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Neural and cognitive correlates of stigma and social rejection in individuals with Serious Mental Illnesses (SMI): a systematic review of literature

Running title: Cognitive neuroscience of stigma and social rejection in Serious Mental Illness

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Introduction

Stereotypes can be defined as common social knowledge shared by people from the same cultural background. They make it possible to rapidly identify and categorize the individuals with whom one interacts and contribute to understanding social situations and shaping behavioral responses (Krendl, 2006). Stigma occurs when stereotypes generate negative emotional responses and behaviors towards the members of a group – or towards oneself in the case of self-stigma (Corrigan, 2002). Self-Stigma - or Internalized Stigma (IS) - is an identity transformation process wherein a person's previously held social identity (defined by social roles such as son, brother, sister, friend, employee or potential partner) is progressively replaced by a devalued and stigmatized view of oneself termed "illness identity" (Yanos, 2008). Stigma Resistance (SR) is defined as one's ability to deflect or challenge stigmatizing beliefs (Thoits, 2011).

According to the US Substance Abuse and Mental Health Services Administration, individuals with "Serious Mental Illness" (SMI) are "persons aged 18 or older who currently or at any time in the past year have had a diagnosable mental, behavioral, or emotional disorder (excluding developmental and substance use disorders) of sufficient duration to meet diagnostic criteria specified within DSM-IV (APA, 1994) that has resulted in serious functional impairment, which substantially interferes with or limits one or more major life activities such as maintaining interpersonal relationships, activities of daily living, self-care, employment, and recreation" (SAMSAH, 2013, p. 13). Serious Mental Illnesses (SMI; SAMSAH, 2014) include schizophrenia (SZ), bipolar disorder (BD), and Borderline Personality Disorder (BPD), as well as Major Depressive Disorder (MDD) and Anxiety Disorders that cause severe and persistent functional impairments. SMI are frequent (1% for SZ; 1.5% for BD; 1.5% for BPD) and heavily stigmatized (Angermeyer, 2013; Ellison, 2013). People with SZ, BD or MDD are more likely to experience discrimination in a range of aspects of their daily life (Thornicroft, 2009; Farrelly, 2014; Lasalvia, 2013). They frequently expect to be discriminated in social contexts even when they

have no previous experience of discrimination (Thornicroft, 2009; Farrelly, 2014; Lasalvia; 2013). Internalized Stigma (IS) is frequent (41.7% of the 1229 participants with SZ and 21.7% of the 1,182 participants with BD in the 2010 GAMIAN-Europe study had moderate to high levels of self-stigma; Brohan, 2010, 2011) and associated with multiple negative consequences: lower therapeutic adherence, self-efficacy, self-esteem, empowerment and hope and a greater intensity of depressive symptoms and suicidal ideation (Livingston et Boyd, 2010; Gerlinger, 2015; Ellison, 2013; Lanfredi, 2015). Stigma resistance concerns a wide range of people with SMI (49.2% of the 1,229 participants with SZ and 49.7% of the 1,182 participants with BD in the 2010 GAMIAN-Europe study had moderate to high levels of self-stigma; Brohan, 2010; 2011). It was associated with higher levels of metacognitive abilities, self-efficacy, self-esteem, empowerment, hope, personal recovery and subjective quality of life (Sibitz, 2011; Nabors, 2014 Firmin, 2016). Several psychosocial interventions (mainly combinations of psychoeducation and Cognitive Behavior Therapy (CBT)) have been designed to reduce IS and its impact on clinical and functional outcomes, with preliminary results on IS, insight, and self-efficacy (Wood, 2015). Their impact on functional brain connectivity remains unknown to date.

Public stigma, i.e. the relatively automatic cognitive and behavioral response in a social context cued by a characteristic related to a stigmatized group (Krendl, 2006), is the most documented area in the literature (Krendl, 2011; 2013; Reihl, 2015). The processes leading to negative or stigmatizing attitudes towards individuals with SMI were investigated and showed the role of the SZ diagnosis, persistent negative symptoms, and functional impairments (mostly on social skills) play in participants' emotional reactions when interacting with people they believed to have SZ (Penn, 2000; Heenan, 2014). More severe negative symptoms and poorer social skills were associated with higher perceived strangeness and desire for social distance when interacting with individuals with SZ (Penn, 2000).

In contrast with public stigma (or endorsement of negative beliefs and discriminating attitudes by the general population), personal stigma refers to the beliefs experiences and attitudes towards mental illness endorsed by the members of a stigmatized group, in this case people with SMI (Gerlinger, 2013). It includes perceived stigma (or one's beliefs and anticipations about the perception and attitudes of the general population towards persons with mental illness), experienced stigma (or the actual experiences of social discrimination lived by the persons with mental illness) and self-stigma. In a recent study anticipated social discrimination mediated the relationships between experienced stigma and self-stigma (Quinn, 2015), showing that these concepts may be interrelated. Three experimental paradigms were used in the literature to investigate the cognitive and neural mechanisms underlying personal stigma. Implicit Association Tests (Greenwald, 2009) and stereotype threat conditions (Steele et Aronson, 2002) directly addressed stigma or self-stigma and the cyberball game (Williams, 2000) was used to investigate social exclusion, a stigma-related concept.

Implicit Association Tests (IAT) are commonly used to assess implicit self-associations, emotional reactions and attitudes towards a concept or a population, as they are less influenced than explicit measures by social desirability biases and have good psychometric properties (Greenwald, 2009). IAT assess the strength of association between concepts by measuring response latencies during computerized categorization tasks: the quicker the stimuli are classified, the more likely they are to match the respondent's associations with a target concept (Greenwald, 2009). IAT are particularly well-suited to investigating automatically activated reactions towards stigmatized individuals, as these reactions can influence outcomes, and because deliberately endorsed stereotypes and negative attitudes towards stigmatized individuals have become less acceptable (Greenwald, 2009). IAT was used to assess automatic stereotyping and negative emotional reactions towards individuals with SMI in the general population (Peris,

2008; Heenan, 2014), in mental health professionals (Stull, 2013), and in participants diagnosed with SZ or BD (Teachman, 2006; Rusch, 2010a; 2011).

The stereotype threat (ST) model is a popular experimental paradigm in social psychiatry that has been used in numerous studies concerning discriminated populations and minorities (Steele et Aronson 2002; Derks, 2008). The ST paradigm refers to situations where one individual is at risk of confirming by his/her actions his/her negative stereotypes about themselves or his/her social group (Derks, 2008). As an individual can suffer simultaneously from various forms of discrimination, Shapiro and Neuberg created a multi-threat framework (Shapiro et Neuberg, 2009). In this model, self and group concept threats imply endorsement by an individual of negative beliefs about oneself or about one's social group, respectively. Own and group reputation threats correspond to one's fear of being identified as possessing stigmatizing attributes and therefore reinforce negative beliefs about his/her own social group (Shapiro et Neuberg, 2007). Given the proximity of these concepts to stigma and self-stigma, the number of studies using ST in individuals with SMI is surprisingly limited (Henry, 2010; Shapiro, 2011; Moritz, 2018).

Social rejection models recreate stigma-related environments under experimental conditions. The most popular paradigm is the cyberball game, a ball-tossing game in which participants believe they are playing with fellow participants, but are in fact randomly assigned to inclusion, exclusion and sometimes over-inclusion conditions and play with computer-controlled players (Williams, 2000). Cyberball is considered to be an ecologically valid paradigm for evaluating emotional reactions following social inclusion or exclusion, and was used in numerous studies involving healthy individuals (Hartgerink, 2015). The neural correlates of acute social exclusion/inclusion in healthy controls (HC) are well known (Eisenberger, 2003; Bolling, 2011; Moor, 2012 Kawamoto, 2012). Enhanced activation of the insula and of the dorsal and ventral

anterior cingulate cortex (ACC) during social exclusion was associated with self-reported experience of rejection (Eisenberger, 2003. Bolling, 2011; Moor, 2012). Enhanced activation of the medio-prefrontal cortex (mPFC), the precuneus and the posterior cingulate cortex during social exclusion were identified as a potential protective mechanism modulating the affective response to acute social rejection (Eisenberger, 2003; Bolling, 2011; Moor, 2012 Kawamoto, 2012). Cyberball was used in individuals with SMI, mostly BPD (Lawrence, 2011; Staebler, 2011; Domsalla, 2014; De Panfilis, 2015; Savage, 2017; Brown, 2017; Euler, 2018; Ernst, 2018; Weinbrecht, 2018).

In summary, the clinical and functional correlates of stigma in individuals with SMI are well known and several strategies have been recently developed to reduce stigma and self-stigma (Griffiths, 2015; Woods, 2016). In contrast, there appears to be surprisingly little cognitive neuroscience research into mental illness stigma. Only a few studies directly addressed the cognitive and neural processes underlying self-stigma or stigma resistance in individuals with SMI (Rusch 2010a; 2010b, 2011; Raij, 2014; Moritz, 2018). These mechanisms remain therefore unclear as the data are heterogeneous and come from various sources and different experimental paradigms (some of which not even directly related to stigma or self-stigma). To our knowledge, no literature review has yet been conducted on this particular topic.

The present review has two objectives: i) to review the cognitive and neural processes underlying the effects of stigma, discrimination and social rejection in individuals with SMI; ii) to evaluate the strengths and limits of the current evidence in order to guide future research.

Methods

A stepwise systematic literature review (PRISMA guidelines) was conducted by searching PubMed, Medline and Web of Science for published, peer-reviewed papers using the following

keywords: “cyberball” OR “stereotype threat” OR “implicit association test” AND “mental illness”. The articles included in this review had to meet all the following criteria: a) reporting on social rejection, stigma, or experiences of discrimination; b) diagnosis of SMI c) available data on the neural and cognitive mechanisms underlying social rejection, experiences of discrimination and stigma or self-stigma.

Results

Our search on July 31st 2018 found 955 articles on PubMed and 3,362 on Web of Science. After manually removing all duplicates, 1,209 articles were retained. Based on their titles and abstracts, 1,153 papers were excluded for lack of relevance. Most of these articles focused on stigma-related experimental paradigms in healthy individuals or in other discriminated populations. Our search strategy yielded 57 full papers. After conducting a full-text analysis of all these papers and after excluding those which did not meet the inclusion criteria we ended up with 34 relevant papers (figure 1).

Figure 1: Review process (Prisma flow diagram)

Neural and cognitive correlates of self-stigma

Nine (23.6%) of the 38 included papers reported directly on self-stigma. However, these studies were characterized by the heterogeneity of samples, methods, and reported outcomes. Two-hundred-fifty-four people with SMI and 148 healthy controls were included. Sample sizes ranged from 36 to 135 participants, mean age from 26 to 45 years, and the proportion of male participants ranged from 12.5% to 75%. Five studies reported data on the participants’ ethnic origins with a proportion of Caucasian participants ranging from 34 to 77% (Teachman, 2006; Rusch, 2010a; 2010b; 2010c; 2011). Four studies investigated a specific psychiatric diagnosis (OCD; Moritz, 2018; SZ; Henry, 2010; Lindner, 2015; Raij, 2014) whereas the other five

included a broader range of diagnoses (SZ-spectrum disorders, BD, unipolar MDD and OCD). Seven studies only included outpatients. One only included inpatients and one did not report the patients' statuses at inclusion. The mean duration of illness was reported in six studies and ranged from 49 months (Raij, 2014) to 15 years (Rusch, 2010a; 2010b; 2010c; 2011; Henry, 2010). The mean number of psychiatric hospitalizations was recorded in four studies (Rusch, 2010a; 2010b; 2010c; 2011) which all came from the same sample. Three studies reported data on patients' current medication status (Henry, 2010; Raij, 2014; Moritz, 2018). Five studies used IAT (Teachman, 2006; Rusch 2010a, 2010b, 2010c; Raij, 2014), one used Lexical Decision Task (Wittenbrink, 2001; Rusch, 2011) and two ST (Henry, 2010; Moritz, 2018). Two studies included f-MRI data, one acquired during passive emotion viewing (Lindner, 2015) with visual stimuli from the Karolinska Directed Emotional Faces (KDEF) catalogue (Lindqvist, 1998) and one during a visuo-motor rating task with stigma-related and non-stigma related visual stimuli (statements about schizophrenia or common cold) (Raij, 2014). Results are shown on Table 1.

Two cognitive models of self-stigma and one of stigma resistance were described. Implicit self-stigma (defined as the combination of implicit negative attitudes towards mental illness and low implicit self-esteem; Rusch 2010c) was strongly correlated with explicit self-stigma and identified as a predictor of subjective quality of life (Rusch, 2010c). Social alienation (or high perceived social loneliness associated with low personality trait agreeableness; Lindner, 2015) was associated with reduced insula activation in participants with SZ when processing covert expressions of disgust (Lindner, 2015). According to the authors, this reflected a decreased sensitivity to subtle signals of social rejection that might protect individuals against social alienation (Lindner, 2015). There was however also a negative association between insula responsiveness to subtle facial expressions of disgust and low agreeableness in the control group (Lindner, 2015).

Stigma resistance (defined as low negative implicit associations between SZ and social inferiority) was associated with the enhanced activation of rvmPFC and decreased activation of the amygdala (Raij, 2014). Acute social rejection, low stigma resistance, and ST conditions led to underperformance in cognitive or social cognitive tasks (Raij, 2014; Savage, 2017; Ernst, 2017; Moritz, 2018) and in social skills (Henry, 2010) in people with SMI. The associations between self-stigma, cognitive performance and social functioning are however unclear as self-stigma did not influence cognitive performance under ST conditions in people with OCD (Moritz, 2018) and was not recorded in the study by Henry *et al.* (Henry, 2010).

Neural and cognitive correlates of social rejection

The consequences of social rejection were investigated in 25 studies (65.7%), with varying samples, methods, and reported outcomes. Most of the 629 participants in the experimental groups had BPD (19 studies; n=475; 75.5%), the other diagnoses represented were SZ (n=55; 8.7%; Gradin, 2012; Engel, 2016), a high clinical risk of psychosis (CHR; n=25; 3.9%; Lincoln, 2017), SAD (n=23; 3.6%; Heeren, 2017), MDD (n= 15; 2.3%; Kumar, 2017) and suicide attempters (SA; n=36; 5.7%; Olié, 2017). No studies were conducted specifically on people with BD. However, four studies recruited participants with type I or II BD in their experimental group (10 to 56% of the total sample; Domsalla, 2014; Renneberg, 2012; Bungert, 2015; Olié, 2017). All studies recruited healthy controls (HC). Seven studies had also patient controls (PC) with SAD (Gutz, 2015; 2016; Weinbrecht, 2018), AD (Lincoln, 2017), MDD (Ernst, 2018; Olié, 2017) or non-suicidal self-injury (Brown, 2017). Sample sizes ranged from 32 to 122 participants, mean age from 19 to 45 years and the proportion of female participants from 15.4% to 100%. Education level was reported in 16 studies and ranged from 10.61 to 15.7 years of education. Three studies reported data on the participants' ethnic origins with a proportion of Caucasian participants ranging from 49 to 80% (Ruocco, 2010; Gratz, 2013; Savage, 2017). Eleven studies were conducted on outpatients only, five on stabilized inpatients (admitted to receive specific

psychotherapy), four had mixed samples and five did not report the participants' status at inclusion. Almost all studies recorded current psychiatric comorbidities. Eleven studies recorded lifetime comorbidities and one recorded the number of past depressive or manic episodes and the age of onset. Fourteen studies reported data on patients' medication with the proportion of participants taking medication at inclusion ranging from 0 to 92%. Most studies used cyberball. Two studies added an over-inclusion condition (i.e. a condition where the participant received the ball more often than the other players) to the conventional experimental paradigm (De Panfilis, 2015; Weinbrecht, 2018) and one a re-inclusion condition (Heeren, 2017). One study used implicit and explicit emotion processing tasks (Schienle, 2015) and one an emotion reappraisal task during f-MRI (Koenigsberg, 2009). Two studies included biological measures (oxytocin and cortisol dosages; Jobst, 2014; 2016), ten studies f-MRI (Koenigsberg, 2009; Ruocco, 2010; Gradin, 2012; Domsalla, 2014; Bungert, 2015; Schienle, 2015; Kumar, 2017; Heeren, 2017; Olié, 2017; Brown, 2017), two EEG (Gutz, 2015; Weinbrecht, 2018) and two cognitive assessments (Go-No Go; Ernst, 2017; Reading Mind in the Eyes Test; Savage, 2017). The results are presented in Table 2.

The relationships between acute social rejection and self-stigma are still largely unknown. However, acute social exclusion results in greater social distress, more negative emotions (i.e. self-blame, more internal attributions, decreased feeling of control) and less use of functional emotion regulation strategies in people with SMI (Staebler, 2011; Gratz, 2013; Olié, 2017; Lincoln, 2017). The response to social rejection was influenced by the psychiatric diagnosis and might be stigma-related. In people with SZ, the results are controversial. Some studies supported the hypothesis that reduced sensitivity to social rejection might be related to social cognition deficits (Gradin, 2012) and protect against social alienation (Lindner, 2015). However, another study found similar negative emotions during social exclusion, less positive emotions during social inclusion and increased negative expectations before the task (Engel, 2016). According to

the authors, the decrease in positive emotions during inclusion was related to social anhedonia and increased negative expectations before exclusion, due to higher anticipatory social anxiety (Engel, 2016). Hypersensitivity to social rejection and increased paranoid beliefs during social exclusion were found in people with CHR and were mediated by difficulties with emotion regulation and self-blaming (Lincoln, 2017). The potential role of self-stigma and of experienced or anticipated discrimination cannot be determined, as these variables were not recorded.

Almost all studies of BPD participants found a hypersensitivity to social rejection during both social exclusion and social inclusion. This hypersensitivity was associated in some studies with enhanced P3 amplitudes and with enhanced activation within the salience network (dorsal anterior cingulate cortex (dACC), dorsal medio prefrontal cortex (dmPFC) and precuneus), supporting the hypothesis of an altered modulation of the affective response to social rejection in people with BPD (Gutz, 2015; Weinbrecht, 2018; Ruocco, 2010; Domsalla, 2014; Brown, 2017). Participants with BPD showed an enhanced activation of the amygdala when processing disgusted faces, this activation being associated with self-disgust (Schienle, 2017). Emotion regulation difficulties were also found in people with BPD with lower amygdala deactivation and lower recruitment of the brain areas involved in cognitive reappraisal in HC (Koenigsberg, 2009). Self-stigma, anticipated social discrimination and stigma resistance might therefore play a role in in the response to social rejection in people with BPD, but their potential role remains unknown to date. Hypersensitivity to social rejection was also found in people with MDD and SAD, with increased difficulties recovering from social rejection in those with SAD. There were no direct correlations with stigma or self-stigma.

Predictors of the response to stigma and social rejection

Socio-demographic characteristics (age, sex, ethnicity, education level), current and past psychiatric comorbidities, current psychotropic medication, insight into illness and global functioning did not appear to influence the cognitive mechanisms underlying the effects of stigma

or social rejection on people with SMI (Rusch, 2007; 2010a, 2010b, 2010c; 2011a; 2011b; Ruocco, 2010; Staebler, 2011; Lawrence, 2011; Gratz, 2013; Raij, 2014; Lindner, 2015; Brown, 2017; Savage, 2017; Ernst, 2018; Euler, 2018). Group identification, implicit shame-related self-associations and implicit self-guilt did however contribute to self-stigma and to a lesser ability to resist stigma (Rusch, 2010a; 2010b; 2010c). The endorsement of genetic causal attributions about mental illness increased implicit self-guilt in individuals with SMI (Rusch 2010a) which has implications when designing anti-stigma campaigns or psychoeducation interventions for people with SMI (Rusch, 2010a). The psychiatric diagnosis did not influence implicit stigma-related self-negative associations in people with SMI (Rusch 2010a; 2010b, 2010c; 2011a). It did however influence the response to social rejection (Rusch, 2007; Staebler, 2011; Renneberg, 2012; Gratz, 2013, Gutz, 2015; 2016; Domsalla, 2014; De Panfilis, 2015; Engel, 2016; Weinbrecht, 2018). This concurs with the literature on explicit self-stigma, which is more frequent in people with SZ (Brohan, 2010; 2011) but affects clinical and psychosocial outcomes in all people with SMI (Livingston et Boyd, 2010). Psychiatric symptoms influenced self-perceptions as symptomatic BD participants had more implicit negative self-associations (Jabben, 2014). The number of BPD features influenced social-cognitive performance after social rejection in people with BPD (Savage, 2017) and the severity of positive symptoms affected the response to social rejection in participants with SZ (Gradin, 2012). Illness duration affected negatively stigma resistance (Raij, 2014). There were no significant differences between inpatients and outpatients with SZ in their response to social rejection (Engel, 2016). The participants' social networks did not influence the response to social exclusion in people with BPD (Gratz, 2013). Baseline non-specific distress was associated with elevated distress during social exclusion (Gratz, 2013) suggesting that chronic social rejection might affect the response to acute social rejection and contribute to social alienation (Gutz, 2016). A history of trauma influenced the biological and behavioural response to social rejection (Jobst, 2015; 2016; Ernst, 2018) and was associated with more shame-related self-associations in people with BPD (Rusch,

2011). However, emotion processing when confronted with disgusted faces (Schienle, 2015) and when distancing from negative social cues (Koenigsberg, 2009) were not affected by a history of trauma. A history of suicidal acts influenced the response to social rejection in people with SMI (Olié, 2017).

Discussion

Overall, the results of the present review can be summarized as follows: Acute social rejection and its consequences on individuals with SMI were the most documented area (25 studies). Hypersensitivity to acute social rejection was found in almost all the studies including people with SMI and was associated with more self-related negative emotions and with the use of less functional and more dysfunctional emotion regulation strategies. Enhanced activation within the salience network was associated with hypersensitivity to acute social rejection. Hypersensitivity to social rejection resulted in an increase in paranoid beliefs in people with CHR. Reduced sensitivity to acute social rejection and reduced activation within the salience network were, however, found in people with SZ and could be related to social cognition deficits or act as a protection mechanism against social alienation. Individuals with SMI under-performed in cognitive and social cognitive tasks when placed in stigma-related environments. Stigma resistance was associated with enhanced activation of the rostro-ventral medio prefrontal cortex (rvmPFC) and decreased activation of the amygdala in people with SZ. Psychiatric symptoms, illness duration and baseline non-specific distress influenced the response to acute social rejection or stigma. The potential role of chronic social discrimination and its effects on people with SMI should be further investigated.

The existing body of research on the cognitive neuroscience of stigma in individuals with SMI has several limitations. Only a few studies directly addressed the consequences of self-stigma on

people with SMI. The samples, methods, experimental paradigms and reported outcomes used in the studies were heterogeneous and therefore difficult to compare. The results mostly came from individual studies that have not yet been replicated. The cognitive and neural correlates of personal stigma remain largely unknown and should therefore be further investigated. Neuroimaging studies may add to the knowledge about the neural mechanisms underlying personal stigma and stigma resistance. Personal stigma is however a complex construct difficult to model precisely in cognitive neuroscience. Studying the effects of experienced and anticipated social discrimination on brain functional connectivity and biological inflammatory response in persons with SMI might improve the understanding of the mechanisms underlying personal stigma but future research will be needed.

Relationships between acute social discrimination and self-stigma

The relationships between acute social rejection and self-stigma are unclear, as most studies did not record self-stigma. Implicit and explicit self-stigma predicted subjective quality of life (Rusch, 2010c; Livingston et Boyd, 2010). As expected, individuals with SMI underperformed in cognitive and social cognitive tasks under stigma-related conditions (stereotype threat or acute social rejection). This supports previous findings that explicit self-stigma is associated with lower cognitive, social and vocational functioning (Lysaker, 2009; Yanos, 2010; Hill et Startup, 2012). Individuals with SMI showed higher rejection expectancy and anticipatory anxiety before social exclusion. They had also more self-related negative emotions during social exclusion and an increased tendency to use avoidant strategies after being excluded when compared with HC (Gratz, 2013; Gutz, 2015; 2016; Engel, 2016). This may back up previous research where anticipated social discrimination mediated the relationship between experienced discrimination and self-stigma in individuals with SMI (Quinn, 2015), and where self-stigma predicted social anxiety in people with SZ (Lysaker, 2010) and was associated with avoidant coping strategies (Vauth, 2007). Anticipated social discrimination and self-stigma may influence the response to

social rejection and their potential role should therefore be investigated further. In people with CHR, social exclusion was associated with hypersensitivity to acute social rejection and increased paranoid beliefs that were mediated by emotion regulation difficulties and self-blaming (Lincoln, 2017). This might be related to self-stigma, associated with hypersensitivity to social rejection and paranoid delusions in a cognitive model of self-stigma in psychosis (Wood, 2017). Two studies found reduced sensitivity to social rejection and reduced activation within the salience network in people with SZ (Gradin, 2012; Lindner, 2015). This might relate to social cognition deficits (Gradin, 2012) and protect against social alienation (Lindner, 2015). It might, however, also more generally reflect the salience network dysfunction described in people with SZ (Palaniyappan, 2012). The "insight paradox" described by P. Lysaker (association between depression and good insight) and its relationships with social cognition and emotion regulation abilities might also explain the differences observed in people with SZ (Lysaker, 2007; 2013). The presence (or the absence) of metacognitive deficits impeding one's abilities to deflect negative beliefs about oneself can also be a potential explaining factor (Nabors, 2014). The relationships between social cognition, metacognitive abilities, self-stigma and the response to acute social rejection should therefore be further investigated.

Although very few studies reported on self-stigma in BPD, there is some evidence supporting its potential role in moderating the response to acute social rejection. Participants with BPD showed an enhanced activation of the amygdala when processing disgusted faces, this activation being associated with self-disgust (Schienle, 2017). As implicit self-disgust contributed to self-stigma by increasing the perceived legitimacy of discrimination and by decreasing the ability to resist stigma (Rusch, 2010b), this hypersensitivity to social rejection in people with BPD might be stigma-related. Emotion regulation difficulties in people with BPD were associated with lower deactivation of the amygdala and lower recruitment of the brain areas involved in cognitive reappraisal in HC (Koenigsberg, 2009). Although affect dysregulation is a key feature of BPD, it

has been suggested that this mechanism might also be related to the internalization of psychiatric disorders or early-life maltreatment (Gunderson, 2018). In contrast stigma resistance was associated with preserved cognitive performance in people with SZ. The f-MRI showed SR to be associated with enhanced activation of the rostro-ventral medio prefrontal cortex (rvmPFC) and decreased amygdala activation in people with SZ after controlling for global functioning, insight and depressive symptoms (Raij, 2014). As the rvmPFC was identified as a regulator of the affective response to social exclusion (Eisenberger, 2004) this could be one of the mechanisms behind stigma resistance (Raij, 2014). Self-stigma, anticipated social discrimination, stigma resistance, and social cognition and emotion regulation ability might influence the response to acute social rejection and their potential role should be investigated in future studies.

Implications for future research

Several predictors of the response to stigma or acute social rejection were identified. Self-stigma was influenced by group identification, implicit shame-related self-associations and implicit self-guilt, but not by psychiatric diagnosis, psychiatric comorbidities or socio-demographic characteristics. The association between implicit shame-related self-associations and self-stigma is also found in a previous study where explicit shame-proneness was identified as a mediator between insight and self-stigma (Hasson-Ohayon, 2012). Stigma resistance was negatively affected by illness duration in accordance with previous results (Sibitz, 2011a). The response to social rejection was not influenced by the participants' status or social network in people with SZ and BPD (Gratz, 2013; Engel, 2016). Further investigation is however needed, as inpatient status and reduced social network were associated with decreased stigma resistance in people with SZ (Sibitz, 2011a; 2011b). The role of the psychiatric diagnosis in moderating the response to acute social rejection remains unclear, as all the studies were diagnosis-specific. The severity of the psychiatric symptoms influenced the response to acute social rejection. The number of BPD features influenced social-cognitive performance after social rejection in people with BPD

(Savage, 2017) and the severity of positive symptoms affected the response to social rejection in participants with SZ (Gradin, 2012). This might be stigma-related as self-blaming, social threat processing dysfunctions and self-stigma can underpin paranoid beliefs in people with psychosis (Corlett, 2010; Lincoln, 2017; Wood, 2017) and explicit self-stigma is associated with increased severity of positive and depressive symptoms (Livingston et Boyd, 2010; Cerit, 2012).

Baseline non-specific distress was associated with elevated distress during social exclusion (Gratz, 2013) suggesting that chronic social rejection might affect the response to acute social rejection and contribute to the development of social alienation (Gutz, 2016). However, research on chronic social rejection is extremely limited in HC and non-existent in people with SMI. Chronic social rejection was investigated in people without SMI, but confronted with prolonged ostracism (social rejection > 3-months; Williams, 2009; Riva, 2014; 2017). In contrast to acute social rejection, chronic social rejection was associated with feelings of resignation, helplessness, unworthiness and low self-worth and ultimately with social alienation and depression (Williams, 2009; Riva, 2014; 2017). An increased sensitivity to acute social exclusion was also found in people suffering from chronic social rejection (Williams, 2009; Riva, 2014; 2017). In people at risk of being ostracized, enhanced spontaneous amygdala resting-state activity and increased connectivity with the salience network were associated with a greater exposure to discrimination, independently of ethnicity, sex or current psychiatric comorbidities (Clark, 2017). Elevated pro-inflammatory cytokines (Il-6 and TNF-alpha) were associated with enhanced dorsal ACC and anterior insula activation after acute social rejection in HC (Slavich, 2010). Exposure to everyday social stressors and to social rejection was associated in HC with elevated inflammatory activity and with MDD (Slavich, 2010; 2014; Beatty, 2014; Van Dyke, 2017). Elevated CRP levels were found in people with SZ, BD or MDD (Miller, 2014; Horsdal, 2017) and associated with more severe depressive symptoms in people with SZ (Faugere, 2018). However, the correlations between inflammatory activity, experiences of discrimination and self-stigma in people with SMI have not been investigated to date. Future research should therefore investigate the potential role

of current, past and anticipated social discrimination in the modulation of biological and neural responses to stigma or acute social rejection in people with SMI.

In conclusion, the studies conducted in the last decade have improved our understanding of the cognitive and neural correlates of stigma, self-stigma and acute social rejection in people with SMI. Several potential mechanisms and predictors have been identified and should be further documented. Future research should investigate the associations between self-stigma, performance under ST conditions and the responses to acute and chronic social rejection in people with SMI. Chronic social rejection in people with mental illness and its cognitive, biological and neural correlates should also be further investigated.

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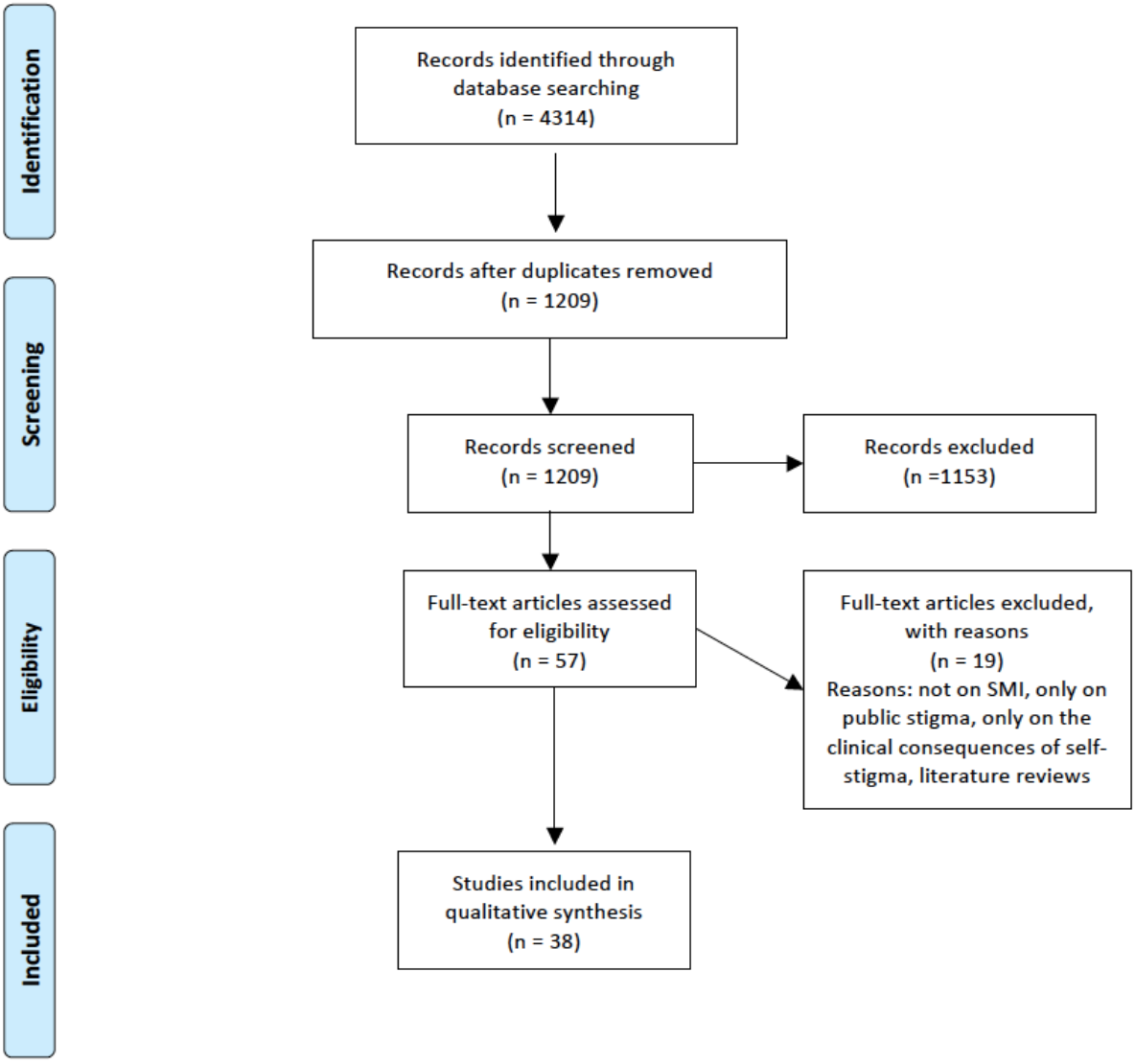

Figure 1: Review process (Prisma flow diagram)

	Socio-demographic characteritics					Psychiatric history					Experimental design	results
	n	Age (mean)	Sex (%)	Ethnicity (%)	Education (mean)	Diagnosis	Current CM	Statut	Psychiatric history	Treatments		
Teachman 2006	35 SMI 36 HC	43	32% women	77% causasian	-	59% psychotic disorders, 31% mood disorders; 31% PD, 13% AD	none	Outpatient	No	-	IAT	Similar implicit negative beliefs and attitudes towards SMI between persons with SMI and controls
Rusch 2011	85 SMI 50 HC	45	32% women	34% caucasian, 58% afro-american	13.5 years	27% SZ, 26% schizoaffective disorders, 30% BD, 12% unipolar MDD	39% SUD	Outpatient	Yes Illness duration: 15 years Mean number of hospitalizations = 9	-	Lexical Decision Task	Reduced automatic stereotyping in persons with SMI compared to controls
Rusch 2010 a	85 SMI 50 HC	45	32% women	34% causasian	13.5	27% SZ, 26% schizoaffective disorders, 30% BD, 12% unipolar MDD	39% SUD	Outpatient	Yes Illness duration: 15 years Mean number of hospitalizations = 9	-	IAT	Endorsement of biogenetic causes (but not neurobiological) of mental illness is associated to increased implicit self-guilt and self reported fear towards people with SMI
Rusch 2010 b	75 SMI	44	69% men	34% causasian	13.5	24% SZ, 28% schizoaffective disorder, 36% BD, 9% unipolar MDD,	43% SUD	Outpatient	Yes Illness duration: 15 years Mean number of hospitalizations = 9	-	IAT	Implicit shame-related associations at baseline predict increased perceived legitimacy of discrimination at 6 months follow-up
Rusch 2010 c	85 SMI	45	68% men	34% causasian	13.5	27% SZ, 26% schizoaffective disorders, 30% BD, 12% unipolar MDD	39% SUD	Outpatient	Yes Illness duration: 15 years Mean number of hospitalizations = 9	-	IAT	Implicit self-stigma predicts lower quality of life independently of explicit self-stigma, depressive symptoms and psychiatric diagnosis
Henry 2010	30 SZ	38	43% men	-	13.4	70% SZ, 30% schizoaffective disorder	none	Outpatient	Yes -Mean illness duration = 15.8 years -Mean age of onset= 23.1 years	100% atypical AP; 343.2 CE	ST with conversation probe role play test	Lower social skills (higher impairment in initiating conversations and switching topics) under ST
Moritz 2018	50 OCD	38 (ST), 43 (PC)	87.5% women (ST), 69.2% (PC)	-		100% OCD	not recorded	Outpatient	No	52% Antidepressants	ST	Lower executive functioning under ST

Lindner 2015	38 SZ 42 HC	30	61% men (SZ) 67.5% (HC)	-	13.1	100% SZ	BDI 12.7 STAI 46.4	Inpatient	Yes Mean illness duration: 6.8 years	-	Passive emotion viewing during fMRI	Reduced insula activation to subtle expressions of disgust and positive correlation between insula activation and social loneliness in participants with SZ
Raij 2014	20 SZ 16 HC	Patients 26 Controls 28	Patients 70% men Controls 75% men	-	13	100% SZ	25% MDD, 20% OCD, 10% SAD, 15% PD	Not recorded	Yes Mean illness duration: 49 months	100% AP (575 CE)	IAT Visuomotor rating task during fMRI	- Lower implicit negative associations in patients in comparison with controls -Negative correlation between implicit associations and rostro ventral medio-prefrontal cortex - Negative correlation between rostro ventral mPFC activation and right amygdala activation

Table 1 Articles reporting directly on self stigma

AD: Anxiety Disorders; AP: Antipsychotics; BD: Bipolar Disorders; BDI: Beck Depression Inventory; CE: Chlormoprazine Equivalent; CM: Comorbidities; fMRI: Functional Magnetic Resonance Imaging; HC : Healthy Controls ; IAT: Implicit Associations Test; MDD: Major Depressive Disorder; mPFC: Medio Prefrontal Cortex; OCD: Obsessive Compulsive Disorder; PC: Patient Controls; PD: Personality Disorder; SAD: Social Anxiety Disorder; SMI: Severe Mental Illness ; ST: Stereotype Threat; STAI: Spielberger Trait Anxiety Inventory; SUD: Substance Use Disorder; SZ: Schizophrenia

	Socio-demographic characteritics				Psychiatric history					Experimental design	Results
	n	Age (mean)	Sex (%)	Education (mean)	Diagnosis	Current CM	Statut	Psychiatric history	Treatments		
Staebler, 2011	35 BPD 33 HC	27.88 to 32.11	100% women	10.61	100% BPD	20% PTSD	Inpatients	Yes Past 54% MDD, 37% SUD	34.28% AD ; 31.4% AP 28.57% none	Cyberball	Women with BPD reported more feeling excluded when included and had less positive and increased negative emotions when excluded
Lawrence, 2011	30 BPD 22 HC	18.56 to 19.33	86 to 90% women	-	75% full BPD; 25% sub-threshold BPD	63% MDD, 46% PTSD; 73% AD	Outpatients	No	66.6% AD, 7.4% BZD, 3.5% AP	Cyberball	No difference in mood rating after social exclusion between young adults with BPD and healthy controls
Renneberg, 2012	30 BPD 30 HC	28.8 BPD 29.03 HC	86.7% women	10.6	100% BPD	30% MDD, 3.3% BD; 60% SUD, 43.3% AD, 36.7% PTSD, 50% ED	Inpatients	Yes Past MDD 50%	60% AD, 23.3% AP, 10% MS, 20% none	Cyberball	-More reported exclusion feelings during social inclusion and exclusion in BPD -More reported anger during social exclusion in BPD
Gratz 2013	53 BPD 34 HC	-	72% women (BPD), 50% (HC)	-	100% BPD	none	Outpatients	No	not recorded	Cyberball	-Hypersensitivity to social rejection and heightened threat to all social needs in BPD -Emotion dysregulation mediated the relationship between BPD and response to the task
Gutz 2016	25 BPD 25 SAD 25 HC	25 to 28	84 to 92% women	11.57	100% BPD	12% MDD, 8% SAD, 24% PTSD, 24% ED, 8% dysthymia	Inpatients	Yes Past 48% MDD	not recorded	Cyberball	-Increased self-focused negative emotions in both SAD and BPD -Increased hostile intent attributions in BPD
De Panfilis 2015	61 BPD 61 HC	40.2 BPD 37.6 HC	77% women (BPD) and 70.5% (HC)	14.8% college / university	100% BPD	36% MDD, 18% ED, 4.9% AD, 3.3% adjustment disorder, 44.3% other PD	Outpatients	No	not recorded	Cyberball	Greater levels of negative reported emotions during social exclusion, inclusion but not during overinclusion in BPD
Euler 2018	23 BPD 28 HC	27.9 BPD 25.7 HC	87% women (BPD), 85% (HC)	12.8	100% BPD	34.8% MDD, 8.7% AD, 26.1% SUD, 13% ED, 8.7% SUD	Inpatients	No	69.6% on medication	Cyberball	Higher threat to social needs levels after social exclusion predicted lower therapeutic alliance in mentalization-based group therapy
Ernst 2017	22 MDD 22 MDD + BPD 20 HC	26.73 to 30.5	100% women	25% college students	100% BPD	Mean BDI 37.4 MDD+ BPD; 33 MDD	Not recorded	No	40% AD	Cyberball and Go-No Go task	-Lower response inhibition in BPD + MDD and correlation with childhood trauma -No improvement of response inhibition during social exclusion in BPD +MDD
Savage, 2017	17 BPD 16 HC	19.65 BPD	56.3% to	-	100% BPD	Mean BDI 21.0, STAI 95.47	Students	No	Not recorded	Cyberball and RMIE	Lower ability to identify correctly neutral faces after social exclusion in young adults

		19.41 HC	64.7% women							test	with BPD features
Gutz 2015	25 BPD 25 SAD 25 HC	25 to 28	84 to 92% women	11.57	100% BPD	12% MDD, 8% SAD, 24% PTSD, 24% ED	Inpatients	Yes Past 48% MDD	-	Cyberball and EEG	More reported feelings of exclusion and enhanced P3b during social inclusion in BPD
Weinbrecht 2018	29 BPD 28 SAD 28 HC	27.86 to 28.86	79 to 86% women	-	100% BPD	7% MDD, 55% AD, 4% SAD,7% other PD	62% inpatients for BPD	Yes Past CM: 48% MDD	35% AD	Cyberball and EEG	-Enhanced P3 amplitude in SAD and BPD compared to controls in all conditions -Stronger self-reported ostracism during social exclusion / inclusion but not overinclusion in SAD and BPD compared to controls -Higher self-reported threats to social needs in all conditions in BPD
Ruocco, 2010	10 BPD 10 HC	22.1 BPD 19.0 HC	100% women	13.2	100% BPD	30% MDD, 20% AD, 10% PTSD	Not recorded	No	80% none, 10% AP, 10% stimulants	fMRI during cyberball	Left hyperactivation of the mPFC in BPD during social exclusion
Domsalla, 2014	20 BPD 20 HC	29.2 BPD 28.7 HC	100% female	12.1	90% BPD, 10% BPD + type II BD	25% PTSD, 75% AD, 40% ED	Outpatients	Yes Past 90% MDD, 25% PTSD, 60% AD, 5% ED	-	Cyberball and fMRI	- Higher reported exclusion feelings during social inclusion task and control condition in BPD - No changes depending on the interaction situation (exclusion/ inclusion) in insula and precuneus responsiveness in BPD
Brown 2017	15 BPD + NSSI 14 NSSI 31 HC	23.3 BPD+ NSSI 15.4 NSSI 14.5 and 23.2 adolescent/ adult HC	76.9% to 100% women	-	100% BPD	100% MDD, 50% PTSD,14.2% AD, 7.1% ED	In and outpatients	Yes Mean number of NSSI: 308.5 (BPD) and 128.8 (NSSI)	85% AD, 7.1% MS	Cyberball f-MRI	-Enhanced feelings of social exclusion in patients groups -Enhanced activation in ventral anterior cingulate cortex in patients groups -Enhanced activation in dorsolateral and mPFC during social inclusion in BPD
Bungert 2015	20 BPD 20 HC	29.2 BPD 28.7 HC	100% women	12.1	90% BPD, 10% BPD + type II BD	25% PTSD, 35% AD, 25% SAD, 5% ED	Outpatients	Yes Past 90% MDD, 25% PTSD; 75% AD; 35% SUD	-	Cyberball f-MRI	-Reduced amygdala activation during pain after social inclusion in BPD -Association between higher rejection sensitivity and lower activation differences during physical pain processing in amygdala and insula after inclusion / exclusion in BPD
Jobst 2014	22 BPD 21 HC	100% women	100% women	-	100% BPD	-	Not recorded	No	68.1% AD ;	Cyberball and	-No differences in cortisol plasma concentrations between BPD and controls

									63.6% AP ; 36.3% MS	oxytocin and cortisol dosages	-Negative association between physical and emotional abuse and return of oxytocin levels at baseline after social exclusion
Jobst, 2016	20 BPD 20 HC	30 BPD 29.71 controls	100% women	11.20	100% BPD	Mean BDI 32.75 25% MDD 15% ED	70% outpatients	No	75% AD, 70% AP, 40% MS	Cyberball and oxytocin and cortisol dosages	-No differences in cortisol plasma concentrations between BPD and controls -Lower oxytocin concentrations in BPD patients with disorganized attachment representations compared to other BPD
Olié 2017	36 SA 41 PC 28 HC	37.6 to 39.48	100% women	14 SA, 15 PC	56% BD in SA group; 36% in PC	SA group , 39.2% AD, 16.8 SAD, 2.8% PTSD, 16.8% ED, PC group BD, 36% AD, 4.8% SAD, 12% ED;	Inpatients	Yes - Mean number of depressive episodes: 3.5 - Mean number of manic episodes: 1 - Age of onset first SA: 22 - Past CM: 25.2% SUD	33.6% on medication (SA); 38.4% (PC)	Cyberball f-MRI	-Higher reported social distress in patients groups -Decreased contrast in the left insula and supramarginal gyrus during the exclusion vs inclusion condition
Gradin 2012	15 SZ 20 HC	41.23 SZ 40.87 HC	84.6% men (SZ) 77.7% (HC)	-	100% SZ	Mean BDI 17.43	Outpatients	No	Not recorded	Cyberball fMRI	Increased activation of the mPFC cortex during social exclusion in HC but not in SZ patients Association between positive symptoms severity and blunted response to exclusion in SZ
Engel 2016	40 SZ 40 HC	36.32 SZ 26.45 HC	50% women	11.1	77.5 % SZ, 17.5% schizoaffective disorder	-	Inpatients	No	92.5% AP	Cyberball	More intense negative anticipations before cyberball in patients Less intense positive emotions during social inclusion in patients
Lincoln 2017	25 CHR 40 AD 40 HC	34.72 CHR, 40.3 HC, 42.2 AD	62.5 to 72% women	15.7	76% APS 8% GR 16% both	96% mood disorders, 36% AD, 16% PTSD, 8% SUD; 8% OCD	Outpatients	No	52% on medication, 16% AP	Cyberball	Stronger increase in paranoid beliefs after social exclusion in CHR mediated by lower levels of functional / higher levels of dysfunctional emotion regulation and by higher self-reported negative emotions
Heeren 2017	23 SAD 23 HC	24.96 SAD 25.30 HC	100% women	13.3	100% SAD	Mean BDI : 15.7 ; STAI : 51.04 ; LSAS : 74.2	Inpatients	No	Not recorded	Cyberball fMRI	-Higher reported feelings of social exclusion in patients -Higher activation within the left inferior frontal gyrus during re-inclusion phase. -Correlation between and feelings of

											exclusion and cerebral activation
Kumar 2017	15 MDD 17 HC	45.27 MDD 41.8 HC	60% women (MDD) 58% (HC)	-	Not recorded	Mean BDI : 22.9; STAI : 54.6	Outpatients	No	-	Cyberball f-MRI	Greater amygdala, insula and ventrolateral prefrontal cortex activation to increasing social exclusion in patients

Table 2: Articles on social rejection in SMI

AD: Anxiety Disorders; AP: Antipsychotics; APS: Attenuated Positives Symptoms Syndrome; BD: Bipolar Disorders; BDI: Beck Depression Inventory; BPD: Borderline Personality Disorder; CHR: Clinical High Risk; CM: Comorbidities; ED: Eating Disorder; EEG: Electroencephalogram; GR: Genetic Risk And Deterioration Syndrome; HC : Healthy Controls; fMRI: Functional Magnetic Resonance Imaging; LSAS: Leibowitz Social Anxiety Scale; MDD: Major Depressive Disorder; mPFC: Medio Prefrontal Cortex; MS: Mood Stabilizers; NSSI: Non Suicidal Self-Injury; PC: Patient Controls; PD: Personality Disorder; PTSD: Post-Traumatic Stress Disorder; RMIE: Reading Mind In the Eyes test; SA: Suicide Attempters; SAD: Social Anxiety Disorder; STAI: Spielberger Trait Anxiety Inventory; SUD: Substance Use Disorder; SZ: Schizophrenia