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Abstract

Hostility and related dimensions like anger, urgency, impulsivity and aggressiveness have been described in non-clinical populations and various serious mental illnesses including schizophrenia. Although representing a mental healthcare challenge, the investigation of such constructs is often limited by the presence of complex and multi-factorial causes and lack of agreement in their conceptualisation and measurement. In this review, we aim to clarify the anatomical basis of hostility-related dimensions in schizophrenia. Imaging studies suggest malfunctioning of a neural circuitry including amygdala, striatum, prefrontal cortex, anterior cingulate cortex, insula and hippocampus to modulate hostile thoughts and behaviours, at least in the subgroup of patients with schizophrenia who exhibit high levels of urgency, impulsivity and aggressiveness.

Hostility, as defined in the International Statistical Classification of Diseases and Related Health Problems (ICD) (World Health Organization, 2016), represents a clinical characteristic that implies the recurring and enduring ‘*tendency to feel anger toward and a desire to inflict harm upon a person or group*’ (Nakagawa *et al.*, 2017). Specifically, it consists of ‘*negative cognitive bias of strong disapproval toward others which implies thoughts and feelings of antagonism, resentment, and alienation*’ (Spielberger *et al.*, 1983). Hostility is associated with negative emotions during interpersonal interactions (Lemerise and Dodge, 2008). Anger, which is related to hostility, can instead be described as an intense but time-limited negative emotional state of displeasure (Ehlers and Clark, 2000). If anger is a state dimension, hostility is a trait leading to temperamental proneness to anger (Smith, 1994). Both hostility and anger are common behavioural features across non-clinical as well as clinical populations (Wang *et al.*, 2014; Fisher *et al.*, 2015; Besteher *et al.*, 2017).

In schizophrenia, the presence of hostility has been reported during the acute phases of the disease (Raja and Azzoni, 2005) and for longer time after hospital discharge (Ochoa *et al.*, 2013). In some cases hostility can lead to verbal or physical aggressiveness. The constructs of hostility and anger are related to that of aggressiveness, which concerns the behavioural dimension of passage to the act. It is present in a variety of mental disorders including schizophrenia, thus representing a serious and compelling issue in mental healthcare. The transition from cognition (hostility) to behaviour (aggressiveness) has been correlated with patients’ lack of compliance, poor social functioning and low quality of life (Galuppi *et al.*, 2010; Ochoa *et al.*, 2013). Furthermore, both hostility and aggressiveness are related to lengthening of hospitalisation, increased costs as well as stigma (Wehring and Carpenter, 2011). In the current review, we aim to clarify the neural basis of hostility and related dimensions in schizophrenia.

Hostility-related behaviours observed in schizophrenia are rooted in complex and multi-factorial causes. In particular, aggressiveness has been linked to both impulsivity and psychotic symptoms (Stahl, 2014; Hoptman, 2015). Impulsivity is a multidimensional construct defined as ‘*a predisposition toward rapid unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to themselves or others*’ (Moeller *et al.*, 2001). It accounts for a substantial proportion of aggressive behaviours in schizophrenia, especially in inpatient settings, and it has been associated with increased suicidal risk in this population (Ouzir, 2013). Impulsive aggressiveness in schizophrenia is situationally bound, reactive and characterised by a lack of clear intent (Leclerc *et al.*, 2018). Impulsivity is related to urgency, representing impulsivity in the context of both positive and negative strong emotions. Also, urgency is elevated in schizophrenia due to affective dysregulation (Hoptman *et al.*, 2014). As for positive symptoms, paranoid delusions, hallucinations and grandiosity may lead to misinterpretation of environmental stimuli and thus episodes of irritability or aggressiveness (Stahl, 2014). The comorbid use of substance represents an additional risk factor for

schizophrenia patients to become aggressive (Fazel *et al.*, 2009; Schiffer *et al.*, 2010). Cognitive deficits have also been implicated in the genesis and maintenance of aggressiveness in schizophrenia through inefficient regulation of negative affective states, with global cognitive impairment, deficits in working memory, and reasoning/problem solving as the most involved (Reinhardt *et al.*, 2014; Ahmed *et al.*, 2018). Finally, social emotion processing deficits such as impaired facial affect recognition have been associated with an increased risk of aggressiveness in psychosis (Malone *et al.*, 2012). A recent study by Krakowski and Czobor (2017) pointed at the existence of two distinct profiles of proneness to aggressiveness in schizophrenia combining personality traits, cognitive function and emotional processes: the first patient group was characterised by impulsivity, psychopathy, deficits in cognition and fear recognition, with proneness to aggressiveness. The second profile was defined by impairment in facial affect processing and cognitive perseveration, and has an inverse relationship with aggression. Another study by Bilgi *et al.* (2017) suggested a relationship among misidentification of emotional faces and patients' irritability, which was in turn related to childhood adversity experienced by some patients with schizophrenia. Interestingly, cognitive remediation and social cognitive training have been recently suggested to complement the action of the traditional (mainly pharmacological) care tools in the management of hostility and aggressiveness in schizophrenia (Darmedru *et al.*, 2018).

The measurement of hostility, impulsiveness and aggressiveness can be critical for patient management and treatment planning. A series of psychometric instruments have been created to assess such dimensions. In particular, the Buss Durkee Hostility Inventory (BDHI) (Buss and Durkee, 1957) is a 75-item self-report inventory comprising height subscales measuring multidimensional aspects of anger/hostility and aggression (i.e. negativism, indirect hostility and irritability). The revision of the BDHI item pool has resulted in the emergence of the Buss-Perry Aggression Questionnaire (BPAQ) (Buss and Perry, 1992) which includes 29 items covering physical aggression, verbal aggression, anger and hostility. Other scales are the Novaco Anger Scale (NAS) (Novaco, 2003), which comprises 25 hypothetical situations that are likely to provoke anger, and the Multidimensional Anger Inventory (MAI) (Siegel, 1986) measuring multiple dimensions of anger, including frequency, duration, magnitude and mode of expression (anger-in or anger-out). The Barratt Impulsiveness Scale (BIS) (Patton *et al.*, 1995) is one of the most common self-report measures of impulsivity. Also instruments routinely used in clinical practice and research like the Positive and Negative Syndrome Scale (PANSS) and the Symptom Checklist 90 (SCL-90) (Derogatis, 1983) include subscales measuring hostility and related behaviour. In particular, the PANSS subscale 'Hostility' is part of the positive scale and measures verbal and non-verbal expressions of anger and resentment, including sarcasm, passive-aggressive behaviour, verbal abuse and physical aggressiveness. The SCL-90 hostility subscale is made up of six items assessing thoughts, feelings and actions related to resentment, irritability, aggression and rage. It has to be specified that different scales measure different shades of the cited constructs therefore the choice of the best scale depends on the specific aspects that clinicians or researchers are interested to measure (see Fernandez *et al.*, 2014 for a detailed review on measures of anger/hostility/aggression in adults).

An extensive understanding of the neurobiological patterns involved in hostility, impulsivity and aggressiveness in

schizophrenia is crucial to comprehend the pathophysiology of these aspects, which directly affect the clinical management of patients. In the current paper, we reviewed the neuroimaging literature on hostility and related dimensions in schizophrenia. We focused on structural magnetic resonance imaging (sMRI) techniques with some findings from functional magnetic resonance imaging (fMRI) studies. A bibliographic search on PUBMED was performed and the search terms were 'hostility', 'impulsivity', 'urgency', 'aggressiveness', 'violence', 'schizophrenia' and 'magnetic resonance imaging'. Aggressive behaviour and impulsivity are the most investigated hostility-related dimensions in neuroimaging investigations in schizophrenia. Hoptman *et al.* (2002) found an association between disrupted white matter in the right inferior frontal area and high level of both impulsiveness and aggressiveness in a group of 14 men with schizophrenia who had shown aggressive behaviour. Other studies reported that higher scores of aggression correlated with larger grey and white matter volumes in the caudate as well as larger left orbitofrontal (OFC) grey matter and bilateral OFC white matter volumes on treatment-resistant patients with schizophrenia (Hoptman *et al.*, 2005, 2006). A more recent study from the same group found a significant reduction in functional connectivity between amygdala and ventral prefrontal cortex (vPFC) regions, where fractional anisotropy (FA) along connecting tracts was inversely related to aggression measured with the BPAQ in patients with schizophrenia (Hoptman *et al.*, 2010). A recent systematic review and effect size analysis of structural MRI studies by Widmayer *et al.* (2018) showed lower total as well as regional prefronto-temporal, hippocampus, thalamus and cerebellum brain volumes and higher volumes of lateral ventricles, amygdala and putamen in aggressive *v.* non-aggressive people with schizophrenia. Impulsivity, on the other hand, has been mostly investigated with fMRI. A comprehensive review of both structural and functional MRI studies in schizophrenia was performed by Ouzir (2013), showing a relationship between impulsivity and activation deficits in dorso-/ventro-lateral prefrontal cortex (DLPFC, VLPFC) and anterior cingulate cortex (ACC). In contrast, a study from Nanda *et al.* (2016) did not show any correlation between BIS impulsivity scores and brain measures in schizophrenia. Neural correlates of urgency have been less intensely studied in schizophrenia *v.* healthy controls. In particular, Hoptman *et al.* (2014) combining an automated MRI and resting state methods showed increased urgency predicting lower cortical thickness in ventral-prefrontal areas, as well as lower connectivity between this region and both limbic and executive brain regions beyond the diagnostic classification. In the same study, urgency and aggressive attitudes were significantly elevated in patients with schizophrenia compared with healthy controls, showing an associated reduced resting-state functional connectivity in the same brain regions only in patients. Overall, studies on schizophrenia showed abnormally higher levels of urgency, impulsivity and aggressiveness. Interestingly, studies comparing aggressive *v.* non-aggressive subjects with schizophrenia suggest different anatomical patterns of altered volumes and connectivity in the two groups, supporting the existence of different profiles of proneness to aggressiveness and related neuroanatomical alterations in this population (Kumari *et al.*, 2009, 2014; Schiffer *et al.*, 2013; Krakowski and Czobor, 2017; Kuroki *et al.*, 2017; Widmayer *et al.*, 2018). In Table 1, we summarise the structural brain imaging studies on the anatomical substrates of hostility-related dimensions in schizophrenia.

Table 1. Structural MRI studies on the neuroanatomical correlates of hostility-related dimensions in schizophrenia

Reference	Participants	Variable	Assessment of hostility-related dimensions	Neuroimaging methods	Main results
Hoptman et al. (2002)	-14 SCZ (only males)	Aggression, impulsivity	BIS	1.5 T MRI DTI (FA and trace) ROIs placed in frontal white matter	-Inferior frontal white matter disruption was associated with impulsivity and aggression in men with schizophrenia
Hoptman et al. (2005)	-49 SCZ or SKZ	Aggression	OAS TAS PANSS hostility score	1.5 T MRI ROI (OFC) manually traced	-Higher scores of aggression correlated with larger left grey matter and bilateral white matter OFC volumes
Hoptman et al. (2006)	-157 treatment resistant SCZ or SKZ	Aggression	OAS PANSS	1.5 T MRI ROI (caudate) manually traced	-Higher scores of aggression correlated with larger grey and white matter volumes in the caudate
Narayan et al. (2007)	-12 SCZ with history of violence -15 SCZ without history of violence -14 antisocial personality disorder with history of violence -15 non-violent HC	Violence	Psychopathy Checklist-Screening Version	1.5 T sMRI (cortical pattern matching; cortical thickness)	-Violence was associated with cortical thinning in the prefrontal cortex (left medial inferior frontal and right lateral sensory motor cortex and surrounding association areas) and intraparietal sulcus bilaterally, irrespective of group -Cortical thinning in left inferior dorsolateral prefrontal regions (Brodmann's area 45) and in right medial dorsal ACC (Brodmann's areas 8, 6, 32, 24) was detected in the SCZ group compared with the non-SCZ groups, irrespective of violence -There are some overlapping (in motor cortices) but also differences in the areas associated with violence in the group of patients with SCZ (thinning of the sensory motor areas) and in subjects with antisocial personality disorder (thinning of the medial prefrontal cortices), compared to the groups with no history of violence
Kumari et al. (2009)	-24 SCZ males -14 HC males	Impulsivity	IVE-7	1.5 T MRI Selected ROIs	-Participants with schizophrenia and a history of violence showed elevated impulsiveness, which in turn is associated with reduced OFC and hippocampal volumes
Hoptman et al. (2010)	-25 SCZ or SKZ -21 HC	Aggression	BPAQ LHA	1.5 T sMRI and resting state	-Patients had significant reductions in FC between amygdala and ventral PFC regions. The strength of connectivity was inversely related to aggression (lower connectivity associated with higher levels of self-rated aggression)
Schiffer et al. (2010)	-12 paranoid SCZ -12 SCZ with comorbid substance use disorders -14 HC -13 patients with substance use disorders	Impulsivity	BIS	1.5 T MRI VBM	-Increased impulsivity in addicted, especially dual-diagnosis patients, which is related to grey matter volume losses in medial OFC, DLPFC, ACC and fronto-polar regions -In contrast to non-addicted schizophrenics, comorbid patients showed exacerbated volume decreases only in ACC and fronto-polar region but not in the medial OFC or DLPFC -Violence is associated with impulsivity that was increased in both addicted groups
Schiffer et al. (2013)	-27 SCZ males preceded by conduct disorder (CD) -23 SCZ males without CD -27 males with only CD -25 HC males	Aggression, violence	LHA Criminal convictions extracted from official criminal records	1.5 T MRI VBM	-SCZ with CD had increased GM volumes in the hypothalamus, the left putamen, the right cuneus/precuneus, and the right IPC and decreased GM volumes in the inferior frontal region compared with SCZ without CD -Aggressive behaviour both prior to age 15 and lifetime tendency, was positively correlated with the GM volume of the hypothalamus
Hoptman et al. (2014)	-33 SCZ or SKZ -31 HC	Urgency	UPPSS BPAQ IPAS LHA	3 T sMRI (cortical thickness) and resting state	-Urgency scores were higher in patients than HC -In the patients group, increased urgency predicted lower cortical thickness in ventral prefrontal areas, as well as lower connectivity between this region and both limbic and executive brain areas
Kumari et al. (2014)	-13 SCZ with history of violence -15 SCZ without history of violence -14 antisocial personality disorder -15 HC without history of violence	Violence	GRSV	1.5 T MRI VBM	-SCZ with history of violence and antisocial personality disorder, but not SCZ, patients had significantly lower ACC volume relative to HC

(Continued)

Table 1. (Continued.)

Reference	Participants	Variable	Assessment of hostility-related dimensions	Neuroimaging methods	Main results
Del Bene <i>et al.</i> (2016)	-37 violent SCZ -26 non-violent SCZ -24 non-psychotic violent subjects -24 HC	Violence	LHA BPAQ BIS	1.5 T MRI ROIs (amygdala, hippocampus, thalamus, ventricles and whole brain volumes)	-Non-violent SCZ showed elevated vCSF volume, smaller left hippocampus and left thalamus volumes compared with other groups -Interaction between violence and diagnosis as regards left amygdala (smaller amygdala size linked to violence in non-psychotic individuals, smaller size was linked to non-violence in psychotic patients). Such double dissociation appeared to be mostly driven by substance abuse
Nanda <i>et al.</i> (2016)	-305 HC -139 SCZ -100 SKZ -125 PBP	Impulsivity	BIS	3 T MRI (regional cortical volumes)	-BIS impulsivity scores were higher in SKZ and PBP than SCZ, which showed higher impulsivity scores than HC -Impulsivity scores were inversely associated with bilateral OFC volume in SKZ and PBP, but not in SCZ
Kuroki <i>et al.</i> (2017)	-34 SCZ males with history of violence -23 SCZ males with no history of violence	Violence	GRSV	3 T MRI VBM	-SCZ group with history of violence showed significant smaller volumes of right inferior temporal area extended to middle temporal gyrus and temporal pole, and in right insular area compared with SCZ with no history of violence

ACC, anterior cingulate cortex; BD, patients with bipolar disorder; BIS, Barratt Impulsiveness Scale; BPAQ, Buss-Perry Aggression Questionnaire; CD, conduct disorder; vCSF, ventricular cerebrospinal fluid; DLPFC, dorso-lateral prefrontal cortex; DTI, diffusion tensor imaging; GM, grey matter; GRSV, Gunn and Robertson Scale for Violence (Gunn and Robertson, 1976); HC, healthy controls; IPAS, Impulsive and Premeditated Aggression Scale (Stanford *et al.*, 2003); IPC, inferior parietal cortex; IVE-7, Impulsiveness-Venturesomeness-Empathy questionnaire (Eysenck *et al.*, 1985); LHA, life history of aggression; OAS, Overt Aggression Scale; OFC, orbito-frontal cortex; PANSS, Positive and Negative Symptoms Scale; PBP, patients with psychotic bipolar disorder; PFC, prefrontal cortex; ROI, region of interest; SCZ, patients with schizophrenia; SKZ, patients with schizophrenia; SMRI, structural magnetic resonance imaging; T, tesla; TAS, Total Aggression Severity score; UPPSS, Urgency, Premeditation, Perseverance and Sensation Seeking scale (Cyders and Smith, 2007); VBM, voxel-based morphometry.

Neuroanatomical observations made in people with schizophrenia are in line with results from non-clinical samples (Besteher *et al.*, 2017; Nakagawa *et al.*, 2017). Specifically, Nakagawa *et al.* (2017) explored the brain structures underlying hostility in a large sample of young healthy subjects showing a positive correlation between hostility scores and regional grey matter density in the anterior midcingulate cortex (amCC), which has been hence suggested as a specific neural node accounting for the cognitive aspect of hostility. This result is in accordance with the role assigned to amCC as integrating emotional and motor information concerning others' intentional behaviour in order to execute goal-directed behaviour (Shackman *et al.*, 2011). In the study of Nakagawa *et al.* (2017), hostility was also positively associated with regional grey matter density of several frontal regions such as DLPFC and the lateral premotor cortex. More recently, a voxel-based morphometry study from our extended group (Besteher *et al.*, 2017) showed a positive correlation of irritability/hostility measured with SCL-90 and grey matter volume in bilateral anterior cingulate, OFC, gyrus rectus, left lingual and postcentral gyri.

Taken together, studies on patients with schizophrenia and in healthy adults with varying levels of hostility/aggressiveness suggest the existence of a broad phenotype covering manifestations of anger, hostility and aggression across clinical and non-clinical populations. A neural network including fronto-limbic and sub-cortical regions would underpin such a phenotype. A neuroanatomical model of impulsivity and aggressiveness has recently been proposed (Coccaro *et al.*, 2011) pointing at the existence of a continuity of hostility-related dimensions ranging from healthy subjects to pathological conditions rather than a specificity of such phenomena for schizophrenia (Narayan *et al.*, 2007; Leclerc *et al.*, 2018). Such model includes brain regions involved in the generation of aggressive responses (brain stem, amygdala and striatum), emotion regulation and impulse control (DLPFC, VLPFC, dorsal ACC and OFC), decision making and socio-emotional information processing (insula, VLPFC, rostral ACC, OFC, dorso-medial prefrontal cortex-PFC and hippocampus). Brain regions included in the model were observed to be altered not only in schizophrenia but also in other clinical groups with increased levels of aggressiveness such as people with bipolar disorder, antisocial personality or conduct disorder (Leclerc *et al.*, 2018). Some of these areas (especially amygdala, OFC, ACC and hippocampus) appear to be reduced in adult healthy controls who experienced childhood adversities (Dannlowski *et al.*, 2012, 2013; Teicher and Samson, 2013), suggesting that early mistreatment experiences can represent a shared risk factor for emotion dysregulation and distress in adult life.

Overall, neuroanatomical investigations of hostility and related dimensions are useful to map target brain areas relevant for both pharmacological and non-pharmacological (i.e. neurostimulation and cognitive remediation) treatments of hostile thoughts and behaviours in schizophrenia. Moreover, further studies comparing clinical groups with emotional dysregulation and healthy controls with and without the presence of hostility and aggressiveness are warranted to deliver more insight into our understanding of hostility-related dimensions in schizophrenia and their neuroanatomical correlates within the continuum from non-clinical conditions to pathology.

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