Neural correlates of social cognition in populations at risk of psychosis: a systematic review

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Abstract

Social cognition refers to the mental operations governing social interactions. Recent research has highlighted the importance of social cognition in determining functional outcome in patients with schizophrenia and in psychosis risk populations. The aim of this review is to investigate the neural correlates of social cognition in different psychosis risk populations, potentially representing different levels of risk i.e. high schizotypy (SR), familial risk (FR) and clinical high risk (CHR). PsychINFO, Web of Science and PubMed were systematically searched, and 39 papers were included in the final review. Results in FR samples were highly inconclusive. In SR samples, findings showed a tendency towards increased task related activity in frontal cortex regions. The most consistent results come from CHR samples, where findings suggest increased task related activity in frontal and cingulate cortices. Interestingly, all studies of CHR populations also report increased activity in temporal cortex and abnormal response to neutral stimuli during emotional processing tasks. These findings are discussed in relation to dopamine models of psychosis due to temporal cortex abnormality.

Key words: psychosis, risk, social cognition, functional neuroimaging, systematic review

List of abbreviations used for neural regions:

ACC – anterior cingulate cortex

dlPFC – dorsolateral prefrontal cortex

dmPFC – dorsomedial prefrontal cortex

IFG – inferior frontal gyrus

mPFC – medial prefrontal cortex

OFC – orbitofrontal cortex

PCC – posterior cingulate cortex

PFC – prefrontal cortex

SFG – superior frontal gyrus

STG – superior temporal gyrus

STS – superior temporal sulcus

TPJ - temporal-parietal junction

vlPFC – ventrolateral prefrontal cortex

vmPFC – ventromedial prefrontal cortex

1. Introduction

Schizophrenia is a severe mental health disorder encompassing a heterogeneous cluster of symptoms such as delusions, hallucinations, cognitive impairment, lack of motivation and observable social cognition biases (among other; Frith, 2014). This debilitating psychiatric condition affects nearly 1% of the general population, thus early clinical intervention has become a major objective of mental health services and research networks (McGorry, Killackey, & Yung, 2008). Crucially, treatment advances have been hampered, because whilst antipsychotic medication has been shown to be efficacious for treating positive symptoms (delusions, hallucinations), these drugs are largely ineffective for the treatment of social cognition deficits that are also prevalent in the disorder (Haddad, Brain, & Scott, 2014). As such, focused research into the pathological neural mechanisms that underlie social cognition deficits is needed to facilitate targeted interventions. This is important because poor social functioning has been linked to a reduced quality of life (Penn, Corrigan, Bentall, Racenstein, & Newman, 1997) and predicts illness outcome in schizophrenia, including relapse, poor illness course and unemployment (Couture, Penn, & Roberts, 2006).

Social cognition refers to the mental operations involved in understanding other people's thoughts and intentions, recognising and perceiving emotions and understanding social interactions (Brothers, 1990; Adolphs, 2001). Although social and non-social cognition share some overlapping operations (e.g. working memory, perception, etc.), some brain regions and networks have specifically been linked to processing social information (Green, Horan, & Lee, 2015). Neural systems involved in processing social-affective stimuli, such as facial emotion and nonverbal social cues, include the amygdala, ventral striatum, ventromedial prefrontal cortex, anterior cingulate cortex and superior temporal regions (Ochsner, 2008; Adolphs, 2009; Fig 1). Higher level social cognition processes, such as inferring the intentions of others, are most commonly associated with activations in a broad 'mentalizing network' including the medial frontal

cortex, paracingulate and posterior cingulate cortex, temporal-parietal junction, superior temporal sulcus, and the temporal pole (Ochsner, 2008; Adolphs, 2009; Fig 2).

FIGURE 1 HERE

Fig 1. Areas involved in the recognition and respone to social-affective stimuli. The amygdala (purple) is responsible for recognising emotional expressions and evaluating stimuli. The ventral striatum (red) is associated with recognising stimuli with learned reward values. The medial prefrontal cortex (yellow) supports the ventral stiatum, a10nd is further involved with interpreting nonverbal social information and the contextual interpretation of complex social information. The anterior cingulate cortex (blue) is associated with like/dislike judgements of social cues and intergrating this with emotional information to motivate behavior. The superior temporal gyrus (green) is imporant for recognising nonverbal social cues.

FIGURE 2 HERE

Fig 2. Areas involved in higher-level mental inference. The medial prefrontal cortex (red) is the most reliably activated structure across these studies. This region is associated with thinking the internal states of others, inferring the current beliefs of others and evaluating their long-term traits. The posterior cingulate cortex (green) is associated with generating knowledge of our mind and those of others. The temporal-parietal junction region (purple) is associated with imaging the perspectives of others and attributing beliefs and internal states to others. The superior temporal sulcus (blue) and the temporal poles around it are associated with representing nonverbal cues (that are relevant to deciphering the intentions of others) and with representing emotional knowledge.

Patients with schizophrenia show widespread impairment in the processing of social information, particularly when processing emotional stimuli and when inferring the intentions of others (Green, Horan, & Lee, 2015; Ventura, Wood, Jomenez, & Hellemann, 2013). These social cognitive deficits can result in misinterpretations of the social intent of others, leading to social withdrawal, impaired day-to-day social functioning (Fett, Viechtbauer, Penn, van Os, & Krabbendam, 2011) and delusional interpretations (Morrison, Renton, Dunn, Williams, & Bentall, 2004). At a neural level, functional Magnetic Resonance Imagining (fMRI) studies in schizophrenia patients have shown *reduced* activation (relative to healthy controls) in a number of brain regions during social cognition tasks, namely the medial prefrontal cortex (mPFC), the anterior insula and the amygdala (Anticevic & Corlett, 2012; Whalley, et al., 2009; Taylor, Liberzon, Decker, & Koeppe, 2002; Takahashi, et al., 2004). Patients with a first-episode psychosis also present with abnormal corticolimbic response to emotional stimuli (Bergé, et al., 2014), with altered neural activity to emotional relative to neutral scenes (Modinos, et al., 2015). These abnormalities are seen in patients with schizophrenia during Theory of Mind (ToM; inferring the intentions of others) tasks, with reduced activity observed in middle/inferior frontal gyrus and insula (Russell, et al., 2000), the mPFC (Lee, et al., 2006; Brunet, Sarfati, Hardy-Bayle, & Decety, 2003) and the TPJ (Brüne, et al., 2008). Conversely however, there are studies that report *increased* activity relative to healthy controls in mPFC, superior temporal sulcus/gyrus (STG) and TPJ during ToM tasks (Shamay-Tsoory, et al., 2007; Pedersen, et al., 2012).

These broadly consistent fMRI findings demonstrating functional abnormalities during social cognition tasks have provided support for the notion that these deficits are a strong candidate endophenotype for schizophrenia (Green, Horan & Lee, 2015). Indeed, social cognition impairments have been found to be longitudinally stable and present during both acute symptom stages of the illness and during clinical remission. Research is also increasingly identifying abnormal neural processing in social cognition tasks in psychosis-risk populations (Braff, Freedman, Schork, & Gottesman, 2006), suggesting the presence of this impairment during the illness prodrome and in other high-risk states. Moreover, social cognition deficits can predict functional outcomes in patients with schizophrenia (Kring & Elis, 2013; Brüne, Schaub, Juckel, &

Langdon, 2011; Alvarez-Jimenez, et al., 2012) and are one of the most predictive traits for future onset of schizophrenia-spectrum disorders in psychosis risk populations (Kwapil, 1998). Thus, specifying the nature and extent of these social cognition deficits, and the corresponding neural abnormalities, in different psychosis risk populations may help built a comprehensive model of the progression of this potential endophenotype during illness prodrome.

The aim of this systematic review is to identify patterns of neural abnormalities associated with social cognition across different psychosis risk populations. Firstly, schizotypal personality traits are believed to represent an underlying vulnerability for psychosis (Raine, 1991; Meehl, 1990, Nelson, Seal, Pantelis, & Phillips, 2013; Ettinger, Meyhöfer, Steffens, Wagner, & Koutsouleris, 2014). Furthermore, research has consistently demonstrated similarities between schizotypy and schizophrenia with parallel, albeit attenuated symptoms and deficits (Nelson, Seal, Pantelis, & Phillips, 2013; Ettinger, et al., 2014). While the majority of healthy individuals with high schizotypal traits (schizotypy risk, SR) do not develop psychosis, the rate of SR participants meeting criteria for a schizophrenia-spectrum diagnosis at a 10-year follow-up assessment is estimated to be around 2% (Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994; Kwapil, Gross, Silvia, & Barrantes-Vidal, 2013; see van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009 for a review).

Thus, research into SR populations may represent a useful paradigm for investigating etiological factors associated with schizophrenia in individuals not presenting with typical confounding factors present in clinical samples (i.e. comorbidities, medication).

Insights into at-risk populations also originate from genetic studies. Previous findings from family, twin and adoption studies conclude that familial factors are important risk predictors for the development of psychosis (familial risk – FR; Fowles, 1992). First-degree nonpsychotic relatives of schizophrenia patients have a 10% risk of developing psychosis (MacDonald & Schulz, 2009). In addition, a link between genetic vulnerability to psychosis and the expression of subclinical psychotic-like experiences has been demonstrated (Fanous, Gardner, Walsh, & Kendler, 2001).

Finally, the research potential of clinical high-risk (CHR) groups has been increasingly recognised. This risk category is used to identify individuals potentially in a prodromal phase of psychosis and is operationally defined by attenuated psychotic symptoms and a decline in social and occupational function (Fusar-Poli, et al., 2013; Yung, et al., 1998; Yung, et al., 2003). CHR individuals have an elevated risk (relative to the general population) of developing a first episode psychosis with transition rates varying form 18% after 6 months of follow-up to 36% after 3 years (Fusar-Poli, et al., 2012).

. We have chosen to focus on these three psychosis risk categories as they outline different risk levels in terms of subsequent development of psychosis and might provide valuable insights into disorder progression and neurofunctional risk trajectories. For each at-risk group, we provide a summary of the key neural findings based on brain region in the frontal cortex, cingulate cortex, limbic and subcortical regions (medial temporal regions, insula cortex, striatum and thalamus) and the lateral temporal cortex across a variety of social cognition tasks (i.e. emotional processing, ToM tasks, social reward tasks).

2. Methods

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Moher, Liberati, Tetzlaff, & Altman, 2009) guideline. The review is registered with Prospero under registration number CRD42018111771.

2.1 Inclusion criteria

The aim was to identify all studies fulfilling the following criteria: fMRI studies investigating social cognition in at-risk for psychosis populations (SR, FR, CHR). Social cognition, as outlined in the Introduction, refers to a diverse range of mental operations underlying social interactions (Adolphs, 2001). Thus, tasks were defined as engaging social cognition mechanisms if they: involved perceiving the

intentions/dispositions of others, perceiving/recognising emotions or otherwise involved processing demands that are elicited by, about, and/or directed towards other people. To be included, studies had to provide enough methodological details to judge the social cognition nature of the tasks (have specific a-priori hypotheses as to how the tasks will activate areas within the social brain network, etc.).

There was no age limit applied to the samples although many CHR samples include individuals between 18 – 35 years of age (Fusar-Poli, et al., 2012; Fusar-Poli, et al., 2013). At-risk populations included samples of healthy participants in the general population scoring high on schizotypy personality traits (SR), participants at familial risk of developing psychosis (FR), and at-risk/high clinical risk populations (CHR; Yung, et al., 1998). Samples consisting of individuals presenting with schizophrenia-like symptoms that do not yet warrant full diagnosis were included in categories depending on the nature of the assessment measure used. Studies had to index at-risk populations via a validated measure (e.g. Schizotypy Personality Questionnaire, Comphrenesive Assessment of at-risk mental states, Structured Clinical Interviews for DSM-V, etc.) or had to clearly define genetic risk (i.e. first-degree relatives of patients with schizophrenia). Studies that utilised social anhedonia measures as representing psychosis risk were included in the SR review, as per previous findings indicating that social anhedonia identifies individuals with current elevated positive and negative schizotypy traits and is an indicator of schizotypy (Blanchard, Gangestad, Brown, & Horan, 2000; Blanchard, Collins, Aghevli, Leung, & Cohen, 2011)..

To qualify for inclusion, studies had to present original work subjected to peer-review. PhD theses matching the aim of the review were included if they were published. Studies that did not report fMRI results in the risk group of interest *relative* to healthy controls were excluded.

2.2 Search strategy and selection of studies

Articles published up to November 2018 were identified through literature searches conducted on PsychINFO, Web of Science and PubMed using search terms following Boolean logic. The initial search on all databases used: ''social cognition'' AND (''neuroimaging'' OR ''functional imaging'') AND schizo*. Secondary searchers to ensure optimal identification used: ''social cognition'' AND (''neuroimaging'' OR

’’functional imaging ‘’) AND schizo* AND (’’clinical high risk’’ OR ’’ultra-high risk’’ OR ’’at risk mental state’’ OR ’’prodromal psychosis’’). References from articles and secondary searches and relevant literature reviews were also examined for possible inclusion in the review.

FIGURE 3 HERE

Fig3. PRISMA flowchart of the systematic review process.

Database hits, exclusion, secondary searches and final inclusion were summarised in a PRISMA diagram (Fig 3). We found 4864 records from initial searches. After adjusting for duplicates, 3597 articles were screened for title and abstract. Out of these, 3558 records were discarded as the studies did not meet the inclusion criteria. The full texts of the remaining 39 articles were assessed for eligibility and 21 of these papers were included in the review. Additionally, the reference lists of these articles were searches for relevant records, this search yielded 27 additional articles. Of these secondary searchers, 18 articles were included in the review. Thus, out of 66 full-text screened papers, the total number of articles that met criteria for inclusion was 39.

A second reviewer (FS) independently screened title and abstract of 15% of the 3597 articles identified from the initial search (541 articles). Subsequently, the same author independently screened 15% (6 articles) of the 66 papers identified for full-text screening (from both database and secondary searches). Disagreements, if present, were solved via research team decision. Two authors (PK, FS) further assessed the full list of 39 final included articles to ensure they meet inclusion/exclusion criteria.

2.3 Data collection

The following information was extracted from each included study: (1) authors and year of publication, (2) sample size, (3) type of measure used to define psychosis risk, (4) methodologies and task specifics, (5) fMRI findings in risk group relative to healthy control and (6) main conclusions.

2.4 Quality assessment

To ascertain quality individual studies were appraised using the STROBE checklist (Von Elm, et al., 2007). This is a structured, standardised checklist consisting of 22 items, each relating to the different sections in an article (i.e. title, abstract, introduction, methods, results, discussion, and funding). The quality scores calculated for each article (total score 22) give comparisons of the relative quality of included studies, a higher score indicating higher quality (Table S1 includes the quality scores for all studies).

3. Results

3.1 Samples, demographics, and study design

The search identified 13 fMRI studies investigating social cognition in SR samples, 16 studies in FR and 10 studies CHR samples. Studies used a variety of established methods to assess risk populations (see Table 1, 2 and 3 for relevant populations).

Samples, demographics, key findings and task details are outlined in Table 1 (SR), Table 2 (FR) and Table 3 (CHR). Sample sizes ranged from 10 to 260 participants (mean sample size 67, standard deviation 97). Total number of SR subjects in this review was 287 (relative to 287 controls), total number of FR was 406 (relative to 613 controls) and total number of CHR subjects was 594 (relative to 525 controls). All studies utilised a cross-sectional design, with no randomised control trials included in the review. Emotional processing tasks were used in 24 studies, ToM tasks were used in 9 studies, and 6 papers outlined different tasks reported to engage social cognition. All studies included in the review reported results relative to healthy controls (or groups low on schizotypy symptomatology for SR studies), and the all results presented here report differences relative to control groups. Subjects in the SR and FR groups were not medicated, a

subset of the CHR subjects were medicated at the time of scanning (the studies that included medication status as confound did not report significant differences, please see supplementary table 2). Due to the small number of medicated subjects (only in CHR groups), we could not assess the effect of medication on the results.

We further conducted analyses based on age and functional task design to rule out systematic differences between the at-risk groups and the controls based on these factors. Lower level social cognition tasks (i.e. emotion processing, emotion viewing tasks, etc.) were used in 10 studies with SR samples, 8 studies with FR samples and 7 studies with CHR samples. Higher level social cognition tasks (e.g. ToM) were used in 3 SR studies, 8 FR studies and 3 CHR studies. The functional task design was not significantly different between risk groups and controls, $x2\ (2) = 2.46$, $p > .05$. No interactions were found between risk groups and controls in terms of age either, $x2\ (2) = .01$, $p > .05$. Finally, the three at-risk populations did not differ significantly on age, $F\ (1,71) = .37$, $p > .05$. Details on age, level of education and type of task are in supplementary table 1. Quality scores for the included studies ranged from 16 to 21. The mean quality score for the SR studies was 17.96, for the FR group was 18.37, for the CHR group was 21.7 (details in supplementary table 1).

The results of this review were categorised in four separate brain networks, namely frontal cortex, cingulate cortex, limbic regions and the lateraltemporal cortex. This organisation broadly represents the separate brain regions and networks involved in social cognition as outlined in the literature (Adolphs, 2009) and serves as a comprehensive framework to use for tabulating results.

Table 1. Summary of included papers investigating SR samples.
Blue shading – decreased activity. Grey shading – increased activity. Orange shading – mixed results.

Study (year)	**Sample size (healthy controls) Measure**	**Task**	**Frontal cortex** (Risk group vs controls)	**Cingulate cortex** (Risk group vs controls)	**Limbic regions** (Risk group vs controls)	**Lateral temporal cortex** (Risk group vs controls)	**Conclusions**
Wang, et al., 2018	34 (30 low schizotypy) Chapman Psychosis Proneness Scales	Facial Emotional Valence Discrimination Task. Emotions: angry, fearful, happy, neutral.	↓ mPFC (neutral condition)** ↑ middle frontal gyrus**	↑ ACC (angry conditions)**	↓ amygdala (fearful and neutral conditions)** ↑ insula (angry conditions)**		Abnormal emotional processing neural correlates. Altered activity in the prefrontal regions may result in the dysregulation of negative emotions, or it might be related to possible compensatory mechanisms. Hyperactivation of the insula observed in the present study may suggest that there may be a stronger negative emotional response to angry faces in social interaction.
Modinos, et al., 2017	23 (25 low schizotypy) O-LIFE	Emotional processing task. Categories: negative high arousal, negative low arousal, positive high arousal, positive low arousal,	↑ mPFC**	↑ ACC**	↑ hippocampus**		Dysfunction of the circuitry underlying emotional processing.

		neutral matched for social content.					
Modinos, Ormel, & Aleman, 2010	17 (17 low schizotypy) CAPE	Passive viewing emotional task. Conditions: negative, reappraise, neutral.	↑ left dmPFC** ↑ right vlPFC**	↑ ACC**			Dysfunction of the circuitry underlying emotional processing. Greater activation of prefrontal cognitive control regions is required to down-regulate the experience of negative emotions.
Huang, et al., 2013	14 (14) SPQ	Dynamic facial expression processing. Emotion – happy. Conditions: Happiness induction interaction cues (praise); happiness reduction interaction cue (blame).		↓ left PCC (blame conditions)** ↓ rACC (happiness disappearing conditions)**		↓ right STG (blame conditions)**	Less deactivation in the ACC in the happiness disappearing condition might suggest alteration of neural activities in the hedonic system of individuals with SPD traits. The more deactivated STG in the 'blame' condition could provide a piece of evidence of neural sensitivity for the negative social interaction cues, which induced unhappiness in

							individuals with SPD traits.
Modinos, Renken, Ormel, & Aleman, 2011	18 (18) CAPE	Self-reflection task (self vs other vs general semantic processing)	↑ right dmPFC** ↑ left vmPFC (positive self vs semantic)** ↑ right dmPFC (negative self vs semantic)**	↓ PCC (self vs other contrasts)** ↑ ACC (negative self vs semantic conditions)**	↑ bilateral insula (negative self vs semantic)**		High PP subjects may make less favourable judgements about the other person. High PP subjects may be characterised with exertion of higher cognitive control to diminish emotional response. High PP subjects may have an increased emotional response to self-related stimuli of positive and negative valence (vmPFC), which is seemingly associated with attempts to diminish this response (activity in dmPFC).
Premkumar, et al., 2012	12 (14) O-LIFE (UE subscale)	Rejection-acceptance task (images depicting social acceptance, social rejection or neutral scenes).	↓ left vmPFC/vlPFC (rejection vs neutral)**	↓ dACC bilaterally (rejection vs neutral conditions)**			HS subjects may be unable to attend to and process rejection cues. HS subjects may be unable to attend to and process rejection cues and may not be

							able to effectively engage prefrontal regions in conflict detection and emotional decision-making.
Wang, et al., 2015	52 (-) Chapman Psychosis Pronesess scales	Theory of Mind task. One or two characters in them.	**Positive correlation** between negative schizotypy and activity in medial frontal gyrus* **Negative correlation** between positive symptoms and activity in the medial frontal gyrus			**Positive correlation** between bilateral middle temporal gyrus activity and negative schizotypy* **Positive correlation** between right TPJ activity and negative schizotypy*	Negative schizotypy associated with poorer social cognition and compensatory mechanisms. Negative schizotypy is associated with poorer social cognition.
Germine, 2012	15 (15) Revised Chapman Social Anhedonia Scales	Emotional faces task - emotion discriminations vs identity discriminations vs pattern discriminations.	↓ anterior portion of the rostral PFC**			↓ right STG** ↑ left fusiform gyrus**	Deactivation of areas during emotion processing. Social anhedonia is related to differences in the neural subtracted responsible for self/other representations.
Modinos , Renken, Shamay-Tsoory, Ormel, & Aleman, 2010	18 (18 low) CAPE ¶	First and second order Theory of Mind Mental state attributions.	↑ anterior mPFC** ↑ lateral PFC bilaterally** ↑ right dmPFC				Require greater effort to integrate separate cognitive operations to correctly mentalize and reach

			(during second order ToM)**				performance equivalent to controls.
Healey, Morgan, Musselman, Olino, & Forbes, 2014	27 (-) Revised Chapman Social Anhedonia Scale	Social Rewards Task – passive viewing task. Face stimuli: either people who gave them positive social feedback or ambiguous social feedback.	**Positive correlation** between mPFC activity and anhedonia scores**				Anhedonia is associated with disrupted neural responding to peer social feedback. Anhedonia might be associated with an abnormal response to mutual liking as if it were aversive or, alternatively, received linking as if it were less salient.
Mohanty, et al., 2005	17 (17) Chapman Psychosis Pronesess scale	Emotional Stroop Task (positive, negative, neutral words).	↑ right middle frontal gyrus** ↑ IFG (negative stimuli)**		↑ amygdala cluster** ↓ nucleus accumbens**		Exaggerated attention to negative stimuli even though they are task irrelevant. Increased IFG activity may indicate a greater effort to inhibit strongly interfering emotional stimuli to achieve normal behavioural performance. Decreased activity in the nucleus accumbens suggests

							mechanisms for dysregulation of inputs form important brain regions in the face of aversive stimuli.
Premkumar, et al., 2013	12 (12) O-LIFE (UE subscale)	Criticism listening task (relative's criticism, positive or neutral comments).	↓ right middle frontal gyrus (positive vs neutral)**		↓ left insula** ↓ right thalamus (positive vs neutral contrasts)**	↓ left STG (positive vs neutral)**	HS subjects may be characterised by reduced capacity to elevate mood in response to reward and by difficulty in positive emotion regulation.
Chan, et al., 2016	28 (-) Chapman Social Anhedonia scale†	Affective Delay Task (emotional stimuli as reward or loss based on RT to the target).			↓ left thalamus ↓ right insula (positive vs neutral)*		Affective incentives may elicit specific activations in high anhedonia subjects.

† low vs high N is not reported for the low-high anhedonia comparison.

¶ same sample as Modinos et al (2011)

* significant at $p<0.005$ or $p<0.001$ uncorrected

** significant at $p < 0.05$ corrected

Table 2. Summary of included papers investigating FR samples.
Blue shading – decreased activity. Grey shading – increased activity. Orange shading – mixed results.

Study (year)	**Sample size (healthy controls) Measure**	**Task**	**Frontal cortex** (Risk group vs controls)	**Cingulate cortex** (Risk group vs controls)	**Limbic regions** (Risk group vs controls)	**Lateral temporal cortex** (Risk group vs controls)	**Conclusions**
Villarreal, et al., 2014	14 (14) Siblings, no SCID-I diagnoses	Basic emotion task, Faces Theory of Mind Task, Eyes Theory of Mind Task Correlated measures – Social Skills Performance Assessment questionnaire; Test for Adaptive Behaviour in Schizophrenia	**Positive correlation** between bilateral dlPFC, bilateral IFG activation and SSPA during basic emotion processing* **Positive correlation** between bilateral SFG, left middle frontal gyrus activation and SSPA during ToM tasks*	**Positive correlation** between left cingulate gyrus and SSPA during ToM*	**Positive correlation** between insula and SSPA during basic emotion processing*		Faulty/alternative brain processing underlying social competence.
Spilka & Goghari, 2017	27 (27) Siblings, no SCID diagnoses	Theory of Mind task. Judge changes in the character's affective state – better, worse, equal compared to preceding picture.	No differences found	↑ PCC**			Posterior ToM regions might be inefficiently hyperactivated. May represent a compensatory mechanism that maintains intact performance.
van Buuren, Vink, Rapcencu, & Kahn, 2011	24 (25) Siblings, no MINI or SCAN diagnoses	Emotional valence rating task. Conditions: negative, positive, neutral.	↑ vmPFC** ↑ dmPFC** ↑ right middle frontal	↑ PCC** ↑ ACC** (emotional relative to neutral)	↑ bilateral amygdala** ↑ hippocampus (emotional relative to	↑ middle temporal gyrus**	Hyperactivity supports the notion of abnormal social cognitive processing in FR subjects.

			gyrus (emotional relative to neutral stimuli)**		neutral)**		Abnormal social cognitive processing. Hyperactivity supports the notion of abnormal social cognitive processing in FR subjects. Abnormalities in the neural circuitry of emotion processing.
Pulkkinen, et al., 2015	51 (52) Siblings, no SCID/SIPS diagnoses	Visual presentation of dynamic happy or fearful faces.	↑ SFG**	↓ anterior paracingulate cortex (happy conditions)**			May not have the same vivid response to dynamic happy faces, which may be a risk factor for social withdrawal due to a lack of enjoyment of social interactions. Trait of increased effort for emotion recognition. Reduced functional connectivity may lead to functional compensations in other brain regions as they take a greater role in processing emotions.
Walter, et al., 2011	42 (18)	ToM task	↓ dmPFC**	↓ PCC**			Impaired neural ToM

	Risk allele carriers (rs1244706)		↓ left lateral PFC**				correlates in RA carriers. Reduced top down influence of the DLPFC on the posterior TOM system, possibly compensated by increased connectivity between the posterior parts of the TOM system and the inferior PFC as part of the mirror neuron system.
de Achával, et al., 2013	13 (13) Siblings, no SCID-I diagnoses	Modified moral dilemmas task. Subject had to judge the character's action based on a dilemma.	↑SFG** ↑IFG**				May represent a compensatory mechanism.
de Achával, et al., 2012	14 (14) Siblings, no SCID-I diagnoses	Basic emotion task, Faces Theory of Mind Task, Eyes Theory of Mind Task.	↓ right prefrontal structures during emotion processing*		↑ bilateral insula*		Failure to recruit right brain structures during emotion processing tasks. May be due to a failure to recruit right brain structures during emotion processing tasks.
Spilka, Arnold, & Goghari, 2015	27 (27) Siblings, no SCID-1	Passive viewing facial emotion	↑ left IFG (fearful vs neutral)**		↑ left insula (fearful vs neutral	↓ fusiform gyrus**	May reflect compensatory

	diagnoses	perception task. Emotions – happy, sad, neutral, fearful, angry).	↑ left OFC (fearful vs neutral)**		contrasts)**	↑ left temporal pole (fearful vs neutral contrast)**	mechanisms. Characterised by under-recruitment of regions involved in processing perceptual features of faces. Under-recruitment of regions involved in processing perceptual features of faces.
van der Meer, et al., 2014	20 (20) Siblings, no SCAN or Mini-Plus diagnoses	Emotion regulation Task. Conditions: attend neutral, attend negative, and reappraise, supress.	↓ left vmPFC*		↓ amygdala*	↓ STG*	Hypoactivation may be related to compromised cognitive control and emotion regulation.
Mohnke, et al., 2015	63 (297) Siblings, no SCID diagnoses	Theory of Mind task. Judge changes in the character's affective state – better, worse, equal compared to preceding picture.	↓ mPFC**			↑ right medial temporal gyrus**	May represent an intermediate phenotype for schizophrenia. Posterior ToM regions might be inefficiently hyperactivated.
Park, et al., 2016	20 (17) Two or more relatives with schizophrenia, SIPS, CAARMS	Implicit facial emotion recognition task (explicit – gender recognition). Emotions: fearful, happy, neutral.	↓ frontal cortex (during fearful conditions)** ↓ IFG and PFC (during neutral		↓ amygdala** (fearful conditions) ↓ amygdala complex (neutral conditions)**	↓ right middle temporal gyrus** ↓ right STG** ↓ fusiform gyrus	Neural correlate of inefficient executive control for decoding of rather ambiguous facial stimuli.

			conditions)**			(fearful conditions)** ↓ fusiform gyrus** ↓ middle temporal gyrus** ↓ hippocampal complex (neutral conditions)**	Aberrant emotional processing across brain regions including amygdala in response to ambiguous social stimuli may indicate a genetic liability for psychosis. Abnormal emotional processing may not be limited to amygdala, but include broad areas related to social brain circuitry.
Marjoram, et al., 2006	12 (13) Two or more relatives with schizophrenia, PSE	Visual Joke Theory of Mind Task (ToM condition requires the attribution of false belief, ignorance or deception).	↑ bilateral medial frontal gyrus				Compensatory overactivation from additional systems.
Li, et al., 2012	12 (12) Siblings, no SCID-NP diagnoses	Facial Emotional Valence Discrimination Task. Emotions: happy, fearful, neutral.	↑ right SFG*				Compensatory brain mechanisms activated.
Dodell-Feder, DeLisi, & Hooker, 2014	19 (19) Siblings, no SCID/SIPS diagnoses	Person Description ToM task. False-Belief ToM task.	↓ right vmPFC** ↓ OFC (emotion vs judgement contrasts)**			↓ TPJ (thoughts/emotions vs physical appearance)**	Genetic vulnerability manifests as disruption to brain regions recruited for ToM tasks.

Rasetti, et al., 2009	29 (20) Siblings, no SCID diagnoses	Face matching task. Emotions - angry, afraid.			No differences in amygdala responses between the groups.		
Barbour, et al., 2010	19 (25) Offspring, no SCID diagnoses	Continuous n-back affective task. Emotions: happy, angry, fearful, sad, neutral.			↓ left amygdala (positively valenced stimuli)*		The decreased amygdala response may be related to a decrease in the salience of positively valenced stimuli.

* significant at $p<0.005$ or $p<0.001$ uncorrected
** significant at $p < 0.05$ corrected

Table 3. Summary of included papers investigating CHR samples.
Blue shading – decreased activity. Grey shading – increased activity. Orange shading – mixed results.

Study (year)	**Sample size (healthy controls) Measure**	**Task**	**Frontal cortex** (Risk group vs controls)	**Cingulate cortex** (Risk group vs controls)	**Limbic regions** (Risk group vs controls)	**Lateral temporal cortex** (Risk group vs controls)	**Conclusions**
Balevich, 2017	28 (32) SPD (SCID-I)	Affective picture processing task. Stimuli – unpleasant, pleasant and neutral pictures, social in nature (social interactions or faces). Response – categorise stimuli.		↑ ACC (novel unpleasant stimuli)**			Increased ACC activation could either contribute to this heightened arousal or reflect an effort to regulate it.
Gee, 2015	200 (129) SIPS	Emotional faces task. Emotional expressions – fear, anger happy, surprised. Affect labelling and matching; gender labelling and matching; shape matching.	↓ vlPFC during affect conditions**	↑ ACC**	↓ amygdala**		Increased ACC activity (or less of a deactivation) may relate to the process of matching affective stimuli. May relate more to the cognitive processes involved in processing complex emotions. Decreased amygdala activation may be specific to deficits in processing emotional stimuli when attention is directed

							toward the affective features.
Brüne, et al., 2011	10 (26) SOPS, BLIPS	ToM task		↑ PCC*		↑ TPJ* ↑ STG* ↑ middle temporal gyrus	The greater activation may represent compensatory overactive brain regions.
Stanfield, et al., 2017	20 (32) SPD (SCID-II)	Social Judgement Approachability Task. Social cognition – face stimuli presented during approachability judgements or gender judgements.	↑ right inferior frontal gyrus when making social decisions		↑ amygdala (social decision conditions)		May represent a compensatory mechanism. Hyperactivation in the amygdala may represent an exaggeration of the threat response.
Takano, et al., 2017	17 (20) SIPS	Theory of Mind Task – control, first order false belief, second order false belief (i.e. social emotion inference).	↓ IFG (social emotion inference conditions)*			↑ left STG (during social emotion inference conditions)*	Deficits in inferring others' social emotions.

Mirzakhanian, 2010	10 (12) SIPS	Emotion-Face matching Task. Emotions: angry, fearful, happy.	↑ right middle frontal gyrus (angry conditions)*		No significant differences were found between prodromal populations and controls in amygdala activation	↑ left fusiform gyrus (angry conditions)*	Abnormalities in frontal brain regions might be trait-like changes. Abnormalities in temporal brain regions might be trait-like changes.
Pelletier-Baldelli, Orr, Bernard, & Mittal, 2018	19 (20) SIPS	Social Rewards Task – passive viewing task. Face stimuli: either people who gave them positive social feedback or ambiguous social feedback.	**Positive correlation** between vmPFC activity and greater reporting of social anhedonia**				Individuals who experience positive feedback as unpleasant report a greater level of social anhedonia. An increased exchange of information between the ventral stiatum and vmPFC in clinical high risk implies down-regulation of reward response behaviour.

Seiferth, et al., 2008	12 (12) BLIPS, PAANS, SCID	Facial Emotions for Brain Activation Task. Emotions: happy, sad, angry, fearful, neutral.	↑ IFG** ↑ SFG (neutral relative to emotional stimuli)**		↑ thalamus (neutral vs emotional stimuli)**	↑ right fusiform gyrus** ↑ hippocampus (neutral vs emotional stimuli)**	Hypersensitivity to affectively irrelevant stimuli in brain areas relevant for affective salience/significance of stimuli. Alternatively, hyperactivation to neutral stimuli may point to neural changes before illness onset. Stronger reactivity in regions associated with visual stimuli and face processing is consistent with the notion of altered brain function already present in perceptual pathways.

Wolf, et al., 2015	260 (220) PS-R, KSADS-PL	Emotion identification Task. Conditions: threatening (anger and fear), nonthreatening (happy and sad).	↑ right middle frontal gyrus (threatening stimuli)** ↓ deactivation in bilateral SFG**		↑ amygdala (threatening stimuli)** ↓ left insula**	↑ left fusiform gyrus**	Abnormal activity in circuitry underlying emotional processing. Amygdala hyperactivity may increase the likelihood of paranoid feelings or ideas. Subclinical illness phenotype rather than a marker of trait vulnerability.
Modinos, et al., 2015	18 (22) BLIPS, CAARMS	Emotional processing task. Categories: negative high arousal, negative low arousal, positive high arousal, positive low arousal, neutral matched for social content.	↑ left IFG (neutral stimuli)** **Positive correlation** between dmPFC activity and CAARMS positive symptoms**		↓ right amygdala** **Positive correlation** between left amygdala activation and arousal ratings to neutral pictures** ↑ left anterior insula (neutral stimuli)**		Abnormal emotional salience engaged areas involved in more cognitive, evaluative and regulatory aspects of emotion. The neural correlates of abnormal salience may involve different cortico-limbic areas depending on illness stage.

3.2. Summary of key findings by brain region across groups.

Altogether, 32 studies reported altered activity in the frontal cortex. Of these, 18 studies reported increased activity; whereas 11 studies reported decreased activity (3 studies had mixed results). Out of the 15 studies reporting altered cingulate cortex activity, 9 studies reported increased activity. Reduced activity was found in 5 studies and 1 study reported mixed results.

Findings regarding limbic regions were particularly inconclusive with 8 studies reporting increased activity, 7 studies reporting decreased activity and 6 studies having mixed results. Findings regarding the lateral temporal cortex were similarly mixed with 8 studies reporting increased activity and 6 studies reporting decreased temporal cortex activity (2 studies had mixed results).

It is of note that out of the 39 included studies in this review, only 2 reported differences in behavioural performance between at-risk populations and healthy controls. Chan et al. (2016) reported that high schizotypy participants rated positive and neutral stimuli as less pleasant compared to controls. Similarly, CHR individuals rated neutral scenes and negative high arousal scenes as more emotionally arousing compared to controls (Modinos, et al., 2015). Thus, 37 out of the 39 studies summarised here discuss differences in neural profiles in the context of similar behavioural performance.

3.3 Key findings in relation to SR

In relation to activity in the frontal cortex, six studies reported overall increased frontal cortex activity, three studies reported decreased activity and two studies had mixed findings. A number of studies consistently report increased activity in the dmPFC in SR samples during emotion processing (Modinos , Renken, Shamay-Tsoory, Ormel, & Aleman, 2010), during self-reflection tasks (self vs semantic judgements contrasts, Modinos, Renken, Ormel, &

Aleman, 2011) and during a second-order ToM task (Modinos, et al., 2010, same sample as Modinos et al., 2011). Hyperactivation of the mPFC was also observed during emotional processing (Modinos, Renken, Shamay-Tsoory, Ormel, & Aleman, 2010) and ToM (Modinos, Ormel, & Aleman, 2010), and a positive correlation has been reported between mPFC activity and scores on anhedonia measures during the processing of social rewards (Healey, et al., 2014). An investigation utilising an emotional Stroop Task found increased right middle frontal gyrus and IFG activity during negative stimuli processing (Mohanty, et al., 2005). Wang et al. (2018) also reported increased middle frontal gyrus activity during a facial emotional processing task that was positively correlated with negative schizotypy scores (Wang, et al., 2015). However, the same group also reported a negative correlation between activity in the middle frontal gyrus (MFG) and positive symptoms (marginally significant, Wang, et al., 2015). Reduced middle frontal gyrus activation was also reported by Premkumar during the processing of positive vs neutral emotional stimuli (2013).

Findings relating to cingulate cortex activity in SR were also inconclusive, with three studies reporting increased activity in the ACC (Wang, et al., 2018; Modinos, et al., 2017; Modinos , Renken, Shamay-Tsoory, Ormel, & Aleman, 2010), two studies reporting decreased activity in the PCC and ACC (Huang, et al., 2013; Premkumar, et al., 2012) and one study reporting mixed results (Modinos, Renken, Ormel, & Aleman, 2011).

Studies that assessed activity in limbic regions reported mixed results. Inconclusively, one study reported increased insula activity (Modinos, et al., 2011) and two studies reported mixed results within the amygdala, insula and the nucleus accumbens (Mohanty, et al., 2005; Wang, et al., 2018). The two studies that consistently reported decreased limbic regions activity in, in the insula and thalamus, reported contrasts for positive vs neutral stimuli (Premkumar, et al., 2013; Chan, et al., 2016).

In relation to temporal cortex activity in SR samples, two studies reported increased activity in the bilateral medial temporal gyrus (MTG; Wang, et al., 2015) and the right TPJ (Modinos, et al., 2017). The only consistent finding was decreased activity in the STG during studies using emotional processing tasks (Germine, 2012; Huang, et al., 2013; Premkumar, et al., 2013).

3.4 Key findings in relation to FR

Studies in FR samples report mixed findings in relation to frontal cortex activity during social cognition, with 7 studies reporting increased activity, six studies reporting decreased activity and one study reporting no differences between FR and healthy control groups (Spilka & Goghari, 2017). Increased mPFC activity has been reported during an emotional valence rating task (van Buuren, Vink, Rapcencu, & Kahn, 2011) and during a ToM task (Marjoram, et al., 2006). Increased IFG and SFG activity has been reported by two studies (de Achával, et al., 2013; Spilka, Arnold, & Goghari, 2015; Li, et al., 2012; Pulkkinen, et al., 2015). Furthermore, positive correlations between dorsolateral PFC (dlPFC) and IFG activation and scores on the Social Skills Performance questionnaire have been reported during basic emotion processing and between SFG and medial frontal gyrus (MFG) and scores on the same questionnaire during ToM processing (Villarreal, et al., 2014).

Reduced frontal cortex activity in FR samples has been reported predominantly for emotional processing tasks, with hypoactivations in the mPFC (de Achával, et al., 2012; van der Meer, et al., 2014; Park, et al., 2016) and in the IFG and PFC during the processing of neutral stimuli in particular (Park, et al., 2016). During ToM tasks, reduced activation has been reported in lateral PFC and dmPFC (Walter, et al., 2011) and in the ventromedial PFC and OFC (Dodell-Feder, DeLisi, & Hooker, 2014).

Results investigating cingulate cortex activity were inconclusive with three studies reporting increased activity in ACC and PCC (Villarreal, et al., 2014; Spilka & Goghari, 2017; van Buuren, et al., 2011) and two studies reporting decreased activity (Pulkkinen, et al., 2015; Walter, et al., 2011).

Studies reporting altered limbic region functioning in FR samples again report inconclusive results. Four studies reported increased limbic activity, whereas three studies reported decreased activity and one study reported no significant differences during an emotion face matching task (Rasetti, et al., 2009). Increased insula activity has been reported during emotion processing (de Achával, et al., 2012; for fearful vs. neutral contrasts, Spilka, et al., 2015), and one study found a positive correlation between insula activity and Social Skills Performance ratings during a basic emotion processing task (Villarreal, et al., 2014). All three studies reporting hypoactivity in limbic regions identified this pattern in the amygdala, with reduced activity found during emotion processing specifically (van der Meer, et al., 2014; Park, et al., 2016; Barbour, et al., 2010).

Two studies report increased temporal cortex activity, three studies reported decreased activity and one study had mixed results (Spilka, Arnold, & Goghari, 2015). Increased temporal cortex activity has been reported during an emotional processing task (van Buuren, et al., 2011) and during a ToM task (Mohnke, et al., 2015). Decreased STG activity has been reported for emotion processing (Park, et al., 2016; van der Meer, et al., 2014). Further, deactivations were observed in the TPJ for the thoughts/emotions vs physical appearance contrasts on a person-description ToM task (Dodell-Feder, DeLisi, & Hooker, 2014), and in the MTG for the neutral conditions of an emotional task (Park, et al., 2016).

3.5 Key findings in relation to CHR

Six studies reported increased activity in the frontal cortex and three reported decreased activity. One of the first studies investigating social cognition in CHR samples using a facial emotional task reported increased activity in the IFG and the SFG for neutral relative to emotional stimuli (emotional stimuli included happy, sad, angry and fearful; Seiferth, et al., 2008). Similarly, Modinos et al. (2015) reported increased left IFG activity for neutral stimuli during an emotional processing task. Increased right MFG activity has been reported during angry (Mirzakhanian, 2010) and threatening stimuli (Wolf, et al., 2015). Stanfield et al. (2017) similarly reported a trend level increase in activation in the right IFG during social decision making in a social judgement task. Furthermore, positive correlations have been reported between increased vmPFC activity and greater scores on social anhedonia symptomatology (Pelletier-Baldelli, Orr, Bernard, & Mittal, 2018) and between dmPFC activity and positive symptoms on a CHR diagnostic interview (i.e. Comprehensive Assessment of At-Risk Mental States; Modinos, et al., 2015). In contrast, Gee (2015) reported reduced vmPFC activity during emotional conditions and Takano et al. (2017) reported decreased IFG activity during the social emotion inference conditions on a ToM task. Decreased activity in the bilateral SFG has also been reported during emotion identification tasks (Wolf, et al., 2015).

The three studies that reported altered activity in the cingulate cortex all reported increased activity relative to healthy controls (for novel unpleasant stimuli; Balevich, 2017; Gee, 2015) and the PCC (Brüne, et al., 2011). The first two used an emotional processing task, whereas the last study utilised a ToM task.

In relation to activity in limbic regions, two studies reported increased activity (Seiferth, et al., 2008; Stanfield, et al., 2017), and one study reported decreased activity in the amygdala during emotion processing (Gee, 2015). Two studies reported mixed limbic

activity during emotional processing tasks (Wolf, et al., 2015; Modinos, et al., 2015). Yet, abnormal activity was observed in relation to neutral stimuli with positive correlations between amygdala activity and arousal ratings to neutral stimuli and increased insula activity to neutral stimuli (Modinos, et al., 2015).

All five studies reporting results for the lateral temporal cortex in the CHR group reported increased activity. During a ToM task Brüne et al. (2011) reported increased activity in the TPJ, the STG and the MTG. Similarly, increased activity in the left STG has been reported during social emotion inference conditions on a ToM task (Takano, et al., 2017) and during an emotional processing task (Wolf, et al., 2015). Increased left fusiform gyrus activity for angry stimuli during an emotional processing task were also reported by Mirzakhanian et al. (2010). Increased right fusiform gyrus (for neutral vs emotional stimuli conditions) during an emotion processing task were reported by Seiferth et al. (2008).

4. Discussion

This systematic review aimed to provide a greater understanding of the neurofunctional correlates of social cognition deficits in different psychosis risk populations.

The at-risk populations included in the review were individuals with schizotypal personality traits, assessed psychometrically (SR), individuals at familial/genetic risk of psychosis (FR) and individuals at clinical high risk for psychosis (CHR). Overall, the results of this systematic review are consistent with findings in schizophrenia populations (Green, Horan, & Lee, 2015; Kring & Elis, 2013), reporting altered, both increased and decreased, functional activation in a range of cortical and subcortical regions during social cognition tasks. However, within this broader picture, there are some consistent findings. Most studies in at-risk populations report increased activations in the frontal cortex and, all studies report

that CHR populations are characterised by increased activity in the lateral and medial temporal cortex during social cognition task. This is consistent with studies indicating that psychosis may emerges from dysfunction in medial temporal and frontotemporal regions due to increased excitatory neurotransmission (Allen, et al., 2019). However, for cingulate and limbic regions activation patterns are more difficult to interpret across at-risk populations, with both increased and decreased functional activation seen during a range of social cognition tasks. Below we discuss our findings according to brain regions.

4.1 Frontal and cingulate cortices

Various prefrontal regions reliably showed differential activations in at-risk groups during social cognition tasks. The mPFC, vl/vmPFC, MFG, IFG and SFG show both increased and decreased patterns of activation in both SR populations (Healey, et al., 2014; Mohanty, et al., 2005; Wang, et al., 2018; Wang, et al., 2015; Modinos, Ormel, & Aleman, 2010; Modinos, Renken, Shamay-Tsoory, Ormel, & Aleman, 2010; Modinos, Renken, Ormel, & Aleman, 2011) and in CHR populations (Seiferth, et al., 2008; Modinos, et al., 2015; Mirzakhian 2010; Wolf, et al., 2015; Stanfield, et al., 2017; Pelletier-Baldelli, et al., 2018).

Neuroimaging studies have implicated the mPFC in inferring the internal states and intentions of others, in regulating emotion, in processing reward and punishment and in the contextual interpretation of complex social information (Phan, Wager, Taylor, & Liberzon, 2002). The consistent patterns of increased activity in the mPFC in at-risk populations during social cognition tasks might represent abnormal processing of socially salient cues leading to abberant beliefs about others and thus contributing to the formation of delusions (Morrison, et al., 2004).

Yet, several studies in at-risk populations (Gee, 2015; Takano, et al., 2017; Dodell-Feder, DeLisi, & Hooker, 2014; de Achával, et al., 2012) and patients with schizophrenia

(Russell et al., 2000; Eack, Wojtalik, Newhill, Keshavan, & Phillips, 2013; Lee, Quintana, Nori, & Green, 2011; Dodell-Feder, et al., 2014) also report findings of decreased frontal cortex activity that may be specifically related to mentalising deficits (Savla et al 2007). Furthermore, based on the finding reported here, no definite conclusions can be drawn regarding activity in the cingulate cortex in SR and FR groups, regardless of the type of social cognition task. However, CHR groups do demonstrate a consistent pattern of increased activity in the ACC and the PCC during both emotional processing and ToM, respectively (Balevich, 2017; Gee, 2015; Brüne, et al., 2011). The ACC is involved in a variety of both affective and cognitive functions, such as conditioned emotional learning, assessment of motivational context and integrating emotional information to motivate behaviour (Devinsky, Morrell, & Vogt, 1995; Fig 1). Consequently, increased ACC activity in CHR groups may be related to abnormal salience processing such that increased activity is either contributing to a general heightened state of arousal or is part of an effort to regulate it (Gee, 2015; Balevich, 2017). Functional disruptions in the ACC have been widely implicated in the illness progress of schizophrenia with gradual changes in grey matter volume in the ACC region of the salience network predictive of conversion to psychosis (Palaniyappan & Liddle, 2012).

Overall, the results in at-risk groups suggest that there is a subnetwork of areas in frontal and ACC regions that are differentially activated in at-risk populations. This pattern of abnormal neural activity supports the notion that the processing of social cues is dysfunctional at the earliest stages of the schizophrenia continuum, and that both the recognition/response to social-affective stimuli and the ability for higher order inferences about social information are impaired.

4.2. Lateral temporal and limbic regions

Lateral regions of the temporal cortex also showed increased activation patterns during social cognition tasks in at-risk populations. Increased activity in the TPJ and the STG are reported in CHR populations during ToM tasks and during emotional processing (Brüne, et al., 2011; Takano, et al.; 2017; Wolf, et al., 2015; Mirzakhanian, 2010; Seiferth, et al., 2008). These regions of the temporal cortex are important for inferring the intentions of others, for recognising nonverbal social cues and for representing non-verbal social cues with emotional content (Ochsner, 2008). Collectively, these results support the notion that increased neural activity in the lateral temporal cortex is associated with abnormal processing of emotional and social information in CHR samples (Seiferth, et al., 2008) as well as emotion processing and mentalising (i.e. TPJ, STG; Shamay-Tsoory, et al., 2007; Pinkham, Gur, & Gur, 2007).

The medial temporal network (including areas in amygdala, hippocampus) along with the ventral striatum has been heavily implicated in the progression of psychosis (Modinos et al. 2015; Allen, et al., 2019). However, results in relation to these regions were inconclusive in all three at-risk groups (see Results section). Interestingly, some single studies utilising emotional processing tasks in CHR participants have reported increased activity in response to neutral stimuli in the insula (Modinos, et al., 2015) and the thalamus (Seiferth, et al., 2008). The insula, particularly the anterior part, has been implicated in the evaluative, experiential or expressive processing of internally generated emotions (Reiman, et al., 1997; Craig & Craig, 2009). The thalamus (particularly the pulvinar thalamus and the superior colliculus) has also been identified as a key region for emotion processing due to its role as a robust excitatory pathway controlling emotional attention through a projection from the amygdala (Pessoa & Adolphs, 2010; Phillips, Drevets, Rauch, & Lane, 2003; Adolphs, 2002). This pattern of increased activity to neutral stimuli in regions involved in affective salience and attention processing suggests a neural hypersensitivity to affectively irrelevant stimuli and may be related to aberrant salience processing. This pattern of activation in psychosis risk groups is

broadly consistent with hyperactivation in limbic regions in response to neutral stimuli that has been reported in patients with chronic schizophrenia (Holt, et al., 2006; Surguladze, et al., 2006; Hall, et al., 2008).

Furthermore, studies have reported abnormal activity in other temporal lobe regions such as the MTG, the fusiform gyrus and the hippocampus in CHR groups during ToM and emotional processing task (Brüne, et al., 2011; Takano, et al.; 2017; Wolf, et al., 2015; Mirzakhanian, 2010; Seiferth, et al., 2008). Collectively, these results support the notion of abnormal processing of emotional and social information in CHR samples. These results appear to be in line with evidence of hippocampal and medial temporal cortex dysfunction during the emergence of psychosis (Allen, et al., 2018; Allen, et al., 2016; Lodge & Grace, 2011; Modinos, et al., 2018). Recent evidence suggests that this pattern of hippocampal hyperactivity in psychosis and psychosis risk groups is associated with the dysregulation of striatal dopamine (Lodge & Grace, 2011; Modinos, Allen, Grace, McGuire 2015) which may also affect salience processing (Winton-Brown et al. 2014). Moreover, another major implication of phasic dopamine dysfunction is its effect on synaptic plasticity. Patients with schizophrenia present with reduced connectivity across neural regions and networks (i.e. reduced interaction between neural regions) and this has been proposed to result from a disturbance in NMDAR-dependent synaptic plasticity (Stephan, Diaconescu, & Iglesias, 2016; for a review see Stephan, Friston, & Frith, 2009). Neuromodulatory transmitters, such as dopamine, exert a regulatory effect on NMDAR-dependent synaptic plasticity, thus the aberrant regulation of dopamine could lead to abnormal functional integration across brain regions in patients with, and at-risk of psychosis (Diaconescu, Hauke, & Borgwardt, 2019) including in regions important for processing of social information..

In particular, dopamine dysregulation in the ventral striatum may leads to reduced gating of information flow from prefrontal areas and a failure to fully engage optimal

cognitive regulation (Grace, 2000). Impairment of this mechanism could lead to abnormal processing of social and emotional information and to the formation of delusions (Mohanty, et al., 2005; Liddle, Lane, & Ngan, 2000). This idea is consistent with the neuroimaging findings from the current systematic review indicating increased activity in prefrontal regions for the processing of neutral relative to valenced stimuli. In CHR population, Modinos et al. (2015) reported increased activity in the IFG in response to neutral stimuli during an emotional processing task. Similarly, Seiferth (2008) reported increased activity in the IFG and the SFG for neutral relative to emotional stimuli in a facial emotional processing task. All CHR studies included in the current review reported neural hypersensitivity to neutrally valenced stimuli in both temporal and frontal lobe regions. Taken together, the results support models that posit widespread over activity to neutral stimuli possibly due to hyperactivity of the striatal dopamine system (Lodge & Grace, 2011; Grace, Floresco, Goto, & Lodge, 2007).

4.3 Conclusions and future directions

Overall, the studies reviewed here consistently show neural activity differences between specific at-risk groups and healthy controls during social cognition tasks. The most predominant findings are observed in frontal cortex where neural hyperactivity in SR and CHR groups is widely reported, indicating impairments in circuits involved in the processing of emotional stimuli. Furthermore, CHR samples were characterised by abnormal responses to neutral stimuli (across all tasks) and hyperactivity in the ACC and temporal lobe regions. These results suggest that CHR samples might present with emerging dysfunction across frontal and temporal regions that may impair salience processing. These findings are in line with recent conceptualizations in schizophrenia, indicating that hyperactivity and dysfunction, particularly in medial temporal regions, lead to dopamine dysregulation, aberrant salience and

delusional ideation. It is known that regions implicated in the neuropathology of schizophrenia (i.e. fronto-striatal circuits, limbic areas, ACC, medial and lateral temporal regions) receive innervation from the limbic hippocampus (Grace & Gomes, 2018; Heinz, et al., 2018). Thus, the abnormal medial temporal cortex functioning observed across many studies may have far-reaching consequences for information processing by disrupting related circuits and influencing higher level (social) cognition (Calcia, et al., 2016; Powers, Mathys, & Corlett, 2017). However, no consistent activity patterns were seen for limbic and cingulate regions across at-risk groups, furthermore the results in FR samples were highly inconsistent.

It should be noted that, alternatively, increased frontal cortex activity could represent compensatory mechanisms during the processing of social information to allow for the same level of behavioural performance. Indeed, the studies in at-risk groups reviewed here showed that SR, FR, CHR participants did not significantly differ from the healthy controls on behavioural measures of social cognition, although widespread differences in neural activity were observed. Higher activity in prefrontal regions during ToM could mean that at-risk groups require greater effort to utilse cognitive operations during mentalization to attain a behavioural performance similar to controls (Modinos, Renken, Shamay-Tsoory, Ormel, & Aleman, 2010). Similarly, greater activation in prefrontal regions might represent a compensatory mechanism such that higher cognitive control is required to down-regulate the experience of negative emotions (Modinos, Ormel, & Aleman, 2010; Wang, et al., 2018). In contrast, a general pattern of decreased frontal activity (which is associated with impaired behavioural performance, Green, et al., 2015) might be indicative of a generalized cognitive impairment. Indeed, some of the networks identified by the studies included in this review are also heavily implicated in general cognition and are responsible for cognitive processes in the broader sense. Medial frontal regions are implicated in wide range of cognitive operations, such as conflict monitoring, error detection, executive control, reward-guided learning and

decision-making (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Euston, Gruber, & McNaughton, 2012; Bechara & Damasio, 2005). Lateral (Buchsbaum, Olsen, Koch, & Berman, 2005; Rauschecker & Scott, 2009) and medial temporal regions (Squire & Zola-Morgan, 1991; Alvarez & Squire, 1994) have been associated with auditory and memory functions, respectively. Discussing impairments in general cognition is beyond the scope of the current review, but future studies should attempt to utilise task paradigms that allow the disassociation of neural patterns associated with social cognition and general cognitive control and/or mnemonic processes.

A caveat of the review is that even though the majority of the discussion relates to the direction of neural activity observed during social cognition tasks, this might simply be a reflection of basal state activation in these at-risk populations. A few studies suggest that SR and CHR populations present with increased resting perfusion, particularly in the hippocampus, midbrain and basal ganglia (Allen, et al., 2018; Allen, et al., 2016; Modinos, et al., 2018). Medication might also affect the fMRI findings reported here, but this was relevant only to a very small subset of the CHR studies and thus not likely to make a difference in the overall interpretation of the neural patterns observed (see supplementary table 1). Finally, there appears to be no associations between level of risk for psychosis and altered activity during a particular social cognition heuristic (i.e. ToM tasks, emotional processing tasks), However, this might be because the majority of studies utilised lower level social cognition tasks (i.e. emotion recognition, emotional valence discrimination). One pattern that does emerge however, is that at-risk populations show aberrant processing of salience in relation to emotional stimuli, in frontal (SR and CHR), and cingulate cortices (CHR), and an abnormal responses to neutral stimuli in both temporal and frontal lobe regions (CHR).

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Conflicts of interest

None

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