Understanding negative symptoms
Klaasen, Nicky Gabriëlle

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Chapter 1

General introduction
Schizophrenia is a severe and chronic psychiatric disorder, characterized by a complex and heterogeneous clinical picture. Next to rather visible positive symptoms like delusions and hallucinations, and cognitive deficits like disruptions in attention, memory, and executive functioning, negative symptoms are key symptoms of schizophrenia (Kahn & Keefe, 2013). Negative symptoms are described as diminutions in behaviors that are considered normal. They form a heterogeneous symptom cluster consisting of blunted affect, alogia, apathy, anhedonia, and asociality (Kirkpatrick et al., 2006).

Negative symptoms are present in the whole spectrum of psychotic disorders ranging from subclinical levels to clinical severity: they have been shown to be present in healthy individuals, individuals at risk for mental illness, first-episode psychosis and chronic schizophrenia, (Kaiser, Heekeren, & Simon, 2011). Negative symptoms have shown a strong relationship with functional outcome: people with higher levels of negative symptoms have shown impairments in occupational, household, social, and recreational functioning and lower quality of life (Foussias et al., 2014a). In addition, negative symptoms are associated with higher caregiver burden and distress (Provencher & Mueser, 1997). Moreover, they have been shown to be often persistent (Herbener & Harrow, 2001) and difficult to treat (Aleman et al., 2017).

Their debilitating and persistent nature strongly underlines the importance of studies to new and improved treatment options for negative symptoms. One of the factors hampering the development of treatment for negative symptoms is that to date not much is known about the cognitive and emotional mechanisms and the underlying neural substrates of negative symptoms (Aleman et al., 2017).

Even though the number of studies to the cognitive, emotional and neural underpinnings of negative symptoms has increased in recent years, a clear picture may currently be obscured by the heterogeneity in findings. For example, although ventral striatal activation during reward anticipation is generally found in association with negative symptoms (Radua et al., 2015), not all studies have reported this association (e.g., Esslinger et al., 2012; Kirschner et al., 2016b; Mucci et al., 2015; Simon et al., 2015). This may, at least partly, be due to heterogeneity in symptoms within the negative symptom cluster (Foussias et al., 2015). It has been proposed that negative symptoms are better characterized as two separate, but interrelated subfactors (Blanchard & Cohen, 2006). This has been confirmed by multiple factor analyses on two often-used scales for the assessment of negative symptoms, the Scale for the Assessment of Negative Symptoms (SANS) and the negative subscale of the Positive and Negative Syndrome Scale (PANSS) (Fervaha et al., 2014b; Liemburg et al., 2013; Stiekema et al., 2016; Strauss et al., 2013). The two negative symptom factors encompass expressive deficits and amotivation and are thought to be a better description of the heterogeneous negative symptom cluster (Messinger et al., 2011). While expressive deficits are thought to reflect disturbances in the outward expression of emotion and speech and consists of blunted affect and alogia, amotivation is thought to reflect reduced self-initiated and maintained behaviors and comprises apathy, asociality, and anhedonia (Foussias et al., 2014a; Messinger et al., 2011). Within the amotivation factor, apathy (or avolition) may serve as a core negative symptom, especially given its strong association with functional outcome (Foussias &
Expressive deficits and amotivation have been shown to be differentially associated with depression, functional and clinical outcome, and quality of life (Fervaha et al., 2014b; Kirkpatrick, 2014; Stiekema et al., 2016; Strauss et al., 2013) and may originate from different cognitive and underlying neural dysfunctions (Ergül & Üçok, 2015; Kaiser, Heekeren, & Simon, 2011). Taken together, assessment of the cognitive and neural substrates of the negative symptom factors separately or even on a symptom level is warranted in order to promote understanding of negative symptoms.

**Box 1. Terminology**

In the negative symptom literature, many different terms for the negative symptom cluster and its components are used. Although not exhaustive, this box gives an overview of the use of the different terms in the literature and in this thesis specifically.

- **Blunted affect** and **affective flattening** refer to a reduced observed expression of emotion, characterized by reduced facial and vocal expression, and expressive gestures. The term flat affect was used previously to describe these phenomena, but is now considered only suitable for description of the extreme end of the spectrum.

- **Alogia** reflects poverty of speech, a reduction of speech or richness of speech.

- **Apathy** and **avolition** are interchangeable terms used to describe a behavioral state characterized by a quantitative reduction of self-generated voluntary and purposeful behaviors.

- **Anhedonia** generally refers reduced experience of positive emotions. A distinction is often made between a reduction in anticipatory pleasure (wanting something) and consummatory pleasure (liking something).

- **Asociality** refers to social withdrawal that originates from indifference or reduced desire for social contact.

- **Expressive deficits** or **diminished expression** are used to refer to the negative symptom factor consisting of blunted affect and alogia.

- **Amotivation** is sometimes used as a synonym to apathy and avolition, but is also used to describe one of the negative symptom factors consisting of apathy, asociality, and anhedonia. In the literature, this factor is sometimes referred to as social amotivation or avolition, but in the current thesis the term amotivation will be used.

- **Deficit syndrome** or **deficit schizophrenia** describes a subgroup of patients with schizophrenia with enduring primary negative symptoms (i.e., not due to anxiety, medication effects, psychotic symptoms, cognitive impairment, or depression).

*In this thesis, the terms blunted affect and apathy will be used to refer to the respective symptoms. The terms expressive deficits and amotivation will be used to refer to the negative symptom factors.*
Underlying mechanisms and neural substrates of negative symptoms
Task-based fMRI studies have found a variety of processes and underlying neural substrates that may be disrupted in patients with negative symptoms. To date, most neuroimaging studies have addressed the negative symptom cluster as a whole. However, more recently a small number of studies have studied the neural correlates of amotivation and expressive deficits or their component symptoms separately, suggesting a differential cognitive and neural substrate for these factors.

Box 2. Functional Magnetic Resonance Imaging (fMRI)
In order to assess the underlying neural correlates of cognitive and emotional processes and possible disruptions thereof, functional Magnetic Resonance Imaging (fMRI) has proven to be a useful tool. It has been shown that neuronal activity induces an increase in oxygenated blood flow to the active region (the hemodynamic response). The resulting change in relative levels of oxyhemoglobin and deoxyhemoglobin (oxygenated or deoxygenated blood) can be detected on the basis of their differential magnetic susceptibility. This effect is referred to as the blood-oxygenated-level dependent (BOLD) contrast. It should be noted that the BOLD contrast, as measured using fMRI, is not a direct measure of neuronal activity, but is nonetheless a good proxy of neural activation (Logothetis, 2002).

Two different types of fMRI paradigms can be distinguished: task-evoked fMRI and resting-state fMRI paradigms. During task-evoked fMRI paradigms, participants are asked to perform a task and task-related changes in BOLD signal are assessed to investigate which areas of the brain are active, or which interactions between regions are involved, during a specific process.

In resting-state paradigms no particular task is performed and participants are asked to lie still, stay awake, in absence of an external task. Using resting-state paradigms circumvents the problem that differences in task performance between groups may influence fMRI results, a problem that is often encountered in task-based fMRI studies (van den Heuvel & Hulshoff Pol, 2010). During wakeful rest, the brain shows intrinsic (or task-unrelated) ongoing neural and metabolic activity, reflected by spontaneous low frequency fluctuations of the BOLD signal (Raichle, 2009). In resting-state studies these spontaneous fluctuations are examined. Interestingly, these fluctuations have been shown to correlate between spatially remote but functionally similar brain areas. Several distinct resting-state networks have been identified including the somatomotor network (Biswal et al., 1995), primary visual and auditory networks (Cordes et al., 2000), default mode network (Greicius et al., 2003), executive cognitive control network (Menon & Uddin, 2010), dorsal and ventral attention networks (Fox et al., 2006), and salience network (Seeley et al., 2007). Resting-state networks been found reflect the underlying structural connections between brain areas (Van Den Heuvel et al., 2009), and have been shown to correspond closely with BOLD dynamics during task (Smith et al., 2009) and to correlate with cognitive performance (van den Heuvel & Hulshoff Pol, 2010), emphasizing their utility in studying the neural underpinnings of psychopathology.
Amotivation
It has been suggested that reduced goal-directed behavior is central to the symptoms that comprise the amotivation factor. Goal-directed behavior requires a large number of processes, most notably, reward and effort processing, executive functioning, and self-initiation of behaviors. Disruptions in any of these processes may lead to reductions in goal-directed behavior and thus to the occurrence of amotivation (Levy & Dubois, 2006).

First, goal-directed behavior requires association of positive affective and emotional associations with ongoing and forthcoming behavior (Levy & Dubois, 2006). This relies on reward-related processes like reward anticipation and the anticipation of a favorable outcome of an action, as well as intact emotional memory (Kring & Barch, 2014). Reward processing has been associated with a variety of brain regions within mesocorticolimbic networks, most notably the ventral striatum, orbitofrontal cortex, and anterior and posterior cingulate cortex (Liu et al., 2011). Indeed, negative symptoms have been found to be related to reduced activation of the ventral striatum during reward processing (Radua et al., 2015) and the anterior cingulate cortex during processing of positive emotional stimuli (Nelson et al., 2015). More specifically to amotivation, ventral striatal activation during reward processing has been found in relation to amotivation, but not expressive deficits (Kirschner et al., 2016a; Simon et al., 2015).

Besides reward processing, computation of the effort needed to execute the action, as well as willingness to expend that effort is needed to engage in goal-directed behavior (Kring & Barch, 2014). If the expected benefit of a certain action exceeds the expected effort, this will lead to the approach motivation needed to prepare and execute the action (Kring & Elis, 2013). On a neural level, effort computation and expenditure is thought to involve the striatum, ventromedial prefrontal cortex, and insula (Treadway et al., 2012). Difficulties in effort cost computation and expenditure have been found in relation to negative symptoms (Fervaha et al., 2013; Gold, Waltz, & Frank, 2015) and difficulties in effort expenditure have been related to less activation in the nucleus accumbens, the posterior cingulate gyrus, and medial frontal gyrus, in patients with schizophrenia compared to healthy controls (Huang et al., 2016). However, how this relates to negative symptoms remains to be investigated.

Furthermore, when the reward/effort ratio is such that one is inclined to engage in the action, intact executive functioning (including processes like allocation of attention, rule finding, set-shifting, and the maintenance of goals and subgoals) is needed to plan the action (Levy & Dubois, 2006). These processes have often been associated with activation and connectivity in a network of frontal, striatal, and parietal regions (Leh, Petrides, & Strafella, 2010). In patients with schizophrenia, disturbances in executive functioning have been found, and have been associated with activation and connectivity in a network (Deserno et al., 2012; Minzenberg et al., 2009). In relation to negative symptoms, reduced activation has been found in the left DLPFC, left premotor cortex, and bilateral nucleus accumbens during processing of novel stimuli (Wolf et al., 2008) and to reduced activation in the right hippocampus, amygdala, superior temporal cortex, fusiform gyrus, and thalamus, the left middle frontal gyrus and lateral parietal cortex, and the bilateral insula, cuneus, and posterior cingulate cortex during
the processing of target stimuli (Shaffer et al., 2015) during auditory oddball paradigms. Moreover, stronger severity of amotivation has been found in association with reduced activation in the thalamus and parietal cortex during planning behavior (Liemburg et al., 2015).

Finally, the initiation or auto-activation of thoughts or behavior is imperative to execute goal-directed action (Levy & Dubois, 2006). Difficulties in action initiation are reflected in reduced activation of mental set and emotional response, and lack of self-generated thoughts (mental emptiness) and self-generated actions. In patients with reduced thought or action initiation, there may be a clear contrast between an obvious reduction of self-generated actions and a normal production of actions in response to external demands. Self-initiation of behavior is thought to rely on the anterior midcingulate cortex and (pre-) supplementary motor area ((pre-) SMA) (Hoffstaedter et al., 2013; Jenkins et al., 2000) and disruptions in these areas are thought to lead to reduced goal-directed behavior and therefore to amotivation (Levy & Dubois, 2006).

Expressive deficits

When it comes to expressive deficits, the body of research concerning this topic is much more limited. However, studies on blunted affect and alogia in patients with schizophrenia suggest that recognition and processing of emotions and allocation of cognitive resources may be disrupted in patients with expressive deficits. In line with the modest number of studies, models regarding the underlying cognitive and neural mechanisms of expressive deficits have not been thoroughly developed.

Studies focusing on blunted affect have found that this symptom was associated with impairments in judging facial affect of others, especially when differences in affect were subtle (Gur et al., 2006). One area that is consistently implicated in the processing of emotional stimuli and facial affect in particular is the amygdala (Wager et al., 2003). This area has consistently been associated with disrupted emotional processing (Aleman & Kahn, 2005), and indeed, during the processing of facial affect, negative symptoms have been associated with reduced activation of the amygdala for positive affect (Lepage et al., 2011; Rahm et al., 2015). Moreover, Gur et al. (2007) showed that blunted affect was related to increased amygdala activation during disrupted processing of fearful faces, suggesting an overstimulation of the amygdala in these patients.

Alogia on the other hand may be due to limited cognitive resources (Cohen et al., 2014). This idea is based on the assumption that at any given time, an individual has a certain amount of cognitive resources that can be allocated towards cognitive functioning. Given the cognitive deficits that are often found in patients with schizophrenia, fewer cognitive resources may be available in patients than in healthy individuals. Patients may therefore lack the resources needed to produce normal levels of speech while having to attend to other cognitive functions as well. Hager et al. (2015) added to this that patients with schizophrenia with more severe expressive deficits showed disruptions in reward-modulated allocation of resources. Using a working memory task with varying levels of performance incentives, patients and healthy controls were expected to allocate resources towards the higher yield, a function thought to be mediated by the anterior cingulate cortex (ACC) (Krebs et al., 2012). Results showed
that patients were less able to adapt cognitive resources towards a rewarding outcome, suggesting that not only limited resources, but also allocation of resources may be underlying expressive deficits.

**Resting-state functional connectivity and negative symptoms**
Similar to task-based fMRI studies, studies using resting-state fMRI have shown a heterogeneous pattern of findings. Although dysconnectivity of large-scale brain networks has long been linked to schizophrenia (Stephan, Baldeweg, & Friston, 2006), to date no clear-cut association has been found between connectivity changes and negative symptoms. Both increased (Bluhm et al., 2007; Cole et al., 2011; Mingoa et al., 2012; Mwansisya et al., 2013; Wang et al., 2015) and decreased functional connectivity (Bluhm et al., 2007; Cole et al., 2011; Lui et al., 2009; Pu et al., 2014; Wang et al., 2014) have been found in relation to negative symptoms, both within and between resting-state networks. However, not in all studies an association with negative symptoms has been found (Orliac et al., 2013; Rotarska-Jagiela et al., 2010; Schilbach et al., 2016; Wang et al., 2016). Specifically, negative symptoms have been associated with altered connectivity between a variety of brain regions, including the lateral and medial prefrontal cortex, anterior and posterior cingulate, precuneus, and several areas in the temporal lobe (Bluhm et al., 2007; Cole et al., 2011; Lui et al., 2009; Mingoa et al., 2012; Mwansisya et al., 2013; Pu et al., 2014; Wang et al., 2015, 2014). How these changes in functional connectivity reflect variations in the negative symptom factors or specific symptoms remains unclear.

More recently, the organization of the brain as a complex graph has received considerable attention. Using graph theory, it has been shown that the brain, like many other complex networks, has a small-world organization or topology, which is characterized by high local clustering, combined with short path lengths between nodes, i.e., brain areas, balancing integration and segregation or specialization of processing (Fornito & Bullmore, 2015). Studies have shown that in patients with schizophrenia the functional organization of the brain is less like a less small-world network than in healthy controls (Kambeitz et al., 2016). Specifically, retained or higher functional integration (e.g., retained or higher global efficiency) and lower segregation (e.g., smaller clustering and modularity coefficients) may imply that network connectivity is more random in patients with schizophrenia (Rubinov et al., 2009). Associations between negative symptom severity and lower (Ma et al., 2012; Yu et al., 2011) and higher integration (Su et al., 2015) have been found, but whether this reflects heterogeneity in negative symptoms remains unknown.

**Aim and outline of this thesis**
The aim of this thesis is to investigate the neural substrate of negative symptoms. Neural correlates of negative symptoms as a whole, as well as those of the expressive deficits and amotivation factor and apathy as core negative symptom are assessed, in order to unravel the neural processes that are disrupted in people with negative symptoms. To this end, task-based brain activation related to reward processing, affective forecasting (i.e., thinking about positive events that may happen in the future), cognitive flexibility, and self-initiative are examined, as well as connectivity during rest (Figure 1). Both studies in patients with schizophrenia and in healthy individuals are included, in order
to take into account a broad range of symptom severity.

In chapter 2, the involvement of reward-related ventral striatal activation is studied in association with negative symptoms. Using quantitative meta-analysis, results from published literature on this topic are combined to assess whether negative symptoms are consistently related to reduced activation of the ventral striatum during reward processing. In chapter 3, we expand the study of reward-related processing to a more broad and personalized representation of rewarding stimuli. To this end, we explore the neural underpinnings of affective forecasting as a possible substrate for negative symptoms in patients with schizophrenia.

In chapter 4, we zoom in further on negative symptoms and examine whether functional brain organization is differently related to the factors of negative symptoms: expressive deficits and amotivation. Brain organization is studied using graph analysis on resting-state data of patients with schizophrenia. The aim of this chapter is to assess whether the graph theoretical properties of the functional networks of these patients are related to expressive deficits, amotivation, or negative symptoms as a whole. In chapter 5, we focus specifically on the amotivation factor and assess reward-related resting-state connectivity in relation to the amotivation factor. Specifically, we assess functional connectivity between a seed consisting of the ventral tegmental area and substantia nigra, and the rest of the brain in patients with schizophrenia.

In chapter 6, the focus is shifted from patients with schizophrenia to healthy individuals with varying levels of apathy. The focus on amotivation is narrowed by assessing the neural correlates of a single core negative symptom, namely apathy. Specifically, in this chapter we assess whether apathy in the healthy population is associated to neural alterations during set-shifting, a crucial component of executive functioning. In chapter 7, the neural correlates of apathy in the healthy population are explored further. In this chapter, the focus lies on the association between apathy and neural activation related
to auto-activation or self-initiative.

Finally, in chapter 8, results are summarized and discussed in relation to the current literature.
PART I

Neural correlates of negative symptoms