improvement of overall negative symptoms (Cella et al., 2017a), but specific effects for apathy are unfortunately rarely reported. In this regard, post-hoc analyses based on data from a previously reported randomized 12-week study with CRT in chronic patients (Lindenmayer et al., 2018) revealed that CRT improved severity of apathy measured with the Positive and Negative Symptoms Scale (PANSS) social amotivation factor (Sevy et al., 2020) (see (Fervaha et al., 2014; Liemburg et al., 2013) for more details on PANSS social amotivation factor). In relation to apathy, cognitive remediation interventions can potentially improve deficits of reward learning, which have been linked to deficits in cognitive functions, in particular, in working memory (Collins et al., 2017). One cognitive remediation trial has suggested that improvement in reward or punishment sensitivity is related to reductions in negative symptoms (Cella et al., 2014).

Furthermore, impairments in the generation of options for action and the planning and execution of actions are potentially amenable to cognitive remediation. However, cognitive remediation studies have not focused on negative symptoms as a primary outcome and specific changes in the two negative symptom dimensions are rarely reported.

2.3.2. Biological interventions

2.3.2.1 Pharmacological treatment

With respect to pharmacological treatment, to our knowledge, almost all clinical trials have focused on total negative symptoms, so conclusions about the two dimensions are extremely limited. Considering findings of deficient reward anticipation and reward learning, pharmacological treatment of apathy should favor dopaminergic neurotransmission or at least impair it to the least extent possible. In this context, it has been suggested that atypical antipsychotics might be beneficial compared to typical antipsychotics. However, this potential advantage concerns negative symptoms secondary to extrapyramidal side-effects (Millan et al., 2014). In contrast, the preferential antagonistic effects of atypical antipsychotics at the 5-HT2a receptor are unlikely to provide an advantage in the treatment of primary negative symptoms (Millan et al., 2014).

Small studies have provided limited evidence for low doses of amisulpride and to a lesser extent olanzapine for patients with predominant negative symptoms (Hasan et al., 2012; Krause et al., 2018). In a recent study, caripiprazine – a novel D2/D3 partial antagonist - was more effective than risperidone in diminishing overall negative symptoms (Nemeth et al., 2017). Antipsychotic add-on treatments to the basic antipsychotic therapy have also been evaluated in the management of negative symptoms. A recent meta-analysis has suggested that aripiprazole, a partial dopamine agonist, might be effective as add-on medication to reduce overall negative symptoms (Galling et al., 2017). However, since aripiprazole was always applied as add-on to D2 antagonists, it is conceivable that its partial dopamine agonistic effects may have served mostly to alleviate secondary negative symptoms arising from the antipsychotic treatment. None of the included studies has specifically reported results for distinct negative symptom domains.

Adjunctive antidepressive therapy is common in daily clinical practice and might be particularly effective in secondary negative symptoms due to depression (see for a review (Kirschner et al., 2017). A recent meta-analysis of 48 randomized controlled trials (n=1905) found a small effect size (-0.3) of antidepressants for total negative symptoms (Helfer et al., 2016). However, no results for distinct negative symptom domains were reported in this meta-analysis. Similar effect sizes were found in another meta-analysis examining antidepressant augmentation to antipsychotics in schizophrenia patients with medium effect sizes for avolition/apathy and anhedonia/asociality factors (Galling et al., 2018).

Another approach is to directly increase dopamine neurotransmission in the nucleus accumbens by applying psychostimulants, such as amphetamines, methylphenidate, modafinil and armodafinil. Low doses of psychostimulants can theoretically improve the coding of rewarding stimuli by increasing phasic dopamine responses (Maia and Frank, 2017a). However, the evidence remains very limited (Veerman et al., 2017). A recent meta-analysis (Sabe et al., 2019) including eleven RCTs on pro-dopaminergic drugs reported no overall effect on total negative symptoms, but a small effect in a subset of four modafinil/armodafinil trials requiring patients to have negative symptoms severity above a certain threshold. Specific effects for either apathy or diminished expression dimensions were not observed, but available data was very limited (Sabe et al., 2019). Nevertheless, these findings support further investigation of pro-dopaminergic drugs in the treatment of apathy.

With respect to transdiagnostic treatment research, inflammation has been increasingly linked to amotivation in depression (Felger and Treadway, 2017). Inflammatory cytokines can potentially reduce dopaminergic neurotransmission and thus diminish motivation. Regarding schizophrenia, treatment with the classical anti-inflammatory drugs, celecoxib and aspirin, has yielded very limited effects for negative symptoms (Nitta et al., 2013). More recently, the antibiotic and anti-inflammatory drug minocycline has gained some interest for negative symptoms (Liu et al., 2014; Zhang et al., 2018), but only one trial has found a specific improvement of avolition (Kelly et al., 2015).

2.3.2.2 Non-invasive brain stimulation

Prefrontal brain stimulation may be beneficial for diminishing motivational symptoms, considering that task-related and resting state fMRI studies, discussed earlier, pointed towards fronto-striatal network abnormalities. Prefrontal brain stimulation has received support by conceptual work combining repetitive transcranial magnetic stimulation (rTMS) and positron emission topography (PET). These studies showed that stimulation of the left DLPFC (Strafella et al., 2001), left primary motor cortex (Strafella et al., 2003) and mPFC (Cho et al., 2015) increased striatal dopamine release. Indeed, clinical trials using rTMS protocols targeting the prefrontal cortex reported promising results in diminishing overall negative symptoms (Aleman et al., 2018). However, high methodological heterogeneity still limits conclusive statements on TMS efficacy for overall negative symptoms. The paucity of data does not allow any conclusion regarding specific effects for apathy and diminished expression.

In sum, these psychosocial and biological interventions represent exciting avenues to improve clinical management of apathy. Treatment effects in clinical trials may be strongly reduced by substantial heterogeneity in their definition of negative symptom domains; thus, in our view, an important step forward would be to design and report clinical trials for apathy and diminished expression separately.

3. The pathophysiology of diminished expression

3.1. Mechanisms related to diminished expression

Research in the pathophysiology of diminished expression has focused on a) emotion expression deficits, b) dysfunction in emotion perception. An additional line of research has postulated that insufficient cognitive resources for speech production and fluency are responsible for diminished expression symptoms (Kohler et al., 2010; Kring and Elis, 2013).

3.1.1. Impairments in processes underlying emotion expression

Some studies have addressed the association of flat affect with motor aspects of emotion expression in patients with schizophrenia (Tremeau et al., 2005; Tron et al., 2016). It has been suggested that patients display poorer, less diverse and mainly neutral facial expressions, possibly related to impairments in motor cognition (Tremeau, 2006), or even low-level disruption of rapid facial mimicry (Varcin et al., 2010). Along these lines, impairments in the imitation or execution of emotional (including facial) expressions have been reported (Lee et al., 2014). Overall, these findings have addressed different aspects of emotion expression and further research is needed to establish a clear link with blunted affect.

3.1.2. Dysfunction in emotion perception

Another line of research in the pathophysiology of diminished expression has focused on impairments in emotion perception (Gur et al., 2006; Lepage et al., 2011).

Limited evidence has pointed to a direct association between emotion perception deficits and overall negative symptoms, with diminished expression symptoms being particularly affected (Gur et al., 2006; Lepage et al., 2011). Gur and colleagues (2006) found that patients with schizophrenia and flat affect were significantly more impaired than those without flat affect using an emotion intensity differentiation task. However, earlier work suggested that negative symptoms might related to a *general* performance deficit, rather

than a specific abnormal emotion perception (Kerr and Neale, 1993). Along the same lines, Kring and colleagues (Kring and Campellone, 2012) suggested that abnormal emotion perception stems from abnormal contextual integration of emotional stimuli in prefrontal cortices, rather than a deficit in low-level emotion perception processes *per se*. Overall, while emotion-processing deficits in patients with schizophrenia have clearly been shown, it remains to be determined whether such deficits contribute directly to the diminished expression dimension (Kohler et al., 2010) or indirectly via general neurocognitive impairment (see (Kring and Elis, 2013; Kring and Moran, 2008) for comprehensive reviews). In sum, these findings provide evidence that links blunted affect to deficits in emotion perception, identification and discrimination and/or perception of nonverbal cues.

3.1.3. Limited cognitive resources

Attempts to conceptualize diminished speech expression have resulted in the cognitive resource limitation model of alogia (Cohen et al., 2014; Cohen et al., 2012). According to this model, speech is dependent on multiple cognitive domains, such as controlled retrieval during verbal fluency tasks (Docherty et al., 2011), semantic memory organization (Sumiyoshi et al., 2005), verbal fluency (Joyce et al., 1996). In support for the limited cognitive resource model, deficits in working memory (Barch and Berenbaum, 1997) and impaired overall cognitive performance (Hartmann-Riemer et al., 2015) have been shown to play a role in alogia.

When patients are exposed to situations with increased cognitive demands (also called “high-load” conditions), such as during social interactions, less cognitive resources will be allocated to speech production. Cohen and colleagues (2012) provided initial evidence in individuals with schizotypy and schizophrenia that diminished expression might be underpinned by a *relative* lack of cognitive resources (Cohen et al., 2014; Cohen et al., 2012). Additional support for a limited cognitive resources model derives from studies reporting that diminished expression is associated with cognitive impairments in patients with schizophrenia (Galderisi et al., 2014; Hartmann-Riemer et al., 2015; Sevy et al., 2020). Taken together, these results indicate that situations with high cognitive demands (e.g. social situations) in an already limited baseline cognitive functioning may

lead to a *relative* insufficiency of cognitive resources and, in turn, may cause symptoms of diminished expression, in particular, alogia.

It is important to underline that in contrast to the apathy domain no comprehensive cognitive models exist for the diminished expression domain, even though alogia and blunted affect load systematically onto the same psychometric factor. Future efforts in this direction are necessary and might be indeed essential for defining specific treatment targets.

3.2. Neural substrates of diminished expression

Scarcer efforts have been dedicated to study the neural correlates of diminished expression compared to the apathy dimension. Neuroimaging studies focusing on diminished expression can be clustered in a) task-based fMRI employing tasks, which require emotional expression, emotion perception and cognitive resources b) rs-fMRI and c) sMRI assessing gray and white matter changes in patients with schizophrenia (see Figure 2, regions in green).

3.2.1. Task-based functional neuroimaging

Few fMRI studies have examined neural activity in relation to diminished expression employing tasks that examine motor components of emotional expression. Using a facial emotion imitation task Lee and colleagues (Lee et al., 2014) showed an association of blunted affect with deficits in motor aspects of emotional expression. Of note, they observed significant negative correlations between severity of blunted affect and brain activity in the mirror neuron system (including premotor cortex, motor cortex, and inferior parietal lobule) during imitation of emotional expression.

Evidence for the cognitive resource limitation model in behavioral studies has been obtained by observing changes in emotional expression “online”, while manipulating cognitive demands (Cohen et al., 2014; Cohen et al., 2012). This or related approaches have, to our knowledge, not been used in functional neuroimaging, and therefore the functional neuroimaging evidence for the cognitive resource limitation model is only indirect. Hager and colleagues (2015) employed a n-back memory task coupled with

monetary reward for performance. Their results showed that activity in the rostral ACC was inversely correlated to the diminished expression dimension and was thought to reflect the incapacity to recruit additional cognitive resources when rewards are at stake. Another study found that the severity of alogia was associated with decreased activity in key components of the basal ganglia, including the right caudate and left pallidum, during an auditory oddball task (Shaffer et al., 2015). The authors speculated that this implication might reflect a disturbance of voluntary motor behavior but may also be related to the crucial role of basal ganglia in language processing.

Finally, other fMRI studies have focused on emotional perception and discrimination in relation to blunted affect (Gur et al., 2007; Lepage et al., 2011; Rahm et al., 2015). One earlier study of emotional face processing in schizophrenia (Gur et al., 2007) observed that amygdala activation in response to fearful faces was correlated with more severe blunted affect. In addition, Lepage and colleagues (2011) employed a gender identification task on sad, happy and neutral emotional facial expressions. Severity of blunted affect was negatively correlated with activity in the amygdala and the parahippocampal gyrus, suggesting that regions involved in emotional face perception may play a role in the emergence of this domain. Rahm and colleagues (2015) also found a significant negative correlation between emotional blunting and neural activation in the amygdala during positive affect processing. Together with the previous study, this work points towards abnormal amygdala function in the development of blunted affect. Another region potentially implicated in the pathophysiology of diminished expression is the ventrolateral prefrontal cortex. Stip and colleagues (2005) employed a passive viewing task and presented sad film excerpts to schizophrenia patients with and without blunted affect. Their results showed heightened VLPFC recruitment in patients without blunted affect vs. those with blunted affect. In addition, patients with blunted affect showed temporal and midbrain hyperactivity, which was interpreted as impaired emotional processing.

In sum, current evidence for neural correlates of either alogia or blunted affect is limited by single studies, heterogeneous task design and lack of replication across different patients' groups. Based on the available data, cortical motor areas and fronto-limbic regions (e.g. VLPFC, rostral ACC, amygdala, basal ganglia) may be involved in the pathophysiology of diminished expression.

3.2.2. Resting-state functional neuroimaging

Resting-state fMRI studies directly addressing neural correlates of diminished expression are scarce. Few studies reported an association between total negative symptoms and abnormal connectivity of the default mode network (DMN) (Bluhm et al., 2007; Mazza et al., 2013; Orliac et al., 2013). Using probabilistic independent component analysis (pICA) to resting state data, Mingoia and colleagues (2012) revealed a pattern of hyper/hypoconnectivity in pre-defined regions of the default mode network (DMN) in patients with schizophrenia. Correlation analysis showed that intrinsic fronto-polar cortex connectivity was negatively correlated with the SANS subscales affective flattening and alogia, while right inferior temporal gyrus intrinsic connectivity was negatively associated with the alogia subscale only. Adding to this, a recent study showed that severity of flat affect was positively associated with functional network connectivity between anterior DMN and salience network (Hare et al., 2018). Together, these findings suggest a specific role for regional and between network dysconnectivity in the development of diminished emotional expression (Millan et al., 2014) beyond well-established DMN abnormalities in schizophrenia (Whitfield-Gabrieli and Ford, 2012; Whitfield-Gabrieli et al., 2009).

3.2.3. Structural neuroimaging

Consistent sMRI findings in relation to diminished expression have yet to emerge. One study found that GM volume in ACC was negatively correlated with the negative subscales scores of emotional withdrawal and difficulty in abstract thinking (Kim et al., 2017). In addition, GM volume of the superior temporal gyrus (STG) correlated negatively with PANSS subscale scores of blunted affect, poor rapport, difficulty in abstract thinking, and stereotyped thinking (Kim et al., 2017). By contrast, another study found positive correlation of GM volume in the STG with alogia and blunted affect symptoms (i.e. higher severity of such symptoms related to higher GM volume in the STG) (Caravaggio et al., 2017). Additionally, the same study found positive correlation of blunted affect severity with GM volumes in bilateral inferior temporal lobes, left fusiform face area, and bilateral supramarginal gyri (Caravaggio et al., 2017).

With respect to white matter changes, integrity of the left superior fronto-occipital fasciculus (SFOF) was negatively correlated with affective flattening (Asami et al., 2014).

In sum, across neuroimaging modalities, evidence suggests a potential role for the rostral ACC, amygdala and basal ganglia as well as the ventro-lateral PFC and temporal cortical regions. It is evident, however, that these emerging findings are not easy to integrate into a pathophysiological model of diminished expression. Therefore, future neuroimaging studies should directly address neural substrates of diminished expression. First, to help define a comprehensive model of this negative symptom dimension, and second to identify novel targets for an individualized treatment of diminished expression.

3.2.4. Pharmacology of diminished expression

The pharmacology of diminished expression is only poorly understood. Research has been hampered by a lack of pathophysiological models and inherent challenges to test hypotheses of diminished expression in animal studies. Oxytocin has been considered a potential pharmacological candidate, given correlations between plasma oxytocin levels and identification of emotions in facial (Goldman et al., 2008) or body expressions (Strauss et al., 2015) in schizophrenia. While some studies showed positives effects of intranasal oxytocin on increased facial expressivity in patients with schizophrenia (Woolley et al., 2017), a recent meta-analysis of intranasal oxytocin yielded no effects for negative symptoms (Zheng et al., 2019) (section 3.4.2 for discussion of treatment). In sum, pharmacological mechanisms of diminished expression remain a field that requires additional research.

3.4 Treatment of diminished expression, related mechanisms and neural substrates

Overall, very little research efforts have been dedicated to the treatment of diminished expression dimension. In the following sections, we emphasize treatment approaches that may have some specificity in this regard.

3.4.1. Psychosocial interventions

Regarding CBT-based interventions, it is important to note that the diminished expression was rarely the therapeutic focus. More recent treatment manuals have

included modules addressing emotional expression and speech production (Klingberg et al., 2011). However, Klingberg and colleagues (2011) reported improvements in diminished expression and apathy after CBT that were not different from improvements within the active control group receiving CRT.

Considering the cognitive resource limitation model, CRT is a potentially interesting approach for improving expressive deficits. As mentioned above, meta-analytic evidence corroborates a positive effect on negative symptoms (Cella et al., 2017a), however, cognitive remediation effects on diminished expression have rarely been reported, with only two exceptions. Ventura and colleagues (2019) compared CRT vs Healthy Behaviors Training (HBT) over a 12 months period in first-episode schizophrenia, and found improvements in the CRT arm for both negative symptom dimensions (apathy and diminished expression). This positive effect on diminished expression was confirmed by Sevy and colleagues (2020) (see section 2.3.1). Taking a transdiagnostic approach, it is worth mentioning that in other neuropsychiatric disorders, the limited-cognitive-resources model has been successfully employed for motor-cognitive dual-task training (Fritz et al., 2015). It would be of high interest to probe whether such interventions could be adopted for diminished expression in schizophrenia.

CRT specifically targeting impaired facial recognition has shown significant improvement in facial emotion recognition and overall negative symptoms, but association with diminished expression has not been reported (Gaudelus et al., 2016; Wolwer and Frommann, 2011). Another potentially interesting approach is speech and language therapy to overcome deficits in pragmatics (e.g. usage of language in a given context) and discourse skills (Joyal et al., 2016). However, no controlled studies targeting negative symptoms and diminished expression in schizophrenia have been reported.

Social skills training programs include a heterogeneous set of modules but expressive skills in verbal and nonverbal behavior are a key components related to diminished expression (Elis et al., 2013). Social skills training has been shown to improve overall negative symptoms, but few studies report specific outcomes for diminished expression (Turner et al., 2018). Social skills training focusing on social cognition domains (e.g. emotional perception, affiliative and interactive skills and so on) has yielded small to medium positive effects on social withdrawal and communication (Rus-Calafell et al.,

2013). Replications in larger cohorts are needed to establish specific social skills training effects on diminished expression. In addition to the diminished expression dimension, social skills training may be useful to target apathy, in particular, asociality (Granholm et al., 2014).

Arts and body-oriented therapies could theoretically improve emotional expression and interpersonal functioning. However, after initial promising results, recent findings from larger studies have been somewhat disappointing (Crawford et al., 2012; Priebe et al., 2016), even though small improvements in expressive deficits were observed with body-oriented psychotherapy (Priebe et al., 2016).

3.4.2. Biological interventions

After initial studies had shown promising results of oxytocin for the treatment of negative symptoms, the results have overall been disappointing (Williams and Burkner, 2017). It is important to note that oxytocin potentially targets cognitive processes and brain regions associated with diminished expression, but specific results for this dimension have rarely been reported. Therefore, it would be of high importance to specifically address the question whether modulation of these processes (e.g. facial expressivity or social cognition) can improve clinical manifestation of diminished expression. However, heterogeneity in the assessment of negative symptoms and varying dosage and duration of oxytocin in current studies are potential limitations that should be addressed in future studies.

4. Discussion and future directions

4.1. Summary

Considerable progress has been made in understanding behavioral, cognitive, and neural mechanisms related to negative symptoms of schizophrenia. However, despite enormous efforts, translation to treatment of negative symptoms has not been achieved and remains a critical unmet need. One major weakness of previous basic and clinical studies is that negative symptoms and their underlying pathophysiology were often treated as if they were a monolithic entity. In addition, research in negative symptoms has yet to account for the heterogeneity in length and course of negative symptoms across the lifespan (Lyne et al., 2018), their fluctuations over time (Savill et al., 2015), their influence by differential baseline levels, premorbid functioning and the duration of untreated psychosis (Lyngstad et al., 2020). The study of the longitudinal evolution of negative symptoms with a pathophysiological multi-level approach, as advocated here, may therefore be crucial to tackle these issues. In this context, recent studies provide accumulating evidence for specific pathological processes of two distinct negative symptom dimensions: apathy and diminished expression. We believe that treatment of negative symptoms can only be advanced by systematically targeting these negative symptom dimensions and uncover the precise pathological mechanisms.

For the apathy dimension, a comprehensive and integrative framework of behavioral and neural mechanisms already starts to emerge. Various aspects of motivation and goal-directed behavior have been directly related to the clinical manifestation of apathy. These deficits include blunted reward anticipation, impaired reward learning and effort-based decision-making, as well as cognitive mechanisms such as neurocognitive deficits and dysfunctional beliefs. Of note, new psychosocial interventions are beginning to specifically target some of these processes, for example, by training anticipatory pleasure. On a neural level, accumulating evidence from different neuroimaging modalities demonstrate that the neural substrates of apathy can be mapped on circumscribed regions within a prefrontal-striatal network. Key structures in this network are the ventral/dorsal striatum, ventromedial PFC/OFC, DLPFC and ACC, all being implicated in normal motivated behavior (Dowd and Barch, 2010; Le Heron et al., 2018;

Millan et al., 2014). In this regard, uncovering distinct prefrontal-striatal pathways related to apathy could be key to improve treatment. First, a precise cortico-striatal mapping of apathy could advance individualized non-invasive brain stimulation approaches. Second, integrating mechanistic models and neurofunctional prefrontal-striatal substrates of apathy may promote new pre-clinical models for drug development. To achieve these goals, it will be crucial to go beyond the conceptualization of apathy in schizophrenia and develop a transdiagnostic understanding of overlapping and distinct features of apathy, anhedonia and depression (Husain and Roiser, 2018; Kirschner et al., 2020).

In contrast to the apathy dimension, mechanistic models and neural substrates of the diminished expression dimension are less developed. Disturbances in three main areas can be distilled from the current literature: impaired emotion expression and emotion perception as well as insufficient cognitive resources for speech production. In all three areas, studies have identified deficits in patients with schizophrenia. However, only very few studies show a direct association with the clinical manifestation of diminished expression. In addition, to our knowledge, none of the hypothesized causal mechanisms of diminished expression has been replicated in independent studies. Thus, this lack of a comprehensive pathophysiological model has clearly undermined efforts to yield significant results for new treatment approaches. Hence, although all of these deficits in emotion processing and cognition are potentially amenable to psychosocial interventions, we are still far away from an individualized treatment of diminished expression. Similar to the research gap regarding pathophysiological models, neural substrates of diminished expression have not been systematically investigated and evidence relies on few heterogeneous studies. So far, neural substrates of diminished expression were described in fronto-limbic regions including the rostral ACC, amygdala, basal ganglia and ventro-lateral PFC, temporal cortical regions and dysconnectivity of the DMN. Of note, some of the neural substrates are structurally overlapping with those from the apathy dimension (e.g. striatum, ACC). However, specificity for the diminished expression dimension could rely on associations to independent and distinct functional neural processes within these regions. Similar to the limited data on mechanistic models, the current literature on relationships between brain abnormalities and diminished expression provide little guidance for the development of dimension-specific biological treatment approaches.

The preceding sections illustrate efforts to define comprehensive, multi-level frameworks for the apathy and diminished expression dimensions. At the same time, the present overview highlights research gaps and limitations in transferring existing knowledge into clinical management of negative symptoms (Box 2). Future work should address this lack of research and incapability in integrating clinical, mechanistic, and neural levels to advance drug development and individualized treatment of negative symptom dimensions/domains. The present review is limited by the fact that very few clinical trials reported separate outcomes for the apathy and diminished expression dimensions. Therefore, the potential specificity of pathophysiological mechanisms and neural substrates in relation to treatment remains somewhat speculative. Furthermore, while some studies made the effort to adequately address the distinction between primary and secondary negative symptoms, a systematic approach is still missing. This hampers the ability to disentangle precise pathological mechanisms of primary negative symptoms, as well as to develop an understanding of potential shared and divergent mechanisms of both primary and secondary negative symptoms. Hence, in our opinion, it is essential to systematically include a differentiated clinical assessment across all levels of investigation in basic science (behavioral, pharmacological, cognitive and neural mechanisms) as well as clinical trials in order to limit cohort heterogeneity.

4.2 Future directions

By deconstructing negative symptoms, recent scientific work started to decipher specific pathophysiological mechanisms related to the dimensions of apathy and diminished expression (Box 3). In this regard, it is relevant to note that recent psychometric studies strongly suggested an even more detailed differentiation into five domains (anhedonia, avolition, asociality, blunted affect, and alogia) (Ahmed et al., 2018; Strauss et al., 2019b; Strauss et al., 2018). Therefore, it would be of high interest to explore whether a higher degree of granularity could also be related to other levels of investigation including behavioral, pharmacological, cognitive, and neural mechanisms as well as treatment development. Irrespective of the degree of examination, it is instrumental to ask how a differentiated view on negative symptom dimensions/domains can provide new avenues in ultimately improving treatment development and patient care. As outlined

before, a differentiated approach allows to systematically define multi-level frameworks for distinct negative symptom dimensions/domains. This will form the basis to identify mechanistic targets for the development of new biological and psychosocial treatments as well as ways to quantify their efficacy. Domain-specific mechanistic and neural models could be translated into pre-clinical models in order to develop new selective pharmaceutical targets. In line with the Research Domain Criteria (RDoC) initiative (Insel et al., 2010), multi-level models of negative symptom dimensions/domains would enable the evaluation of clinical outcome in treatment trials on several levels including clinical, biological, behavioral and neural measures.

A dimension-specific understanding of neural mechanisms could also advance treatment of negative symptoms with non-invasive brain stimulation. Specific neural networks and systems could guide decision-making for treatment selection as well as serving as targets for individualized TMS treatment. Of note, this potential application could also be employed in other forms of non-invasive brain stimulation, such as real-time fMRI neurofeedback. Although this approach is still in its infancy, promising results of successful self-regulation of the reward system in healthy individuals and addiction (Kirschner et al., 2018; MacInnes et al., 2016; Sulzer et al., 2013) as well as treatment trials in depression (Young et al., 2017) suggest a potential translation as treatment approach for negative symptoms.

Furthermore, a differentiated view on pathophysiological models of negative symptom dimensions/domains may advance the integration of biological and psychosocial intervention into comprehensive treatment approaches. This integration of treatments on a biological and psychological level is relatively little explored but deserves more attention. One pressing question in this regard is how biological treatments could contribute to the efficacy of a psychosocial intervention. To give a very simplified example, imagine a patient with apathy showing reduced reward anticipation and impaired learning from positive outcomes. A CBT approach to improving reward anticipation would be an obvious treatment option. However, beneficial effects may be hampered by the patient's amotivation and inability to learn from positive outcomes, both being the basis for most CBT treatments. In this scenario, the selective use of pro-dopaminergic drugs or neuroimaging-guided non-invasive brain stimulation of the reward system may potentially

improve motivation and learning from positive outcomes. Hence, the efficacy of CBT and treatment adherence might improve considerably.

Taken together, one of the most important clinical consequences of systematically employing a dimension-specific approach to negative symptoms could be the development of individualized treatment. In the near future, it might be possible that comprehensive, multi-level frameworks of negative symptom dimensions guide clinicians to precisely define inter-individual differences between patients. Specifically, clinicians may be able to differentiate complex clinical pictures (apathy vs. diminished expression, primary vs. secondary) and directly relate symptoms to dysfunctional mechanisms and neural substrates. Based on these personalized symptom models, it might be possible to tailor treatment to the individual needs of our patient and provide successful care of these debilitating symptoms.

Box 1

Box 1 adapted from Marder and Galderisi (2017)) and following the NIMH consensus statement on negative symptoms (Kirkpatrick et al., 2006)

Negative symptoms	**Definition**
Avolition	Diminished motivation and lack of drive resulting in reduced initiation and maintenance of goal-directed activities.
Anhedonia	Diminished experience of pleasure related to current and/or future activities. Two types of anhedonia are usually distinguished: - *Consummatory anhedonia* = pleasure experience is decreased during the unfolding of the activity. Generally, preserved in patients with schizophrenia. - *Anticipatory anhedonia* = pleasure experience is decreased during anticipation for upcoming activities. Generally, impaired in patients with schizophrenia.
Asociality	Reduced social activities and interactions accompanied by decreased interest in forming close relationships with others.
Blunted affect	Decrease in spontaneous or elicited expression of emotion and reactivity to events including facial mimicry, prosody and expressive gestures.
Alogia	Reduction in quantity of speech and spontaneous elaboration.

Box 2. Key points review

- Negative symptoms can be mapped on at least two dimensions: apathy and diminished expression.
- There is increasing evidence for negative symptom dimensions-specific multi-level framework including behavioral, cognitive and neural mechanisms.
- For apathy, a comprehensive model including different behavioral mechanisms and fronto-striatal function essential to goal-directed behavior is starting to emerge.
- For diminished expression, different underlying cognitive mechanisms have been proposed. Only few studies have investigated neural substrates of diminished expression and comprehensive multi-level remains to be established.
- Treatment research has only recently begun to specifically target the negative symptom dimensions of apathy and diminished expression.

Box 3. Future Directions

- A differentiated view on negative symptom dimensions/domains is instrumental to define comprehensive, multi-level frameworks of pathophysiological mechanisms.
- Developing multi-level models of distinct negative symptom dimensions/domains form the basis to identify mechanistic targets for the development of new biological and psychosocial treatments.
- Multi-level models of distinct negative symptom dimensions/domains (1) provide an avenue to integrate different biological and psychosocial approaches in combined treatment approaches and (2) could advance clinical-decision making and treatment tailored to the individual needs of our patient.

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Figure captions

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Figure 1: Schematic representation of negative symptom dimensions and individual negative symptom domains.

Figure 2: Schematic summary of pathophysiological processes and brain regions implicated with apathy (red) and diminished expression (green) and potential targets for treatment. Abbreviations: ACC, anterior cingulate cortex; AMY, amygdala; CBT, cognitive-behavioral therapy; DS, dorsal striatum; OFC, orbito-frontal cortex; rACC, rostral ACC; DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; VS, ventral striatum.