

Social functioning and brain imaging in individuals at clinical high-risk for psychosis: A systematic review

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ABSTRACT

Impairments in social functioning are a core impairment in psychosis and are associated with poor outcomes. These deficits are found in those at clinical high-risk (CHR) for psychosis, and can persist even in the absence of transition. However, the neurobiological underpinnings of social functioning remain unclear, therefore we conducted a systematic review of brain metrics that have been associated with social functioning in youth at CHR for psychosis.

Five databases (MEDLINE, CINAHL, EBM reviews, Embase, and PsycINFO) were searched from inception to May 5, 2020. Studies were selected if they examined brain imaging, and social functioning in youth at CHR for psychosis. Of the 9629 citations found through online database searching, 12 studies with 696 CHR participants met inclusion criteria. Too few studies were focused on the same brain region using the same methodology to perform a meta-analysis, however, loci within the prefrontal cortex were most often associated with social functioning. Few studies have linked social functioning to brain imaging metrics, suggesting that future work should focus on this relationship.

1. Introduction

Social functioning involves the ability to fulfill social roles and achieve social milestones, such as establishing social networks, including friendships and family relationships, as well as more subjective measures of satisfaction with those social roles/networks (Burns and Patrick, 2007). Impairments in social functioning are a core feature of schizophrenia and other psychotic disorders (Couture et al., 2006; Velthorst et al., 2017). Social functioning has been associated with both negative symptoms (Robertson et al., 2014) and social cognition (Mike et al., 2019); good social functioning has been recognized as an important index of treatment success (Fowler et al., 2019). However, only a small percentage (~14%) of diagnosed schizophrenia patients achieve and maintain clinical and socio-functional recovery (Jääskeläinen et al., 2013).

The brain changes that potentially underlie these social functioning deficits in schizophrenia patients have been explored in many studies,

and many different regions and types of changes have been implicated. For example, poorer social functioning has been found to be associated with bilateral shape deflation in the hippocampus (Brambilla et al., 2013), lower levels of thalamic glutamate and glutamine levels (Aoyama et al., 2011), as well as lower activity in the supplementary motor area during a cognitive empathy task (Smith et al., 2015), and in the left medial prefrontal cortex during a social cognition task (Lee et al., 2006). The variability in the imaging findings suggest that the neural indices of social functioning may be widespread, dependent on imaging modality and experimental type, and difficult to disentangle from those of correlated symptoms (e.g. negative symptoms and social cognition).

Furthermore, decreased social functioning has been found in first degree relatives of those with schizophrenia (Glatt et al., 2006), as well as youth that are at clinical high-risk (CHR) for psychosis (Addington et al., 2017; Carrión et al., 2011). These deficits in social functioning persist in individuals at CHR even in the absence of transition to a diagnosable psychotic disorder (Addington et al., 2019; Carrión et al.,

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2013).

The majority of those at CHR will not go on to develop a psychotic disorder, however, poor social functioning, as well as decline in social functioning over time in individuals at CHR is a predictor of transition to psychosis (Addington et al., 2017; Carrión et al., 2011, 2013). Therefore, the brain changes that accompany this loss of function may be important in characterizing the progression of psychosis. Furthermore, as most schizophrenia patients take anti-psychotics, medication represents a significant confounding factor when examining brain imaging and social functioning. As some individuals at CHR are medication-naïve, this group may provide clarity on the relationships between social functioning and changes in brain structure and function in unmedicated individuals.

The aim of this review was to identify the literature linking brain imaging measures with social functioning in those at CHR for developing schizophrenia. Our specific objective was to understand the relationship between social functioning and structural and functional brain imaging in individuals at CHR for psychosis, in order to identify which brain metrics may be affected. We hypothesized that many of changes in structure and function observed in individuals at CHR would be localized to the prefrontal cortex or its connections.

2. Methods

2.1. Protocol

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). This review was registered a priori through PROSPERO (CRD 42020187342).

2.2. Search strategy

Altogether, five databases were systematically searched including: MEDLINE, CINAHL, EBM reviews, Embase, and PsycINFO. The following search strategy containing medical subject heading (MeSH) terms and keywords were used: ((“ultra high risk” OR “uhr” OR “clinical at risk” OR “clinically at risk” OR “clinical high risk” OR “clinically high risk” OR “clinically high-risk” OR “clinical high-risk” OR “psychosis risk syndrome” OR “blips”) AND (“imaging” OR “brain imaging” OR “neuroimaging” OR “magnetic resonance imaging” OR “MRI” OR “functional magnetic resonance imaging” OR “fMRI” OR “structural magnetic resonance imaging” OR “sMRI” OR “diffusion tensor imaging” OR “diffusion weighted imaging” OR “DTI” OR “DWI” OR “voxel based morphometry” OR “VBM” OR “graph theory” OR “fractional anisotropy” OR “FA” OR “electroencephalography” OR “EEG” OR “event related potentials” OR “ERP” OR “magnetoencephalography” OR “MEG” OR “beamforming” OR “positron emission tomography” OR “PET”) AND ((social*) AND (function* OR scale* OR assess* OR outcome*)) OR (sofas OR “Social and Occupational Functioning Assessment Scale” OR sfs OR “Social Functioning Scale” OR ssis OR “Social Skills Improvement Scale”)).

A grey literature search in Google scholar was also conducted using the same key search terms listed above. All searches were executed on May 5, 2020 where only records published in English were included, and no other date or geographic restrictions applied.

2.3. Screening and selection criteria

Screening records were conducted in two phases. First, by titles and abstracts, and second, full-text articles were screened. All citations were reviewed in duplicate (T.P., A.B., D.B., K.B., & M.C.) for inclusion and a third reviewer (P.M.) resolved any conflicts.

The inclusion criteria for this review were as follows: (1) individuals who are at risk for psychosis via meeting established CHR or ultra high risk (UHR) criteria for psychosis; (2) measures of social functioning

including but not limited to the following scales: Global functioning: social (GF:S) (Cornblatt et al., 2007), the Social Adjustment Scale (SAS) (Weissman and Bothwell, 1976), the Social and Occupational Functioning Assessment Scale (SOFAS) (Rybarczyk, 2011), the Social Functioning Scale (SFS) (Birchwood et al., 1990), plus any functioning scale with a social functioning component; (3) imaging measures examining brain structure or function (e.g. voxel/region activity, functional connectivity, fractional anisotropy (FA), surface area, grey matter volume (GMV), cortical thickness, event related potentials (ERPs), spectral power, graph theoretic properties); (4) observational studies (retrospective cohort, prospective cohort, case-control, cross-sectional) or intervention studies (randomized controlled trial, single arm intervention trial).

Studies that only examined individuals diagnosed with a DSM-IV disorder, schizotypy, first-episode psychosis, nonhumans, or healthy controls were excluded. In addition, general functioning measures such as the Global Assessment of Functioning scale, which includes questions about both social and role functioning and is influenced by clinical status, were excluded. Case studies, reviews, protocols, and conference proceedings (non peer reviewed) were also excluded.

2.4. Data extraction

All data was extracted in duplicate including: study characteristics (country, year, study design, sample size, and duration of study), individual participant characteristics (age, sex), specific features of social functioning and features of the individual imaging techniques (magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), structural magnetic resonance imaging (sMRI), diffusion tensor imaging (DTI), diffusion weighted imaging (DWI), voxel based morphometry (VBM), electroencephalography (EEG), magnetoencephalography (MEG), or positron emission tomography (PET)).

2.5. Quality assessment

Quality of the included studies was assessed using a 13 item checklist similar to previously published quality assessments for imaging review studies (Fusar-Poli et al., 2013; Walter et al., 2016). The categories scored in the quality assessment checklist were: (1) role of the funding source in data interpretation and analysis; (2) sample size; (3) clearly reported inclusion criteria; (4) exclusion criteria and substance abuse information; (5) sex distribution; (6) race distribution; (7) IQ, educational level; (8) previous antipsychotic medication; (9) drop out rate; (10) psychopathological ratings and in the case of manual tracing; (11) inter-rater reliability; (12) intra-rater reliability; and (13) blindness of rater. As per Walter et al. (2016), each item in the checklist was assigned a score of 0–2, with 0 being the lowest quality and 2 being the highest quality. In cases where the information was partially reported, a score of 1 was assigned.

2.6. Data synthesis

Characteristics and results of the included studies were synthesized descriptively. Due to the heterogeneity in the social functioning tools and the brain imaging outcomes, the included studies were summarized qualitatively, and a meta-analysis was deemed inappropriate to conduct.

3. Results

3.1. Search yield

There were 9629 citations found through the online database searches. After duplicates were removed, 8098 citations were screened at the title and abstract screening phase. The title and abstract screening phase involved rejecting all manuscripts that: 1) were not focused on humans, 2) did not include the population of interest (i.e., individuals at

CHR), or 3) were of an unacceptable type (i.e., conference proceeding, case report, protocol, or review). Then, the remaining 191 full-text articles were screened for inclusion. Overall, 12 studies met our inclusion criteria, of which seven were structural studies and five were functional studies. See Fig. 1 for details.

3.2. Participant characteristics

Table 1 outlines the demographics and participant characteristics of the included studies. Of the 12 studies included in this review, there were 1231 study participants and of those, 696 were individuals at CHR for psychosis. Ten of the 12 studies included a comparison group of healthy controls, one study did not have a comparison group (Lepock et al., 2019), and one study included both healthy controls and individuals with schizophrenia, comparing individuals at CHR to each of the two groups independently (Takahashi et al., 2018). The mean age of the CHR participants ranged from 16.8–27.1 years, the healthy controls ranged from 17.7–27.6 years and the patients with schizophrenia had a mean age of 28.0 years. The percentage of males in the CHR samples, healthy controls, and schizophrenia patients ranged from 43.33–86.67%, 48.00–63.79%, and 46.03%.

CHR status was determined using the Structured Interview for Prodromal Syndromes (McGlashan et al., 2010) in seven of the included studies, and in the remaining five studies, the Comprehensive

Assessment of At-Risk Mental States was used (Yung et al., 2005), although Reniers et al., (2017) used the Brief Psychiatric Rating Scale (Faustman and Overall, 1999) to establish CHR status for participants that were recruited prior to 1999.

3.3. Study characteristics

Table 2 describes the brain imaging characteristics of the included studies, as well as describing their relationships to social functioning measures, and Fig. 2 depicts the quality assessment results for the included studies.

The included studies utilized many different brain imaging metrics, many of which are incommensurable with one another. The two types of functional imaging that were included in this review are fMRI and EEG studies. EEG provides a direct measure of the changes in electrical activity in the brain resulting primarily from changes in local field potentials whereas fMRI, (specifically fMRI using blood oxygenation level dependent (BOLD) signal), measures the metabolic aftereffects of local brain activity via the differences in the magnetic field properties of oxygenated versus deoxygenated hemoglobin. For the fMRI studies, the two metrics that are reported herein are BOLD activity, which is a within region measurement as it assesses activity changes within voxels (volumetric pixels in the brain), and BOLD connectivity, which is a between region measurement indexing the correlation between BOLD

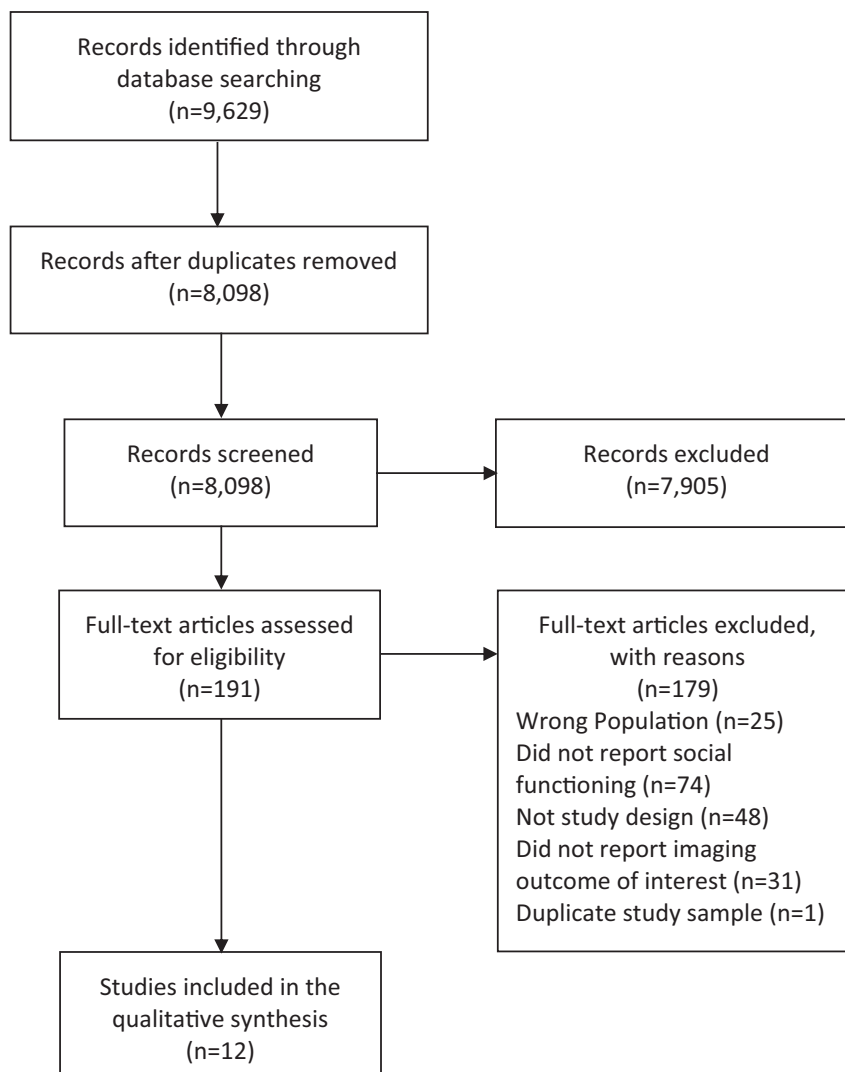


Fig. 1. PRISMA flow diagram of included studies.

Table 1
Demographic and study characteristics.

Author & year	Country	Study design	Total sample size	Number of at-risk participants (percentage of males)	Age (SD)	Comparison group(s)	Number of comparators (percentage of males)	Age (SD)
<i>Structural studies</i>								
Karlsgodt et al., 2009	USA	Ln	61	36 (75.00%)	17.02 (3.37)	HC	25 (48.00%)	17.69 (3.40)
Koutsouleris et al., 2018	Multi-country ^a	Ln	232	I: 66 (51.52%), UI: 50 (48.00%)	I: 23.6 (4.7), UI: 24.5 (5.5)	HC	116 (50.00%)	27.6 (4.6)
Krakauer et al., 2017	Denmark	C	90	45 (48.89%)	23.71 (4.65)	HC	45 (48.89%)	23.80 (5.15)
Krakauer et al., 2018	Denmark	Ln	53	30 (43.33%)	24.07 (5.12)	HC	23 (56.52%)	24.48 (5.81)
Lavoie et al., 2014	Australia	C	184	N: 77 (57.14%), P: 49 (59.18%)	N: 20.6 (3.6), P: 19.5 (3.3)	HC	58 (63.79%)	21.4 (3.2)
Reniers et al., 2017	Australia	Ln	109	109 (49.54%)	19.5 (3.6)	NA	NA	NA
Takahashi et al., 2018	Japan	C	162	38 (63.16%)	18.4 (3.9)	HC, SZ	HC: 61 (54.46%), SZ: 63 (46.03%)	HC: 25.6 (3.2), SZ: 28.0 (9.4)
<i>Functional studies</i>								
Carrión et al., 2015	USA	C	67	34 (52.94%)	17.07 (2.18)	HC	33 (54.55%)	18.18 (2.97)
Colibazzi et al., 2016	USA	C	105	56 (73.21%)	20.75 (3.1)	HC	49 (63.27%)	21.17 (3.79)
Lepock et al., 2019	Canada	C	35	35 (62.86%)	20.6 (3.3)	NA	NA	NA
Pelletier-Baldelli et al., 2015	USA	C	69	36 (69.44%)	19.03 (1.4)	HC	34 (50.00%)	18.68 (1.7)
Sabb et al., 2010	USA	Ln	64	N:20 (75.00%), P:15 (86.67%)	N: 16.8 (3.1), P: 18.4 (4.2)	HC	24 (50.00%)	18.5 (3.2)

Abbreviations: NA = not applicable; NR = not recorded; C = cross-sectional; Ln = longitudinal; HC = healthy control; SZ = schizophrenia; I = impaired functioning; UI = unimpaired functioning; N = did not transition to psychosis; P = did transition to psychosis.

^a Included Germany, Finland, Switzerland, Italy, and England.

activity time courses in disparate brain regions. The EEG studies that are included in this review measure event related potentials (ERPs), which are small changes in voltage that are time locked to specific stimuli, and are seldom localized to a particular brain region. Generally, ERP analyses focus on specific components of an ERP waveform, e.g. the N400, or the mismatch negativity (MMN).

The structural studies employed either sMRI or DTI. sMRI measures the size, volume, shape, and density of structures in the brain and can be used to differentiate between tissue types. In this review, the sMRI metrics that have been reported are GMV, which measures the amount of grey matter, grey matter density (GMD), which measures the proportion of grey matter to other tissue types, and gyrosulcal morphology, which classifies the shape of a brain structure. DTI measures the diffusion of water through the brain in order to assess the properties of white matter (i.e. axonal) connections. Fractional anisotropy (FA) is the most commonly reported measure of white matter microstructure in DTI studies but other metrics like axial diffusivity (AD) and mode of anisotropy (MO) provide additional information about axonal pathology and the orientation of crossing white matter fibres.

Seven of the included studies were focused on structural imaging (Karlsgodt et al., 2009; Koutsouleris et al., 2018; Krakauer et al., 2017, 2018; Lavoie et al., 2014; Reniers et al., 2017; Takahashi et al., 2018); whereas the remaining five were functional imaging studies (Carrión et al., 2015; Colibazzi et al., 2016; Lepock et al., 2019; Pelletier-Baldelli et al., 2015; Sabb et al., 2010). For the seven structural imaging studies, three measured within region metrics (e.g. GMV) (Koutsouleris et al., 2018; Reniers et al., 2017; Takahashi et al., 2018), one measured within region morphology (Lavoie et al., 2014), and the other three studies measured white matter structure using DTI (Karlsgodt et al., 2009; Krakauer et al., 2017, 2018). For the five functional imaging studies, two examined functional activity using fMRI (Colibazzi et al., 2016; Sabb et al., 2010), one examined functional connectivity using fMRI (Pelletier-Baldelli et al., 2015), and two studies measured ERPs using EEG

(Carrión et al., 2015; Lepock et al., 2019). Of these five functional imaging studies, one was resting state (Pelletier-Baldelli et al., 2015) while the other four studies employed task paradigms. Each of the four tasks was unique to that particular study: one of the ERP studies (Carrión et al., 2015) used an auditory oddball paradigm that presented either standard or deviant tones to elicit an MMN response, the other ERP study (Lepock et al., 2019) used a semantic priming task whereby related or unrelated pairs of words were presented in order to elicit a differential N400 response. For the fMRI studies, one study (Colibazzi et al., 2016) used the Simon spatial compatibility task to elicit changes in the need for cognitive control, and the other (Sabb et al., 2010) examined changes in brain activity in individuals at CHR during a blocked naturalistic language processing task, as deficits in this ability are commonly found in schizophrenia patients.

3.4. Imaging findings related to social functioning

Four of the seven structural studies found a significant relationship between social functioning and brain imaging metrics (Karlsgodt et al., 2009; Koutsouleris et al., 2018; Krakauer et al., 2017; Reniers et al., 2017). Three of these studies found that social functioning measures had a positive relationship with at least some regions/tracts, while Koutsouleris et al. (2018) found both positive and negative relationships between social functioning measures and GMV. Notably three of the four studies with significant relationships employed a longitudinal design; Karlsgodt et al. (2009) focused on white matter connectivity measures (using DTI) whereas Koutsouleris et al. (2018) and Reniers et al. (2017) focused on within-region measurements (GMV and GMD). The remaining three structural imaging studies were cross sectional, and only Krakauer et al. (2017), which examined white matter connectivity, found a significant positive relationship between brain metrics and social functioning measures. Four of the structural studies used a whole brain analysis (Koutsouleris et al., 2018; Krakauer et al., 2017, 2018;

Table 2

Imaging characteristics and relationships to social functioning.

Author & year	Social Functioning Scale	Imaging/measurement type	Field strength	Manual or automatic segmentation	Whole brain/ROI	Analysis method	Relationship between social functioning and brain imaging measures	Statistic
<i>Structural studies</i>								
Karlsgodt et al., 2009	GF:S	DTI	1.5 T	Automatic	ROI (ATR, CB, ILF, MTL, SLF, UF)	FSL	Positive correlation with FA in R ILF at 15 months	6 months L ILF: $F_{(3,21)} = 2.86$, $p = 0.033^a$ R ILF: $F_{(3,21)} = 2.46$, $p = 0.071^a$ 15 months R ILF: $F_{(3,8)} = 12.39$, $p = 0.001$ R MTL: $F_{(3,8)} = 5.83$, $p = 0.074^a$ R ATR: $F_{(3,8)} = 6.33$, $p = 0.073^a$ Cross-validation threshold map corresponding to an α level of 0.05 (exact p -values not given)
Koutsouleris et al., 2018	GF:S	sMRI (GMV)	1.5 T & 3.0 T	Automatic	Whole brain	Freesurfer, SPM12, Neurominer	Positive relationship with baseline GMV in mPFC, Cing, OFC, insulae, temporal, parietal and occipital regions. Negative relationship with baseline GMV in cerebellum, DMPFC, and DLPFC	
Krakauer et al., 2017	SOFAS	DTI	3.0 T	Automatic	Whole brain	FSL, PLSC	Positively correlated with FA in L ILF, AD in L IFF and R SLF, MO in R IFF, L SLF, and R ATR	FA in L ILF: $p = 0.022$ AD in L IFF: $p = 0.007$ AD in L SLF: $p = 0.045$ MO in R IFF (cluster 1 & 2): $p = 0.006, 0.005$ MO in L SLF: $p = 0.018$ MO in R ATR: $p = 0.044$ Baseline FA and SOFAS correlations (positive and negative): $p = 0.87^a$ & $p = 0.15^a$ FA change and SOFAS change correlations (positive and negative): $p = 0.40^a$ & $p = 0.59^a$ L OFC: $R^2 = 0.011$, $p = 0.65^a$ R OFC: $R^2 = 0.018$, $p = 0.50^a$ mPFC (cluster 1, 2, & 3): $p = 0.017, 0.018, 0.018$ Cingulate gyrus: $p = 0.021$ ACC (cluster 1, 2, & 3): $p = 0.021, 0.030, 0.028$ Subcallosal gyrus: $p = 0.034$ Declive: $p = 0.033$ Spearman's $\rho = 0.15$, $p = 0.373^a$
Krakauer et al., 2018	SOFAS	DTI	3.0 T	Automatic	Whole brain	FSL	NS	
Lavoie et al., 2014	SOFAS	sMRI (gyrusulcal morphology)	1.5 T	Manual	ROI (OFC)	FSL	NS	
Reniers et al., 2017	SOFAS & QLS	sMRI (GMD)	1.5 T (80%) 3.0 T (20%)	Automatic	Whole brain	SPM8, VBM8 Toolbox	Positively correlated with mPFC, CG, ACC, AFC, SCG, declive	
Takahashi et al., 2018	SOFAS	sMRI (GMV)	3.0 T	Manual	ROI (pituitary)	Dr. View software	NS	
<i>Functional studies</i>								
Author & year	Social Functioning Scale	Imaging/measurement type	Field strength	Task	Whole brain/ROI	Analysis method	Relationship between social functioning and brain imaging measures	Statistic
Carrión et al., 2015	GF:S	EEG	32 electrodes	Auditory stimuli with visual distractor task	ROI (10 fronto-central sites)	Brain Vision Analyzer 2	Negative correlation with MMN amplitude response to frequency, duration, and intensity deviations	Frequency MMN: $r = -0.22$, $p = 0.03$ Intensity MMN: $r = -0.30$, $p = 0.01$ Duration MMN: $r = -0.44$, $p < 0.001$ Multiple comparison corrected p -value of $p < 0.05$ (exact p -values not given)
Colibazzi et al., 2016	GF:S	fMRI	3.0 T	Simon task	Whole brain	SPM8	Positively correlated with DLPFC and fusiform gyrus	
	GF:S	EEG			Whole brain		NS	

(continued on next page)

Table 2 (continued)

Author & year	Social Functioning Scale	Imaging/measurement type	Field strength	Task	Whole brain/ROI	Analysis method	Relationship between social functioning and brain imaging measures	Statistic
Lepock et al., 2019			32 electrodes	Semantic priming task		Not reported		N400, 300 ms SOA: Spearman's $\rho = -0.09^a$ N400, 750 ms SOA: Spearman's $\rho = -0.17^a$
Pelletier-Baldelli et al., 2015	GF:S	fMRI	NR	Resting state	ROI (SN and DMN)	FSL	Negative correlation with connectivity between SN and cuneal cortex in UHR	False-discovery rate corrected p -value of $p < 0.05$ (exact p -values not given)
Sabb et al., 2010	SAS	fMRI	3.0 T	Naturalistic language processing task	ROI (IFG, IT/MTG, ACC, caudate, SFG)	FSL	Negatively correlated with ACC and L IFG during reasoning minus rest contrast	Reasoning minus rest contrast ACC: $R = -0.41$, $p < 0.009$ L IFG: $R = -0.43$, $p < 0.007$ IT/MTG: $R = -0.33$, $p < 0.04^a$ SFG: $R = -0.35$, $p < 0.03^a$ Reasoning minus topic maintenance contrast ACC: $R = -0.30$, $p < 0.06^a$ Caudate: $R = 0.03$, $p < 0.85^a$ L IFG: $R = -0.26$, $p < 0.11^a$ IT/MTG: $R = -0.27$, $p < 0.10^a$ SFG: $R = -0.29$, $p < 0.07^i$

Abbreviations: NA = not applicable; NR = not recorded; NS = non-significant; ROI = region of interest; T = Tesla; DTI = diffusion tensor imaging; sMRI = structural magnetic resonance imaging; fMRI = functional magnetic resonance imaging; EEG = electroencephalogram; GMV = grey matter volume; GMD = grey matter density; L = left; R = right; B = bilateral; ILF = inferior longitudinal fasciculus; ATR = anterior thalamic radiation; CB = cingulate bundle; MTL = medial temporal lobe structures; SLF = superior longitudinal fasciculus; UF = uncinate fasciculus; IFF = inferior fronto-occipital fasciculus; SLF = superior longitudinal fasciculus; ATR = anterior thalamic radiation; ACC = anterior cingulate cortex; CG = cingulate gyrus; OFC = orbitofrontal cortex; mPFC = medial prefrontal cortex; AFC = anterior frontal cortex; SCG = subcallosal gyrus; DLPFC = dorsolateral prefrontal cortex; SN = salience network; DMN = default mode network; IFG inferior frontal gyrus; IT/MTG = Inferior temporal/middle temporal gyrus; SFG = superior frontal gyrus; GF:S = Global Functioning: Social Scale; SOFAS = Social and Occupational Functioning Assessment Scale; SAS = Social Anxiety Scale; SPM = Statistical Parametric Mapping; VBM = voxel based morphometry; FSL = FMRIB Software Library.

^a Statistically non-significant results

Reniers et al., 2017) whereas three used regions of interest (ROIs); Lavoie et al. (2014) and Takahashi et al. (2018) used manually delineated ROIs and Karlsgodt et al. (2009) selected DTI tracts of interest a priori. The only structural imaging study that did not examine white matter microstructure or within-region measurements focused instead on morphology, specifically gyrosulcal morphology and sulcal counts within the orbitofrontal cortex (OFC) (Lavoie et al., 2014), but no significant relationship to social functioning was found.

Four of the five functional imaging studies found a significant relationship between social functioning and brain imaging metrics (Carrión et al., 2015; Colibazzi et al., 2016; Pelletier-Baldelli et al., 2015; Sabb et al., 2010). The two studies that examined fMRI activity (Colibazzi et al., 2016; Sabb et al., 2010) found a positive relationship between social functioning and activation, whereas a negative relationship was found between social functioning and the MMN amplitude in an ERP study (Carrión et al., 2015), and social functioning was negatively correlated with fMRI connectivity between the salience network and the cuneus during a resting state study (Pelletier-Baldelli et al., 2015).

Of the studies that found a significant relationship between social functioning and functional imaging, only Sabb et al. (2010) was a longitudinal study, and it found a significant negative relationship between baseline brain activity in the anterior cingulate cortex (ACC) and left inferior frontal gyrus (IFG) and social functioning measures at follow-up

while performing a language processing task. Four of the functional imaging studies were cross-sectional (Carrión et al., 2015; Colibazzi et al., 2016; Lepock et al., 2019; Pelletier-Baldelli et al., 2015), and three found significant relationships with social functioning measures, all using different imaging modalities or analysis techniques; Carrión et al. (2015) used EEG, and two used fMRI. Of the two fMRI studies, Pelletier-Baldelli et al. (2015) was focused on functional connectivity, whereas Sabb et al. (2010) examined functional activity. However, for all three of these studies, the correlated activity was found in the prefrontal lobe (or in a functional connection to a network involving the prefrontal lobe). Pelletier-Baldelli et al. (2015) found a relationship between brain metrics and social functioning in both healthy controls and individuals at CHR; however, this relationship was positive for healthy controls and negative for individuals at CHR. Colibazzi et al. (2016) and Lepock et al. (2019) employed a whole brain analysis, whereas Carrión et al. (2015), Pelletier-Baldelli et al. (2015), and Sabb et al. (2010) used ROIs. All three of the ROI studies found statistically significant associations with social functioning measures. Carrión et al. (2015) and Lepock et al. (2019) were the two EEG studies included in this review, both of which examined ERPs from different experimental paradigms. Lepock et al. (2019) used a semantic priming task and found non-significant results, whereas Carrión et al. (2015) found a significant negative relationship between social functioning and the frequency, intensity, and duration of

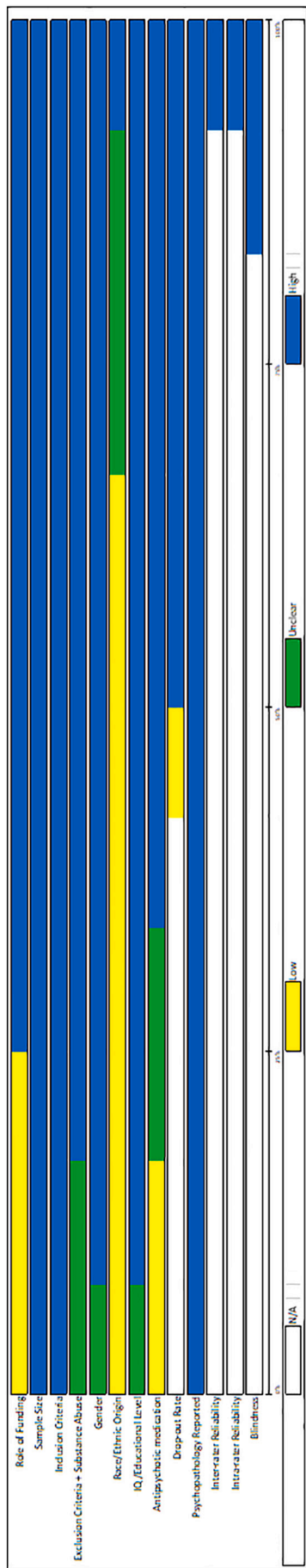


Fig. 2. Quality assessment summary chart for neuroimaging studies (adapted from (Fusar-Poli et al., 2013) and (Walter et al., 2016)). For these ratings: 0 = low, 1 = unclear, and 2 = high. Areas in white indicate studies for which the criteria were not applicable.

the auditory MMN.

In many cases, the results from the studies showed agreement in terms of the directionality of the relationships and the regions found to be involved. For instance, the medial prefrontal cortex (mPFC) was found to be positively related to social functioning in two of the structural imaging studies (Koutsouleris et al., 2018; Reniers et al., 2017). Also, the ACC was associated with social functioning in two of the structural (Koutsouleris et al., 2018; Reniers et al., 2017) and one of the functional imaging studies (Sabb et al., 2010). For the structural studies, there was a positive relationship between ACC and social functioning, whereby decreases in structural metrics were associated with poorer social functioning. In contrast, the functional study identified a negative relationship, whereby a larger difference in the contrast of the reasoning condition versus rest was associated with poorer social functioning. In the DTI studies, FA in the left inferior longitudinal fasciculus (ILF) was positively associated with social functioning measures in two of the structural imaging studies (Karlsgodt et al., 2009; Krakauer et al., 2017), however, in Karlsgodt et al. (2009), the association was only trend level. There were also cases of conflicting results, where particular regions/ tracts, including the orbitofrontal cortex (OFC) and the anterior thalamic radiation (ATR), were significantly associated with social functioning in some but not all of the included studies.

4. Discussion

Taken together, the results of this systematic review suggest that there are widespread and subtle brain changes that are associated with social functioning in youth at CHR for psychosis. Significant relationships between social functioning and brain measures were found in eight of the 12 included studies. Notably, some of the same brain regions were found to be related to social functioning using very different imaging modalities.

As was hypothesized, many of these regions are found in the pre-frontal cortex, including the ACC, mPFC, OFC, and the DLPFC, and have been associated with the pathophysiology of schizophrenia (Brugger and Howes, 2017; Guo et al., 2019; Minzenberg et al., 2014; Mwansisya et al., 2017). However, these results may have been influenced by selective outcome reporting, as half of the included studies used an ROI approach and did not examine changes in structure or function in the whole brain.

The structural imaging studies either examined white matter connectivity using DTI, within-region metrics (e.g. GMV), or morphological features within a region. In the DTI studies, the most consistent finding was a positive relationship between FA in the left ILF and social functioning. Changes in white matter microstructure in the ILF has been found in chronic schizophrenia patients (Friedman et al., 2008), as well as medication naïve patients in their first psychotic episode (Cheung et al., 2008). A recent review examining the functional role of the ILF suggests that disruptions are associated with deficits in visual cognition including hallucinations, as well as socio-emotional impairments (Herbet et al., 2018). In all three of the DTI studies, the relationship between diffusion measures and social functioning was positive, that is, poorer white matter integrity was associated with poorer social functioning, even when the relationship between the two was non-significant.

In the studies that focused on structural within-region metrics, the regions that were most commonly found to be related to social functioning were the ACC and mPFC. Two of the studies found that the mPFC and ACC was positively related to social functioning, using two different measures, GMV and GMD. This agreement supports the idea that these regions are impacted by disease processes as GMV and GMD exhibit considerable variability across regions and can be weakly correlated or even anti-correlated (Gennatas et al., 2017). The only morphological study in this review did not find a significant relationship with social functioning. The structural studies were evenly split between cross-sectional and longitudinal designs; however, three of the four longitudinal studies found a significant relationship with social functioning,

whereas only one of the cross-sectional ones found a significant relationship. The three longitudinal studies that found significant results correlated baseline scan metrics with social functioning measures at follow-up. Positive associations between brain metrics and social functioning were found all the structural imaging studies with significant results; only Koutsouleris et al. (2018) also found some regions with a negative association between social functioning and regional GMV.

Functional imaging studies examined functional activity using fMRI, functional connectivity using fMRI, or examined specific ERPs using EEG. The functional activity studies found that social functioning was correlated with brain activity primarily localized to the prefrontal cortex. Colibazzi et al. (2016) found a positive relationship between social functioning and conflict related activity in the DLPFC and fusiform gyrus, whereas Sabb et al. (2010) found a negative relationship between the magnitude of the reasoning-rest contrast in ACC and left IFG and social functioning measures. Although there is a difference in the valence of these relationships, it is not clear whether this result is dependent on the brain regions found to be involved, the differences in the experimental design and contrast choice, or some combination of these factors. These studies employed very different paradigms (e.g., the Simon task, where levels of conflict and the need for cognitive control are manipulated, versus a naturalistic language processing task, where participants listened to dialogue and indicated whether a response made sense), and it is important to note that the first study contrasted two active conditions (e.g. congruent and incongruent) whereas the second contrasted an active condition (e.g. reasoning) versus a rest condition. These variations in experimental design and analysis strategy add to the complexity in comparing results from studies in the same population. The functional connectivity study performed by Pelletier-Baldelli et al. (2015) was notable in that it found that the valence of the brain and social functioning relationship differed for healthy controls and individuals at CHR while performing a resting state scan, which suggests that the relationship between these networks is altered at an early stage. The EEG studies were focused on ERPs that are related to early sensory and cognitive processing. The Carrión et al. (2015) study, which focused on the MMN (an early sensory process) found a significant relationship with social functioning, specifically the MMN was smaller in individuals at CHR with poorer social functioning. This may suggest that sensory deficits are more closely related to social functional outcomes, but much more evidence is required.

Despite the importance of social functioning as a predictor of transition to a psychotic illness (Cornblatt et al., 2012), relatively few imaging studies have sought to identify significant relationships between social functioning and brain measures. One possible reason might be that social functioning is a complex construct that requires social skills, social cognition, and social motivation (Fulford et al., 2018). Individuals at CHR report lower motivation than age matched peers (Schlosser et al., 2014), and negative symptoms in individuals at CHR have been associated with social functioning deficits (Devoe et al., 2020; Schlosser et al., 2015). This interplay between social functioning and negative symptoms has been hypothesized to result from failures in low level sensory processing (Pelletier-Baldelli and Holt, 2020); but empirical evidence is required. Previous studies have found that social cognition is not related to negative symptoms (Barbato et al., 2015), nor is it associated with transition to psychosis (Piskulic et al., 2016), suggesting that further work is required to clarify the relationships between social functioning, social cognition, and negative symptoms in CHR.

Furthermore, there have been concerns that current methods of measuring negative symptoms in CHR are inadequate, as numerous conceptual and methodological issues have been identified in the negative symptom subscales of commonly used instruments for determining CHR status (Strauss et al., 2020), including the use of items that are based on outdated concepts, and the lack of differentiation between objective and experiential components of negative symptoms.

In addition to the issues with complexity of the social functioning construct and its relations to other negative symptoms, the lack of

significant results in this literature is also likely to be related to the variability in the experimental design and analysis methods in neuro-imaging experiments. Although, there are a limited number of studies included in this review, they vary in several ways such as: the field strength of the MRI, the use of cross-sectional or longitudinal designs, the software used for the analysis, preprocessing and data cleaning steps, the scope of the analysis (e.g. within a voxel/region, functional connections between regions), whole brain or ROI, manual or automated segmentations in structural analyses, task choice in functional imaging experiments, choice of ERPs and channels to examine in EEG experiments, and choice of comparison group. All these decisions can play a role in the observed results, and there is no established method to determine the ideal experimental parameters.

The results of this review suggest that there appear to be subtle and widespread changes in brain structure and function in individuals at CHR that are associated with social functioning, and many of these changes appear to be localized or connected to the prefrontal cortex. However, given the discussion above regarding the variability in imaging parameters and analysis decisions, some useful steps that could be taken include the preregistration of studies to reduce the number of studies that obtain non-reported negative results, using standardized experimental paradigms and analysis procedures to facilitate the interpretation of results, and to increase sample sizes via multi-site collaborations. A similar push towards the standardization of the clinical criteria that are used to establish CHR status is currently underway as part of the NIMH funded Psychosis-Risk Outcomes Network. This work will help to reduce the differences between participants that are classified as being at CHR which may lead to more robust results.

There were several limitations to this review that should be noted. First, very few studies report relationships between social functioning and brain imaging metrics, which, in addition to the variability between studies mentioned above, necessitated a qualitative review, rather than a meta-analysis. Second, the included studies varied in sample sizes, with the number of CHR individuals numbering as few as 30 or as many as 109. Although CHR samples >20 counted as high quality in the Quality Assessment, the relationships between brain imaging and social functioning should be interpreted with caution as many of these studies were likely underpowered. With respect to the limitations that were reported in the individual studies, the most commonly mentioned issues were small sample sizes and that some of the participants were taking medication, although several of the studies attempted to control for this by testing for significant differences between medicated and unmedicated participants. Another issue that was raised in multiple papers were difficulties in matching the demographics of healthy controls and individuals at CHR, particularly in terms of years of education and smoking/substance use.

To our knowledge, this review is the first attempt to synthesize what is known about brain changes associated with social functioning in individuals at CHR for psychosis, and thus provides a comprehensive look at the current state of the field, as well as highlighting the need for further research in this area.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

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References

- Addington, J., Liu, L., Perkins, D.O., Carrion, R.E., Keefe, R.S.E., Woods, S.W., 2017. The role of cognition and social functioning as predictors in the transition to psychosis for youth with attenuated psychotic symptoms. *Schizophr. Bull.* 43, 57–63. <https://doi.org/10.1093/schbul/sbw152>.
- Addington, J., Stowkowy, J., Liu, L., Cadenhead, K.S., Cannon, T.D., Cornblatt, B.A., McGlashan, T.H., Perkins, D.O., Seidman, L.J., Tsuang, M.T., Walker, E.F., Bearden, C.E., Mathalon, D.H., Santesteban-Echarri, O., Woods, S.W., 2019. Clinical and functional characteristics of youth at clinical high-risk for psychosis who do not transition to psychosis. *Psychol. Med.* 49, 1670–1677. <https://doi.org/10.1017/S0033291718002258>.
- Aoyama, N., Théberge, J., Drost, D.J., Manchanda, R., Northcott, S., Neufeld, R.W.J., Menon, R.S., Rajakumar, N., Pavlosky, W.F., Densmore, M., Schaefer, B., Williamson, P.C., 2011. Grey matter and social functioning correlates of glutamatergic metabolite loss in schizophrenia. *Br. J. Psychiatry* 198, 448–456. <https://doi.org/10.1192/bjp.bp.110.079608>.
- Barbato, M., Liu, L., Cadenhead, K.S., Cannon, T.D., Cornblatt, B.A., McGlashan, T.H., Perkins, D.O., Seidman, L.J., Tsuang, M.T., Walker, E.F., Woods, S.W., Bearden, C.E., Mathalon, D.H., Heinssen, R., Addington, J., 2015. Theory of mind, emotion recognition and social perception in individuals at clinical high risk for psychosis: findings from the NAPLS-2 cohort. *Schizophr. Res. Cogn.* 2, 133–139. <https://doi.org/10.1016/j.schres.2015.04.004>.
- Birchwood, M., Smith, J., Cochrane, R., Wetton, S., Copstake, S., 1990. The Social Functioning Scale. The development and validation of a new scale of social adjustment for use in family intervention programmes with schizophrenic patients. *Br. J. Psychiatry* 157, 853–859. <https://doi.org/10.1192/bjp.157.6.853>.
- Brambilla, P., Perlini, C., Rajagopalan, P., Saharan, P., Rambaldelli, G., Bellani, M., Dusi, N., Cerini, R., Pozzi Mucelli, R., Tansella, M., Thompson, P.M., 2013. Schizophrenia severity, social functioning and hippocampal neuroanatomy: three-dimensional mapping study. *Br. J. Psychiatry* 202, 50–55. <https://doi.org/10.1192/bjp.bp.111.105700>.
- Brugger, S.P., Howes, O.D., 2017. Heterogeneity and homogeneity of regional brain structure in schizophrenia: a meta-analysis. *JAMA Psychiatry* 74, 1104–1111. <https://doi.org/10.1001/jamapsychiatry.2017.2663>.
- Burns, T., Patrick, D., 2007. Social functioning as an outcome measure in schizophrenia studies. *Acta Psychiatr. Scand.* 116, 403–418. <https://doi.org/10.1111/j.1600-0447.2007.01108.x>.
- Carrión, R.E., Goldberg, T.E., McLaughlin, D., Auther, A.M., Correll, C.U., Cornblatt, B.A., 2011. Impact of neurocognition on social and role functioning in individuals at clinical high risk for psychosis. *Am. J. Psychiatry* 168, 806–813. <https://doi.org/10.1176/appi.ajp.2011.10081209>.
- Carrión, R.E., McLaughlin, D., Goldberg, T.E., Auther, A.M., Olsen, R.H., Olvet, D.M., Correll, C.U., Cornblatt, B.A., 2013. Prediction of functional outcome in individuals at clinical high risk for psychosis. *JAMA Psychiatry* 70, 1133–1142. <https://doi.org/10.1001/jamapsychiatry.2013.1909>.
- Carrión, R.E., Cornblatt, B.A., McLaughlin, D., Chang, J., Auther, A.M., Olsen, R.H., Javitt, D.C., 2015. Contributions of early cortical processing and reading ability to functional status in individuals at clinical high risk for psychosis. *Schizophr. Res.* 164, 1–7. <https://doi.org/10.1016/j.schres.2015.01.030>.
- Cheung, V., Cheung, C., McAlonan, G.M., Deng, Y., Wong, J.G., Yip, L., Tai, K.S., Khong, P.L., Sham, P., Chua, S.E., 2008. A diffusion tensor imaging study of structural dysconnectivity in never-medicated, first-episode schizophrenia. *Psychol. Med.* 38, 877–885. <https://doi.org/10.1017/S0033291707001808>.
- Colibazzi, T., Horga, G., Wang, Z., Huo, Y., Corcoran, C., Klahr, K., Brucato, G., Girgis, R., Gill, K., Abi-Dargham, A., Peterson, B.S., 2016. Neural dysfunction in cognitive control circuits in persons at clinical high-risk for psychosis. *Neuropsychopharmacology* 41, 1241–1250. <https://doi.org/10.1038/npp.2015.273>.
- Cornblatt, B.A., Auther, A.M., Niendam, T., Smith, C.W., Zinberg, J., Bearden, C.E., Cannon, T.D., 2007. Preliminary findings for two new measures of social and role functioning in the prodromal phase of schizophrenia. *Schizophr. Bull.* 33, 688–702. <https://doi.org/10.1093/schbul/sbm029>.
- Cornblatt, B.A., Carrion, R.E., Addington, J., Seidman, L., Walker, E.F., Cannon, T.D., Cadenhead, K.S., McGlashan, T.H., Perkins, D.O., Tsuang, M.T., Woods, S.W., Heinssen, R., Lencz, T., 2012. Risk factors for psychosis: impaired social and role functioning. *Schizophr. Bull.* 38, 1247–1257. <https://doi.org/10.1093/schbul/sbr136>.
- Couture, S.M., Penn, D.L., Roberts, D.L., 2006. The functional significance of social cognition in schizophrenia: a review. In: *Schizophrenia Bulletin*. Oxford University Press, p. S44. <https://doi.org/10.1093/schbul/sbl029>.
- Devoe, D.J., Braun, A., Seredynski, T., Addington, J., 2020. Negative symptoms and functioning in youth at risk of psychosis: a systematic review and meta-analysis. *Harv. Rev. Psychiatry*. <https://doi.org/10.1097/HRP.0000000000000273>.
- Faustman, W.O., Overall, J.E., 1999. Brief Psychiatric Rating Scale. In: *The Use of Psychological Testing for Treatment Planning and Outcomes Assessment*, 2nd ed. Lawrence Erlbaum Associates Publishers, Mahwah, NJ, US, pp. 791–830.
- Fowler, D., Hodgekins, J., French, P., 2019. Social recovery therapy in improving activity and social outcomes in early psychosis: current evidence and longer term outcomes. *Schizophr. Res.* 203, 99–104. <https://doi.org/10.1016/j.schres.2017.10.006>.
- Friedman, J.I., Tang, C., Carpenter, D., Buchsbaum, M., Schmeidler, J., Flanagan, L., Golembo, S., Kanellopoulou, I., Ng, J., Hof, P.R., Harvey, P.D., Tsopoulos, N.D., Stewart, D., Davis, K.L., 2008. Diffusion tensor imaging findings in first-episode and chronic schizophrenia patients. *Am. J. Psychiatry* 165, 1024–1032. <https://doi.org/10.1176/appi.ajp.2008.07101640>.
- Fulford, D., Campellone, T., Gard, D.E., 2018. Social motivation in schizophrenia: how research on basic reward processes informs and limits our understanding. *Clin. Psychol. Rev.* <https://doi.org/10.1016/j.cpr.2018.05.007>.
- Fusar-Poli, P., Smieskova, R., Kempton, M.J.J., Ho, B.C.C., Andreasen, N.C.C., Borgwardt, S., 2013. Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. *Neurosci. Biobehav. Rev.* 37, 1680–1691. <https://doi.org/10.1016/j.neubiorev.2013.06.001>.
- Gennatas, E.D., Avants, B.B., Wolf, D.H., Satterthwaite, T.D., Ruparel, K., Ciric, R., Hakonarson, H., Gur, R.E., Gur, R.C., 2017. Age-related effects and sex differences in gray matter density, volume, mass, and cortical thickness from childhood to young adulthood. *J. Neurosci.* 37, 5065–5073. <https://doi.org/10.1523/JNEUROSCI.3550-16.2017>.
- Glatt, S.J., Stone, W.S., Faraone, S.V., Seidman, L.J., Tsuang, M.T., 2006. Psychopathology, personality traits and social development of young first-degree relatives of patients with schizophrenia. *Br. J. Psychiatry* 189, 337–345. <https://doi.org/10.1192/bjp.bp.105.016998>.
- Guo, J.Y., Ragland, J.D., Carter, C.S., 2019. Memory and cognition in schizophrenia. *Mol. Psychiatry*. <https://doi.org/10.1038/s41380-018-0231-1>.
- Herbet, G., Zemmoura, I., Duffau, H., 2018. Functional anatomy of the inferior longitudinal fasciculus: from historical reports to current hypotheses. *Front. Neuroanat.* <https://doi.org/10.3389/fnana.2018.00077>.
- Jääskeläinen, E., Juola, P., Hirvonen, N., McGrath, J.J., Saha, S., Isohanni, M., Veijola, J., Miettinen, J., 2013. A systematic review and meta-analysis of recovery in schizophrenia. *Schizophr. Bull.* 39, 1296–1306. <https://doi.org/10.1093/schbul/sbs130>.
- Karlsgodt, K.H., Niendam, T.A., Bearden, C.E., Cannon, T.D., 2009. White matter integrity and prediction of social and role functioning in subjects at ultra-high risk for psychosis. *Biol. Psychiatry* 66, 562–569. <https://doi.org/10.1016/j.biopsych.2009.03.013>.
- Koutsouleris, N., Kambeitz-Ilanovic, L., Ruhrmann, S., Rosen, M., Ruef, A., Dwyer, D.B., Paolini, M., Chisholm, K., Kambeitz, J., Haidl, T., Schmidt, A., Gillam, J., Schultze-Lutter, F., Falkai, P., Reiser, M., Riecher-Rössler, A., Upthegrove, R., Hietala, J., Salokangas, R.K.R., Pantelis, C., Meisenzahl, E., Wood, S.J., Beque, D., Brambilla, P., Borgwardt, S., 2018. Prediction models of functional outcomes for individuals in the clinical high-risk state for psychosis or with recent-onset depression: a multimodal, multisite machine learning analysis. *JAMA Psychiatry* 75, 1156–1172. <https://doi.org/10.1001/jamapsychiatry.2018.2165>.
- Krakauer, K., Ebdrup, B.H., Glenthøj, B.Y., Raghava, J.M., Nordholm, D., Randers, L., Rostrop, E., Nordentoft, M., 2017. Patterns of white matter microstructure in individuals at ultra-high-risk for psychosis: associations to level of functioning and clinical symptoms. *Psychol. Med.* 47, 2689–2707. <https://doi.org/10.1017/S0033291717001210>.
- Krakauer, K., Nordentoft, M., Glenthøj, B.Y., Raghava, J.M., Nordholm, D., Randers, L., Glenthøj, L.B., Ebdrup, B.H., Rostrop, E., 2018. White matter maturation during 12 months in individuals at ultra-high-risk for psychosis. *Acta Psychiatr. Scand.* 137, 65–78. <https://doi.org/10.1111/acps.12835>.
- Lavoie, S., Bartholomeuz, C.F., Nelson, B., Lin, A., McGorry, P.D., Velakoulis, D., Whittle, S.L., Yung, A.R., Pantelis, C., Wood, S.J., 2014. Sulcogyrar pattern and sulcal count of the orbitofrontal cortex in individuals at ultra high risk for psychosis. *Schizophr. Res.* 154, 93–99. <https://doi.org/10.1016/j.schres.2014.02.008>.
- Lee, K.H., Brown, W.H., Egleston, P.N., Green, R.D.J., Farrow, T.F.D., Hunter, M.D., Parks, R.W., Wilkinson, I.D., Spence, S.A., Woodruff, P.W.R., 2006. A functional magnetic resonance imaging study of social cognition in schizophrenia during an acute episode and after recovery. *Am. J. Psychiatry* 163, 1926–1933. <https://doi.org/10.1176/appi.ajp.2006.163.11.1926>.
- Lepock, J.R., Ahmed, S., Mizrahi, R., Gerritsen, C.J., Maheandiran, M., Drvaric, L., Bagby, R.M., Korostil, M., Light, G.A., Kiang, M., 2019. Relationships between cognitive event-related brain potential measures in patients at clinical high risk for psychosis. *Schizophr. Res.* <https://doi.org/10.1016/j.schres.2019.01.014>.
- McGlashan, T., Walsh, B.C., Woods, S.W., 2010. *The Psychosis-risk Syndrome: Handbook for Diagnosis and Follow-up*. Oxford University Press, New York, NY.
- Mike, L., Guimond, S., Kelly, S., Thermeos, H., Meshulam-Gately, R., Eack, S., Keshavan, M., 2019. Social cognition in early course of schizophrenia: exploratory factor analysis. *Psychiatry Res.* 272, 737–743. <https://doi.org/10.1016/j.psychres.2018.12.152>.
- Minzenberg, M.J., Laird, A.R., Thelen, S., Carter, C.S., Glahn, D.C., 2014. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. *Arch. Gen. Psychiatry* 66, 811–822. <https://doi.org/10.1001/archgenpsychiatry.2009.91>.
- Mwansiyi, T.E., Hu, A., Li, Y., Chen, X., Wu, G., Huang, X., Lv, D., Li, Z., Liu, C., Xue, Z., Feng, J., Liu, Z., 2017. Task and resting-state fMRI studies in first-episode schizophrenia: a systematic review. *Schizophr. Res.* <https://doi.org/10.1016/j.schres.2017.02.026>.
- Pelletier-Baldelli, A., Holt, D.J., 2020. Are negative symptoms merely the “real world” consequences of deficits in social cognition? *Schizophr. Bull.* 46, 236–241. <https://doi.org/10.1093/schbul/sbz095>.
- Pelletier-Baldelli, A., Bernard, J.A., Mittal, V.A., 2015. Intrinsic functional connectivity in salience and default mode networks and aberrant social processes in youth at

- ultra-high risk for psychosis. *PLoS One* 10, e0134936. <https://doi.org/10.1371/journal.pone.0134936>.
- Piskulic, D., Liu, L., Cadenhead, K.S., Cannon, T.D., Cornblatt, B.A., McGlashan, T.H., Perkins, D.O., Seidman, L.J., Tsuang, M.T., Walker, E.F., Woods, S.W., Bearden, C.E., Mathalon, D.H., Addington, J., 2016. Social cognition over time in individuals at clinical high risk for psychosis: findings from the NAPLS-2 cohort. *Schizophr. Res.* 171, 176–181. <https://doi.org/10.1016/j.schres.2016.01.017>.
- Reniers, R.L.E.P., Lin, A., Yung, A.R., Koutsouleris, N., Nelson, B., Cropley, V.L., Velakoulis, D., McGorry, P.D., Pantelis, C., Wood, S.J., 2017. Neuroanatomical predictors of functional outcome in individuals at ultra-high risk for psychosis. *Schizophr. Bull.* 43, 449–458. <https://doi.org/10.1093/schbul/sbw086>.
- Robertson, B.R., Prestia, D., Twamley, E.W., Patterson, T.L., Bowie, C.R., Harvey, P.D., 2014. Social competence versus negative symptoms as predictors of real world social functioning in schizophrenia. *Schizophr. Res.* 160, 136–141. <https://doi.org/10.1016/j.schres.2014.10.037>.
- Rybarczyk, B., 2011. Social and Occupational Functioning Assessment Scale (SOFAS). In: Kreutzer, J.S., DeLuca, J., Caplan, B. (Eds.), *Encyclopedia of Clinical Neuropsychology*. Springer New York, New York, NY, p. 2313. https://doi.org/10.1007/978-0-387-79948-3_428.
- Sabb, F.W., van Erp, T.G.M., Hardt, M.E., Dapretto, M., Caplan, R., Cannon, T.D., Bearden, C.E., 2010. Language network dysfunction as a predictor of outcome in youth at clinical high risk for psychosis. *Schizophr. Res.* 116, 173–183. <https://doi.org/10.1016/j.schres.2009.09.042>.
- Schlosser, D.A., Fisher, M., Gard, D., Fulford, D., Loewy, R.L., Vinogradov, S., 2014. Motivational deficits in individuals at-risk for psychosis and across the course of schizophrenia. *Schizophr. Res.* 158, 52–57. <https://doi.org/10.1016/j.schres.2014.06.024>.
- Schlosser, D.A., Campellone, T.R., Biagianti, B., Delucchi, K.L., Gard, D.E., Fulford, D., Stuart, B.K., Fisher, M., Loewy, R.L., Vinogradov, S., 2015. Modeling the role of negative symptoms in determining social functioning in individuals at clinical high risk of psychosis. *Schizophr. Res.* 169, 204–208.
- Smith, M.J., Schroeder, M.P., Abram, S.V., Goldman, M.B., Parrish, T.B., Wang, X., Derntl, B., Habel, U., Decety, J., Reilly, J.L., Csernansky, J.G., Breiter, H.C., 2015. Alterations in brain activation during cognitive empathy are related to social functioning in schizophrenia. *Schizophr. Bull.* 41, 211–222. <https://doi.org/10.1093/schbul/sbu023>.
- Strauss, G.P., Pelletier-Baldelli, A., Visser, K.F., Walker, E.F., Mittal, V.A., 2020. A review of negative symptom assessment strategies in youth at clinical high-risk for psychosis. *Schizophr. Res.* <https://doi.org/10.1016/j.schres.2020.04.019>.
- Takahashi, T., Higuchi, Y., Komori, Y., Nishiyama, S., Takayanagi, Y., Sasabayashi, D., Kido, M., Furuichi, A., Nishikawa, Y., Nakamura, M., Noguchi, K., Suzuki, M., 2018. Pituitary volume and socio-cognitive functions in individuals at risk of psychosis and patients with schizophrenia. *Front. Psychiatry* 9, 574. <https://doi.org/10.3389/fpsy.2018.00574>.
- Velthorst, E., Fett, A.K.J., Reichenberg, A., Perlman, G., Van Os, J., Bromet, E.J., Kotov, R., 2017. The 20-year longitudinal trajectories of social functioning in individuals with psychotic disorders. *Am. J. Psychiatry* 174, 1075–1085. <https://doi.org/10.1176/appi.ajp.2016.15111419>.
- Walter, A., Suenderhauf, C., Harrisberger, F., Lenz, C., Smieskova, R., Chung, Y., Cannon, T.D., Bearden, C.E., Rapp, C., Bendfeldt, K., Borgwardt, S., Vogel, T., 2016. Hippocampal volume in subjects at clinical high-risk for psychosis: a systematic review and meta-analysis. *Neurosci. Biobehav. Rev.* 71, 680–690. <https://doi.org/10.1016/j.neubiorev.2016.10.007>.
- Weissman, M.M., Bothwell, S., 1976. Assessment of social adjustment by patient self-report. *Arch. Gen. Psychiatry* 33, 1111–1115. <https://doi.org/10.1001/archpsyc.1976.01770090101010>.
- Yung, A.R., Yuen, H.P., McGorry, P.D., Phillips, L.J., Kelly, D., Dell'olio, M., Francey, S.M., Cosgrave, E.M., Killackey, E., Stanford, C., Godfrey, K., Buckby, J., Yung, A.R., Pan Yuen, H., McGorry, P.D., Phillips, L.J., Kelly, D., Dell'olio, M., Francey, S.M., Cosgrave, E.M., Killackey, E., Stanford, C., Godfrey, K., Buckby, J., 2005. Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. *Aust. N. Z. J. Psychiatry* 39, 964–971. <https://doi.org/10.1080/j.1440-1614.2005.01714.x>.