Malevolent Voices in Schizophrenia

Amygdala Resting State Functional Connectivity Based on Emotional Valence of Auditory Hallucinations

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Abstract

The present study explored functional connectivity of the laterobasal amygdala in a group of schizophrenia patients and healthy control subjects during rest to investigate underlying neural correlates of emotion processing related to auditory hallucinations. Beliefs About the Voices Questionnaire was used to separate hallucinating patients into a group with malevolent voices, and a group with benevolent voices to investigate neural correlates of the voices emotional valence. Patients with auditory hallucinations ($N = 20$), non-hallucinating patients ($N = 25$), and healthy controls ($N = 54$) underwent a resting-state fMRI scan. Functional connectivity analysis of the laterobasal amygdala was conducted to investigate differences between hallucinating patients and control groups. A second analysis was conducted to compare patients with malevolent voices and benevolent voices. Results show that hallucinating patients have different resting state functional connectivity of the laterobasal amygdala, compared with non-hallucinating patients and healthy controls. These areas include the paracingulate gyrus, anterior cingulate cortex, inferior frontal gyrus, temporal pole, inferior parietal lobule and precuneus. The hallucinating patients with malevolent voices have decreased resting state functional connectivity between the laterobasal amygdala and the medial prefrontal cortex, compared to hallucinating patients with benevolent voices. There was also a gender effect, where women experienced more malevolent and omnipotent voices compared to men. Women also experienced more depression, anxiety, general psychopathology and negative symptoms. The results suggest that intrinsic activation of regions involved with emotion processing are different depending on symptoms in schizophrenia.

Keywords: amygdala, AVH, BAVQ-R, emotion, functional connectivity, resting state fMRI, schizophrenia

Sammendrag

Nevrale sammenhenger med emosjonsprosessering relatert til auditive verbale hallusinasjoner (AVH) ble undersøkt ved "resting state fMRI". Funksjonelle hjernekoblinger ble målt hos schizofreni-pasienter med AVH, uten AVH og en kontrollgruppe. "Beliefs About Voices Questionnaire" ble brukt for å dele pasienter med AVH inn i en gruppe med "onde" stemmer, og en gruppe med "snille" stemmer. En analyse av funksjonelle hjernekoblinger ble utført med laterobasal amygdala som "region of interest" for å undersøke forskjeller mellom AVH pasienter og kontrollgrupper, og AVH undergruppene med "snille" og "onde" stemmer. Resultatene viser at pasienter med AVH har forskjellige hjernekoblinger med laterobasal amygdala, sammenlignet med schizofreni-pasienter uten AVH. Hjerneregioner med økte eller reduserte koblinger bestod av paracingulate gyrus, anterior cingulate cortex, inferior frontal gyrus, temporal pole, inferior parietal lobule og precuneus. AVH-pasienter med "onde stemmer" har svakere koblinger mellom laterobasal amygdala og medial prefrontal cortex, sammenlignet med AVH-pasienter med "snille stemmer". I dette utvalget var det kun menn som rapporterte mer "snille stemmer" enn "slemme stemmer", og kvinner hadde en høyere score av "slemme stemmer" sammenlignet med menn. Kvinner hadde også høyere forekomst av depresjon, angst, generell psykopatologi og negative symptomer. Resultatene tyder på at det er forskjeller hos schizofreni-pasienter i spontane nevrale fyringer av regioner involvert i emosjonsprosessering basert på ulike symptomer.

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1 Introduction

The scope of this thesis regards functional connectivity of emotional brain networks in hallucinating schizophrenia patients. The region of interest is the amygdala due to its central role in emotion processing. The motivation of this study was to see if there are differences in emotional brain networks between hallucinating and non-hallucinating schizophrenia patients and a healthy control group. The main hypothesis is that there will be differences between hallucinating patients with malevolent and benevolent voices.

1.1 Schizophrenia

Schizophrenia is a heterogeneous disease with symptoms of positive, negative and disorganized character (Stephan, Friston & Frith, 2009). Positive, or psychotic symptoms include delusions and hallucinations and involve a loss of contact with reality (Aleman & Kahn, 2005). Delusions are defined by the diagnostic and statistical manual of mental disorders (5th ed.; DSM-5; American Psychiatric Association, 2013) as fixed beliefs that are consistent in spite of conflicting evidence. Negative symptoms indicate a "subtraction of emotions" including flat affect, apathy and anhedonia (Aleman & Kahn, 2005). The most prominent negative symptoms of schizophrenia are diminished emotional expression and avolition (American Psychiatric Association, 2013). Diminished emotional expression includes reduced facial expressions and intonation of speech, and avolition is the reduced motivation to self-initiate in activities (American Psychiatric Association, 2013). The disorganized symptoms include difficulties in memory, attention and executive functioning (van Os & Kapur, 2009), e.g. disorganized thinking, speech or abnormal motor behaviour (American Psychiatric Association, 2013).

Schizophrenia is preceded by a number of prodromal symptoms, including eccentric behaviour, social isolation, blunted affect, poverty of speech, poor attention span and lack of

motivation (Kandel, Schwartz, Jessell, Siegelbaum & Hudspeth, 2013). The schizophrenia spectrum encompasses several diagnoses, differing in duration. Brief psychotic disorder has a duration from 1 day – 1 month, schizophreniform disorder lasts less than 6 months, and a diagnosis for schizophrenia requires an illness duration of minimum 6 months, and at least 1 month of active-phase symptoms (American Psychiatric Association, 2013). The lifetime prevalence for schizophrenia is about 1%. There are some gender differences, where the most prominent is an average of 3-4 years later onset in women (Häfner, 2003). The peak age at onset for the first psychotic episode is in the early- to mid-20s for men and late-20s for women (American Psychiatric Association, 2013). Women tend to have a more favourable socio-economic outcome than men, believed to be related to the later onset of illness, as women might have started their education or careers when they first experience symptoms (Häfner, 2003). The later onset in women has also been associated with a protective effect of estrogen, supported by the "second outburst" of symptoms in women around the age of menopause (American Psychiatric Association, 2013). Earlier age at onset has been associated with worse prognosis (American Psychiatric Association, 2013). However, there are no overall differences in symptomatology between men and women, and both sexes experience the same level of positive symptoms (Leung & Psych, 2000). Although, women seem to experience more auditory hallucinations than men (Rector & Seeman, 1992). Rector and Seeman (1992) suggest that the larger prevalence of AVH in women could be related to greater emotionality and reactivity to stress in women, which could predispose them to AVH. Another study found that women expressed more affective symptoms, which covaried with psychotic symptoms, while men had more negative symptoms that covaried with their psychotic symptoms (Goldstein & Link, 1988).

There is no clear consensus for the aetiology of schizophrenia, however a neurodevelopmental model has been proposed, concerning both genetic and environmental

aspects (Rapoport, Addington, Frangou & Psych, 2005). Risk factors include pre- or perinatal complications, paternal age, being born in winter, urban upbringing, cannabis, trauma, and there is also a larger prevalence in minority groups (van Os, Kenis & Rutten, 2010). There is a heritability vulnerability of around 80%, indicated from twin studies (van Os & Kapur, 2009). Susceptibility genes are being revealed (Harrison & Weinberger, 2005), with each risk allele contributing only a small amount to the total population variance (American Psychiatric Association, 2013). Risk alleles for schizophrenia are also associated with other mental disorders, including bipolar disorder, depression, and autism spectrum disorder (American Psychiatric Association, 2013).

1.1.1 Brain abnormalities.

Schizophrenia is characterized by certain abnormalities in brain anatomy that can be seen in post-mortem studies and with structural and functional magnetic resonance imaging (fMRI). Thinning of specific areas of the prefrontal, temporal and parietal cerebral cortex are the most prominent findings (Kandel et al., 2013). Thinning in the temporal lobe has been traced to grey matter reduction in the superior temporal gyrus, the temporal pole, the amygdala, and the hippocampus (Kandel et al., 2013). Further, impairment of functions that are dependent on the prefrontal cortex (PFC) has been particularly well documented. Patients with schizophrenia perform worse than controls in tasks concerning working memory and cognitive control, which are correlated in fMRI with reduced activity in the dorsolateral prefrontal cortex (Weinberger, Berman & Zec, 1986).

The volume reductions that are found in schizophrenia are not associated with neuronal loss, but rather increased neuronal density (Selemon & Goldman-Rakic, 1999). Others have found decreased number of interneurons in the anterior cingulate cortex (Benes et al., 1991). Selemon & Goldman-Rakic (1999) suggest that cortical volume reduction is due to

decreased neuropil: grey matter that consist of unmyelinated axons and dendrites (Drevets, Savitz & Trimble., 2008), and neuronal size because of altered synaptic, dendritic and axonal organization. Feinberg (1983) suggests that schizophrenia could be caused by a defect in synaptic pruning. Infants of 1-2 years of age has about 50% above adult mean in synaptic density. The reduction of synaptic density occurs around puberty, and appears to be stable from age 16-72 years (Huttenlocher, 1979). Excessive pruning has been observed in schizophrenia patients, resulting in decreased dendritic organization (Feinberg, 1983).

Instead of being a risk factor for developing schizophrenia, these structural abnormalities could also be caused by illness-related degeneration or medication effects. However, volume reductions are also found in drug-naïve individuals with high-risk of developing psychosis (Borgwardt et al., 2007; Pantelis et al., 2003), indicating that at least some of the volume reductions are not caused by antipsychotic medication or duration of illness. Volume reductions could therefore be related to increased susceptibility for developing schizophrenia. This indicates that the brain is considerably affected in schizophrenia; in addition to the anatomical differences there are also functional differences which are a topic of intense research in how they relate to symptoms.

1.2 Auditory Hallucinations

Auditory verbal hallucinations (AVH) refer to hearing voices in the absence of external stimulus (Alderson-Day, McCarthy-Jones, & Fernyhough, 2015). Auditory hallucinations are one of the most prominent positive symptoms in schizophrenia, affecting more than 70% of the patients (Hugdahl, 2009). However, AVH may also occur in other psychiatric disorders or even as an isolated symptom independently of any need for psychiatric care (Johns et al., 2014). Therefore, psychosis has been considered on a continuum, ranging from normal functioning to disturbed functioning (Daalman, Diederen, Hoekema, Lutterveld & Sommer,

2016; Johns & van Os, 2001; van Os, Linscott, Myin-Germeys, Delespaul & Krabbendam 2009). Evidence suggests that disturbed functioning depends on the intrusiveness and frequency of voices, psychopathological co-morbidities, and personal and cultural factors like coping, illness behaviour, social tolerance and possible developmental impairments (Johns & van Os, 2001).

The neural correlates of AVH in schizophrenia and other groups experiencing AVH is a topic of intense research. Functional and structural magnetic resonance imaging (MRI) is a useful tool to investigate whether the brains of individuals with AVH differ from non-hallucinating individuals. This information can help us understand the brain regions and networks that are responsible for generating AVH, and therefore assist with developing new therapy approaches for people suffering from AVH. A prominent finding of individuals experiencing auditory hallucinations during fMRI-scanning has been activations in the primary auditory cortex in absence of external auditory stimuli (Diederen et al., 2012; Dierks et al., 1999; Kompus, Westerhausen & Hugdahl, 2011). This is remarkable because the primary auditory cortex does not activate during auditory imagery or in inner speech (Mcguire et al., 1996). Others have found stronger activations in the right homologues of language areas during auditory hallucinations, especially the inferior frontal area (Sommer et al., 2008). Brown and Thompson (2010) found that 70% of the reviewed studies reported increased neural activity in the right middle temporal gyrus and/or in the right superior temporal cortex in individuals with AVH who were hallucinating during scanning. Activations have also been found in structures important for emotion processing, including hippocampus, parahippocampus, cingulate cortex and orbitofrontal cortex (Silbersweig et al., 1995). Silbersweig et al. (1995) suggest that deep brain structures could generate or modulate hallucinations, while neo-cortical activity could affect the perceptual content of the hallucinations. Fewer studies have been conducted regarding the emotional components of

schizophrenia. And the emotional deficits related to the negative symptoms of schizophrenia have received more attention than the emotional aspects of psychotic symptoms (Aleman & Kahn, 2005). Patients with psychotic symptoms often experience a surplus of emotional reactions to the often emotionally threatening content of their hallucinations or delusions (Aleman & Kahn, 2005). It would therefore be of interest to investigate whether there are differences between hallucinating patients based on voice appraisal.

1.2.1 Qualia of AVH

Recently, researchers have started focusing more on the content of AVH, because this can give valuable information on the mechanisms of how AVHs are generated. Suhail and Cochrane (2002) suggest that immediate environment and life experiences are important for hallucination content. This might explain why technological content is common today, while religion was determined as the most common source of hallucinations in the 1930s. Doctors, scanners, television and radio were the most common perceived sources in the 1980s (Mitchell and Vierkant, 1989). Okulate and Jones (2003) found that malevolent voice content was more common among patients in the UK compared to Nigerian patients. In addition, it was more common for the patients to be addressed in third person by the voices in the UK. Religious content is more common in Saudi Arabia, compared to the UK, where instructions and running commentary is more common (Kent and Wahass, 1996).

Individuals with AVH with and without a need of psychiatric care report broadly similar perceptual experiences and topographical features, e.g. localization (internal/external), loudness and number of voices (Johns et al., 2014). Voice hearers report on average three different voices (Larøi et al., 2012). Both groups tend to attribute their voices to a real person or entity (Johns et al., 2014). Evidence from fMRI studies suggest that the neural correlates of experiencing AVH are the same in individuals irrespective of need for care (Diederen et al.,

2012). However, there are also differences between the “clinical” and “non-clinical” voice-hearers. The differences between individuals with AVH with and without need for care involve the frequency and duration of voices, age of onset, and degree of negative voice content (Johns et al., 2014). The nonclinical group tends to have an earlier age of onset compared to the clinical group. The clinical group tends to have a higher degree of negative voice content, whereas nonclinical cases report mostly neutral or pleasant voice content (Johns et al., 2014). This is interesting because it suggests that the emotional content of AVH can give information that is important in predicting the clinical outcome of voice-hearers. In a follow-up of non-clinical AVH, Daalman et al. (2016) found that total distress of AVH and depression at baseline were significant predictors of need for care five years later.

Distress is often associated with having a malevolent voice. Malevolent voices are comprised of commands, personal insults, and abuse (Larøi et al., 2012). These voices tend to be male, dominant and have degrading themes (Larøi et al., 2012). Individuals with malevolent voices often report that they have little control over their voices´ onset or offset, while benevolent voices are associated with greater control and positive attribution (Larøi et al., 2012). The experience of abusive and emotionally threatening content in auditory hallucinations has been reported to be distressing for a majority of patients (Nayani & David, 1996). Over 75% of hallucinating patients reported that they were highly distressed by their voices (Birchwood, Meaden, Trower, Gilbert, & Plaistow, 2000). Another study found that over half of the patients worried “a lot” about their hallucinations, while only 19% reported that they did not worry (Carter, Mackinnon & Copolov, 1996). The majority of the patients who worried, reported that they used coping strategies. Coping strategies included yelling or talking back to the voices, listening to music, talking to someone, deliberately going to sleep, physical exercise, and relaxation. The authors further noted that the most frequently tried coping strategies were not necessarily effective.

Worrying is also associated with stronger feelings about AVHs and greater negative content (Copolov, Mackinnon & Trauer, 2004). This could mean that worrying about the voices contributes to the negative content, or simply that negative content leads to worrying. The lack of control over the voices could lead to feelings of hopelessness and helplessness resulting in depression. Negative voice content and severity of hallucinations has also been associated with depression and low self-esteem (Smith et al., 2006). Comorbidity with depression in schizophrenia was found to be 45% in one study (Leff, Tress & Edwards, 1988). Further, positive symptoms have been found to be more strongly related to anxiety and depression compared to negative symptoms (Norman & Malla, 1994). This could further be one of the reasons why suicidal ideation are high in patients with malevolent hallucinations (Fialko et al., 2006). Approximately 5-6% of individuals with schizophrenia die by suicide, about 20% attempt suicide on one or more occasions, (American Psychiatric Association, 2013), and a large-sample study showed that 41% had some degree of suicidal ideation (Fialko et al., 2006).

This suggests that negative voice content could be one of the most important aspects differing between clinical and non-clinical AVH, and that the emotional content of AVH deserves more attention in research. The prominence of positive voices in non-clinical situations implies that voice-hearing per se is not the main cause for distress. It is the emotional experience that the voice causes the patient that is associated with distress. Exploring the underlying neural mechanisms of malevolent voices could hopefully provide some help in developing interventions to target malevolent voices and improving life quality of patients with psychosis.

1.2.2 Beliefs about voices.

The revised beliefs about voices questionnaire (BAVQ-R) is a reliable and valid measure for the assessment of voice appraisal (Chadwick, Lees & Birchwood, 2000). The questionnaire has a 35-item, 4-point response rate: 'disagree', 'unsure', 'agree slightly' and 'agree strongly'. The 3 scales: malevolence (e.g. "my voice is punishing me for something I have done"), benevolence (e.g. "my voice wants to protect me") and omnipotence (e.g. "I cannot control my voices") consist of six questions in each category. In addition, the questionnaire measures engagement and resistance, which both contain emotional and behavioural items. E.g. emotional resistance: "my voice frightens me" and emotional engagement: "my voice reassures me", behavioural resistance: "when I hear my voice I usually tell it to leave me alone", and behavioural engagement: "when I hear my voice I usually listen to it because I want to" (Chadwick et al., 2000).

The present study used the BAVQ-R to assess participants' appraisal of auditory hallucinations, and to further group hallucinating patients based on their reports of malevolent and benevolent voices. Voice appraisal separates it from voice content, as some may have benevolent voice content, and still view the voice as malevolent and vice versa (Chadwick & Birchwood, 1994). One study found that in 31% of cases, beliefs were incongruent with content (Chadwick & Birchwood, 1994). Most malevolent voices lead to resistance of the voices and feelings of anger, fear, depression and anxiety, whereas most benevolent voices lead to engaging with the voices and feelings of amusement, reassurance, calm and happiness (Chadwick & Birchwood, 1994). A previous study found that most patients view their voices as omnipotent (Chadwick & Birchwood, 1994), however a more recent study only found a correlation between malevolent voices and omnipotence, and no correlations with benevolent voices (Chadwick et al., 2000). Malevolent voices have also been associated with depression and anxiety (Chadwick et al., 2000). Further, depression in voice hearers have been associated

with omnipotence and resistance of voices (Chadwick et al., 2000). Comorbidities with affective disorders further demonstrates how important it is to look at the phenomenology of voices, due to the higher prevalence of affective disorders in hallucinating patients with malevolent voices.

1.3 Cognitive theories of hallucinations

There are several models and theories for the aetiology of auditory hallucinations, including memory-based models, inner speech models, and the misattribution theory. Some researchers argue that AVHs should be subcategorized based on phenomenology, and that these subcategories could have different underlying neurocognitive mechanisms (Jones, 2010; McCarthy-Jones et al., 2014). Jones (2010) propose two cognitive models for explaining different AVHs: an inner speech model, and a memory-based model. The memory-model is based on the observation that some psychotic hallucinations are related to memories of traumatic events (Jones, 2010). The inner speech model is consistent with a large number of AVHs, in that inner speech and AVHs are both regulatory, linked to ongoing events, they include the perspectives and voices of others, and it is creative in nature. Another phenomenological study discovered four subcategories of patients' auditory hallucinations (McCarthy-Jones et al., 2014). The most common was "constant commanding and commenting AVHs", which is especially seen in malevolent voices. The second category was "Replay AVH" which was identical to memories. A third category was "own thoughts AVHs", these were similar to memories, but not identical. The fourth category was "nonverbal auditory hallucinations" that are believed to be due to spontaneous activity of the superior temporal gyrus. Evidence for this is based on external electrical stimulation of the temporal cortex, which elicits auditory hallucinations of music, crowds, and overheard conversations (Penfield & Perot, 1963).

Another popular perspective on theoretical understanding of AVH is to view them as internal events that are misattributed to an external source. Intrusive thoughts, metacognition and cognitive dissonance have been implicated in the cognitive bias models of AVH (Morrison, Haddock & Tarrier, 1995). The suggested mechanism involves misattribution of intrusive thoughts to an external source due to metacognitive beliefs that create cognitive dissonance (Morrison et al., 1995). In a metacognition questionnaire, schizophrenia patients with AVH exhibited positive beliefs about worry (e.g. "worrying helps me cope") in addition to negative beliefs about controllability of thoughts (e.g. "I cannot ignore my worrying thoughts") and corresponding danger (e.g. "worrying is dangerous for me") (Baker & Morrison, 1998). Baker and Morrison (1998) argue that holding both beliefs would increase the likelihood of cognitive dissonance. In summary, the patients experience intrusive thoughts which are unpleasant (at least for the malevolent voices), they hold strong metacognitive beliefs that they should control their thoughts, and when they are not able to, cognitive dissonance arises, which leads to misattribution of the thoughts.

In accordance with this, schizophrenia patients with AVH made more errors in an "attribution task" when the words had negative emotional content (Johns & McGuire, 1999). This tendency suggests that the malevolent content of AVH could reflect a bias where the patients attribute unpleasant thoughts about him or herself to somebody else (Johns & McGuire, 1999). The same bias was also found in a group of hallucination-prone subjects (Larøi, Linden & Marczewski, 2004), indicating that the bias is not related to full-blown psychosis, but could be an underlying trait in hallucination-prone subjects. Morrison et al. (1995) argue that hallucinations arise from intrusive thoughts that are externalised in an effort to reduce the experienced negative affect. This holds not only for malevolent voices, as benevolent voices have also been associated with increased anxiety (Lung, Shu & Chen, 2009). Anxiety has further been found to be the strongest predictor of hallucination intensity

(Delespaul & van Os, 2002), where intensity ranged from "can hardly be heard" to "extremely disrupting". Anxiety levels are also elevated before the first report of an AVH (Delespaul & van Os, 2002), and studies have shown elevated hypothalamic-pituitary-adrenal (HPA) axis activity months before the onset of psychosis in subjects with ultra-high risk for developing psychosis (Garner et al., 2005). This suggests that emotional stress could be triggering voices. Chadwick and Birchwood (1994) further propose that distress and resistance in relation to malevolent voices, increases the likelihood of voice activity, which could lead to further distress. This results in a vicious cycle where emotional stress triggers voices, and the voices increases distress, which maintains voices. The ability to control or reappraise emotional stress could possibly have an effect on the occurrence or intensity of hallucinating voices. Exploring the brain functioning involved with emotional responses could possibly contribute in developing interventions to relieve distress from hallucinating voices.

1.4 Amygdala

The amygdala has been associated with a range of emotional processes, including emotional learning and memory, emotional influences on attention and perception, emotional and social behaviour, and emotion inhibition and regulation (Phelps & LeDoux, 2005). Based on the central role of the amygdala in processing emotions, there could be different functional connections with the amygdala based on the emotional content of the hallucinating voices.

The amygdala consists of a collection of nuclei, located subcortically in the left and right temporal lobe (Kandel et al., 2013). The amygdala is however often subdivided into three groups of nuclei: the laterobasal (LB), centromedial and superficial amygdala. These subdivisions differ in function, architecture and connectivity (Amunts et al., 2005).

The amygdala nuclei receive input from all sensory cortices, and projects back to the earliest stages of sensory processing (LeDoux, 2000). A key function of the amygdala is to

connect external stimuli with aversive or rewarding consequences (Kandel et al., 2013). Most studies of the amygdala have focused on fear extinction (LeDoux, 2000). However, the amygdala has been associated with both aversive and pleasant stimuli (Liberzon, Phan, Decker & Taylor, 2003). Therefore, it has been suggested that the amygdala could play a part in general processing of the salience of stimuli, detecting both aversive and pleasant stimuli.

1.4.1 Amygdala anatomy

The amygdala volume is larger in men, and negatively correlated with age in healthy subjects (Brierley Shaw & David, 2002). One study has found the opposite in schizophrenia patients, with 8% decreased amygdala volume in men, and 10.5% increased volume in women (Gur et al., 2000). Further, increased volume was related to greater symptom severity in men, and less severity of negative symptoms in women (Gur et al., 2004).

Information about amygdala connections derives mainly from tracing studies in animals, and there is evidence for similar organization of cortical pathways in all mammalian species (Mcdonald, 1998). The central nucleus and the basolateral amygdala (BLA) have been particularly implicated in the control of emotional processes (Cardinal, Parkinson, Hall & Everitt, 2002). The BLA comprises the lateral, basal and accessory basal nuclei. The BLA is able to influence complex behaviour via projections to the ventral striatum and prefrontal cortex (Cardinal et al., 2002). The BLA also projects to the central nucleus, which further projects to the hypothalamus, midbrain reticular formation and brain stem through which it regulates behavioural, autonomic and neuroendocrine responses (Cardinal et al., 2002).

1.4.1.1 Afferent connections of the amygdala

Input to the amygdala can be separated into two groups, from cortical and thalamic afferents, and hypothalamic and brain stem afferents (Sah, Faber, De Armentia & Power,

2003). Cortical and thalamic afferents provide information from sensory areas and memory-related areas, whereas the hypothalamic and brain stem input provide information from regions involved in behaviour and autonomic systems. Most cortical afferents originate in unimodal and polymodal association areas, rather than the primary sensory areas. The polymodal sensory areas include the prefrontal cortex, perirhinal cortex and hippocampus. The prefrontal cortex projects mainly to the basal nucleus of the amygdala (Sah et al., 2003). Further, Aggleton, Burton and Passingham (1980), investigating the afferent projections to the primate amygdala using horseradish peroxidase found afferent projections from the orbital frontal cortex, anterior cingulate gyrus, subcallosal gyrus, temporal pole and anterior insula which terminated in the laterobasal nuclei. This indicates that these structures could be in a position to influence amygdala responsivity.

1.4.1.2 Efferent connections of the amygdala

Tracing studies in monkeys show that the amygdala projects to regions of frontal, insular, temporal and occipital cortices (Amaral & Price, 1984). The amygdala also has strong reciprocal connections to the long-term declarative memory areas that include the perirhinal cortex, entorhinal cortex, parahippocampal cortex, and the hippocampus (Sah et al., 2003). The connectivity with memory systems makes the amygdala able to modulate memory processes during emotional arousal (McGaugh, 2004). Further, the basolateral nuclei projects to the nucleus accumbens, thalamus and prefrontal cortex. Nucleus accumbens is associated with reward, and has dense innervation of dopaminergic neurons. The Efferents from the basolateral nuclei arise from pyramidal-like neurons and are thought to be glutamatergic (Sah et al., 2003), meaning that they are excitatory rather than inhibitory.

1.4.2 Functional connectivity of the amygdala

The recent technological advances in imaging techniques have made it possible to study the human brain in vivo. These studies confirm many of the findings from tracing studies concerning amygdala connectivity. Recent fMRI-studies (Ball et al., 2007; Frühholz & Grandjean, 2013; Roy et al., 2009) have found functional distinctions of amygdala subdivisions using cytoarchitectonic probability maps based on post-mortem studies, developed by Amunts et al. (2005). Roy et al. (2009) studied both total amygdala as well as amygdala subdivisions of healthy subjects in resting state fMRI. They found positively-predicted ventral and negatively-predicted dorsal networks associated with the total amygdala. The ventral network included the medial prefrontal cortex, insula, thalamus and striatum (Roy et al., 2009). The subdivisions of amygdala demonstrated distinct and partly hemispherically lateralized connectivity patterns. Spontaneous activity in the laterobasal nuclei predicted bilateral activity in temporal and frontal regions (Roy et al., 2009). The LB nuclei are further connected with visual cortices and associative sensory areas that process higher-level visual and auditory input, including the associative auditory cortex, inferior occipital gyrus, posterior superior temporal sulcus, frontal eye field, precuneus and hippocampus (Bzdok et al., 2013).

Right LB activity predicted bilateral activity in medial frontal gyrus, superior frontal gyrus, anterior cingulate cortex, and precentral and postcentral gyri (Roy et al., 2009). Others have found that the right LB nuclei are connected with the medial prefrontal cortex, temporal pole, inferior parietal cortex, and the precuneus (Bzdok et al., 2013).

Activity in the centromedial nuclei predicted activity in the striatum, globus pallidus, dorsal anterior cingulate cortex, insula and cerebellum. The centromedial nuclei are connected to brain areas implicated in motor behaviour, perceptual modulation, as well as visceral and somatosensory processing (Bzdok, Laird, Zilles, Fox & Eickhoff, 2013). The superficial

nuclei are connected to brain areas that are important for processing olfaction as well as affective and vegetative processing, and reward prediction (Bzdok et al., 2013)

The amygdala has been suggested to belong to a ventral system of emotion perception, together with the insula, ventral striatum, and ventral regions of the anterior cingulate gyrus and prefrontal cortex (Phillips, Drevets, Rauch & Lane, 2003). The ventral system is believed to be important for emotional salience, or identifying the emotional significance of external stimuli and production of affective states (Philips et al., 2003). The dorsal system is believed to be the location of integration between emotional input and cognitive processes. The dorsal system includes the hippocampus and dorsal regions of anterior cingulate gyrus and prefrontal cortex (Philips et al., 2003).

In summary, the amygdala has extensive connections throughout the brain that can be explored in humans using non-invasive neuroimaging techniques. These methods have shown that, especially the laterobasal nuclei seem to be in a position to coordinate high-level sensory input for processing of emotion and cognition.

1.4.3 The Amygdala in Schizophrenia

Studies of amygdala activation in schizophrenia patients have in general shown an under-recruitment in different task-based fMRI paradigms comparing emotional stimuli with neutral stimuli (Aleman & Kahn, 2005). For instance, schizophrenia patients exhibit reduced activation in the amygdala during recognition of emotional, compared with neutral facial expressions (Mier et al., 2014; Gur et al., 2002). This has also been associated with schizophrenia patients' impaired ability to discriminate happy and sad facial expressions (Schneider et al., 1998).

Williams et al. (2004) found differences between paranoid and non-paranoid schizophrenia patients in skin conductance responses and activity in amygdala and medial

PFC in response to pictures of fearful faces. Paranoid patients exhibited hyper-arousal in the skin conductance response and decreased amygdala and medial PFC activity, compared to non-paranoid patients, indicating a discrepancy between autonomic and central systems for processing threatening stimuli (Williams et al., 2004). The author further proposed that paranoid cognition may reflect a misattribution caused by aberrant functions of regulating mechanisms of incoming fear signals (Williams et al., 2004). A recent study of paranoid patients found increased activity of the left amygdala during resting state, and decreased task-related activation of the amygdala compared to non-paranoid schizophrenia patients and healthy controls (Pinkham et al., 2015). Paranoid ideation is thus associated with increased amygdala activity in resting state, and decreased task-related activation.

Increased amygdala activation during emotion processing has been found in depression and anxiety (Hahn et al., 2011; Stein, Simmons, Feinstein & Paulus, 2007). Negative symptoms (e.g. flat affect, poverty of speech, inability to persist in goal-directed behaviour) have also been correlated with reduced amygdala activity (Schneider et al., 1998). Amygdala activation correlated with induced sadness in healthy participants, but not in schizophrenia patients with predominantly negative symptoms, despite subjective ratings showing negative affect (Schneider et al., 1998). However, this study compared activations in an emotion-task with a neutral task, which means that the results could be due to elevated baseline activation of the amygdala. Anticevic et al. (2012) argue that amygdala hypo-activation is only present in studies that employ a neutral versus emotion contrast, and not in studies directly comparing patients and controls in the emotion condition. They further suggest that patients with schizophrenia have a normal amygdala response (relative to a resting baseline) to affectively aversive stimuli, and that the apparent hypo-activation mentioned in the studies above is due to an elevated response to emotionally neutral stimuli.

If the amygdala is hyperactive to neutral stimuli, then the comparison between the neutral and emotional stimuli would result in a smaller effect.

Others have also found a tendency for schizophrenia patients to have greater responses to neutral stimuli compared to controls. Kring and Neale (1996) compared schizophrenia patients with controls watching neutral, positive and negative emotional film clips. Schizophrenia patients tend to have reduced facial expressions in response to the emotional stimuli, but reported experiencing as much negative and positive emotions as controls (Kring & Neale, 1996). In addition, schizophrenia patients exhibited increased skin conductance reactivity compared to controls (Kring & Neale, 1996). Skin conductance can be used to measure levels of arousal. The schizophrenia patients showed increased arousal, not only to the emotional stimuli, but also to the neutral stimuli.

A heightened response to neutral stimuli is coherent with the hypothesis of an aberrant salience network in psychosis (Kapur, 2003). Kapur suggests that schizophrenia (and more specifically, psychosis) may be characterized as a state of aberrant assignment of salience to insignificant stimuli. Evidence suggest that the neurotransmitter dopamine is important for directing attention towards rewarding stimuli (Kandel et al., 2013). Elevated dopamine levels as seen in psychosis could lead to aberrant salience to external objects and internal representations (Kapur, 2003). Kapur further argues that dopamine dysregulation could be providing the driving force of psychotic experiences, but that it is the subject's own cognitive cognitive, psychological and cultural context that provide the content of psychotic experiences. Psychosis is thus seen as a dynamic interaction between a bottom-up neurochemical drive and a top-down psychological process (Kapur, 2003).

1.4.4 Task-based functional connectivity of AVH patients

Schizophrenia patients with AVH responded to emotional words (that were common in their hallucinations) with stronger activation in the orbitofrontal cortex, temporal cortex, insula, middle and posterior cingulate and amygdala compared to healthy controls (Sanjuan et al., 2007; Martí-Bonmatí et al., 2007). However, the study by Sanjuan et al. (2007) did not include a schizophrenia control group without hallucinations. In another study, using the same task, patients with AVH showed greater activation in the amygdala and the parahippocampal gyrus compared to controls and patients without hallucinations (Escartí et al., 2010). This could signify that the patients associated the words with adverse emotional responses retrieved from their memory. It could also be evidence for amygdala abnormalities being associated with the affective component of positive symptoms of schizophrenia (Escartí et al., 2010). The study by Escartí et al. (2010) did however not account for whether or not the patients were hallucinating during the scanning, which could be a confounding factor for the results. Threatening words have been associated with left posterior cingulate activation when compared to neutral words in healthy participants (Maddock & Buonocore, 1997). It is possible that some of these structures have increased amygdala connectivity due to the threatening content of malevolent voices.

It is also possible that there is a difference between schizophrenia patients with malevolent and benevolent voices, especially in the ¨orbitofrontal cortex¨ known to regulate the amygdala. There have been no studies comparing amygdala functional connectivity in individuals with malevolent and benevolent voices during resting state fMRI that the author is aware of. It is possible that the activated regions during processing of negative emotional words will have aberrant connectivity with the amygdala during a resting state condition in hallucinating patients with malevolent voices compared to hallucinating patients with benevolent voices.

1.5 Brain structures involved with emotion regulation

The ability to regulate emotions is important to modify the spontaneous reaction to arousing stimuli. The amygdala has consistently been found to be regulated by the cingulate, orbitofrontal, insular and dorsolateral prefrontal cortices (Stein & Wiedholz et al., 2007).

FMRI-studies of specific emotions have been conducted to see which brain regions are involved with the experience of different emotions, and possibly for emotion processing in general. In a review of PET and fMRI studies of emotions, the medial prefrontal cortex seemed to have a general role in emotion processing (Phan et al., 2002). Further, the basal ganglia were activated in 70% of the studies that induced happiness (Phan et al., 2002). The basal ganglia are richly innervated by dopaminergic neurons, known to be important in reward and addiction (Kandel et al., 2013). The same review found that sadness was associated with subcallosal cingulate cortex activation (BA25) (Phan et al., 2002). This structure has consistently been associated with depression (Drevets et al., 2008; Price & Drevets, 2010), and is located ventral to the genu (anterior part of the corpus callosum). Considering the association between malevolent voices and depression, it is possible that there will be decreased amygdala – subgenual coupling in patients with malevolent voices compared to benevolent voices in the present study. Damasio et al. (2000) used PET to look at functional correlates of self-generated recall for sadness, happiness, anger and fear. Structures related to all emotions included insula, secondary somatosensory cortex, cingulate cortex, brainstem and hypothalamus. These structures are also implicated in regulating homeostasis, indicating a close connection between emotion and homeostasis. The review by Phan et al. (2002) also found insula and anterior cingulate activation associated with recall of emotions.

The studies of neural correlates related to induced emotions, investigates bottom-up processes. Top-down processes can be investigated in fMRI by having participants regulate

their emotions. Emotion regulation strategies include reappraisal and expressive suppression. Reappraisal refers to cognitive transformation of the meaning of a situation (Goldin, McRae, Ramel & Gross, 2008; Ochsner et al., 2004a), often in response to negative emotional stimuli. Expressive suppression on the other hand is a strategy where individuals inhibit emotional responses (e.g. facial expressions) (Goldin et al., 2008). This top-down control of behaviour is mediated by the prefrontal cortex (Miller & Cohen, 2001). The amygdala is closely interconnected with the prefrontal cortices, especially the medial and orbital prefrontal cortices (Price & Drevets, 2010). The amygdala is in a position to directly influence PFC output, whereas the PFC is in a position to modulate the amygdala response indirectly through inhibitory connections (Hariri, Mattay, Tessitore, Fera & Weinberger, 2003).

Reduction of experienced negative affect is associated with reduced amygdala activity and increased orbitofrontal activity (Ochsner et al., 2004a), indicating that the orbitofrontal cortex has a modulatory role on the amygdala. Others have also found that the strength of coupling between the amygdala and the orbitofrontal/dorsomedial PFC predicts successful emotion regulation, as indexed by reduction in self-reported negative affect (Banks, Eddy, Angstadt, Nathan & Phan, 2007). Stronger amygdala – medial prefrontal cortex connectivity measured in a resting state study also predicted lower anxiety (Kim, Gee, Loucks, Davis & Whalen, 2011). A stronger coupling between these two areas could be associated with more efficient emotion regulation. A deficient amygdala – PFC connectivity could further be associated with malevolent voice content. It is possible that these patients use inefficient emotion regulation mechanisms. Carter et al. (1996) found that the most common coping strategies included yelling or talking back to the voices, listening to music, talking to someone, deliberately going to sleep, physical exercise, and relaxation. These reports indicate that the most common coping mechanism is related to distractions.

Increased use of expressive suppression (but not reappraisal) has been associated with

higher levels of anxiety and decreased levels of happiness in both in schizophrenia patients with AVH and healthy controls (Badcock, Paulik & Maybery, 2011). Reappraisal increases activity in medial, dorsolateral and ventrolateral PFC regions and decreases activity in amygdala and insula (Goldin et al., 2008). Further, suppression reduces negative emotion experience and behaviour, but sustains elevated amygdala and insula activity. Suppression as an emotion regulation strategy in AVH has been associated with increased severity of AVH (frequency, duration, and loudness) and greater disruption in daily life (Badcock et al., 2011).

Taken together, different brain regions have been identified for processing of specific emotions, and for regulating emotions. It is possible that hallucinating patients may have aberrant connections between these brain regions, resulting in the emotional content of their voices.

1.6 Functional Connectivity in Schizophrenia Patients

Schizophrenia has been conceptualized as a disease of aberrant brain networks (Stephan et al., 2009). The dysconnectivity theory postulates that schizophrenia might be due to abnormal (increased as well as decreased) functional integration among brain regions (Stephan et al., 2009). Functional connectivity has been defined as the temporal dependence of neuronal activity in separated brain regions (Van Den Heuvel & Pol, 2010).

Lynall et al. (2010) looked at functional connectivity and functional network topology in schizophrenia patients and healthy controls measured by resting-state fMRI. They found decreased functional connectivity and increased diversity of functional connections in schizophrenia patients. Another study found altered small-world properties in prefrontal, parietal and temporal lobes, which correlated with illness duration of schizophrenia patients (Liu et al., 2008). In addition, the higher associative networks in schizophrenia has been

found to be less efficiently wired, and the hubs of the network tends to be abnormally clustered and connected to other nodes than in controls (Bassett et al., 2008).

Most studies of patients with schizophrenia have found increased connectivity within the default mode network and greater connectivity, or reduced negative correlations, with brain regions not normally considered part of the default mode network (Karbasforoushan & Woodward, 2012). Specifically, one study found increased connectivity in the posterior areas of the default mode network (Whitfield-Gabrieli et al., 2009). Reduced resting-state connectivity of the PFC, particularly the dorsolateral PFC has also been consistently reported in patients with schizophrenia (Karbasforoushan & Woodward, 2012). The dorsolateral PFC is important for working memory processing, which is often reduced in schizophrenia patients (Weinberger et al., 1986). It is also important to notice that fMRI can not detect whether functional connectivity is inhibitory or excitatory. Increased activation could mean increased inhibition or increased excitation, and decreased activation could indicate decreases in normal inhibitory or excitatory activation.

1.6.1 Resting state fMRI.

Resting state functional connectivity of the amygdala in healthy subjects (Stein & Wiedholz et al., 2007; Roy et al., 2009) corresponds with findings from anatomical studies (Van Den Heuvel & Pol, 2010) and task-based studies (Bzdok et al., 2013), suggesting that intrinsic activity of the amygdala indexes functionally relevant circuits. Resting state functional connectivity explores brain regions that correlate in their spontaneous activity when idle or at rest. In fMRI, such spontaneous correlations occur due to low-frequency fluctuations in the hemodynamic response (Alderson-Day et al., 2015). This type of brain activation data is of interest in hallucination research because auditory hallucinations can be seen as intrinsic, spontaneous neural activity. Previous research on auditory hallucinations

and emotion processing have focused mostly on task based paradigms (Escartí et al., 2010; Sanjuan et al., 2007). Exploring resting-state connectivity of specific brain regions could reveal dysfunctional neural networks which could underlie the variation in the self-generated neural activity, giving rise to AVH, without being confounded by task influences on activation.

There are two general classes of methods used to measure functional connectivity: seed-based region-of-interest (ROI) and independent component analysis (Karbasforoushan & Woodward, 2012). The latter is generally better suited at examining multiple networks simultaneously and for generating novel hypotheses (Karbasforoushan & Woodward, 2012). Seed-based methods are well-suited for testing hypotheses about connectivity between a set of predefined areas or specific brain regions. This method involves extracting the BOLD time-course signal from a pre-defined ROI, and correlating the ROI time course with the time courses of every voxel in the brain (Karbasforoushan & Woodward, 2012). This method shows the strength of connectivity between the ROI and every voxel in the brain (Karbasforoushan & Woodward, 2012). The present study will use the seed-based method with the amygdala as region of interest to investigate resting state functional connectivity of brain regions underlying emotion processing.

1.6.2 Region of interest.

Most imaging studies of the amygdala have looked at the total amygdala due to ambiguous anatomical borders and proximity to other structures (Brierley et al., 2002). Structural ROIs are generally defined based on macroanatomy, such as gyral anatomy (Poldrack, 2007). However, many borders of structures like the amygdala, hippocampus and entorhinal cortex do not match sulcal landmarks (Amunts et al., 2005). Microscopic anatomy can localize the borders of these brain regions with more precision (Amunts et al., 2005).

Therefore, Amunts et al. (2005) have created probabilistic maps of neocortical areas and subcortical fibre tracts based on histological analysis of ten human post-mortem brains. Probability maps are defined as the relative frequency with which a cytoarchitectonic structure is present in each voxel of the anatomical MNI space (Amunts et al., 2005). The amygdala structure had low inter-subject variability, which make the probability maps a valid tool for anatomical localization in brain imaging (Amunts et al., 2005).

Considering the amygdala as a single unit could potentially overlook the independent functions and patterns of connectivity of the individual subdivisions (Roy et al., 2009). Some brain regions have opposing patterns of connectivity with the different amygdala subdivisions. For instance, the laterobasal nuclei were positively associated, and the centromedial nulcei were negatively associated with regions of medial PFC and the temporal lobe (Roy et al., 2009). Further, the laterobasal nuclei had negative associations, and the centromedial nuclei had positive associations with the striatum. Even within the amygdala, the resting state activity of the right centromedial subdivision, negatively predicts laterobasal activity (Roy et al., 2009).

The probability maps of Amunts et al. (2005) have successfully been used by other researchers studying amygdala subdivisions (Roy et al., 2009; Bzdok et al., 2013; Ball et al., 2007). Bzdok and colleagues (2013) found an overlap of approximately 80% for the bilateral subdivisions in healthy subjects when comparing amygdala subdivisions probability maps with connectivity-based parcellations. Left LB amygdala had an overlap of 96%, and right LB had an overlap of 98% with one of the clusters found by the connectivity-based parcellation (Bzdok et al., 2013).

Further, a meta-analysis of 114 task based fMRI and PET studies concerned with the amygdala found that approximately half of the reported responses were located in the amygdala with high probability (≥80%), including responses related to stimuli of positive and

negative emotional valence (Ball et al., 2009). The majority of peaks (96.3%) were found in the laterobasal and superficial subdivisions, while 3.7% of peaks were found in the centromedial subdivision (Ball et al., 2009). This yields support for using the laterobasal nuclei as region of interest in the present study, as the superficial nucleus is rather small, and mostly involved with olfaction.

Right and left laterobasal amygdala will be used as regions of interest in this thesis because of the connections with cortical structures, like the frontal cortex, and because it is the most activated subdivision in task-based fMRI studies. The laterobasal group consists of the lateral nucleus, basolateral, basomedial and paralaminar nuclei (Amunts et al., 2005).

1.7 Aims and hypotheses

The novel contribution of this thesis regards examining the relationship between resting-state brain connectivity measured using fMRI and the emotional appraisal of AVH, measured using a specialized self-report scale on appraisal of auditory hallucinations, Beliefs About Voices Questionnaire (BAVQ-R) (Chadwick et al., 2000). Because the amygdala is central for emotion processing, there will be a focus on the amygdala, and the approach will be seed-voxel based. The laterobasal nuclei are chosen as region of interest because of the anatomical connections with prefrontal cortices known to be involved with emotion regulation. The assumption is that the resting-state connectivity of LB amygdala with the rest of the brain will be different across the patients depending on the emotional appraisal of their voices. In addition, hallucinating patients will be compared to schizophrenia patients without AVH and healthy controls.

The main hypothesis is that there will be differences in the amygdala's laterobasal nuclei connectivity with other brain regions, in particular the frontal lobe, depending on how strongly the patients experience negative emotions in response to their hallucinations. Other

regions that might be implicated is the temporal cortex, insula, anterior and posterior cingulate and the parahippocampal gyrus. The second hypothesis is that there will be differences in LB amygdala connectivity between the hallucinating group and both control groups.

2 Materials and Methods

2.1 Ethics

The thesis is part of the Bergen Psychosis Project 2. Ethical approvals have been provided by the Norwegian Medicines Agency/ EudraCT, and the Research Ethics Committee (REK Vest). Written informed consent was obtained from participants. The study is a pragmatic, rater-blind and randomized trial. This project concentrates on data that are already gathered, and will consist of a novel analysis of the resting-state fMRI data, combined with the BAVQ-R scores.

2.2 Subjects

The total sample consisted of 99 participants, after 11 participants (1 HC, 5 H, 5 NH) were omitted due to lack of fMRI-data. The healthy control group (HC) consisted of 54 participants and were matched in age, gender and handedness to the schizophrenia groups. Schizophrenia patients with no experience of hallucinations (NH) consisted of 25 participants matched in age, gender, handedness and duration of illness with the hallucinating group. The 20 patients (14 men and 6 women) included in the hallucinating group were 18-39 (M = 25.65, SD = 5.88) years of age with symptoms of psychosis in the schizophrenia spectrum or with a paranoid psychosis.

Antipsychotic drug treatment was indicated using the oral formulation of the drugs. Psychosis was defined by a score of ≥ 3 in the Positive and Negative Syndrome Scale (PANSS) on hallucinatory behaviour item. Hallucinating participants were divided into either a malevolent voices group (n = 13) or a benevolent voices group (n = 7) based on whether they had a higher malevolence or benevolence score. The group with malevolent voices consisted of 7 men, and 6 women (age 18-34) while the group with benevolent voices consisted of 7 men, (age 20-39).

2.3 Questionnaires

2.3.1 Positive and negative syndrome scale.

The positive and negative syndrome scale (PANSS) was used to obtain information about participant's symptoms and to establish the hallucinating group. Participants were evaluated with the PANSS rating criteria by a clinician at hospitalization in Sandviken Sykehus. PANSS is a 30-item, 7-point rating instrument ranging from 1 (absent) to 7 (extreme) in negative and positive symptoms of schizophrenia and general psychopathology (Kay, Fiszbein & Opfer, 1987). Three different mean scores were computed from the positive, negative and general psychopathology items. The positive symptoms score (α = .73) and the negative symptoms score (α = .72) consisted of 7 items each with a total possible score of 47. And the general psychopathology score (α = .80) consisted of 16 items with a total possible score of 112. The inclusion requirement for the hallucinating group was a score of ≥ 3 on the item for hallucinatory behaviour. A score of 3 on hallucinatory behaviour indicates a mild symptom with "one or two clearly formed but infrequent hallucinations, or else a number of vague abnormal perceptions which do not result in distortions of thinking or behaviour".

2.3.2 Beliefs about voices questionnaire

The revised beliefs about voices questionnaire (BAVQ-R) was used to obtain information about appraisal of voices. This separates it from voice content, because there can be discrepancies between voice content and voice appraisal (Chadwick & Birchwood, 1994). BAVQ-R items were computed into 5 different sum scores, including 3 scores with 6 items and a total possible score of 18: malevolence (α = .90), benevolence (α = .90) omnipotence (α = .85), and engagement (α = .75) with 8 items and a total possible score of 24 and resistance (α = .86) with 9 items and a total possible score of 27.

2.4 Statistical Analysis

Statistical tests were conducted using IBM SPSS Statistics (22) for Windows to compare demographic variables and PANSS and BAVQ-scores between groups. Independent samples t-tests were conducted to assess differences between groups. A Pearson product-moment coefficient was computed to assess the relationship between variables from PANSS and BAVQ-R questionnaires in hallucinating patients.

2.5 Data Acquisition and Pre-processing

The fMRI data was gathered using a GE 3.0 T MR scanner at the Department of Radiology, Haukeland University Hospital. The patients went through a series of different scans in a research protocol including a structural MRI and resting-state fMRI acquisition (duration 5 minutes). In the resting state condition, participants were instructed to relax. 160 contiguous functional brain volumes were obtained at a repetition time of TR = 2000 ms, and echo time of TE = 30 ms (flip angle = 90 degrees, slices = 26, slice thickness 3 mm, slice spacing 3,5 mm, matrix = 60 x 9664, field of view = 220x220 mm^2, effective voxel size = 1.72*1.72*3).

Image pre-processing was conducted with the SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Pre-processing steps consisted of realigning the functional images to the first image in the series to correct for head motion, and spatial normalization to the Montreal Neurological Institute (MNI) standard brain. Spatial smoothing of the fMRI data was not conducted. Smoothing the data reduces the number of performed independent statistical tests, and evens out the differences in anatomy between subjects (Aguirre, 2006). By not using spatial smoothing, the statistical sensitivity for small focal areas of activation increases.

2.6 Definition of ROI

The region of interest (ROI) was defined based on probabilistic cytoarchitectonic maps (Amunts et al., 2005), using the SPM anatomy toolbox version 2.1 (http://www.fz-juelich.de/). Individual masks were created for the right and left laterobasal amygdala. The laterobasal subdivision included the lateral, basolateral, basomedial, and paralaminar nuclei (Amunts et al., 2005).

2.7 Functional Connectivity and Statistical Analysis

The functional connectivity analysis of the amygdala was performed using the CONN toolbox (https://www.nitrc.org/projects/conn), using the recommended pre-processing steps. The fMRI data was filtered between 0.01 to 0.09 Hz, and time courses from white matter and cerebrospinal fluid were removed from the data as confounds. Within each ROI, the average time course was calculated. The whole-brain connectivity maps were estimated separately for the left and right laterobasal amygdala ROIs. This resulted in two connectivity maps for each subject, expressing for every voxel the Fisher-transformed bivariate correlation coefficient with the seed ROI in the left and right hemisphere, respectively.

The single-subject connectivity maps were entered into a factorial design in SPM8. An ANOVA was used to assess significant differences for main effect of group (schizophrenia with no hallucinations, hallucinating schizophrenia patients, healthy controls), main effect of hemisphere (left, right), and group*hemisphere interaction. Images were assessed for cluster-wise significance corrected for family-wise error (FWE) using a threshold of $p < .001$. Further, post hoc t-tests were performed to examine differences between the groups.

After estimating the functional connectivity between the amygdala and other brain regions, the BAVQ scores of the individual patients was used in a covariance analysis to find

the connections modulated by the differing emotional content of the voices. Participants were divided into either a malevolent group or a benevolent group based on whether they had a higher malevolence or benevolence score.

Comparing all the voxels of the brain that are connected to the laterobasal amygdala to find significant differences between groups would result in significant results that could differ by noise alone, if not corrected for multiple comparisons (Aguirre, 2006). Correction was conducted to control false-positives, the family-wise error rate (FWE) was used to increase the significance level as the number of comparisons increased.

Two brain Atlases in FSL (FMRIB Software Library) were used to determine structures from the coordinates given in SPM. The Harvard-Oxford Cortical and Subcortical structural atlas were used for the tables, and includes 48 cortical and 21 subcortical structural areas. The Jülich histological atlas was used supplementary to determine regions in ambiguous areas. This atlas is based on 10 human post-mortem brains and includes 52 grey matter structures and 10 white matter structures.

3 Results

3.1 Descriptive Statistics of hallucinating patients

A Pearson product-moment coefficient was computed to assess the relationship between variables from PANSS and BAVQ-R questionnaires. Table I shows that sex had positive correlations with malevolent voices, depression, anxiety, omnipotence, negative symptoms, and symptoms of general psychopathology. Table II shows that this effect was related to females having a higher score in these variables compared to males. Further, malevolent voices had positive correlations with sex, depression, omnipotence of voices and resistance towards voices (r = .638, p < .01). In addition to the correlations mentioned in table I, age and duration of illness had a significant positive correlation (.478, , p < .05). Age, handedness and duration of illness did not significantly correlate with any of the other measures. Benevolent voices and engaging with voices had a significant positive correlation (r = .612, p < .01). Engaging with voices and resistance towards voices had a negative correlation (r = -.521, , p < .05). Positive symptoms and general psychopathology had a positive correlation (r = .569, p < .01).

Table I. *Correlations between variables from PANSS and BAVQ-R in hallucinating patients.*

	Mal	Sex	Depr	Anx	Omni	Neg	Psych
Mal	1	.708**	.497*	.382	.871**	.413	.368
Sex		1	.607**	.520*	.614**	.514*	.530*
Depr			1	.521*	.464*	.182	.567**
Anx				1	.384	.448*	.574**
Omni					1	.294	.449*
Neg						1	.498*
Psych							1

Note. Mal = malevolent voices, Depr = depression, Anx = anxiety, Omni = Omnipotent voices, Psych = general psychopathology. ** p < .01, * p < .05.

Independent-samples t-tests were conducted to assess differences between hallucinating and non-hallucinating patients. There were no significant differences between patients in age, sex, handedness, duration of illness or negative symptoms ($p < .05$). Hallucinating patients had significantly higher scores than non-hallucinating patients in general psychopathology (t (43) = -3.09, $p < .001$), positive symptoms (t (43) = -4.61, p = .003), and anxiety t (43) = -2.52, p = .016). In addition, the Levene's test of unequal variance showed that there was unequal variance in the hallucinating and non-hallucinating groups in depression, the differences were however still significant when this was accounted for (t (29.47) = -2.58, p = .015), where hallucinating patients also had a higher score compared to non-hallucinating patients (see appendix C).

An independent-samples t-test showed that there were significant gender differences in the hallucinating group in symptomatology (table II). There was a significant difference between male and female reports of malevolent voices, where females (M = 2.27, SD = .45) reported more malevolent voices than males (M = .85, SD = .83). Hallucinating women also reported more omnipotent voices, in addition to higher general psychopathology, anxiety, depression, and negative symptoms compared to hallucinating men. Anxiety and depression scores were only measured by a single-item. There were no significant differences (< .05) between hallucinating women and men in age, handedness, duration of illness, benevolent voices (this group consisted of only men), engagement to voices, resistance to voices, or positive symptoms.

Table II. *Significant differences between hallucinating women and men.*

	Women		Men				
	M	*SD*	*M*	SD	*t*	*df*	*p*
Malevolent voices	2.27	.45	.85	.83	-3.91	17	< .001
Omnipotent voices	2.11	.66	1.07	.64	-3.30	18	.004
Depression	4.50	1.05	2.43	1.40	-3.24	18	.005
General psychopathology	2.60	.60	2.02	.38	-2.65	18	.016
Anxiety	4.50	.55	3.00	1.36	-2.58	18	.019
Negative symptoms	2.91	.80	2.10	.58	-2.54	18	.021

3.2 Functional Connectivity

An ANOVA was conducted to assess main effect of hemisphere. Six clusters were detected when corrected for family-wise error ($p < .05$). Differences between left and right laterobasal nuclei across groups were observed in left laterobasal amygdala, left superior frontal gyrus, left middle frontal gyrus, right laterobasal amygdala, right temporal pole and right planum temporale. There was no group-hemisphere interaction effect when corrected for multiple comparisons, however five clusters were detected for uncorrected ($p < .001$). Uncorrected group-hemisphere interactions were observed in the cerebellum, precentral gyrus, temporal lobe white matter, middle frontal gyrus and precuneus.

3.2.1 Conjunction analysis.

A conjunction analysis was performed to compare the healthy control group with both schizophrenia groups. Table III illustrates the functional connectivity of the bilateral laterobasal amygdala between the healthy control group and both schizophrenia groups. The schizophrenia groups had decreased functional connectivity between the bilateral laterobasal amygdala and the postcentral gyrus, inferior frontal gyrus, anterior cingulate cortex, insular cortex, posterior supramarginal gyrus, putamen, and anterior parahippocampal gyrus. Both

schizophrenia groups had stronger functional connectivity between the laterobasal amygdala and the thalamus, precuneus and white matter callosal body, compared to healthy controls.

Table III. *Effect of bilateral laterobasal amygdala functional connectivity between both schizophrenia groups and healthy controls.*

		Local maxima		
Structure	Side	K	Z	x, y, z
Schizophrenia patients < healthy controls				
Postcentral gyrus	R	32	6.49	48, -6, 24
Inferior frontal gyrus	R	50	6.09	60, 26, 20
Anterior cingulate gyrus	L	260	7.95	-6, -6, 44
Insular cortex	R	27	5.94	36, 4, 0
Posterior supramarginal gyrus	R	47	6.00	68, -36, 24
Putamen	L	125	7.48	-30, 6, 6
Parahippocampal gyrus, anterior	L	45	6.52	-16, -4, -40
Parahippocampal gyrus, anterior	R	103	6.30	24, -10, -38
Schizophrenia patients > healthy controls				
Thalamus	R	42	6.13	2, -14, 14
WM below splenium	R	22	5.62	6, -36, 6
Precuneus	R	143	5.75	2, -82, 48

Note. WM = white matter. $p < .05$ (corrected, FWE) $k = 20$ voxels

3.2.2 Main effect of groups.

A one-way ANOVA was conducted to assess main effect of group, which detected a significant main effect of group in 33 clusters of the brain when corrected for family-wise error ($p < .001$, $k = 20$). Post-hoc t-tests were conducted to look at differences between the specific groups. Independent-samples t-tests for main effect of groups are shown in table IV. Results generally show *decreased* functional connectivity between laterobasal amygdala and brain regions of schizophrenia patients, compared to healthy controls. Further, schizophrenia

patients show *increased* functional connectivity between laterobasal amygdala and posterior regions of the brain, especially occipital and superior parietal areas compared to healthy controls. Non-hallucinating patients (NH), specifically showed *decreased* functional connectivity between laterobasal amygdala and the subgenual area and caudal posterior cingulate cortex, and *increased* with dorsal posterior cingulate cortex, compared to both hallucinating patients and healthy controls (HC). Hallucinating patients (H) had *increased* functional connectivity between the laterobasal amygdala and paracingulate gyrus, and the temporal pole, compared to non-hallucinating patients, and *decreased* functional connectivity in the dorsal anterior cingulate cortex.

Table IV. *Effect of bilateral laterobasal amygdala functional connectivity between groups.*

			Local maxima		
Structure	Side	Contrast	K	Z	x, y, z
Superior frontal gyrus	R	NH < HC	58	7.07	6, 56, 28
Callosal body (WM)	L	NH < HC	26	6.16	-18, 28, 24
Precentral gyrus	R	NH < HC	108	7.21	62, 24, 24
Orbitofrontal cortex, subgenual area	L	NH < HC NH < H	53	7.26	-12, 10, -18
Anterior cingulate gyrus	L	NH < HC	56	6.81	-2, 4, 32
Insular cortex	L	NH < HC	25	6.43	-38, 2, -6
Insular cortex	L	NH < HC	60	6.96	-34, 0, 8
Precentral gyrus	R	NH < HC	114	6.85	64, -2, 42
Anterior parahippocampal gyrus (most likely outside the brain)	L	NH < HC	32	7.04	-16, -4, -40
Juxtapositional lobule cortex	L	NH < HC	194	> 8	-8, -6, 46
Anterior parahippocampal gyrus	R	NH < HC	40	7.38	24, -12, -36
WM close to secondary somatosensory cortex	R	NH < HC	83	7.16	54, -16, 20
Posterior cingulate gyrus, caudal	R	NH < HC	32	6.51	6, -52, 22
Cerebellum	R	NH < HC	35	7.37	32, -40, -36

Frontal pole, superior frontal gyrus	R	NH > HC	35	6.66	22, 38, 40
Callosal body (WM)	R	NH > HC	30	6.16	4, -34, 4
Posterior cingulate gyrus, dorsal	R	NH > HC	102	7.15	4, -34, 44
		NH > H			
Superior longitudinal fascicle (WM)	R	NH > HC	22	6.47	30, -36, 32
Precuneus	R	NH > HC	47	6.54	4, -64, 54
Cerebellum	L	NH > HC	30	> 8	-2, -64, -48
Cerebellum	L	NH > HC	69	7.74	-52, -70, -36
Cerebellum	R	NH > HC	98	7.82	46, -80, -22
Occipital pole	R	NH > HC	207	7.38	28, -92, 36
Occipital pole	L	NH > HC	66	7.29	-16, -100, 20
Anterior cingulate gyrus	L	H < HC	54	7.50	-6, 14, 34
Insular cortex	L	H < HC	65	6.78	-30, 8, 8
Insular cortex	R	H < HC	105	7.58	34, 6, 2
Anterior cingulate gyrus	R	H < HC	63	7.77	12, 6, 42
Central opercular cortex	R	H < HC	25	6.35	54, 4, 0
White matter close to primary somatosensory cortex	R	H < HC	51	> 8	44, -6, 26
Central opercular cortex	L	H < HC	168	7.38	-44, -8, 8
Posterior cingulate gyrus	R	H < HC	571	> 8	2, -16, 46
Precentral gyrus	L	H < HC	40	6.40	-8, -18, 60
Brain stem	R	H < HC	113	7.25	16, -26, -30
Superior temporal gyrus	R	H < HC	75	7.35	70, -32, 24
Occipital pole	L	H < HC	63	7.26	-34, -90, 10
Middle temporal gyrus, posterior	R	H > HC	69	7.27	60, -16, -26
Thalamus	R	H > HC	28	6.30	4, -16, 16
Posterior cingulate	R	H > HC	26	6.35	8, -38, 4
Precuneus		H > HC	35	6.48	0, -62, 66
Lateral occipital cortex	R	H > HC	27	6.36	16, -70, 54

Intracalcarine cortex	L	H > HC	60	6.83	-6, -80, 16
Supracalcarine cortex		H > HC	120	7.75	0, -80, 52
Posterior cingulate gyrus dorsal	R	H < NH HC < NH	47	6.55	4, -34, 44
WM close to supramarginal gyrus	L	H < NH	22	6.43	-26, -38, 42
Occipital pole	L	H < NH	62	7.06	-14, -100, 18
Paracingulate gyrus		H > NH	22	6.46	0, 42, 28
Orbitofrontal cortex, subcallosal area	L	H > NH HC > NH	49	6.74	-12, 10, -18
Temporal pole	R	H > NH	38	7.34	50, 6, -34
Posterior cingulate gyrus, caudal	R	H > NH HC > NH	29	6.33	4, -52, 22

Note. HC = healthy controls, H = hallucinating patients, NH = non-hallucinating patients, WM = white matter. $p < .001$ (corrected: FWE) k = 20 voxels.

3.2.3 Malevolent versus benevolent voice appraisal.

The hallucinating group was divided into two groups to investigate the effect of emotional valence on functional connectivity of the LB amygdala. Nothing passed correction (k = 0 voxels, $p < .05$) for hemisphere*group interaction or hemisphere main effect (k = 0 voxels, $p < .05$). Table V show the differences in LB amygdala functional connectivity between hallucinating patients with malevolent and benevolent voices. The left frontal pole, left fusiform cortex and right hippocampus exhibited stronger coupling with LB amygdala in the group with benevolent voices compared to the group with malevolent voices. Figure 1 shows the frontal pole area where hallucinating patients with benevolent voices had increased functional connectivity with the LB amygdala compared to patients with malevolent voices.

Nothing passed correction in the malevolent > benevolent contrast. The uncorrected comparison ($p < .001$) revealed that the hallucinating group with malevolent voices exhibited stronger functional connectivity between the laterobasal amygdala and two clusters in the cerebellum compared to the patients with benevolent voices.

Table V. *Effect of bilateral laterobasal amygdala functional connectivity between hallucinating patients with malevolent and benevolent voices.*

Benevolent > malevolent voices		Local maxima		
Structure	Side	K	Z	x, y, z
Frontal pole	L	20	6.07	-4, 60, 14
Temporal occipital fusiform cortex	L	35	6.14	-32, -56, -8
WM or Hippocampus*	R	26	6.09	34, -32, 0

Note. *94% white matter according to Harvard-structural atlas, optic radiation according to Jülich (6% hippocampus). $p < .05$ (corrected: FWE) $k = 20$ voxels

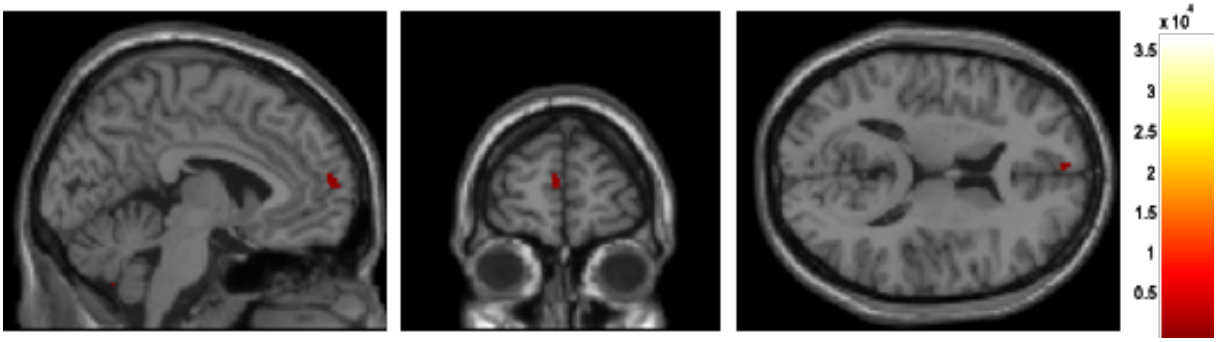

Figure 1. Hallucinating patients with benevolent voices show stronger coupling between the amygdala and the medial prefrontal cortex, compared to hallucinating patients with malevolent voices.

4 Discussion

Measuring spontaneous low frequency correlations with the laterobasal amygdala as region of interest revealed differences in functional connectivity between hallucinating patients and control groups. Hallucinating patients had increased coupling between the LB amygdala and temporal pole and paracingulate gurus compared to non-hallucinating patients. This indicates that there might be differences in how the two groups process or regulate emotions.

Comparing the hallucinating patients with malevolent voices and benevolent voices revealed reduced functional connectivity between the LB amygdala and the left frontal pole, fusiform gyrus and right hippocampus in patients with malevolent voices. Malevolent voices were also associated with increased depression, omnipotent voices and resistance of voices.

The discussion will focus mainly on the hallucinating patients, compared to non-hallucinating and healthy controls, with a particular focus on the subgroups of malevolent and benevolent voices. The differences between hallucinating patients and control groups could tell us something about underlying neural mechanisms of hallucinations, that are independent of emotional valence, while comparing the hallucinating subgroups could tell us something about the neural mechanisms of negative and positive valence of emotions, respectively.

4.1 Differences in Symptoms between Schizophrenia groups

Hallucinating patients had significantly more affective symptoms compared to non-hallucinating patients. Hallucinating patients experienced more symptoms of depression and anxiety, in addition to more general psychopathology. Previous studies have also found that positive symptoms are more strongly related to anxiety and depression compared to negative symptoms (Norman and Malla, 1994). These differences in symptoms were not related to age,

gender or duration of illness, as the groups did not significantly differ in demographic variables.

4.2 Functional Connectivity of the Amygdala

The results suggest that schizophrenia patients have reduced LB amygdala- functional connectivity with various brain regions involved with emotion processing compared to healthy controls. This reduction was seen in connections that are both positive and negatively correlated in healthy participants. However, the schizophrenia patients also exhibited increased connectivity between the LB amygdala and especially posterior regions of the brain (that are normally negatively or uncorrelated). This indicates that schizophrenia patients have extended amygdala connections with regions not seen in healthy participants during resting state. Roy et al. (2009) found that activation of regions involved in cognitive processes and effortful regulation of affect, such as superior frontal gyrus, middle frontal gyrus, posterior cingulate cortex, and precuneus, were negatively predicted by amygdala activity in healthy subjects. These regions tended to have stronger connectivity with the amygdala in schizophrenia patients compared to healthy controls in the present study. The abnormal connections could be explained as neuronal hyper or hypo-excitability or an abnormal increase or decrease in synaptic connections (Zhou et al., 2007).

The subgenual area (which had decreased amygdala-coupling in non-hallucinating patients) was the only observed ventral prefrontal region in the present study. This is surprising, considering the consistent finding of anatomical and functional connections between the amygdala and the orbitofrontal cortex (Banks et al., 2007; Ochsner et al., 2004b; Price & Drevets, 2010). It is possible that these connections would have been detected with a more liberal significance threshold. Further, it is not likely that other parts of the amygdala would be more involved than the LB amygdala considering that Roy et al. (2009) found

orbitofrontal connections with the LB amygdala in their study of healthy participants. Since the present study only looked at contrasts between groups, it is possible that there were no differences in amygdala functional connectivity with ventral prefrontal regions between groups. Phillips et al. (2003) has suggested that the ventral prefrontal cortex is important for rapid appraisal of emotional stimuli, while the dorsal prefrontal cortex is involved with effortful regulation of affective states. This would imply that schizophrenia patients experience normal appraisal of emotional stimuli. However, the aberrant connections between the amygdala and dorsal regions of the prefrontal cortex found in the present study may contribute to the observed affective symptoms in the hallucinating patients.

4.2.1 Emotion processing

This section goes through the findings related to structures known to interact with the amygdala in emotion processing. Any reductions or increases in coupling with the amygdala in these structures could explain aberrant emotion processing in hallucinating patients.

4.2.1.1 Stronger amygdala – precuneus coupling in schizophrenia patients.

The coupling of LB Amygdala and precuneus (predominantly right) (x, y, z = 2, -82, 48) was *increased* in schizophrenia patients compared to healthy controls. The precuneus has been found to be negatively correlated with the amygdala in healthy controls during resting state (Zhang & Li, 2012; Roy et al., 2009). However, Roy et al. (2009) also found a positive correlation in a large cluster of the left precuneus. A stronger coupling with the amygdala as shown in the present study in schizophrenia patients could indicate a stronger negative correlation compared to healthy controls, or a positive correlation.

The connectivity of the precuneus is related to higher associative cortical and subcortical structures (Cavanna & Trimble, 2006). The overall function is believed to be

related to processing internal stores of information, instead of exogenous perceptual processing (Cavanna & Trimble, 2006). It has been suggested that the precuneus has a role in consciousness and self-awareness due to deactivation in various unconscious states (e.g. sleep, hypnosis, anaesthesia, and vegetative state) (Cavanna & Trimble, 2006). The precuneus is one of the most active areas during rest, and is part of the default mode network (Cavanna & Trimble, 2006). Together with the posterior cingulate and retrosplenial area, it consumes more glucose than any other area of the cerebral cortex (Gusnard & Raichle, 2001). The default mode network has been found to be overactive in schizophrenia patients (Whitfield-Gabrieli et al., 2009). Further, increased precuneus activation has been observed in schizophrenia patients during an approachability judgment task in fMRI, compared to healthy controls (Mukherjee et al., 2014).

The precuneus is also involved with mental imagery and retrieval of episodic memory (Shallice et al., 1994; Fletcher et al., 1995). The stronger negative correlation or positive correlation between amygdala and precuneus in schizophrenia patients could be related to episodic memories or aberrant stress regulation. Veer et al. (2011) found increased amygdala-precuneus functional connectivity in a stress recovery phase after participants had gone through a psychosocial stressor task. The authors suggested that increased connectivity between the amygdala and precuneus (during resting state) could be related to stress and memory consolidation of negative experiences. The precuneus has been associated with episodic memory retrieval (Cavanna & Trimble, 2006). If the amygdala and precuneus are coupled during stress regulation, increased connectivity during resting state could indicate a hypersensitive stress response or aberrant stress regulation in schizophrenia patients.

Individuals with prodromal symptoms for psychosis have been found to have reduced precuneus volume (Borgwardt et al., 2007). Others have found increased precuneus volume in schizophrenia patients (Antonova et al., 2005). Larger volume was further associated with

greater number of psychotic episodes and hospitalizations, but also better verbal memory in schizophrenia patients. In the healthy control group of Antonova et al's. (2005) study however, larger precuneus volume was associated with poorer verbal working memory. This could imply that schizophrenia patients use different strategies in cognitive tasks, maybe because of aberrant connections or reduced volume in prefrontal cortices involved with working memory (Weinberger et al., 1986).

4.2.1.2 Weaker amygdala – insula coupling in schizophrenia patients.

Both schizophrenia groups showed *decreased* functional connectivity between LB amygdala and an area close to the insular cortex compared to healthy controls. Amygdala and insula have reciprocal connections (Amaral & Price, 1984; Aggleton et al., 1980), and are also both positively and negatively correlated in resting state (Roy et al., 2009). The conjunction analysis showed decreased activation of the right insula, while the t-test comparing non-hallucinating with healthy controls showed decreased left insula-amygdala connectivity. Hallucinating patients showed decreased connectivity bilaterally. No differences were found in amygdala-insula connectivity between the hallucinating and non-hallucinating group. Reduced insula volume has been observed in individuals with prodromal symptoms for psychosis (who later developed psychosis) (Borgwardt et al., 2007). Further, hallucination severity correlates negatively with insula grey matter volume (Wylie & Tregellas, 2010). Others have also found reduced amygdala – insula coupling in schizophrenia patients in an approachability task (Mukherjee et al., 2014).

The anterior part of the insula is connected to the amygdala (Wylie & Tregellas, 2010). Insula, amygdala and anterior cingulate cortex are important for emotional salience, detecting emotional significance of external stimuli and producing affective states (Phillips et al., 2003). Insula is also connected to sensory systems, emotion systems and memory regions

(Nagai Kashi & Kato, 2007). These connections make the insula able to detect bottom–up salience, and facilitate access to the brain's attentional and working memory resources (Menon & Uddin, 2010). The multiple connections indicate a role in processing/integrating multimodal information. The anterior insula has especially been implicated in mediating dynamic interactions between externally oriented attention and internally oriented or self-related cognition (Menon & Uddin, 2010).

The insula may be involved with the misattribution error found in schizophrenia patients, including self-recognition and discriminating sources of sensory input. Schizophrenia patients have been found to attribute self-generated stimuli to others (Waters, Woodward, Allen, Aleman & Sommer, 2012). Activation of the left insula has been associated with making correct attributions (Allen et al., 2005).

The insula has also been associated with interoception (Wylie & Tregallas, 2010). Interoception is the interpretation of how you are feeling, based on the sense of the physiological condition of the body (Craig, 2002). This could be relevant for the negative symptoms of schizophrenia, that is characterized by flat affect, anhedonia and avolition.

4.2.1.3 Stronger amygdala – temporal pole coupling in hallucinating patients.

Increased functional connectivity was observed between LB amygdala and the right temporal pole (50, 6, -34) in hallucinating patients compared to non-hallucinating patients. The temporal pole (BA38) covers the most anterior part of the temporal lobe, and have dense reciprocal connections with the amygdala (Höistad & Barbas, 2008). Still, the resting state study of Roy et al. (2009) did not detect a LB amygdala – temporal pole coupling, indicating that these structures are not normally correlated during rest. The right anterior temporal lobe is especially associated with feelings of familiarity and retrieval of biographical information (Olson, McCoy, Klobusicky, Ross, 2013).

Evidence suggest that the temporal pole is an integration area of highly processed sensory stimuli with emotional responses (Olson, Plotzker & Ezzyat, 2007). The temporal pole is frequently activated in complex emotional tasks, such as theory of mind, also called mentalizing (Olson et al., 2007). These tasks have socially important narratives that requires analysing another agent´s emotions, intentions or beliefs. One example of such a task is the Heider and Simmel (1944) animation where participants observe human-like interaction among three geometric figures.

Decreased temporal pole volume has been associated with severity of psychotic and disorganized symptoms (Crespo-Facorro et al., 2004). Increased connectivity between amygdala and temporal pole in hallucinating patients could be involved with the content of hallucinations, as the temporal pole is involved with autobiographical memory (Gallagher & Frith, 2003). The temporal pole has further been associated with representing and retrieving social knowledge (Olson et al., 2013); including memory about people and abstract forms of social memory like traits and social concepts. Reflective tasks concerning self, other people or social issues also activates the temporal pole in fMRI (D'Argembeau et al., 2005). The content or appraisal of hallucinations have been linked to "interpersonal schemas". Birchwood et al. (2004) found that depression and subordination to voices was caused by "interpersonal schemas" related to a person's social sense of being powerless and controlled by others. It was further the feeling of powerlessness in relation to the dominant malevolent voice that was linked to distress and depression. Benevolent voices could be rooted in positive interpersonal schemas. Interpersonal schemas are based on previous experiences, and depends on autobiographical memory (Baldwin, 1992). The role of the temporal pole in autobiographical memory could be related to the content or appraisal of both benevolent and malevolent voices. Although these are speculative assumptions that need to be supported by future

research, they provide a possible explanation for the aberrant amygdala – temporal pole connections seen in the hallucinating patients.

4.2.1.4 Weaker amygdala – inferior parietal lobule coupling in hallucinating patients.

Decreased LB amygdala coupling with the right inferior parietal lobule was observed in both schizophrenia groups in the conjunction analysis (with a significance threshold of $p <$ .05). However, the hallucinating group compared to healthy controls was the only contrast to appear in the t-tests with a significance threshold of $p < .001$. This indicates that the hallucinating patients had a larger decrease compared to non-hallucinating patients. Previous studies have found negative correlations between the right inferior parietal lobe and the right laterobasal amygdala (Roy et al., 2009). Decreased negative correlations between the right inferior parietal lobule and laterobasal amygdala in hallucinating patients could mean that they have either weaker negative correlations or slight positive correlations.

The inferior parietal lobule has not received much attention in schizophrenia research. This could be because it is a relatively difficult area to study due to late maturation and great variation in gyral pattern (Torrey, 2007). The inferior parietal lobule includes the supramarginal gyri and the angular gyri, and the evidence for abnormalities in schizophrenia patients are inconsistent (Shenton, Dickey, Frumin & McCarley, 2001). Abnormalities include decreased volume, increased volume, no differences between schizophrenia patients and controls, different lateralization, and correlations between decreased volume and severity of symptoms (Torrey, 2007). The inconsistent findings in schizophrenia patients could be related to the heterogeneity of the disorder, indicating that abnormalities in this structure is symptom-specific.

Normal function of inferior parietal lobe includes agency judgements and self-other distinctions (Brunet-Gouet & Decety, 2006). Inferior parietal lobule functions detected to be impaired in schizophrenia patients include sensory integration, body image, concept of self, and executive functions (Torrey, 2007). Acute abnormal function of the inferior parietal lobe includes permeability to others thoughts and behaviour, feeling of being intruded by others, influence syndrome and hallucinations (Brunet-Gouet & Decety, 2006). These abnormal functions are "classic" psychotic symptoms, and is in agreement with the suggestion that this structure could be abnormal in specific symptoms of schizophrenia. Further, chronic abnormal function includes merging of self and others, and external event bias. These abnormal functions are also seen in schizophrenia patients. Increased activation of the right supramarginal gyrus has also been associated with with decreased negative affect during reappraisal of emotion (Ochsner, Bunge, Gross & Gabrieli, 2002), indicating that this region could have some role in emotion regulation.

4.2.1.5 Weaker amygdala – subgenual coupling in non-hallucinating patients.

Hallucinating patients seemed to have a normal LB amygdala – subgenual area connectivity. The non-hallucinating patients showed *decreased* LB amygdala functional connectivity with this area compared to hallucinating patients and healthy controls. Strong positive amygdala – subgenual coupling is seen in healthy subjects (Stein & Wiedholz et al., 2007). Subgenual activation has been associated with self-induced sadness in healthy participants (Phan et al., 2002; Vogt, 2005). Decreased activation of this area has been associated with depression and decreased dopamine release (Drevets et al., 2008). Decreased coupling between amygdala and the subgenual area has also been associated with anxiety (Kim et al., 2011). PET-studies also show decreased cerebral blood flow and glucose metabolism in this area in depressed individuals. Further, the most prominent volumetric abnormality reported in major depressive disorder and bipolar disorder is a reduction in the

left subgenual area (Price & Drevets, 2010). The literature suggest that decreased activation or coupling of the subgenual area could be related to deficient regulation of sadness. Considering that hallucinating patients experienced more depression and anxiety compared to non-hallucinating patients it is surprising that the latter had decreased subgenual-coupling. No differences were detected between healthy controls and hallucinating patients in the subgenual area. This further indicates that the hallucinating group had a normal response. The increased dopamine levels in hallucinating patients could maybe be a "protective" factor of amygdala-subgenual connectivity. Although, this assumption would possibly hold more support if the hallucinating patients had increased coupling compared to healthy controls, which was not the case. Further research is required to provide evidence for these speculations.

4.2.2 Emotion Regulation

One interpretation of negative correlations between the amygdala and brain structures involved with emotion processing has been viewed as a regulating role of these structures of the amygdala. These assumptions are based on task-based studies showing an association between effective reduction of negative emotions and negative correlations between prefrontal cortices and the amygdala (Banks et al., 2007). This section goes through the structures that are believed to contribute in regulating the amygdala.

4.2.2.1 Weaker amygdala – inferior frontal gyrus coupling in schizophrenia groups.

The conjunction analysis showed that both schizophrenia groups had *decreased* functional connectivity between LB amygdala and the right inferior frontal gyrus compared to healthy controls (x, y, z = 60, 26, 20). The area detected in the non-hallucinating group and

healthy controls was classified as the right precentral gyrus by the Harvard-Oxford structural atlas, and as Broca's area by the Jülich histological atlas. The area observed between the healthy control group and the hallucinating group was classified as the central opercular cortex by the Harvard-Oxford structural atlas, and Broca's area by Jülich histological atlas. This area was situated ventral and caudal compared to the area observed in non-hallucinating patients, at the border to the superior temporal gyrus.

The inferior frontal gyrus has not been found to correlate with LB amygdala during resting state in previous studies (Roy et al., 2009). Relevant for the hallucinating patients, the right homologue of Broca's area have been found to activate during active hallucinations in fMRI (Sommer et al., 2008).

The inferior frontal gyrus is highly lateralized in function, and the right side is normally involved with nonverbal material and intrinsic processing (Lyoo et al., 2004). Volume reductions of right inferior frontal gyrus have been found in high-risk patients who later developed psychosis (Pantelis et al., 2003), and in bipolar I disorder (Lyoo et al., 2004). The right inferior frontal gyrus plays an important role in response inhibition (Aron, Robbins & Poldrack, 2004). Response inhibition is defined as the mechanism that the prefrontal cortex applies to implement executive control of subcortical and posterior regions (Aron et al., 2004). Evidence suggest that the right inferior frontal gyrus subserve inhibitory processes underlying switching from performing one task, to another (Aron et al., 2004). Aron et al. (2004) suggest that the response inhibition performed by the inferior frontal gyrus could be associated with the inhibition of unwanted memory, whenever we try to "push" (or suppress) unpleasant events or memories out of mind. Aberrant coupling between the amygdala and inferior frontal gyrus could possibly be related to an inability to suppress intrusive thoughts, that could lead to hallucinations. However, considering that non-hallucinating patients also had aberrant connections between these structures, it is more likely that it might subserve

some other aberrant functions in response inhibition. The right inferior frontal gyrus has also been implicated in processing of ambiguous facial expressions that might be associated with inhibition of emotional responses (Nomura et al., 2003). Taken together, it is unclear what the weaker amygdala – inferior frontal gyrus connections observed in schizophrenia patients could indicate, but it is possible that it is associated with aberrant response inhibition that has been detected in schizophrenia patients.

4.2.2.2 Weaker amygdala – anterior cingulate cortex coupling in schizophrenia patients.

In general, schizophrenia patients showed *decreased* functional connectivity between the LB amygdala and anterior cingulate gyrus (ACC), compared to healthy controls. The conjunction analysis revealed an area close to the left premotor cortex. Three other clusters were detected in the t-contrasts. Non-hallucinating patients exhibited *decreased* amygdala-functional connectivity with the left anterior cingulate gyrus corresponding to the mid-cingulate cortex in Vogt (2005), and in a subgenual area compared to healthy controls and hallucinating patients. Hallucinating patients had *decreased* amygdala-functional connectivity with the left dorsal anterior cingulate (x, y, z = -6, 14, 34), and an area close to the right premotor cortex, compared to healthy controls. The anterior cingulate cortex was negatively correlated with the LB amygdala in a previous study (Roy et al., 2009), implying that decreased coupling in schizophrenia patients could mean a weaker negative correlation.

Post-mortem studies have revealed a significant reduction of GABA interneurons in layer II of the anterior cingulate cortex in schizophrenia patients (Benes, McSparren, Bird, SanGiovanni & Vincent, 1991). Layer II receive projections from the basolateral nucleus of the amygdala (Benes, 2009). Benes (2009) suggest that the observed disturbance of inhibitory

activity in this layer of the anterior cingulate cortex in schizophrenia patients might be due to an increased inflow of activity originating in the amygdala.

The anterior cingulate cortex has connections to motor cortices, amygdala, anterior insula, ventral striatum, periaqueductal grey, orbitofrontal and dorsolateral prefrontal cortices (Devinsky, Morrell & Vogt, 1995). The ACC is thus highly interconnected with both the amygdala and prefrontal structures, which makes it ideally situated to mediate top-down regulation of the amygdala. In Roy et al's. study (2009) the laterobasal amygdala correlated negatively with the anterior cingulate cortex. Weaker amygdala – ACC connectivity has also been found in a study of veterans with post-traumatic stress disorder (PTSD). Sripada, Wang, Sripada & Liberzon (2012) found reduced negative correlations between amygdala and dorsal and rostral ACC compared to combat controls without PTSD. It is possible that the decreased connections observed in the present study is also related to reduced negative correlations.

The anterior cingulate cortex plays an important part in detecting conflicts in information processing, to further signal in situations that require cognitive control (Botvinick, Braver, Barch, Carter & Cohen, 2001). This attention to conflicts in information processing serves to regulate both cognitive and emotion processing (Bush, Luu & Posner, 2000). Further, the dorsal ACC is involved with appraisal and expression of negative emotion, while ventral ACC is involved with emotion regulation (Etkin, Egner & Kalisch, 2011). Phillips et al. (2003) however, includes the dorsal ACC in emotion regulation, and the ventral ACC in autonomic response regulation.

Weaker amygdala – dorsal anterior cingulate cortex coupling in hallucinating patients.

Hallucinating patients had decreased functional connectivity between the amygdala and left dorsal anterior cingulate cortex (x, y, z = -6, 14, 34), compared to healthy controls.

The non-hallucinating patients showed a similar effect, caudal to the area found in hallucinating patients (mid-cingulate) (x, y, z = -2, 4, 32). The dorsal ACC and amygdala have a negative correlation in healthy subjects (Roy et al., 2009), indicating that the hallucinating patients have a weaker negative correlation between amygdala and dorsal ACC.

Dorsal ACC is consistently activated in fear conditioning (Mechias, Etkin & Kalisch, 2010), and has been associated with emotional distress related to social and physical pain (Eisenberger & Lieberman, 2004). Individuals higher in neuroticism showed more ACC reactivity to a discrepancy detection task (Eisenberger & Lieberman, 2005). Neuroticism is associated with an increased alert system of perceived threatening stimuli. The increased reactivity of ACC to ambiguous stimuli could be an underlying neural mechanism for the "hight alert" and distress seen in anxious individuals. (Eisenberger & Lieberman, 2005). Further, paranoid patients also tend to have an excessive alertness or sensitivity to the external environment. Etkin, Egner, Peraza, Kandel & Hirsch (2006) suggest that the dorsal ACC is implicated in response conflict monitoring, irrespective of whether stimuli is cognitive or emotional.

The right side of the dorsal anterior cingulate cortex (6, 14, 32) was identified in a reappraisal study of emotion regulation, where increased activation of dorsal anterior cingulate cortex was associated with decreased negative affect in response to negative pictures (Ochsner et al., 2002). This implies a role for the dorsal anterior cingulate cortex in effective reappraisal of negative affect. Decreased coupling between amygdala and dorsal anterior cingulate cortex could indicate poorer emotion regulation skills.

Weaker negative correlations of the amygdala and dorsal ACC in hallucinating patients could possibly be related to the increased attention to insignificant stimuli that has been associated with psychosis (Kapur, 2003).

4.2.3 Stronger amygdala - paracingulate coupling in hallucinating patients.

Hallucinating patients had increased amygdala-paracingulate connectivity compared to non-hallucinating patients. The observed area was in the dorsomedial area of the prefrontal cortex (0, 42, 28). Previous studies have found strong negative correlations between the amygdala and dorsomedial PFC in healthy subjects (Roy et al., 2009; Stein & Wiedholz et al., 2007). This means that when activation of the dorsomedial PFC increase, amygdala activation decrease. Increased coupling in hallucinating patients could represent a stronger negative correlation, or even a positive correlation.

The aberrant connections could be associated with the observed anatomical increases in medial PFC volume that has been found in individuals with poor reality monitoring ability (Buda, Fornito, Bergström & Simons, 2011). The increased medial PFC volume is further negatively correlated with the length of the paracingulate sulcus (Buda et al., 2011), which has a 19.2mm mean reduction in hallucinating schizophrenia patients compared to non-hallucinating schizophrenia patients (Garrison et al., 2015). So hallucinating patients could have increased medial PFC volume because of a shorter or absent paracingulate sulcus, and the increased medial PFC volume is also associated with poor reality monitoring ability.

The paracingulate has consistently been associated with mentalizing, also called "theory of mind" (Gallagher et al., 2000; Brunet-Gouet & Decety, 2006). Mentalizing is defined as the ability to predict the behaviour of others by imagining their mental states concerning beliefs, desires, emotions or intentions (Gallagher & Frith, 2003). Schizophrenia patients tend to perform poorer than controls in mentalizing tasks (see Harrington, Siegert & McClure, 2005 for review). The review by Harrington et al. (2005) however, found that hallucinating patients did not perform worse than controls. Another study found poorer mentalizing performance in schizophrenia patients during an acute episode of psychosis, compared to non-schizophrenia inpatients (Drury, Robinson & Birchwood, 1998). When

these participants were tested again at recovery, no differences were found compared to controls. The authors suggested that theory of mind deficits could be a result of information-processing overload while patients are in a psychotic state. It could be hypothesised that hallucinating patients are more often involved with mentalizing, because they try to interpret the meaning or intentions of their voices.

Activity in the amygdala and dorsomedial and dorsolateral PFC has been proposed to reflect amount of emotional conflict (Etkin et al., 2006). Etkin et al. (2006) suggest that emotional conflict is generated in the amygdala, while the response conflict involves the dorsomedial and dorsolateral PFC. These structures are also involved with non-emotional attentional processes. The dorsomedial PFC is activated by uncertain or ambiguous stimuli, which can induce anxiety and relates to emotional conflict (Nomura et al., 2003). In a resting state study however, high anxious subjects showed amygdala–dorsomedial PFC activity that was uncorrelated, while low anxious subjects showed negatively correlated activity during resting state fMRI (Kim et al., 2011). It is possible that non-hallucinating patients had negatively correlated activity (normal response), and that the greater coupling in hallucinating patients represents uncorrelated functional connectivity.

Stronger (negative) amygdala – dorsomedial PFC coupling has been associated with successful emotion regulation in task-based fMRI (Banks et al., 2007), implicating that the dorsomedial PFC is able to suppress amygdala activation. Etkin & Wager (2007) suggest that hypo-activation of dorsomedial prefrontal cortex and dorsal anterior cingulate cortex could be related to a decrease in the experience or impact in negative emotion. Hallucinating patients in the present study had increased amygdala – dorsomedial PFC coupling, and decreased dorsal anterior cingulate cortex coupling. The dorsomedial PFC and dorsal ACC recruit rostral anterior cingulate cortex for emotion regulation (Etkin et al., 2006). The rostral anterior cingulate is closely connected to the frontal pole, which had increased functional

coupling with the amygdala in hallucinating patients with benevolent voices. Increased activity of this region is believed to reduce activation in the amygdala and thereby reduce emotional responsivity (Etkin et al., 2006). Dorsomedial PFC and dorsal ACC could be viewed as facilitating emotion regulation for the rostral ACC.

4.3 Amygdala coupling Based on Emotional Valence of the AVH

4.3.1 Gender differences and descriptives of malevolent and benevolent voices.

Hallucinating patients were grouped into malevolent or benevolent voices groups based on whether they had a higher score in e.g. benevolent voices compared to malevolent voices. Three of the men who were grouped as having malevolent voices had an average response equivalent to 'unsure' or 'disagree' in the BAVQ-R malevolence score. This means that they most likely did not see their voices as malevolent. However, they still had a higher malevolence score compared to benevolence score, indicating that they did not view their voices as benevolent either. Ideally these individuals should have been excluded or grouped in a third category of "neutral voices". The BAVQ-R however does not account for neutral voices. Theses results indicate that some patients do not view their voices as predominantly benevolent or malevolent. It is possible that some patients view their voices as neutral, and therefore do not agree on any of the items in the BAVQ-R questionnaire. It could also be that some patients are unsure of their voices' agenda, possibly because they have not had them for very long, or that their voices do not comment on them personally.

Further, women had a worse outcome compared to men in the present study based on the PANSS and BAVQ-scores. Women had significantly more severe depression, anxiety, negative symptoms, general psychopathology and both malevolent and omnipotent voices compared to men. In addition, the benevolent voices group consisted of only men (n = 7), while the malevolent voices group consisted of seven men and six women. A larger sample

would probably have evened out the groups as other researchers have not mentioned a similar gender effect on appraisal of voices (Chadwick & Birchwood, 1994; Chadwick et al., 2000). Women did however, not have more severe hallucinations than men (see appendix B, table III), measured by PANSS hallucinatory behaviour item. This indicates that severity of hallucinations is not associated with increased levels of distress, which is in agreement with previous studies (Badcock et al., 2011). Two of the men had severe hallucinations or a score of six on this item, while three men and three women had a score of five or moderate/severe hallucinations. A score of six means that "hallucinations are present almost continuously, causing major disruption of thinking and behaviour. Patient treats these as real perceptions, and functioning is impeded by frequent emotional and verbal responses to them". The two men with severe hallucinations also had malevolent voices.

The present study found that malevolent voices were resisted, and benevolent voices were engaged with, which is supported by the literature (Chadwick & Birchwood, 1994). Malevolent voices were also correlated with omnipotence and depression, which is in agreement with previous studies (Chadwick et al., 2000; Fialko et al., 2006). The association between malevolent voices and depression was probably a gender effect, as women were more depressed compared to men, and sex and depression had a higher correlation than malevolent voices and depression.

Women had an average depression score between moderate and moderate/severe in the PANSS. Moderate symptoms include "Distinct feelings of sadness or hopelessness, which may be spontaneously divulged, but depressed mood has no major impact on behaviour or social functioning and the patient usually can be cheered up" (PANSS). Moderate/severe symptoms include "distinctly depressed mood that is associated with obvious sadness, pessimism, loss of social interest, psychomotor retardation and some interference in appetite and sleep. The patient cannot be easily cheered up" (PANSS). Men had an average of

minimum/mild symptoms in the depression score, indicating symptoms at the upper extreme of normal limits and expressions of some sadness.

4.3.1.1 Anxiety.

Men had an average score of three in the anxiety item of the PANSS, indicating mild symptoms with some worry, overconcern or subjective restlessness, but with no evidence of somatic or behavioural consequences. Women on the other hand had an average between moderate and moderate/severe. Moderate symptoms of anxiety indicate that the patient reports distinct symptoms of nervousness, which are reflected in mild physical manifestations such as fine hand tremor and excessive perspiration. A Moderate Severe score indicate that "the patient reports serious problems of anxiety which have significant physical and behavioural consequences, such as marked tension, poor concentration, palpitations or impaired sleep".

Differences in anxiety could also explain why women reported more malevolent voices than men. Women in this study reported significantly more anxiety compared to men. However, there was no significant correlation between malevolent voices and anxiety, indicating that the men in the malevolent voices group experienced less anxiety. Anxiety disorders have been found to be more prevalent and more disabling in women than in men (McLean, Asnaani, Litz & Hofmann, 2011). Also, there is some evidence for the assumption that women tend to worry than men (Häfner, 2003). A tendency to worry more could possibly affect the perceived malevolence of voices. Goldstein and Link (1988) found more affective disorder comorbidity with psychosis in women compared to men. This would be in agreement with the present study as women scored higher on general psychopathology, depression, anxiety and negative symptoms. This could further be related to greater emotionality and reactivity to stress in women (Rector & Seeman, 1992).

Differences in reports of malevolent voices between women and men could be due to different experiences of childhood trauma. Auditory hallucinations have been linked to childhood trauma, especially sexual abuse (Bentall, Wickham, Shevlin & Varese, 2012). Fisher et al. (2009) found an association between adverse childhood experiences and psychosis in women, but not in men. Another study found that a history of childhood sexual abuse was reported by 10/26 patients and was linked to more malevolent voices (Offen, Waller & Thomas, 2003).

4.3.2 Malevolent voices and decreased amygdala-coupling

Stronger LB amygdala functional connectivity was observed with the left medial frontal gyrus (frontal pole), left fusiform cortex and right hippocampus in the hallucinating group with benevolent voices compared to the group with malevolent voices. These resting state functional connections have also been found in healthy subjects (Roy et al., 2009). Since no comparisons were made between the hallucinating subgroups and the control group, one can only assume, based on the comparison with Roy et al. (2009) that the benevolent group have a normal response in these regions.

Using a more liberal significance threshold ($p < .05$), the hallucinating patients had decreased functional connectivity between the amygdala and the right frontal pole (x, y, z = 2, 66, 10), compared to non-hallucinating patients (data not shown). The similar connection seen in the hallucinating – non-hallucinating contrast could be due to the patients with malevolent voices, because they were in a greater number than the patients with benevolent voices (mal n = 13, ben n = 7). This indicates that the patients with benevolent voices could be similar to the non-hallucinating patients in the amygdala – frontal pole connection.

4.3.2.1 Weaker amygdala – frontal pole coupling in patients with malevolent voices.

The area of stronger functional connectivity between laterobasal amygdala and left medial prefrontal cortex in hallucinating patients with a higher benevolent- compared to malevolent score, corresponded with area 10p in Öngür, Ferry and Price (2003). This area is often referred to as the anterior/rostral frontal pole or anterior/rostral medial prefrontal cortex, and is part of Brodmann area 10. BA 10 is the largest architectonic area of the prefrontal cortex (Öngür et al., 2003). Roy et al. (2009) found a more ventral area that was positively correlated with the right laterobasal amygdala.

The medial prefrontal cortex is involved with intrinsic processes like remembering the past, prospection of the future and theory of mind (Buckner & Carroll, 2007). The medial prefrontal cortex is one of the most active regions during rest, and is implicated in the default mode network (Gusnard & Raichle, 2001).

The human frontal pole cooperates with the orbitofrontal cortex, temporal pole, and amygdala to process social and emotional information (Olson et al., 2007). Both hallucinating patients with malevolent and benevolent voices had stronger functional connectivity between amygdala and temporal pole. This could mean that the temporal pole is important for processing both positive and negative valence of emotional stimuli. Further, stronger amygdala functional connectivity with the frontal pole could be important for positive valence. It is also possible that stronger coupling is related to perceived control, as benevolent voices are associated with greater control and positive attribution (Larøi et al., 2012).

The frontal pole area (x, y, z = 2, 60, 6) that was detected in the study of Veer et al. (2011) in the stress recovery phase was in the same area observed in the present study. This could indicate a role for the frontal pole in regulating the stress-response in amygdala. It could be that a stronger connectivity between the amygdala and the frontal pole in hallucinating patients with benevolent voices makes them more adept in emotion regulation. In accordance

with this assumption, reappraisal of negative emotions increases activity in medial PFC (x, y, z = -11, 67, 18) and has been associated with reduced activations of the amygdala and insula (Goldin et al., 2008). This indicates that the observed effect of stronger functional connectivity between the amygdala and medial PFC in benevolent AVH could be related to effective emotion regulation. Stronger amygdala-medial PFC connectivity measured in a resting state study also predicted lower anxiety (Kim et al., 2011). However, the medial region in the study of Kim et al. (2011) was located ventral to the area detected in this study. Further, individuals with high anxiety levels had negative correlations between amygdala and ventromedial PFC (Kim et al., 2011). Anxiety was not associated with malevolent voices in the present study, but showed a significant gender effect where women tended to be more anxious compared to men. The decreased connectivity between amygdala and medial PFC could still be related to anxiety, since women had higher malevolent scores compared to men.

The anterior medial PFC has also been associated with focusing on subjective emotional responses (Lane, Fink, Chau & Dolan, 1997). In one study, subjects viewed emotional (pleasant and unpleasant) and neutral picture sets and responded whether pictures were pleasant, unpleasant or neutral (internal focus condition) or whether the scene in the pictures were indoors or outdoors (external focus condition). The internal focus condition represents subjective emotional responses. The internal focus condition elicited increased activity in rostral anterior cingulate (close to the region observed in the present study), compared to the external condition (Lane et al., 1997). This could also be associated with participants focusing on themselves as the medial PFC (x, y, z = -4, 52, -1) is active during self-reflection (D'Argembeau et al., 2005).

Others have observed activation in the area equivalent to BA10p during evaluation of pleasant arousing words compared to neutral words in healthy participants, using fMRI. This effect was not seen in the neutral versus unpleasant words condition (Maddock, Garrett &

Buonocore, 2003). Another study found that medial PFC (-4, 56, 14) activation was positively correlated with more positive subjective ratings of pictures with emotional content (Grimm et al., 2006). Phan et al. (2002) observed medial PFC activation in emotion processing of both positive and negative emotions. Which makes it unclear whether this region is associated with positive emotions only or emotion processing in general.

The hallucinating patients with malevolent voices were more depressed compared to hallucinating patients with benevolent voices. Johnson, Nolen-Hoeksema, Mitchell & Levin (2009) found decreased activity in medial PFC in participants with major depressive disorder compared to healthy controls when they were induced to self-reflect with valence-neutral cues. Tendency to ruminate was negatively correlated with activity in medial PFC when participants were cued to think about who they strive to be, and why things turn out as they do (Johnson et al., 2009). The decrease in depressed individuals could indicate that the medial PFC could be involved with positively valenced self-reflection, supported by the results in the present study with increased connectivity in AVH patients with benevolent voices.

Depression is also associated with diminished serotonin levels. A study investigating the phenotype of the human serotonin transporter gene (SLC6A4) in healthy participants found that having the s-allele increased coupling between amygdala and medial PFC (-15, 52, -8) in response to aversive stimuli (Heinz et al., 2005). The authors concluded that increased coupling between amygdala and medial PFC could reflect an increased capacity for regulating emotions (Heinz et al., 2005).

4.3.2.2 Weaker amygdala - hippocampus coupling in patients with malevolent voices.

Hallucinating patients with malevolent voices had decreased amygdala functional connectivity with the right hippocampus, compared to patients with benevolent voices.

The hippocampus has strong connections to the amygdala, and these regions cooperate in memory and learning, especially in modulating memory processes during emotional arousal (McGaugh, 2004). The decreased coupling between the amygdala and hippocampus in patients with malevolent voices could be related to the distress associated with these voices, or it could be related to previous experienced trauma (which was not measured in the present study). Trauma is associated with smaller hippocampal volume due to its role in the stress response, modulated by the hypothalamic-pituitary-adrenal-axis (Kandel et al., 2013). The hippocampus is part of the feedback loop and contains receptors for cortisol. An enhanced level of glucocorticoids which are released in response to stress makes the hippocampus inhibit excessive release of cortisol releasing hormone from the hypothalamus (Kandel et al., 2013). Excessive levels of glucocorticoids, especially in early life inhibits neurogenesis in the hippocampus (Sapolsky, 2000). Higher cortisol levels have been associated with smaller left hippocampal volume in first-episode psychosis (Mondelli et al., 2010).

4.3.2.3 Schizophrenia and trauma

The malevolent content of voices could be related to negative cognitive schemas, poor self esteem, early life stress, which could further lead to aberrant brain connections. Shin, Rauch and Pitman (2006) found increased amygdala, and diminished medial PFC responsivity, diminished hippocampal volumes and impaired hippocampal function in PTSD, compared to trauma-exposed individuals without PTSD. This indicates that hallucinating patients with malevolent voices could have some similar underlying neural mechanisms as individuals with PTSD. There is a stronger relationship between hallucinations and recalled childhood trauma compared with other psychotic symptoms (Read, Os, Morrison & Ross, 2005). Further, a significant proportion of psychotic disorders arise as a response to trauma, and PTSD-like symptoms can be developed in response to people's experience of psychotic

episodes (Morrison, Frame & Larkin, 2003). Andrew, Gray and Snowden (2008) found that both hallucinating patients with a schizophreniform disorder and a non-clinical group with hallucinations, reported high prevalence of traumatic life events. The schizophreniform group however, had significantly more symptoms sufficient for a diagnosis of PTSD. Childhood sexual abuse was also more common in patients with a schizophreniform disorder. The non-clinical groups had predominantly benevolent voices, while the schizophrenia group had predominantly malevolent voices (Andrew et al., 2008). This indicates that trauma might be related to developing AVH, but the severity of trauma might be related to beliefs about voices. Acute psychosis and PTSD comorbidity was found to have a prevalence of 67% in one study (Frame & Morrison, 2001).

Dorahy et al. (2009) explored differences between hallucinating schizophrenia patients with no childhood maltreatment, hallucinating schizophrenia patients with a childhood maltreatment history and dissociative identity disorder. The schizophrenia group with maltreatment history and the dissociative identity disorder group both experienced voices "telling them what to do and feeling controlled by voices". The majority in each group reported voice content to be incongruent with their own mood (Dorahy et al., 2009).

In a study of 47 schizophrenia patients, 74% reported experiencing at least one life threatening event, which led to subjective distress, and 13% of the participants had current PTSD (Resnick, Bond & Mueser, 2003). Symptoms of PTSD was further associated with greater emotional distress, but not with schizophrenia-specific symptoms. However, the study by Resnick et al. (2003) did not include a control group, meaning that the same prevalence could be present in the general population. Read, Perry & Moskowitz (2001) suggest that PTSD, dissociative disorders and schizophrenia should be viewed as interacting components of a process beginning with adaptive responses to early aversive events and evolving into a range of maladaptive disturbances later in life. Sadeh, Spielberg, Warren, Miller & Heller

(2014) further propose that strong negative medial PFC-amygdala connectivity could be a transdiagnostic indicator cutting across disorders with prominent hyperarousal symptoms. The Traumagenic Neurodevelopmental model postulates that a central effect of trauma on children's brains is increased sensitivity to stress (Read et al., 2001).

Moskovitz and Corstens (2008) suggest that dissociation could be underlying all forms of auditory hallucinations. Dissociation is considered as a lack of normal integration of thoughts, feelings and experiences in consciousness and memory (Bernstein & Putnam, 1986). Dissocation is often associated with trauma, and is also seen in PTSD. Moskovitz and Corstens (2008) argue that AVH behaves similar to a trauma in that it is the person's response to the trauma or AVH, and the extent to which they can incorporate it into their existing schemas that determines need for care. Further, AVH is often preceded by a highly stressful experience (Romme & Escher, 1989). Likewise, elevated anxiety levels and elevated HPA-axis activity has been found before first report of AVH (Delespaul & van Os, 2002; Garner et al., 2005). AVH has been associated with childhood trauma in a large sample of individuals in the general population (Bentall et al., 2012). If the voices are indeed rooted in traumatic events, then it is possible that hallucinating schizophrenia patients with malevolent voices and PTSD patients may share some underlying neural mechanisms, possibly constituted by elevated stress levels. These speculations need to be interpreted with caution, as the present study did not include a measure of experienced trauma. Further work is required to make any conclusions.

4.4 Future directions

Whether patients experience benevolent or malevolent voices appears to be very important for life quality and clinical outcome, as the content of negative or malevolent voices seems to elicit adverse emotional responses and distress to the patient. Exploring the

brain functioning that leads a patient to have either benevolent or malevolent voices, could hopefully contribute in developing interventions specifically to target the malevolent voices.

Considering the detrimental effects of malevolent voices, more research should be conducted regarding both underlying neural and psychological mechanisms of malevolent voices. Based on these preliminary results, the author suggests that future MRI studies of underlying structural and functional mechanisms should look at hallucinating patients with malevolent and benevolent voices separately. Important differences between these two groups could be cancelled out by only looking at them as one hallucinating group. Hallucinating patients with malevolent voices may also have experienced trauma, which makes it important to include a measure of traumatic experiences. The results further support the importance of separating schizophrenia groups based on specific symptoms when investigating underlying neural mechanisms in neuroimaging. The gender effects that were observed might be because of the small sample size, however this is also something that future studies should look into. A similar study could also be conducted with the insula as region of interest, as the insula is important for somatic sensation of negative emotions (interoception).

4.5 Limitations

The present study has several limitations, some of which have already been discussed. The observed sex differences could be due to the small sample size (6 females; 14 males in hallucinating group). The benevolent voices group consisted of only men. The malevolent/benevolent voices groups were divided based on the participants higher score relative to the other. So a participant could have a score of 2 on benevolence and 3 on malevolence, and be placed in the malevolence group. Further, the participants were instructed to rate the appraisal of their dominant voice (if the participant experienced several voices then this would in theory be the malevolent voice, as they are often perceived as more

dominant). However, it is unclear if the participants were considering all their voices when they filled out the questionnaire or if they focused on reporting only regarding the dominant voice, given that the results showed that some had almost equally high or low score on both malevolence and benevolence items. It could also be that some patients have a dominant voice that is appraised as both benevolent and malevolent. In hindsight there should probably have been a third group consisting of participants with both malevolent and benevolent voices.

The fMRI analyses were not controlled for gender, age, or duration of illness. Gender and age effects are consistently found in the brain, and these effects should have been controlled for. Duration of illness can also have an effect because of longer use of medication, and brain morphologies that may evolve during the disease. The malevolent and benevolent voices groups were not compared to the control groups. It would have been fruitful to see if the benevolent voices group were any different from the non-hallucinating patients or healthy controls, as they experienced less distress measured in the PANSS-score.

Participants were not drug-naïve, which means that antipsychotic drug effects could be responsible for the observed differences in amygdala-connections. Differences between groups with malevolent and benevolent voices are at least not related to drug effects, as these were both on medication.

Because of the small sample size, differences could be due to limited statistical power. Small sample size increases the risk of false-positives, however the use of a stringent threshold and FWE correction makes it more likely that the study suffers from false-negative results. Any generalizations are further limited to auditory hallucinations in the schizophrenia spectrum disorders.

5 Concluding Remarks

The findings are in accordance with the view of schizophrenia as a "dysconnectivity syndrome". Schizophrenia patients had aberrant amygdala- functional connectivity with brain regions involved with emotion processing. Strengthened coupling was in general found between amygdala and posterior regions of the brain in schizophrenia patients. Hallucinating patients especially showed aberrant connections between the amygdala and dorsomedial PFC and dorsal ACC, areas that have been associated with emotion processing. These regions have also been implicated in a role of facilitating emotion regulation in the rostral ACC. The rostral ACC is adjacent to the frontal pole area that had stronger amygdala coupling in AVH with benevolent voices. This indicates that stronger connections between these structures could underlie the benevolent appraisal of voices, and perhaps better abilities to regulate emotions.

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Appendix

Appendix A – Demographic data

Table. I

Demographic data for schizophrenia patients

				Age				Duration of illness			
	N	Fem	Male	range	*M*	*Mdn*	*SD*	range	*M*	*Mdn*	*SD*
NH	25	7	18	20-66	30.48	27	11.17	8-632	2.89	1.15	3.37
H	20	6	14	18-39	23.65	25	5.88	3-889	3.11	1.09	4.3
Mal	13	6	7	18-34	25.92	26	5.81	3-889	3.87	1.73	5.11
Ben	7	0	7	20-39	25.14	22	6.44	8-329	1.80	1.09	2.11

Note. NH = non-hallucinating, H = hallucinating, Mal = malevolent voies, Ben = benevolent voices, Fem = female. Duration of illness is noted in years (except for range, which is in weeks).

Table II.

Demographic data for schizophrenia patients with malevolent and benevolent voices.

	Malevolent voices		Benevolent voices	
	M	*SD*	*M*	*SD*
Positive symptoms	2.81	.72	2.55	.66
Negative symptoms	2.57	.74	1.92	.54
General psychopathology	2.28	.55	2.04	.45
Depression	3.38	1.56	2.43	1.62
Anxiety	3.85	1.14	2.71	1.50
Omnipotent voices	1.63	.83	.93	.50
Malevolent voices	1.86	.81	.33	.96
Benevolent voices	.56	.70	1.43	.90

Note. Duration of illness is noted in years

Appendix B – Descriptive statistics

Table III.

Descriptive statistics of gender and hallucinatory behaviour item of PANSS

	Mild 3	Moderate 4	Moderate/ severe 5	Severe 6	Total
Women		3	3		6
Men	5	4	3	2	14
Total	5	7	6	2	20

Table IV.

Descriptive statistics of gender and mean score of malevolence and benevolence item

	Malevolence item		Benevolence item	
	Male	Female	Male	Female
Disagree	7		4	3
Unsure	3		7	4
Agree slightly	2	3	2	
Agree strongly	1	3	1	

Appendix C – Independent samples t-tests

Table V.

Significant differences between hallucinating women and men.

	Women		Men				
	M	*SD*	*M*	*SD*	*t*	*df*	*p*
Malevolence	2.27	.45	.85	.83	-3.91	17	< .001
Omnipotence	2.11	.66	1.07	.64	-3.30	18	.004
Depression	4.50	1.05	2.43	1.40	-3.24	18	.005
General psychopathology	2.60	.60	2.02	.38	-2.65	18	.016
Anxiety	4.50	.55	3.00	1.36	-2.58	18	.019
Negative symptoms	2.91	.80	2.10	.58	-2.54	18	.021

Note. Only showing significant differences.

Table VI.

Significant differences between hallucinating and non-hallucinating patients.

	Hallucinating		Non-hallucinating				
	M	*SD*	*M*	*SD*	*t*	*df*	*p*
Positive symptoms	2.72	.69	1.75	.71	-4.61	43	< .001
General psychopathology	2.19	.52	1.72	.50	-3.09	43	.003
Depression*	3.05	1.61	2.00	.96	-2.58	29.47	.015
Anxiety	3.45	1.36	2.52	1.12	-2.52	43	.016

Note. Only showing significant differences. *equal variances not assumed in Levene's test for equality of variances.

Appendix D – functional connectivity analysis of the amygdala

Table VII.

Hemisphere main effect for schizophrenia groups and healthy controls

Structure	Side	Coordinates	Z-score	Cluster size	*t*-contrasts
Laterobasal Amygdala	L	-22, -2, -24	> 8	1278	Left > right
Superior frontal gyrus	L	-6, 22, 64	6.55	271	Left > right
Middle frontal gyrus	L	-32, -2, 64	5.75	97	Left > right
Laterobasal Amygdala	R	24, 0, -22	> 8	1167	Right > left
Temporal pole	R	54, 10, -4	5.82	89	Right > left
Planum temporale	R	52, -22, 12	5.52	26	Right > left

Note. $p < .05$ (FWE) $k = 20$ voxels

Table VIII.

*Group*hemisphere interaction for schizophrenia groups and healthy controls*

Structure	Coordinates	Z-score	Cluster size
Cerebellum	-48, -64, -28	3.83	23
Precentral gyrus	12, -22, 80	3.72	50
WM temporal lobe*	26, -24, -2	3.57	12
Middle frontal gyrus	-32, 28, 30	3.45	12
Precuneus	8, -60, 54	3.31	17

Note. WM = white matter. *Optic radiation according to Jülich. $p < .001$ (uncorrected) $k = 10$ voxels

Appendix E – BAVQ-R questionnaire

There are many people who hear voices. It would help us to find out how you are feeling about your voices by completing this questionnaire. Please read each statement and tick the box which best describes the way you have been feeling in the *past week*.

If you hear more than one voice, please complete the form for the voice which is dominant.

Thank you for your help.

		Disagree	Unsure	Agree slightly	Agree strongly
1	My voice is punishing me for something I have done				
2	My voice wants to help me				
3	My voice is very powerful				
4	My voice is persecuting me for no good reason				
5	My voice wants to protect me				
6	My voice seems to know everything about me				
7	My voice is evil				
8	My voice is helping to keep me sane				
9	My voice makes me do things I really don't want to do				

		Disagree	Unsure	Agree slightly	Agree strongly
10	My voice wants to harm me				
11	My voice is helping me to develop my special powers or abilities				
12	I cannot control my voices				
13	My voice wants me to do bad things				
14	My voice is helping me to achieve my goal in life				
15	My voice will harm or kill me if I disobey or resist it				
16	My voice is trying to corrupt or destroy me				
17	I am grateful for my voice				
18	My voice rules my life				
19	My voice reassures me				
20	My voice frightens me				
21	My voice makes me happy				
22	My voice makes me feel down				
23	My voice makes me feel angry				
24	My voice makes me feel calm				
25	My voice makes me feel anxious				
26	My voice makes me feel confident				

When I hear my voice, *usually* …

		Disagree	Unsure	Agree slightly	Agree strongly
27	I tell it to leave me alone				
28	I try to take my mind off it				
29	I try to stop it				
30	I do things to prevent it talking				
31	I am reluctant to obey it				
32	I listen to it because I want to				
33	I willingly follow what my voice tells me to do				
34	I have done things to start to get in contact with my voice				
35	I seek the advice of my voice				

Scoring Guidelines

All items have a four-point response range, Disagree (score 0), Unsure (score 1), Agree slightly (score 2) and Agree strongly (score 3).

The questionnaire has three scales measuring meaning given to the voice:

Malevolence (items 1, 4, 7, 10, 13, 16)
Benevolence (items 2, 5, 8, 11, 14, 17)
Omnipotence (items 3, 6, 9, 12, 15, 18)

These three scales therefore have a range of possible scores 0–18.

Following the original BAVQ, the questionnaire also measures Resistance and Engagement, two ways of relating to voices. Resistance and Engagement both contain emotional and behavioural items.

Resistance
- Emotion (items 20, 22, 23, 25): range 0–12
- Behaviour (items 27, 28, 29, 30, 31): range 0–15

Engagement
- Emotion (items 19, 21, 24, 26): range 0–12
- Behaviour (items 32, 33, 34, 35): range 0–12

Emotion and behaviour scores can either be totalled to give one overall score for Resistance (range 0–27) and Engagement (range 0–24), or looked at separately, or both.

Appendix F – PANSS

POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS) RATING CRITERIA

GENERAL RATING INSTRUCTIONS

Data gathered from this assessment procedure are applied to the PANSS ratings. Each of the 30 items is accompanied by a specific definition as well as detailed anchoring criteria for all seven rating points. These seven points represent increasing levels of psychopathology, as follows:

1- absent

2- minimal

3- mild

4- moderate

5- moderate severe

6- severe

7- extreme

In assigning ratings, one first considers whether an item is at all present, as judging by its definition. If the item is absent, it is scored 1, whereas if it is present one must determine its severity by reference to the particular criteria from the anchoring points. The highest applicable rating point is always assigned, even if the patient meets criteria for lower points as well. In judging the level of severity, the rater must utilise a holistic perspective in deciding which anchoring point best characterises the patient's functioning and rate accordingly, whether or not all elements of the description are observed.

The rating points of 2 to 7 correspond to incremental levels of symptom severity:

- A rating of 2 (minimal) denotes questionable or subtle or suspected pathology, or it also may allude to the extreme end of the normal range.

- A rating of 3 (mild) is indicative of a symptom whose presence is clearly established but not pronounced and interferes little in day-to-day functioning.

- A rating of 4 (moderate) characterises a symptom which, though representing a serious problem, either occurs only occasionally or intrudes on daily life only to a moderate extent.
- A rating of 5 (moderate severe) indicates marked manifestations that distinctly impact on one's functioning but are not all-consuming and usually can be contained at will.

- A rating of 6 (severe) represents gross pathology that is present very frequently, proves

highly disruptive to one's life, and often calls for direct supervision.

- A rating of 7 (extreme) refers to the most serious level of psychopathology, whereby the manifestations drastically interfere in most or all major life functions, typically necessitating close supervision and assistance in many areas.

Each item is rated in consultation with the definitions and criteria provided in this manual. The ratings are rendered on the PANSS rating form overleaf by encircling the appropriate number following each dimension.

PANSS RATING FORM

		absent	minimal	mild	moderate	moderate severe	severe	extreme
P1	Delusions	1	2	3	4	5	6	7
P2	Conceptual disorganisation	1	2	3	4	5	6	7
P3	Hallucinatory behaviour	1	2	3	4	5	6	7
P4	Excitement	1	2	3	4	5	6	7
P5	Grandiosity	1	2	3	4	5	6	7
P6	Suspiciousness/persecution	1	2	3	4	5	6	7
P7	Hostility	1	2	3	4	5	6	7
N1	Blunted affect	1	2	3	4	5	6	7
N2	Emotional withdrawal	1	2	3	4	5	6	7
N3	Poor rapport	1	2	3	4	5	6	7
N4	Passive/apathetic social withdrawal	1	2	3	4	5	6	7
N5	Difficulty in abstract thinking	1	2	3	4	5	6	7
N6	Lack of spontaneity & flow of conversation	1	2	3	4	5	6	7
N7	Stereotyped thinking	1	2	3	4	5	6	7

G1	Somatic concern	1	2	3	4	5	6	7
G2	Anxiety	1	2	3	4	5	6	7
G3	Guilt feelings	1	2	3	4	5	6	7
G4	Tension	1	2	3	4	5	6	7
G5	Mannerisms & posturing	1	2	3	4	5	6	7
G6	Depression	1	2	3	4	5	6	7
G7	Motor retardation	1	2	3	4	5	6	7
G8	Uncooperativeness	1	2	3	4	5	6	7
G9	Unusual thought content	1	2	3	4	5	6	7
G10	Disorientation	1	2	3	4	5	6	7
G11	Poor attention	1	2	3	4	5	6	7
G12	Lack of judgement & insight	1	2	3	4	5	6	7
G13	Disturbance of volition	1	2	3	4	5	6	7
G14	Poor impulse control	1	2	3	4	5	6	7
G15	Preoccupation	1	2	3	4	5	6	7
G16	Active social avoidance	1	2	3	4	5	6	7

SCORING INSTRUCTIONS

Of the 30 items included in the PANSS, 7 constitute a **Positive Scale**, 7 a **Negative Scale**, and the remaining 16 a **General Psychopathology Scale**. The scores for these scales are arrived at by summation of ratings across component items. Therefore, the potential ranges are 7 to 49 for the Positive and Negative Scales, and 16 to 112 for the General Psychopathology Scale. In addition to these measures, a Composite Scale is scored by subtracting the negative score from the positive score. This yields a bipolar index that ranges from –42 to +42, which is essentially a difference score reflecting the degree of predominance of one syndrome in relation to the other.

POSITIVE SCALE (P)

P1. **DELUSIONS** - Beliefs which are unfounded, unrealistic and idiosyncratic.
Basis for rating - Thought content expressed in the interview and its influence on social relations and behaviour.
1 Absent - Definition does not apply
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits
3 Mild - Presence of one or two delusions which are vague, uncrystallised and not tenaciously held. Delusions do not interfere with thinking, social relations or behaviour.
4 Moderate - Presence of either a kaleidoscopic array of poorly formed, unstable delusions or a few well-formed delusions that occasionally interfere with thinking, social relations or behaviour.
5 Moderate Severe - Presence of numerous well-formed delusions that are tenaciously held and

occasionally interfere with thinking, social relations and behaviour.
6 Severe - Presence of a stable set of delusions which are crystallised, possibly systematised, tenaciously held and clearly interfere with thinking, social relations and behaviour.
7 Extreme - Presence of a stable set of delusions which are either highly systematised or very numerous, and which dominate major facets of the patient's life. This frequently results in inappropriate and irresponsible action, which may even jeopardise the safety of the patient or others.

P2. **CONCEPTUAL DISORGANISATION -** Disorganised process of thinking characterised by disruption of goal-directed sequencing, e.g. circumstantiality, loose associations, tangentiality, gross illogicality or thought block.
Basis for rating - Cognitive-verbal processes observed during the course of interview.
1 Absent - Definition does not apply
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits
3 Mild - Thinking is circumstantial, tangential or paralogical. There is some difficulty in directing thoughts towards a goal, and some loosening of associations may be evidenced under pressure.
4 Moderate - Able to focus thoughts when communications are brief and structured, but becomes loose or irrelevant when dealing with more complex communications or when under minimal pressure.
5 Moderate Severe - Generally has difficulty in organising thoughts, as evidenced by frequent irrelevancies, disconnectedness or loosening of associations even when not under pressure.
6 Severe - Thinking is seriously derailed and internally inconsistent, resulting in gross irrelevancies and disruption of thought processes, which occur almost constantly.
7 Extreme - Thoughts are disrupted to the point where the patient is incoherent. There is marked loosening of associations, which result in total failure of communication, e.g. "word salad" or mutism.

P3. **HALLUCINATORY BEHAVIOUR -** Verbal report or behaviour indicating perceptions which are not generated by external stimuli. These may occur in the auditory, visual, olfactory or somatic realms.
Basis for rating - Verbal report and physical manifestations during the course of interview as well as reports of behaviour by primary care workers or family.
1 Absent - Definition does not apply
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits
3 Mild - One or two clearly formed but infrequent hallucinations, or else a number of vague abnormal perceptions which do not result in distortions of thinking or behaviour.
4 Moderate - Hallucinations occur frequently but not continuously, and the patient's thinking and behaviour are only affected to a minor extent.
5 Moderate Severe - Hallucinations occur frequently, may involve more than one sensory modality, and tend to distort thinking and/or disrupt behaviour. Patient may have a delusional interpretation of these experiences and respond to them emotionally and, on occasion, verbally as well.
6 Severe - Hallucinations are present almost continuously, causing major disruption of thinking and behaviour. Patient treats these as real perceptions, and functioning is impeded by frequent emotional and verbal responses to them.
7 Extreme - Patient is almost totally preoccupied with hallucinations, which virtually dominate thinking and behaviour. Hallucinations are provided a rigid delusional interpretation and provoke verbal and behavioural responses, including obedience to command hallucinations.

P4. **EXCITEMENT -** Hyperactivity as reflected in accelerated motor behaviour, heightened responsivity to stimuli, hypervigilance or excessive mood lability.
Basis for rating - Behavioural manifestations during the course of interview as well as reports of behaviour by primary care workers or family.
1 Absent - Definition does not apply
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits
3 Mild - Tends to be slightly agitated, hypervigilant or mildly overaroused throughout the interview, but without distinct episodes of excitement or marked mood lability. Speech may be slightly pressured.
4 Moderate - Agitation or overarousal is clearly evident throughout the interview, affecting speech and general mobility, or episodic outbursts occur sporadically.
5 Moderate Severe - Significant hyperactivity or frequent outbursts of motor activity are observed, making it difficult for the patient to sit still for longer than several minutes at any given time.
6 Severe - Marked excitement dominates the interview, delimits attention, and to some extent affects personal functions such as eating or sleeping.
7 Extreme - marked excitement seriously interferes in eating and sleeping and makes interpersonal interactions virtually impossible. Acceleration of speech and motor activity may result in incoherence and exhaustion.

P5. **GRANDIOSITY -** Exaggerated self-opinion and unrealistic convictions of superiority, including delusions of extraordinary abilities, wealth, knowledge, fame, power and moral righteousness.
Basis for rating - Thought content expressed in the interview and its influence on behaviour.
1 Absent - Definition does not apply
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits
3 Mild - Some expansiveness or boastfulness is evident, but without clear-cut grandiose delusions.
4 Moderate - Feels distinctly and unrealistically superior to others. Some poorly formed delusions about special status or abilities may be present but are not acted upon.
5 Moderate Severe - Clear-cut delusions concerning remarkable abilities, status or power are expressed and influence attitude but not behaviour.
6 Severe - Clear-cut delusions of remarkable superiority involving more than one parameter (wealth, knowledge, fame, etc) are expressed, notably influence interactions and may be acted upon.
7 Extreme - Thinking, interactions and behaviour are dominated by multiple delusions of amazing ability, wealth, knowledge, fame, power and/or moral stature, which may take on a bizarre quality.

P6. **SUSPICIOUSNESS/PERSECUTION -** Unrealistic or exaggerated ideas of persecution, as reflected in guardedness, ad distrustful attitude, suspicious hypervigilance or frank delusions that others mean harm.
Basis for rating – Thought content expressed in the interview and its influence on behaviour.
1 Absent - Definition does not apply
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits
3 Mild - Presents a guarded or even openly distrustful attitude, but thoughts, interactions and behaviour are minimally affected.
4 Moderate - Distrustfulness is clearly evident and intrudes on the interview and/or behaviour, but there is no evidence of persecutory delusions. Alternatively, there may be indication of loosely formed persecutory delusions, but these do not seem to affect the patient's attitude or interpersonal relations.
5 Moderate Severe - Patient shows marked distrustfulness, leading to major disruption of interpersonal relations, or else there are clear-cut persecutory delusions that have limited impact on interpersonal relations and behaviour.
6 Severe - Clear-cut pervasive delusions of persecution which may be systematised and significantly

interfere in interpersonal relations.
7 Extreme - A network of systematised persecutory delusions dominates the patient's thinking, social relations and behaviour.

P7. **HOSTILITY -** Verbal and nonverbal expressions of anger and resentment, including sarcasm, passive-aggressive behaviour, verbal abuse and assualtiveness.
Basis for rating – Interpersonal behaviour observed during the interview and reports by primary care workers or family.
1 Absent - Definition does not apply
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits
3 Mild - Indirect or restrained communication of anger, such as sarcasm, disrespect, hostile expressions and occasional irritability.
4 Moderate - Presents an overtly hostile attitude, showing frequent irritability and direct expression of anger or resentment.
5 Moderate Severe - Patient is highly irritable and occasionally verbally abusive or threatening.
6 Severe - Uncooperativeness and verbal abuse or threats notably influence the interview and seriously impact upon social relations. Patient may be violent and destructive but is not physically assualtive towards others.
7 Extreme - Marked anger results in extreme uncooperativeness, precluding other interactions, or in episode(s) of physical assault towards others.

NEGATIVE SCALE (N)

N1. **BLUNTED AFFECT -** Diminished emotional responsiveness as characterised by a reduction in facial expression, modulation of feelings and communicative gestures.
Basis for rating - Observation of physical manifestations of affective tone and emotional responsiveness during the course of the interview.
1 Absent - Definition does not apply
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits
3 Mild - Changes in facial expression and communicative gestures seem to be stilted, forced, artificial or lacking in modulation.
4 Moderate - Reduced range of facial expression and few expressive gestures result in a dull appearance
5 Moderate Severe - Affect is generally 'flat' with only occasional changes in facial expression and a paucity of communicative gestures.
6 Severe - Marked flatness and deficiency of emotions exhibited most of the time. There may be unmodulated extreme affective discharges, such as excitement, rage or inappropriate uncontrolled laughter.
7 Extreme – Changes in facial expression and evidence of communicative gestures are virtually absent. Patient seems constantly to show a barren or 'wooden' expression.

N2. **EMOTIONAL WITHDRAWAL -** Lack of interest in, involvement with, and affective commitment to life's events.
Basis for rating - Reports of functioning from primary care workers or family and observation of interpersonal behaviour during the course of the interview.
1 Absent - Definition does not apply
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits
3 Mild - Usually lack initiative and occasionally may show deficient interest in surrounding events.
4 Moderate - Patient is generally distanced emotionally from the milieu and its challenges but, with encouragement, can be engaged.

5 Moderate Severe - Patient is clearly detached emotionally from persons and events in the milieu, resisting all efforts at engagement. Patient appears distant, docile and purposeless but can be involved in communication at least briefly and tends to personal needs, sometimes with assistance.
6 Severe - Marked deficiency of interest and emotional commitment results in limited conversation with others and frequent neglect of personal functions, for which the patient requires supervision.
7 Extreme – Patient is almost totally withdrawn, uncommunicative and neglectful of personal needs as a result of profound lack of interest and emotional commitment.

N3. **POOR RAPPORT -** Lack of interpersonal empathy, openness in conversation and sense of closeness, interest or involvement with the interviewer. This is evidenced by interpersonal distancing and reduced verbal and nonverbal communication.
Basis for rating - Interpersonal behaviour during the course of the interview.
1 Absent - Definition does not apply
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits
3 Mild - Conversation is characterised by a stilted, strained or artificial tone. It may lack emotional depth or tend to remain on an impersonal, intellectual plane.
4 Moderate - Patient typically is aloof, with interpersonal distance quite evident. Patient may answer questions mechanically, act bored, or express disinterest.
5 Moderate Severe - Disinvolvement is obvious and clearly impedes the productivity of the interview. Patient may tend to avoid eye or face contact.
6 Severe - Patient is highly indifferent, with marked interpersonal distance. Answers are perfunctory, and there is little nonverbal evidence of involvement. Eye and face contact are frequently avoided.
7 Extreme - Patient is totally uninvolved with the interviewer. Patient appears to be completely indifferent and consistently avoids verbal and nonverbal interactions during the interview.

N4. **PASSIVE/APATHETIC SOCIAL WITHDRAWAL -** Diminished interest and initiative in social interactions due to passivity, apathy, anergy or avolition. This leads to reduced interpersonal involvements and neglect of activities of daily living.
Basis for rating – Reports on social behaviour from primary care workers or family.
1 Absent - Definition does not apply
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits
3 Mild - Shows occasional interest in social activities but poor initiative. Usually engages with others only when approached first by them.
4 Moderate – Passively goes along with most social activities but in a disinterested or mechanical way. Tends to recede into the background.
5 Moderate Severe - Passively participates in only a minority of activities and shows virtually no interest or initiative. Generally spends little time with others.
6 Severe - Tends to be apathetic and isolated, participating very rarely in social activities and occasionally neglecting personal needs. Has very few spontaneous social contacts.
7 Extreme – Profoundly apathetic, socially isolated and personally neglectful.

N5. **DIFFICULTY IN ABSTRACT THINKING -** Impairment in the use of the abstract-symbolic mode of thinking, as evidenced by difficulty in classification, forming generalisations and proceeding beyond concrete or egocentric thinking in problem-solving tasks.
Basis for rating - Responses to questions on similarities and proverb interpretation, and use of concrete vs. abstract mode during the course of the interview.
1 Absent - Definition does not apply
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits

3 Mild - Tends to give literal or personalised interpretations to the more difficult proverbs and may have some problems with concepts that are fairly abstract or remotely related.
4 Moderate - Often utilises a concrete mode. Has difficulty with most proverbs and some categories. Tends to be distracted by functional aspects and salient features.
5 Moderate Severe - Deals primarily in a concrete mode, exhibiting difficulty with most proverbs and many categories.
6 Severe - Unable to grasp the abstract meaning of any proverbs or figurative expressions and can formulate classifications for only the most simple of similarities. Thinking is either vacuous or locked into functional aspects, salient features and idiosyncratic interpretations.
7 Extreme - Can use only concrete modes of thinking. Shows no comprehension of proverbs, common metaphors or similes, and simple categories. Even salient and functional attributes do not serve as a basis for classification. This rating may apply to those who cannot interact even minimally with the examiner due to marked cognitive impairment.

N6. LACK OF SPONTANEITY AND FLOW OF CONVERSATION - Reduction in the normal flow of communication associated with apathy, avolition, defensiveness or cognitive deficit. This is manifested by diminished fluidity and productivity of the verbal interactional process.
Basis for rating - Cognitive-verbal processes observed during the course of interview.
1 Absent - Definition does not apply
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits
3 Mild – Conversation shows little initiative. Patient's answers tend to be brief and unembellished, requiring direct and leading questions by the interviewer.
4 Moderate – Conversation lacks free flow and appears uneven or halting. Leading questions are frequently needed to elicit adequate responses and proceed with conversation.
5 Moderate Severe - Patient shows a marked lack of spontaneity and openness, replying to the interviewer's questions with only one or two brief sentences.
6 Severe - Patient's responses are limited mainly to a few words or short phrases intended to avoid or curtail communication. (e.g. "I don't know", "I'm not at liberty to say"). Conversation is seriously impaired as a result and the interview is highly unproductive.
7 Extreme - Verbal output is restricted to, at most, an occasional utterance, making conversation not possible.

N7. STEREOTYPED THINKING - Decreased fluidity, spontaneity and flexibility of thinking, as evidenced in rigid, repetitious or barren thought content.
Basis for rating - Cognitive-verbal processes observed during the interview.
1 Absent - Definition does not apply
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits
3 Mild - Some rigidity shown in attitude or beliefs. Patient may refuse to consider alternative positions or have difficulty in shifting from one idea to another.
4 Moderate - Conversation revolves around a recurrent theme, resulting in difficulty in shifting to a new topic.
5 Moderate Severe - Thinking is rigid and repetitious to the point that, despite the interviewer's efforts, conversation is limited to only two or three dominating topics.
6 Severe – Uncontrolled repetition of demands, statements, ideas or questions which severely impairs conversation.
7 Extreme - Thinking, behaviour and conversation are dominated by constant repetition of fixed ideas or limited phrases, leading to gross rigidity, inappropriateness and restrictiveness of patient's communication.

GENERAL PSYCHOPATHOLOGY SCALE (G)

G1. **SOMATIC CONCERN -** Physical complaints or beliefs about bodily illness or malfunctions. This may range from a vague sense of ill being to clear-cut delusions of catastrophic physical disease.

Basis for rating - Thought content expressed in the interview.

1 Absent - Definition does not apply

2 Minimal - Questionable pathology; may be at the upper extreme of normal limits

3 Mild - Distinctly concerned about health or bodily malfunction, but there is no delusional conviction and overconcern can be allayed by reassurance.

4 Moderate - Complains about poor health or bodily malfunction, but there is no delusional conviction, and overconcern can be allayed by reassurance.

5 Moderate Severe - Patient expresses numerous or frequent complaints about physical illness or bodily malfunction, or else patient reveals one or two clear-cut delusions involving these themes but is not preoccupied by them.

6 Severe - Patient is preoccupied by one or a few clear-cut delusions about physical disease or organic malfunction, but affect is not fully immersed in these themes, and thoughts can be diverted by the interviewer with some effort.

7 Extreme – Numerous and frequently reported somatic delusions, or only a few somatic delusions of a catastrophic nature, which totally dominate the patient's affect or thinking.

G2. **ANXIETY -** Subjective experience of nervousness, worry, apprehension or restlessness, ranging from excessive concern about the present or future to feelings of panic.

Basis for rating - Verbal report during the course of interview and corresponding physical manifestations.

1 Absent - Definition does not apply

2 Minimal - Questionable pathology; may be at the upper extreme of normal limits

3 Mild - Expresses some worry, overconcern or subjective restlessness, but no somatic and behavioural consequences are reported or evidenced.

4 Moderate - Patient reports distinct symptoms of nervousness, which are reflected in mild physical manifestations such as fine hand tremor and excessive perspiration.

5 Moderate Severe - Patient reports serious problems of anxiety which have significant physical and behavioural consequences, such as marked tension, poor concentration, palpitations or impaired sleep.

6 Severe - Subjective state of almost constant fear associated with phobias, marked restlessness or numerous somatic manifestations.

7 Extreme - Patient's life is seriously disrupted by anxiety, which is present almost constantly and at times reaches panic proportion or is manifested in actual panic attacks.

G3. **GUILT FEELINGS** - Sense of remorse or self-blame for real or imagined misdeeds in the past.

Basis for rating - Verbal report of guilt feelings during the course of interview and the influence on attitudes and thoughts.

1 Absent - Definition does not apply

2 Minimal - Questionable pathology; may be at the upper extreme of normal limits

3 Mild – Questioning elicits a vague sense of guilt or self-blame for a minor incident, but the patient clearly is not overly concerned.

4 Moderate - Patient expresses distinct concern over his responsibility for a real incident in his life but is not pre-occupied with it and attitude and behaviour are essentially unaffected.

5 Moderate Severe - Patient expresses a strong sense of guilt associated with self-deprecation or

the belief that he deserves punishment. The guilt feelings may have a delusional basis, may be volunteered spontaneously, may be a source of preoccupation and/or depressed mood, and cannot be allayed readily by the interviewer.

6 Severe - Strong ideas of guilt take on a delusional quality and lead to an attitude of hopelessness or worthlessness. The patient believes he should receive harsh sanctions as such punishment.

7 Extreme - Patient's life is dominated by unshakable delusions of guilt, for which he feels deserving of drastic punishment, such as life imprisonment, torture, or death. There may be associated suicidal thoughts or attribution of others' problems to one's own past misdeeds.

G4. **TENSION -**Overt physical manifestations of fear, anxiety, and agitation, such as stiffness, tremor, profuse sweating and restlessness.

Basis for rating - Verbal report attesting to anxiety and thereupon the severity of physical manifestations of tension observed during the interview.

1 Absent - Definition does not apply

2 Minimal - Questionable pathology; may be at the upper extreme of normal limits

3 Mild - Posture and movements indicate slight apprehensiveness, such as minor rigidity, occasional restlessness, shifting of position, or fine rapid hand tremor.

4 Moderate - A clearly nervous appearance emerges from various manifestations, such as fidgety behaviour, obvious hand tremor, excessive perspiration, or nervous mannerisms.

5 Moderate Severe - Pronounced tension is evidenced by numerous manifestations, such as nervous shaking, profuse sweating and restlessness, but can conduct in the interview is not significantly affected.

6 Severe - Pronounced tension to the point that interpersonal interactions are disrupted. The patient, for example, may be constantly fidgeting, unable to sit still for long, or show hyperventilation.

7 Extreme - Marked tension is manifested by signs of panic or gross motor acceleration, such as rapid restless pacing and inability to remain seated for longer than a minute, which makes sustained conversation not possible.

G5. **MANNERISMS AND POSTURING –** Unnatural movements or posture as characterised be an awkward, stilted, disorganised, or bizarre appearance.

Basis for rating - Observation of physical manifestations during the course of interview as well as reports from primary care workers or family.

1 Absent - Definition does not apply

2 Minimal - Questionable pathology; may be at the upper extreme of normal limits

3 Mild - Slight awkwardness in movements or minor rigidity of posture

4 Moderate – Movements are notably awkward or disjointed, or an unnatural posture is maintained for brief periods.

5 Moderate Severe - Occasional bizarre rituals or contorted posture are observed, or an abnormal position is sustained for extended periods.

6 Severe - Frequent repetition of bizarre rituals, mannerisms or stereotyped movements, or a contorted posture is sustained for extended periods.

7 Extreme - Functioning is seriously impaired by virtually constant involvement in ritualistic, manneristic, or stereotyped movements or by an unnatural fixed posture which is sustained most of the time.

G6. **DEPRESSION** - Feelings of sadness, discouragement, helplessness and pessimism.

Basis for rating - Verbal report of depressed mood during the course of interview and its observed influence on attitude and behaviour.

1 Absent - Definition does not apply

2 Minimal - Questionable pathology; may be at the upper extreme of normal limits
3 Mild - Expresses some sadness of discouragement only on questioning, but there is no evidence of depression in general attitude or demeanor.
4 Moderate - Distinct feelings of sadness or hopelessness, which may be spontaneously divulged, but depressed mood has no major impact on behaviour or social functioning and the patient usually can be cheered up.
5 Moderate Severe - Distinctly depressed mood is associated with obvious sadness, pessimism, loss of social interest, psychomotor retardation and some interference in appetite and sleep. The patient cannot be easily cheered up.
6 Severe - Markedly depressed mood is associated with sustained feelings of misery, occasional crying, hopelessness and worthlessness. In addition, there is major interference in appetite and or sleep as well as in normal motor and social functions, with possible signs of self-neglect.
7 Extreme - Depressive feelings seriously interfere in most major functions. The manifestations include frequent crying, pronounced somatic symptoms, impaired concentration, psychomotor retardation, social disinterest, self neglect, possible depressive or nihilistic delusions and/or possible suicidal thoughts or action.

G7. **MOTOR RETARDATION –** Reduction in motor activity as reflected in slowing or lessening or movements and speech, diminished responsiveness of stimuli, and reduced body tone.
Basis for rating - Manifestations during the course of interview as well as reports by primary care workers as well as family.
1 Absent - Definition does not apply
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits
3 Mild - Slight but noticeable diminution in rate of movements and speech. Patient may be somewhat underproductive in conversation and gestures.
4 Moderate - Patient is clearly slow in movements, and speech may be characterised by poor productivity including long response latency, extended pauses or slow pace.
5 Moderate Severe – A marked reduction in motor activity renders communication highly unproductive or delimits functioning in social and occupational situations. Patient can usually be found sitting or lying down.
6 Severe - Movements are extremely slow, resulting in a minimum of activity and speech. Essentially the day is spent sitting idly or lying down.
7 Extreme - Patient is almost completely immobile and virtually unresponsive to external stimuli.

G8. **UNCOOPERATIVENESS -** Active refusal to comply with the will of significant others, including the interviewer, hospital staff or family, which may be associated with distrust, defensiveness, stubbornness, negativism, rejection of authority, hostility or belligerence.
Basis for rating - Interpersonal behaviour observed during the course of the interview as well as reports by primary care workers or family.
1 Absent - Definition does not apply
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits
3 Mild - Complies with an attitude of resentment, impatience, or sarcasm. May inoffensively object to sensitive probing during the interview.
4 Moderate - Occasional outright refusal to comply with normal social demands, such as making own bed, attending scheduled programmes, etc. The patient may project a hostile, defensive or negative attitude but usually can be worked with.
5 Moderate Severe - Patient frequently is incompliant with the demands of his milieu and may be characterised by other as an "outcast" or having "a serious attitude problem". Uncooperativeness is reflected in obvious defensiveness or irritability with the interviewer and possible unwillingness to address many questions.

6 Severe - Patient is highly uncooperative, negativistic and possibly also belligerent. Refuses to comply with the most social demands and may be unwilling to initiate or conclude the full interview.
7 Extreme - Active resistance seriously impact on virtually all major areas of functioning. Patient may refuse to join in any social activities, tend to personal hygiene, converse with family or staff and participate even briefly in an interview.

G9. **UNUSUAL THOUGHT CONTENT** - Thinking characterised by strange, fantastic or bizarre ideas, ranging from those which are remote or atypical to those which are distorted, illogical and patently absurd.
Basis for rating - Thought content expressed during the course of interview.
1 Absent - Definition does not apply
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits
3 Mild - Thought content is somewhat peculiar, or idiosyncratic, or familiar ideas are framed in an odd context.
4 Moderate - Ideas are frequently distorted and occasionally seem quite bizarre.
5 Moderate Severe - Patient expresses many strange and fantastic thoughts, (e.g. Being the adopted son of a king, being an escapee from death row), or some which are patently absurd (e.g. Having hundreds of children, receiving radio messages from outer space from a tooth filling).
6 Severe - Patient expresses many illogical or absurd ideas or some which have a distinctly bizarre quality (e.g. having three heads, being a visitor from another planet).
7 Extreme - Thinking is replete with absurd, bizarre and grotesque ideas.

G10. **DISORIENTATION** - Lack of awareness of one's relationship to the milieu, including persons, place and time, which may be due to confusion or withdrawal.
Basis for rating - Responses to interview questions on orientation.
1 Absent - Definition does not apply
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits
3 Mild - General orientation is adequate but there is some difficulty with specifics. For example, patient knows his location but not the street address, knows hospital staff names but not their functions, knows the month but confuses the day of the week with an adjacent day, or errs in the date by more than two days. There may be narrowing of interest evidenced by familiarity with the immediate but not extended milieu, such as ability to identify staff but not the mayor, governor, or president.
4 Moderate - Only partial success in recognising persons, places and time. For example, patient knows he is in a hospital but not its name, knows the name of the city but not the borough or district, knows the name of his primary therapist but not many other direct care workers, knows the year or season but not sure of the month.
5 Moderate Severe - Considerable failure in recognising persons, place and time. Patient has only a vague notion of where he is and seems unfamiliar with most people in his milieu. He may identify the year correctly or nearly but not know the current month, day of week or even the season.
6 Severe - Marked failure in recognising persons, place and time. For example, patient has no knowledge of his whereabouts, confuses the date by more than one year, can name only one or two individuals in his current life.
7 Extreme - Patient appears completely disorientated with regard to persons, place and time. There is gross confusion or total ignorance about one's location, the current year and even the most familiar people, such as parents, spouse, friends and primary therapist.

G11. **POOR ATTENTION** - Failure in focused alertness manifested by poor concentration, distractibility from internal and external stimuli, and difficulty in harnessing, sustaining or shifting

focus to new stimuli.
Basis for rating – Manifestations during the course of interview.
1 Absent - Definition does not apply
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits
3 Mild - Limited concentration evidenced by occasional vulnerability to distraction and faltering attention toward the end of the interview.
4 Moderate - Conversation is affected by the tendency to be easily distracted, difficulty in long sustaining concentration on a given topic, or problems in shifting attention to new topics.
5 Moderate Severe - Conversation is seriously hampered by poor concentration, distractibility, and difficulty in shifting focus appropriately..
6 Severe - Patient's attention can be harnessed for only brief moments or with great effort, due to marked distraction by internal or external stimuli.
7 Extreme - Attention is so disrupted that even brief conversation is not possible.

G12. LACK OF JUDGEMENT AND INSIGHT - Impaired awareness or understanding of one's own psychiatric condition and life situation. This is evidenced by failure to recognise past or present psychiatric illness or symptoms, denial of need for psychiatric hospitalisation or treatment, decisions characterised by poor anticipation or consequences, and unrealistic short-term and long-range planning.
Basis for rating – Thought content expressed during the interview.
1 Absent - Definition does not apply
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits
3 Mild - Recognises having a psychiatric disorder but clearly underestimates its seriousness, the implications for treatment, or the importance of taking measures to avoid relapse. Future planning may be poorly conceived.
4 Moderate - Patient shows only a vague or shallow recognition of illness. There may be fluctuations in acknowledgement of being ill or little awareness of major symptoms which are present, such as delusions, disorganised thinking, suspiciousness and social withdrawal. The patient may rationalise the need for treatment in terms of its relieving lesser symptoms, such as anxiety, tension and sleep difficulty.
5 Moderate Severe - Acknowledges past but not present psychiatric disorder. If challenged, the patient may concede the presence of some unrelated or insignificant symptoms, which tend to be explained away by gross misinterpretation or delusional thinking. The need for psychiatric treatment similarly goes unrecognised.
6 Severe - Patient denies ever having had a psychiatric disorder. He disavows the presence of any psychiatric symptoms in the past or present and, though compliant, denies the need for treatment and hospitalisation.
7 Extreme - Emphatic denial of past and present psychiatric illness. Current hospitalisation and treatment are given a delusional interpretation (e.g. as punishment fro misdeeds, as persecution by tormentors, etc), and the patient thus refuse to cooperate with therapists, medication or other aspects of treatment.

G13. DISTURBANCE OF VOLITION – Disturbance in the wilful initiation, sustenance and control of one's thoughts, behaviour, movements and speech.
Basis for rating - Thought content and behaviour manifested in the course of interview.
1 Absent - Definition does not apply
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits
3 Mild - There is evidence of some indecisiveness in conversation and thinking, which may impede verbal and cognitive processes to a minor extent.
4 Moderate - Patient is often ambivalent and shows clear difficulty in reaching decisions.

Conversation may be marred by alteration in thinking, and in consequence, verbal and cognitive functioning are clearly impaired.
5 Moderate Severe - Disturbance of volition interferes in thinking as well as behaviour. Patient shows pronounced indecision that impedes the initiation and continuation of social and motor activities, and which also may be evidence in halting speech.
6 Severe - Disturbance of volition interferes in the execution of simple automatic motor functions, such as dressing or grooming, and markedly affects speech.
7 Extreme – Almost complete failure of volition is manifested by gross inhibition of movement and speech resulting in immobility and/or mutism.

G14. **POOR IMPULSE CONTROL** - Disordered regulation and control of action on inner urges, resulting in sudden, unmodulated, arbitrary or misdirected discharge of tension and emotions without concern about consequences.
Basis for rating – Behaviour during the course of interview and reported by primary care workers or family.
1 Absent - Definition does not apply
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits
3 Mild - Patient tends to be easily angered and frustrated when facing stress or denied gratification but rarely acts on impulse.
4 Moderate - Patient gets angered and verbally abusive with minimal provocation. May be occasionally threatening, destructive, or have one or two episodes involving physical confrontation or a minor brawl.
5 Moderate Severe - Patient exhibits repeated impulsive episodes involving verbal abuse, destruction of property, or physical threats. There may be one or two episodes involving serious assault, for which the patient requires isolation, physical restraint, or p.r.n. sedation.
6 Severe - Patient frequently is impulsive aggressive, threatening, demanding, and destructive, without any apparent consideration of consequences. Shows assualtive behaviour and may also be sexually offensive and possibly respond behaviourally to hallucinatory commands.
7 Extreme - Patient exhibits homicidal, sexual assaults, repeated brutality, or self-destructive behaviour. Requires constant direct supervision or external constraints because of inability to control dangerous impulses.

G15. **PREOCCUPATION -** Absorption with internally generated thoughts and feelings and with autistic experiences to the detriment of reality orientation and adaptive behaviour.
Basis for rating - Interpersonal behaviour observed during the course of interview.
1 Absent - Definition does not apply
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits
3 Mild - Excessive involvement with personal needs or problems, such that conversation veers back to egocentric themes and there is diminished concerned exhibited toward others.
4 Moderate - Patient occasionally appears self-absorbed, as if daydreaming or involved with internal experiences, which interferes with communication to a minor extent.
5 Moderate Severe - Patient often appears to be engaged in autistic experiences, as evidenced by behaviours that significantly intrude on social and communicational functions, such as the presence of a vacant stare, muttering or talking to oneself, or involvement with stereotyped motor patterns.
6 Severe - Marked preoccupation with autistic experiences, which seriously delimits concentration, ability to converse, and orientation to the milieu. The patient frequently may be observed smiling, laughing, muttering, talking, or shouting to himself.
7 Extreme - Gross absorption with autistic experiences, which profoundly affects all major realms of behaviour. The patient constantly may be responding verbally or behaviourally to hallucinations and show little awareness of other people or the external milieu.

G16. **ACTIVE SOCIAL AVOIDANCE** - Diminished social involvement associated with unwarranted fear, hostility, or distrust.

Basis for rating - Reports of social functioning primary care workers or family.

1 Absent - Definition does not apply

2 Minimal - Questionable pathology; may be at the upper extreme of normal limits

3 Mild - Patient seems ill at ease in the presence of others of others and prefers to spend time alone, although he participates in social functions when required.

4 Moderate - Patient begrudgingly attends all or most social activities but may needs to be persuaded or may terminate prematurely on account of anxiety, suspiciousness, or hostility.

5 Moderate Severe - Patient fearfully or angrily keeps away from many social interactions despite others' efforts to engage him. Tends to spend unstructured time alone.

6 Severe - Patient participates in very few social activities because of fear, hostility, or distrust. When approached, the patient shows a strong tendency to break off interactions, and generally he tends to isolate himself from others.

7 Extreme - Patient cannot be engaged in social activities because of pronounced fears, hostility, or persecutory delusions. To the extent possible, he avoids all interactions and remains isolated from others