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Resting-state functional connectivity in treatment response and resistance in schizophrenia: A systematic review

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ABSTRACT

Background: Treatment-resistant schizophrenia (TRS) and treatment-responsive schizophrenia may exhibit distinct pathophysiology. Several functional magnetic resonance imaging (fMRI) studies have used resting-state functional connectivity analyses (rs-FC) in TRS patients to identify markers of treatment resistance. However, to date, existing findings have not been systematically evaluated.
Methods: A systematic literature search using Embase, MEDLINE, PsycINFO, ProQuest, PUBMED, and Scopus was performed. The query sought fMRI articles investigating rs-FC in treatment response or resistance in patients with schizophrenia. Only studies that examined treatment response, operationalized as the explicit categorization of patients by their response to antipsychotic medication, were considered eligible. Pairwise comparisons between patient groups and controls were extracted from each study.
Results: The search query identified 159 records. Ten studies met inclusion criteria. Five studies examined not TRS (NTRS), and 8 studies examined TRS. Differences in rs-FC analysis methodology precluded direct comparisons between studies. However, disruptions in areas involved in visual and auditory information processing were implicated in both patients with TRS and NTRS. Changes in connectivity with sensorimotor network areas tended to appear in the context of TRS but not NTRS. Moreover, there was some indication that this connectivity could be affected by clozapine.
Conclusions: Functional connectivity may provide clinically meaningful biomarkers of treatment response and resistance in schizophrenia. Studies generally identified similar areas of disruption, though methodological differences largely precluded direct comparison between disruption effects. Implementing data sharing as standard practice will allow future reviews and meta-analyses to identify rs-FC correlates of TRS.

1. Introduction

Schizophrenia is an illness with significant morbidity, characterized by a combination of positive, negative, and cognitive symptoms (van Os and Kapur, 2009). Antipsychotic medications are the mainstay treatment for schizophrenia (Leucht et al., 2013). While most patients respond to "first-line" (non-clozapine) antipsychotics (Elkis, 2007; Lindenmayer, 2000), 35% of patients with schizophrenia fail to respond to first-line antipsychotics (Kahn et al., 2018). These patients with "treatment-resistant schizophrenia" (TRS) are more likely to experience persistent and severe psychotic symptoms, leading to poorer outcomes (Black et al., 2001; Kennedy et al., 2014).

Converging evidence suggests that heterogenous etiologies underlie differences in antipsychotic treatment responses. The dopamine hypothesis describes how dopaminergic dysregulation may lead to psychotic symptoms (Abi-Dargham, 2004; Davis et al., 1991; Howes and Kapur, 2009; Kapur and Mamo, 2003), but dopaminergic regulation in TRS may be distinct from its treatment-responsive counterpart (Abi-Dargham et al., 2000; Demjaha et al., 2012; Gillespie et al., 2017; Mouchlianitis et al., 2016; Nakajima et al., 2015). Clozapine, the only antipsychotic with demonstrated efficacy for TRS, remits psychotic symptoms in 30% to 70% of patients (Buchanan et al., 1998; Chakos et al., 2001; Conley and Kelly, 2001; Kahn et al., 2018; Kane et al., 1988) despite exhibiting low dopamine receptor D_2 occupancy compared to other antipsychotics (Kapur and Seeman, 2001; Seeman et al., 1976;

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Tauscher et al., 1999). The efficacy of clozapine in successfully-treated patients with TRS implies that clozapine may exert its effects via non-dopaminergic mechanism(s) of action (Nucifora et al., 2017), and it has been proposed that aberrant interactions between dopaminergic and glutamatergic signaling pathways might be complementary (Brennan et al., 2013; Caravaggio et al., 2015; Veerman et al., 2014). These interactions are described in part by the dysconnection hypothesis of schizophrenia, which conceptualizes the underlying psychopathology of schizophrenia as an aberrant modulation of synaptic connectivity leading to widespread disruptions of communication between neuronal circuits and brain networks (Friston, 1998; Friston and Frith, 1995; Lynall et al., 2010; Sheffield and Barch, 2016; van den Heuvel and Fornito, 2014). Notably, dysfunction of glutamatergic synapses involving *N*-methyl-D-aspartate receptors has emerged as an important component of the hypothesis (Friston et al., 2016). Given such empirical evidence, investigations of synaptic connectivity that could mediate antipsychotic treatment response in schizophrenia have emerged as an important research priority (Gillespie et al., 2017; Mouchlianitis et al., 2016; Paul and Sharfman, 2016).

Functional neuroimaging can be used to investigate the relationships between brain activities and neurocognitive functions. A review surveyed longitudinal studies that compared resting-state functional MRI (fMRI) before and after antipsychotic medication treatment and noted considerable heterogeneity across studies (Kani et al., 2017) – a finding echoed by other reviews of fMRI in schizophrenia (Minzenberg et al., 2009; Sheffield and Barch, 2016). Another review discussed fMRI and antipsychotic treatment response, noting the heterogeneity of treatment responses and that fMRI differences have been reported between treatment-resistant and treatment-responsive patients; however, the authors found conclusions difficult to draw (Tarcijonas and Sarpal, 2018). Recent studies have emphasized delineating functional "links" between anatomically distinct brain regions through correlational analyses of brain activation, which could serve useful for identifying disruptions in brain networks and circuitry (Buckner et al., 2013). Resting-state functional connectivity (rs-FC) attempts to quantize such links, which is most commonly derived from blood oxygen level dependent (BOLD) fMRI. One review identified two patterns of rs-FC disruptions in schizophrenia: reduced connectivity between the prefrontal cortex, basal ganglia, thalamus, and cerebellum; and abnormal connectivity between the task-positive functional network, including the anterior cingulate gyrus and insula, and the default mode network, including the precuneus, posterior cingulate cortex, and medial frontal gyrus (Sheffield and Barch, 2016). Thus, neuroimaging differences between patients with schizophrenia and HCs are discernable. Whether neuroimaging can differentiate patients with TRS from patients with treatment-responsive schizophrenia is a separate question.

Two comprehensive systematic reviews of all neuroimaging findings addressed this question and independently concluded that no neuroimaging correlates were able to distinguish treatment-responsive schizophrenia from TRS (Mouchlianitis et al., 2016; Nakajima et al., 2015). However, only three studies on rs-FC in TRS (Alonso-Solis et al., 2015; Vercammen et al., 2010; Wolf et al., 2011) had been conducted by the time the more recent review was conducted in April 2015 (Mouchlianitis et al., 2016). In contrast, a short review focusing on functional connectivity suggested that rs-FC could differentiate patients with treatment-responsive schizophrenia from patients with TRS (Paul and Sharfman, 2016). Functional connectivity has also been posited to distinguish patients who might respond well to antipsychotics from those who might not at the earliest stages of the illness (Sarpal et al., 2016). However, research has not yet converged on any specific hypothesis of aberrant functional connectivity that might mediate antipsychotic treatment response, though disrupted rs-FC between subcortical and cortical structures (Tarcijonas and Sarpal, 2018) or between the insula and the saliency network (Paul and Sharfman, 2016) have been implicated.

Since Nakajima et al. (2015) and Mouchlianitis et al. (2016) were conducted, seven additional studies specifically examining treatment response and rs-FC in schizophrenia have been published. Thus, this review approaches the field of rs-FC in schizophrenia with two specific aims: (1) to assess the clinical potential of rs-FC to derive markers of treatment response and resistance; and (2) to examine lines of inquiry that may most successfully advance the clinical and scientific applications of rs-FC in treatment response and resistance of schizophrenia.

2. Methods

Embase, MEDLINE, PsycINFO, ProQuest, PUBMED, and Scopus were searched using the following terms: (1) "treatment resist*" OR "treatment refract*" OR "treatment respon*" OR clozapine (2) AND schizophren* (3) AND "resting state" OR "rs" (4) AND "functional magnetic resonance imaging" OR "fMRI" OR "f-MRI" (5) AND "functional connectivity". Terms were searched in the following fields: "Keyword" for MEDLINE, Embase, and PsycINFO; "Anywhere except full text – NOFT" for ProQuest; "All Fields" for PUBMED; and "Article title, Abstract, Keywords" for Scopus. No time span was specified for the database queries. Additional sources were sought from reference sections of major neuroimaging reviews in TRS (Mouchlianitis et al., 2016; Nakajima et al., 2015). Search results were deduplicated and screened, and only records specifying peer-reviewed primary research articles written in the English language were considered for full-text review.

Full-text articles were assessed for satisfaction of inclusion criteria by two independent reviewers (NC & JK). The date of the last search was August 1st, 2018. A study was included in this review if the following inclusion criteria were all affirmatively satisfied: (1) participants included patients with schizophrenia; (2) interventions included treatment with antipsychotic medication and assessment with resting-state fMRI; (3) comparisons included contrasts between schizophrenia patient groups differentiated (i.e. categorized) by treatment response or TRS patients compared to healthy controls (HCs); (4) outcomes included resting-state functional connectivity measures or surrogate measures such as resting-state functional network connectivity; and (5) study design included (a) cross-sectional studies that compared TRS to other subtypes of schizophrenia or healthy controls or (b) longitudinal studies that investigated treatment response using a priori criteria to separate antipsychotic or clozapine responders from nonresponders.

To assess the quality of studies reviewed, the risk of bias for all studies that met inclusion criteria was assessed using the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) by two independent reviewers (NC & JK) (Kim et al., 2013). Six domains (selection of participants, confounding variables, measurement of exposure, blinding of outcome assessments, incomplete outcome data, and selective outcome reporting) were considered, and each domain was rated as high, low, or unclear risk.

Participant groups and pairwise comparisons were extracted from all studies that met inclusion criteria. Extracted schizophrenia patient groups were classified into two mutually exclusive categories: "treatment-resistant schizophrenia" (TRS), defined as schizophrenia that fails to respond to at least 2 antipsychotic medication trials; and "not treatment-resistant schizophrenia" (NTRS), defined as schizophrenia that does not meet this criterion. A failure to respond to antipsychotic treatment was defined by the studies themselves. Some studies provided additional information to characterize antipsychotic treatment response. With respect to antipsychotic regimen, patient groups treated with non-clozapine antipsychotics are suffixed with "-A" (e.g. NTRS-A, TRS-A), and those treated with clozapine are suffixed with "-C" (e.g. TRS-C). No suffix was included if the use of clozapine was unclear. With respect to treatment responsiveness, patient groups that responded well to their respective antipsychotic are described as "responders" (e.g. NTRS responders; TRS-C responders), and those that failed to respond are described as "nonresponders" (e.g. NTRS-A

nonresponders, TRS-C nonresponders). The absence of responder/nonresponder qualifiers indicates that antipsychotic treatment response status was not specified (e.g. TRS-C patients, meaning TRS patients whose response to clozapine is unclear). Fig. 1 provides a breakdown of labels used and how each patient group was categorized within this review.

3. Results

A total of 159 records were identified using the methods described above, and 67 remained after deduplication. Twenty-six records were excluded by publication type, leaving 41 unique primary research articles eligible for full-text review. Thirty-one studies did not meet all inclusion criteria and were deemed ineligible. The 10 remaining studies were ultimately included in this review: 8 studies were selected from search records, 1 study (Vercammen et al., 2010) was identified from both Nakajima et al. (2015) and Mouchlianitis et al. (2016), and 1 study (White et al., 2016) was identified from Paul and Sharfman (2016). Fig. 2 details the strategy used for assessing papers for inclusion. Table 1 contains a summary of articles included in this review. Additional findings for associations between TRS or NTRS patients and antipsychotic dose or psychiatric symptoms can be found in Appendix A.

As assessed by the RoBANS criteria, there was a low risk of bias across all studies for the domains of confounding variables, measurement of exposure, blinding of outcome assessments, and incomplete outcome data. Bias for the selection of participants could not be determined for four studies generally because of insufficient information with respect to the selection of HCs (Alonso-Solis et al., 2015; McNabb et al., 2017; Sarpal et al., 2017; Vercammen et al., 2010), and one study was rated as high risk of bias due to self-reported measures for the assessment of HCs (White et al., 2016). Bias for selective outcome reporting could not be determined for two studies due to the novelty of the approach used (Ganella et al., 2018) and the lack of clarity for the identification and selection of components within an independent component analysis (McNabb et al., 2018). Supplementary Fig. 1 and Supplementary Fig. 2 (in Appendix A) summarize the risk of bias assessments.

3.1. Functional connectivity in NTRS patients

Five studies contained comparisons with NTRS patients (Alonso-Solis et al., 2015; McNabb et al., 2017; Sarpal et al., 2016; Sarpal et al., 2017; White et al., 2016). Table 2 contains a summary of comparisons with patients with TnRS.

3.1.1. NTRS patients as compared to HCs

Three studies contained comparisons between NTRS patients and HCs (Alonso-Solis et al., 2015; McNabb et al., 2017; White et al., 2016). Analysis methods were not comparable between studies. Two studies specifically examined NTRS-A responders (Alonso-Solis et al., 2015; McNabb et al., 2017). Alonso-Solis et al. (2015) reported increased rs-FC compared to HCs between seed ROIs in the posterior inferior parietal lobule and retrosplenial cortex to several loci within the bilateral occipital lobe. Graph analysis in McNabb et al. (2017) found no difference in functional network connectivity compared to HC, though mean connection strength was weaker amongst the NTRS-A responders. White et al. (2016) examined NTRS-A patients and found reduced rs-FC compared to HCs between a dorsal caudate seed ROI to loci in the prefrontal and visual cortices.

3.1.2. NTRS-A responders as compared to NTRS-A nonresponders

Two longitudinal studies examined first-episode schizophrenia patients that were antipsychotic-free during the baseline scan (Sarpal et al., 2016; Sarpal et al., 2017). Patients were administered antipsychotics after the baseline scan, and a priori criteria for antipsychotic treatment response was used to distinguish NTRS-A responders from NTRS-A nonresponders. In the first study, Sarpal et al. (2016) reported that greater baseline striatal connectivity with posterior regions of the brain predicted better treatment response, whereas lesser baseline striatal connectivity with anterior regions of the brain predicted worse treatment response (Sarpal et al., 2016). Areas that frequently exhibited connections with the striatum included the insular cortex, opercular cortex, anterior cingulate cortex, thalamus, orbitofrontal cortex, and posterior cingulate cortex (Sarpal et al., 2016). In the follow-up study, Sarpal et al. (2017) reported that greater duration of untreated psychosis (DUP) predicted worse treatment response, and that the DUP effect on treatment response was mediated by a measure of corticostriatal connectivity (Sarpal et al., 2017). Greater DUP predicted increased rs-FC between striatal ROIs and loci in the frontal lobes, while greater DUP predicted reduced rs-FC between striatal ROIs and the supramarginal gyrus, middle frontal gyrus, and cingulate gyrus (Sarpal et al., 2017).

3.2. Functional connectivity in TRS patients

Eight studies contained comparisons with TRS patients (Alonso-Solis et al., 2015; Ganella et al., 2017; Ganella et al., 2018; McNabb et al., 2018; McNabb et al., 2017; Vercammen et al., 2010; White et al., 2016; Wolf et al., 2011). Table 3 summarizes comparisons with TRS patients.

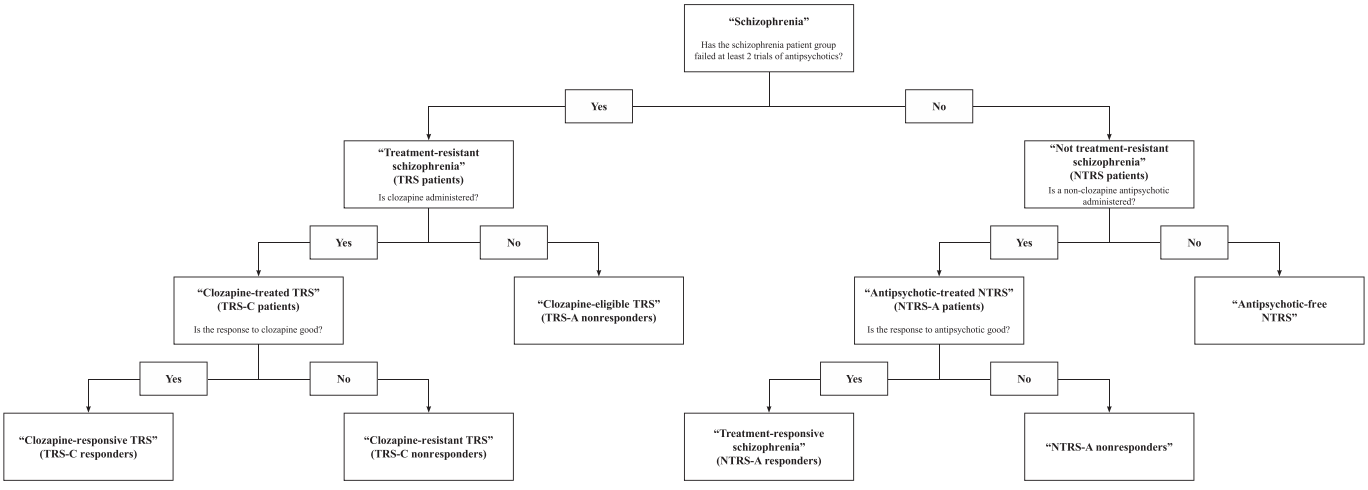

Fig. 1. Taxonomy of nomenclatures for treatment response and resistance in schizophrenia.

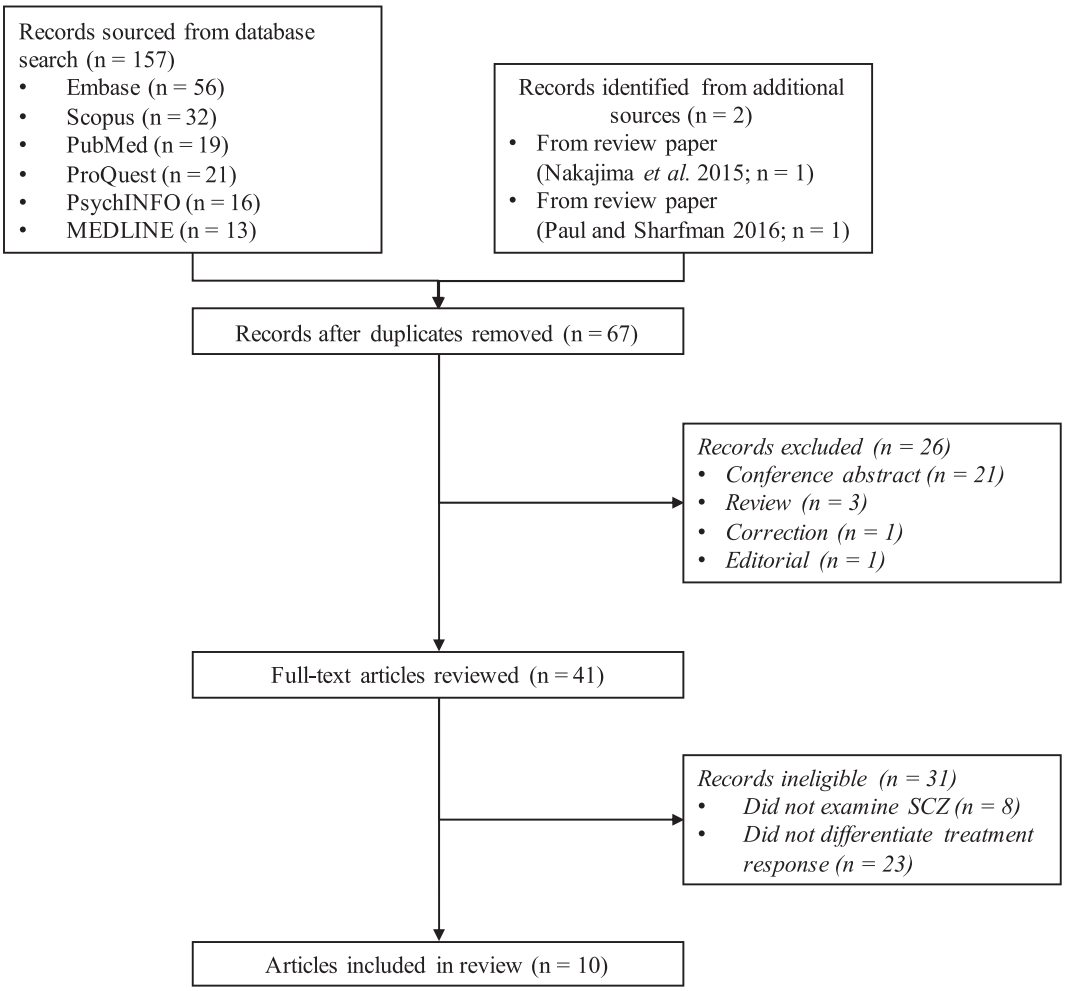

Fig. 2. Flowchart of search strategy and selection process. Abbreviations: SCZ = schizophrenia.

3.2.1. TRS patients as compared to healthy controls

Six studies contained comparisons between TRS and HCs (Alonso-Solis et al., 2015; Ganella et al., 2017; McNabb et al., 2017; Vercammen et al., 2010; White et al., 2016; Wolf et al., 2011). Two studies examined cortical rs-FC in TRS patients, though the analysis methods and ROIs examined differed between studies (Alonso-Solis et al., 2015; Vercammen et al., 2010). Vercammen et al. (2010) examined 10 bilateral ROIs involved in speech and verbal processing and reported broad reductions in rs-FC between the left temporo-parietal junction ROI to the right homotrope of Broca's area. Alonso-Solis et al. (2015) used seed ROIs for whole-brain analysis and reported increased rs-FC between a dorsomedial prefrontal cortex seed ROI to the bilateral central opercular cortex, bilateral insular cortex, bilateral precentral gyrus, and bilateral superior temporal gyrus and between a temporal pole seed ROI to the cerebellum. Reduced rs-FC was additionally reported between a ventromedial prefrontal cortex seed ROI to several loci in the bilateral cingulate gyrus, as well as between a hippocampal formation seed ROI to the bilateral posterior cingulate cortex and bilateral precuneus cortex (Alonso-Solis et al., 2015). As described in Section 3.1.1, the finding of increased rs-FC between seed ROIs in the posterior inferior parietal lobule and retrosplenial cortex to several loci within the bilateral occipital lobe was also found in TRS patients compared to HCs (Alonso-Solis et al., 2015).

The remaining 4 studies examined either mostly TRS-C patients (n = 11/16) (White et al., 2016), all TRS-C responders (McNabb et al., 2017), or all TRS-C patients (Ganella et al., 2017). Two studies used a graph analysis approach (Ganella et al., 2017; McNabb et al., 2017). McNabb et al. (2017) reported no differences between TRS-C responders and HCs (McNabb et al., 2017), while Ganella et al. (2017) reported reduced rs-FC in all lobes of TRS-C patients relative to HCs especially in fronto-temporal, fronto-occipital, temporo-occipital, and temporo-temporal connections (Ganella et al., 2017). The remaining two studies did not use comparable analysis methods (White et al., 2016; Wolf et al., 2011). White et al. (2016) reported reduced rs-FC in TRS-C patients relative to HCs between a ventral striatum seed ROI to the middle frontal gyrus, between a dorsal caudate seed ROI to the sensorimotor cortex, and between a ventrorostral putamen seed ROI to loci in the striatum (White et al., 2016). Wolf et al. (2011) identified reduced rs-FC in TRS-C patients relative to HCs between a left fronto-temporo-parietal resting-state network (RSN) to loci in the bilateral cingulate cortex and between an executive control RSN to the left precuneus (Wolf et al., 2011). Increased rs-FC was reported between loci in the right frontal lobe to both the executive control RSN and a right fronto-parietal RSN and between the left fronto-temporo-parietal RSN to loci in the bilateral temporal lobe (Wolf et al., 2011).

One study also investigated TRS-C nonresponders compared to HCs (McNabb et al., 2017). McNabb et al. (2017) reported that TRS-C nonresponders had weaker functional network connectivity compared to HCs within a cerebellar-frontal network, a cingulo-frontal-temporal network, and a fronto-parietal network.

3.2.2. TRS-C patients as compared to unaffected first-degree family members and HCs

One study by Ganella et al. (2018) examined TRS-C patients compared to unaffected first-degree family members (UFMs) and HCs using a graph analysis approach. The TRS-C and HC groups are the

Table 1
Summary of articles included in review. Abbreviations: ACC = anterior cingulate gyrus; AP = antipsychotic; CLZ = clozapine; CPZ = chlorpromazine; DMN = default mode network; DSM = Diagnostic and Statistical Manual of Mental Disorders; FC = functional connectivity; FLR = first-line responder; HC = healthy control; HP = hallucinating patient; ICA = independent component analysis; MR-AVH = medication-resistant auditory-verbal hallucinations; nHP = non-hallucinating patient; NTRS = not treatment-resistant schizophrenia; NTRS-A = antipsychotic-treated NTRS; NR-SCZ = non-refractory schizophrenia; PANSS = Positive and Negative Syndrome Scale; ROI = region of interest; SCZ = schizophrenia; TPJ = temporo-parietal junction; TRS = treatment-resistant schizophrenia; TRS-A = non-clozapine antipsychotic treated TRS; TRS-C = clozapine-treated TRS; UFM = unaffected first-degree family member; UTRS = ultra treatment-resistant schizophrenia.

Authors	Year	Participant groups (*label in original study*)	TRS definition	FC analysis method	Treatment for SCZ	Diagnostic criteria
Alonso-Solis et al.	2015	TRS (*HP;* n = 19); NTRS-A responders (*nHP; n* = 14); HC (*n* = 20)	Daily occurrence of AVH in past year despite ≥2 different AP trials (equivalent dose of 600 mg/day CLZ)	Seed-based ROI (cortical seeds in the DMN)	AP monotherapy for NTRS-A responders; AP mono- or polytherapy for TRS; (AP included CLZ, but further detail not provided)	DSM-IV-TR
Ganella et al.	2017	TRS-C (n = 42); HC (*n* = 42)	At least 2 unsuccessful trials over 4–10 weeks of 2 or more different AP types (equivalent dose of 1000 mg/day CPZ) within last 5 years and PANSS ≥90	Graph analysis	CLZ (therapeutic regime not specified)	Not specified
Ganella et al.	2018	TRS-C (n = 42); UFM (*n* = 16); HC (n = 42)	At least 2 unsuccessful trials over 4–10 weeks of 2 or more different AP types (equivalent dose of 1000 mg/day CPZ) within last 5 years and PANSS ≥90	Graph analysis	CLZ (therapeutic regime not specified)	Not specified
McNabb et al.	2017	TRS-C responders (*n* = 18); NTRS-A responders (*FLR; n* = 18); TRS-C nonresponders (*UTRS; n* = 16); HC (*n* = 17)	At least 2 unsuccessful trials over 6–8 weeks of atypical APs	Graph analysis	AP monotherapy for NTRS-A responders; CLZ monotherapy for TRS-C responders; CLZ polytherapy for TRS-C nonresponders	DSM-IV
McNabb et al.	2018	TRS-A nonresponders (n = 15); NTRS-A responders (*FLR; n* = 10)	At least 2 unsuccessful 6-week trials with first-line APs	ICA	AP mono- or polytherapy for TRS-A nonresponders and NTRS-A responders	DSM-5
Sarpal et al.	2016	SCZ (*N* = 41) split by treatment response: NTRS-A responders (*responders*; *n* = 24); NTRS-A nonresponders (*nonresponders*; n = 17)	N/A	Seed-based ROI (striatal seeds)	None at time of scan; AP monotherapy prescribed after scan	Not specified
Sarpal et al.	2017	SCZ (*N* = 83) split by treatment response: NTRS-A responders (*responders*; *n* = 48); NTRS-A nonresponders (*nonresponders; n* = 35)	N/A	Seed-based ROI (striatal seeds)	None at time of scan; AP monotherapy prescribed after scan	Not specified
Vercammen et al.	2010	TRS (*MR-AVH;* n = 27); HC (*n* = 27)	Daily occurrence of AVH despite ≥2 different AP trials	ROI connectivity (TPJ, ACC, Broca's area, amygdala, insula)	AP (therapeutic regime not specified)	DSM-IV
White et al.	2016	Mostly TRS-C (n = 16); NTRS-A (*NR-SCZ;* n = 22); HC (n = 20)	Persistent psychotic symptoms of at least moderate severity on ≥1 PANNS positive subscale and ≤ 59 on the Global Assessment of Function, despite ≥2 sequential 4-week AP trials (equivalent dose of 400–600 mg/day CPZ)	Seed-based ROI (striatal seeds)	AP monotherapy for treatment-responsive schizophrenia; AP mono- or polytherapy for TRS (CLZ for 11 of 16 TRS patients)	DSM-IV
Wolf et al.	2011	TRS-C (*MR-AVH;* n = 14); HC (n = 10)	Persistent hallucinations despite ≥2 different AP trials for at least 6 weeks	ICA	CLZ mono- or polytherapy	DSM-IV

Table 2
Comparisons of rs-FC including NTRS patients. Abbreviations: AP = antipsychotic; CLZ = clozapine; HC = healthy controls; NTRS = not treatment-resistant schizophrenia; NTRS-A = antipsychotic-treated NTRS; rs-FC = resting-state functional connectivity; ROI = region of interest; Rx = prescription.

Authors	Year	Participants of interest	Comparison group	Findings
NTRS patients compared to HC				
Alonso-Solis et al.	2015	NTRS-A responders (n = 14) Rx: AP, potentially including CLZ but proportion not specified	HC (n = 20)	Increased rs-FC between seed ROI for posterior inferior parietal lobule and bilateral occipital fusiform gyrus, bilateral lingual gyrus, left inferior occipital cortex. Increased rs-FC between seed ROI for retrosplenial cortex and bilateral occipital cortex and bilateral occipital fusiform gyrus.
McNabb et al.	2017	NTRS-A responders (n = 18) Rx: AP	HC (n = 17)	No significant differences in functional network connectivity, though NTRS-A responders had weaker mean connection strength.
White et al.	2016	NTRS-A (n = 22) Rx: AP	HC (n = 20)	Reduced rs-FC betweed seed ROI for dorsal caudate and rostral prefrontal cortex, dorsolateral prefrontal cortex, visual cortex.
NTRS-A responders compared to NTRS-A nonresponders				
Sarpal et al.	2016	NTRS-A responders (n = 24) Rx: None at time of scan; AP given after scan	NTRS-A nonresponders (n = 17) Rx: None at time of scan; AP given after scan	Greater baseline striatal connectivity with posterior regions of the brain and lesser baseline striatal connectivity with anterior regions of the brain predicted better treatment response. Areas that frequently appeared in striatal connections included the insular cortex, opercular cortex, anterior cingulate cortex, thalamus, orbitofrontal cortex, and posterior cingulate cortex.
Sarpal et al.	2017	NTRS-A responders (n = 48) Rx: None at time of scan; AP given after scan	NTRS-A nonresponders (n = 35) Rx: None at time of scan; AP given after scan	Duration of untreated psychosis predicted poor treatment response; increased rs-FC between seed ROIs for ventral striatum/nucleus accumbens and subcallosal cortex, orbitofrontal cortex, and medial frontal pole; and reduced rs-FC between seed ROIs for striatal regions and supramarginal gyrus, middle frontal gyrus, and cingulate gyrus. Greater duration of untreated psychosis mediated the relationship between rs-FC and treatment response.

same groups described in Ganella et al. (2017). Connections from the temporal lobe, including the fusiform gyrus, and the occipital lobe, including the middle occipital gyrus, were reduced in both TRS-C patients and UFMs compared to HCs. Connections from the frontal lobe, including the paracentral lobule and rolandic operculum, and the temporal lobe, including Heschl's gyri, were reduced in TRS-C patients but not UFMs compared to HCs. Both global and local efficiency were increased in UFMs and TRS-C patients compared to HCs but not between UFMs and TRS-C patients.

3.2.3. TRS-C responders as compared to TRS-C nonresponders

One study compared TRS-C responders to TRS-C nonresponders (McNabb et al., 2017). McNabb et al. (2017) reported no statistical differences in functional network connectivity between the groups.

3.3. Functional connectivity in TRS patients compared to NTRS patients

Four cross-sectional studies contained comparisons between TRS patients and NTRS patients (Alonso-Solis et al., 2015; McNabb et al., 2018; McNabb et al., 2017; White et al., 2016). Table 4 contains a summary of these comparisons. Two studies examined cortical rs-FC, though the analysis methods differed between studies (Alonso-Solis et al., 2015; McNabb et al., 2018). In Alonso-Solis et al. (2015), rs-FC contrasts described earlier between TRS patients and HCs were also found between TRS patients and NTRS responders, with the exception of rs-FC involving seed ROIs in the posterior inferior parietal lobule and retrosplenial cortex to several loci within the bilateral occipital lobe (Alonso-Solis et al., 2015). Some regions that exhibited increased rs-FC in Alonso-Solis et al. (2015) were similarly identified as increased in McNabb et al. (2018) in an independent component analysis for TRS-A nonresponders compared to NTRS-A responders, which identified increased rs-FC in a sensorimotor network (McNabb et al., 2018). These regions included the bilateral precentral gyrus, bilateral insulae, bilateral central opercular cortex, and cerebellum (Alonso-Solis et al., 2015; McNabb et al., 2018).

The 2 remaining studies respectively compared mostly TRS-C patients (White et al., 2016) or all TRS-C responders (McNabb et al., 2017). White et al. (2016) reported reduced rs-FC in TRS-C patients compared to NTRS-A patients between a ventral striatum seed ROI to the substantia nigra, and between a dorsocaudal putamen seed ROI to the pulvinar of the thalamus (White et al., 2016). White et al. (2016) also reported increased rs-FC between a seed ROI for the dorsal caudate and medial and superior prefrontal cortex (White et al., 2016). McNabb et al. (2017) reported no significant differences in functional network connectivity between TRS-C responders and NTRS responders (McNabb et al., 2017).

4. Discussion

Functional connectivity is altered amongst patients with schizophrenia, but the nature of this altered connectivity remains unclear (Sheffield and Barch, 2016). Differentiating patients with schizophrenia by treatment response may be a pragmatic approach for managing heterogeneity in rs-FC findings, especially for delineating illness and treatment-related effects. In brief, studies that investigated striatal functional connectivity found rs-FC differences between patients with schizophrenia based on treatment response (Sarpal et al., 2016; Sarpal et al., 2017; White et al., 2016). Intriguingly, the insular cortex, the central opercular cortex, and areas in the sensorimotor cortex were often identified together in patient groups that were associated with antipsychotic treatment-resistance (Alonso-Solis et al., 2015; Ganella et al., 2017; Ganella et al., 2018; McNabb et al., 2018; Sarpal et al., 2016; White et al., 2016). Across all patients with schizophrenia, rs-FC in regions of occipital lobe were commonly disrupted (Alonso-Solis et al., 2015; Ganella et al., 2017; Ganella et al., 2018; White et al., 2016; Wolf et al., 2011).

Table 3
Comparisons of rs-FC including TRS patients. Abbreviations: AP = antipsychotic; CLZ = clozapine; HC = healthy control; rs-FC = resting-state functional connectivity; ROI = region of interest; RSN = resting-state network; Rx = prescribed medication; SCZ = schizophrenia; TRS = treatment-resistant schizophrenia; TRS-C = clozapine-treated TRS.

Authors	Year	Participants of interest	Comparison group	Findings
TRS compared to HC				
Alonso-Solis et al.	2015	TRS (n = 19) Rx: AP, potentially including CLZ but proportion not specified	HC (*n* = 20)	Increased rs-FC between seed ROI for posterior inferior parietal lobule and bilateral occipital fusiform gyrus, bilateral lingual gyrus, and left occipital pole. Increased rs-FC between seed ROI for retrosplenial cortex and bilateral lateral occipital cortex, bilateral intracalcarine cortex, left occipital fusiform gyrus, bilateral lingual gyrus, left occipital fusiform gyrus. Increased rs-FC between seed ROI for dorsomedial prefrontal cortex and bilateral central opercular cortex, bilateral insular cortex, bilateral precentral gyrus, bilateral superior temporal gyrus. Increased rs-FC between seed ROI for temporal pole and cerebellum. Reduced rs-FC between seed ROI for ventromedial prefrontal cortex and bilateral paracingulate cortex, bilateral anterior cingulate cortex, bilateral subcallosal cortex. Reduced rs-FC between seed ROI for hippocampal formation and bilateral posterior cingulate cortex and bilateral precuneus cortex.
Ganella et al.	2017	TRS-C (n = 42) Rx: CLZ	HC (n = 42)	Reduced rs-FC mainly in fronto-temporal, fronto-occipital, temporo-occipital, and temporo-temporal connections. Global efficiency was reduced, but local efficiency was increased. In temporal lobe, reduced connectivity between Heschl's gyrus and frontal lobe. In occipital lobe, reduced connectivity between cuneus and frontal lobe. In frontal lobe, reduced connectivity between paracentral lobule and occipital lobe.
McNabb et al.	2017	TRS-C responders (n = 18) Rx: CLZ monotherapy	HC (n = 17)	No significant differences in functional network connectivity.
McNabb et al.	2017	TRS-C nonresponders (n = 16) Rx: CLZ polytherapy	HC (n = 17)	Reduced functional network connectivity in a cerebellar-frontal network. Reduced functional network connectivity in a cingulo-frontal-temporal network. Reduced functional network connectivity in a fronto-parietal network. Mean connection strength was weakest overall in TRS-C nonresponders in comparison with HC.
Vercammen et al.	2010	TRS (n = 27) Rx: AP	HC (n = 27)	Broadly reduced rs-FC in left temporo-parietal junction, though only reduced rs-FC between ROI for left temporo-parietal junction and right homotrope of Broca's area was statistically significant.
White et al.	2016	Mostly TRS-C (n = 16) Rx: AP, including CLZ for 11 of 16 TRS	HC (n = 20)	Reduced rs-FC between seed ROI for ventral striatum and middle frontal gyrus. Reduced rs-FC between seed ROI for dorsal caudate and sensorimotor cortex. Reduced rs-FC between seed ROI for ventrorostral putamen and within intrastriatal regions.
Wolf et al.	2011	TRS-C (n = 14) Rx: CLZ	HC (n = 10)	Increased rs-FC in left fronto-temporo-parietal RSN (composed of the bilateral prefrontal cortex and left temporoparietal regions) between left middle temporal gyrus and bilateral superior temporal gyrus. Increased rs-FC in right frontoparietal RSN (composed of right prefrontal regions, superior and inferior parietal regions, parts of the cingulate cortex, and the precuneus) between right middle frontal gyrus. Increased rs-FC in executive control (composed of bilateral prefrontal, bilateral middle temporal, and bilateral interior parietal regions and the cingulate cortex) RSN between right middle frontal gyrus and superior frontal gyrus. Reduced rs-FC in left fronto-temporo-parietal RSN between left anterior cingulate cortex and right posterior cingulate cortex. Reduced rs-FC in executive control RSN between left precuneus.
TRS-C compared to UFM and HC				
Ganella et al.	2018	TRS-C (n = 42) Rx: CLZ	UFM (n = 16); HC (n = 42)	Reduced rs-FC associated with familial risk in temporal areas including the fusiform gyrus. Reduced rs-FC associated with familial risk in occipital areas including middle occipital lobe. Reduced rs-FC associated with precipitating risk/illness effects in frontal areas including paracentral lobule and rolandic operculum. Reduced rs-FC associated with precipitating risk/illness effects in temporal areas including Heschl's gyrus. Global and local efficiency increased in UFM and TRS compared to HC, but no difference in efficiency between UFM and TRS.
TRS-C responders compared to TRS-C nonresponders				
McNabb et al.	2017	TRS-C responders (n = 18) Rx: CLZ monotherapy	TRS-C nonresponders (n = 16) Rx: CLZ polytherapy	No significant differences in functional network connectivity. Mean connection strength was weakest overall in TRS-C nonresponders, but the effect was not significant compared to TRS-C responders.

Two groups investigated antipsychotic treatment response and striatal functional connectivity (Sarpal et al., 2016; Sarpal et al., 2017; White et al., 2016). Sarpal et al. (2016) reported that an anterior-posterior gradient of baseline striatal connections predicted treatment response in patients with first-episode schizophrenia *prior to receiving antipsychotic treatment* (Sarpal et al., 2016). An increase in striato-anterior rs-FC was associated with worse treatment response and vice versa (Sarpal et al., 2016). They also reported that the DUP might mediate treatment response via a corticostriatal-FC-related measure (Sarpal et al., 2017). While the antipsychotic-free NTRS patients in Sarpal et al. (2016, 2017) are not directly analogous to the TRS-C patients studied in White et al. (2016), White et al. (2016) reported increased rs-FC between the dorsal caudate to the superior and medial prefrontal cortex in mostly TRS-C patients compared to NTRS-A patients. Read together, these findings suggest that a marker of corticostriatal rs-FC between striatal sub-regions and anterior cortical

Table 4
Comparisons of rs-FC between TRS and NTRS patients. Entries in subsections are sorted from least or unknown to greatest number taking clozapine Abbreviations: AP = antipsychotic; CLZ = clozapine; HC = healthy control; NTRS = not treatment-resistant schizophrenia; NTRS-A = antipsychotic-treated NTRS; rs-FC = resting-state functional connectivity; ROI = region of interest; Rx = prescribed medication; SCZ = schizophrenia; TRS = treatment-resistant schizophrenia; TRS-A = non-clozapine antipsychotic-treated TRS; TRS-C = clozapine-treated TRS.

Authors	Year	Participants of interest	Comparison group	Findings
TRS compared to NTRS				
McNabb et al.	2018	TRS-A nonresponders (n = 15) Rx: AP	NTRS-A responders (n = 10) Rx: AP	Increased rs-FC in sensorimotor network, including motor cortices, primary somatosensory cortices, bilateral insulae, central opercular cortices, bilateral crus VI of the cerebellum, and left thalamus. Increased rs-FC in precuneus, including precuneus cortex, intracalcarine cortex, supracalcarine cortex, lingual gyrus, cuneal gyrus, and posterior cingulate gyrus.
Alonso-Solis et al.	2015	TRS (n = 19) Rx: AP, potentially including CLZ but proportion not specified	NTRS-A responders (n = 14) Rx: AP, potentially including CLZ but proportion not specified	Increased rs-FC in seed ROI for dorsomedial prefrontal cortex and bilateral central opercular cortex, bilateral insular cortex, bilateral precentral gyrus, and bilateral superior temporal gyrus. Increased rs-FC in seed ROI for temporal pole and cerebellum. Reduced rs-FC in seed ROI for ventromedial prefrontal cortex and bilateral paracingulate cortex, bilateral anterior cingulate cortex, and bilateral subcallosal cortex. Reduced rs-FC in seed ROI for hippocampal formation and bilateral posterior cingulate cortex and bilateral precuneus cortex.
White et al.	2016	Mostly TRS-C (n = 16) Rx: AP, including CLZ for 11 of 16 TRS	NTRS-A (n = 22) Rx: AP	Increased rs-FC in seed ROI for dorsal caudate and medial prefrontal cortex and superior frontal cortex. Reduced rs-FC in seed ROI for ventral striatum and substantia nigra. Reduced rs-FC in seed ROI for dorsal caudal putamen and pulvinar of the thalamus.
McNabb et al.	2017	TRS-C responders (n = 18) Rx: CLZ monotherapy	NTRS-A responders (n = 18) Rx: AP	No significant differences in functional network connectivity. Mean connection strength was weaker in NTRS-A responders compared to TRS-C responders, though the effect was not significant.

loci could be developed to predict antipsychotic treatment resistance in patients with schizophrenia. This potential marker(s) might be detectable at the earliest stages of schizophrenia and persist through antipsychotic treatment trials.

Across studies of TRS patients, a cluster of brain regions including the insular cortex, central opercular cortex, and sensorimotor cortex seemed to be associated with antipsychotic treatment resistance. Earlier discussed studies on corticostriatal connectivity by Sarpal et al. (2016) and White et al. (2016) listed these regions in rs-FC contrasts between schizophrenia patient groups (Sarpal et al., 2016; White et al., 2016), while McNabb et al. (2018) identified these regions amongst others as part of a sensorimotor resting-state network. Curiously, these areas exhibited increased rs-FC in TRS nonresponders versus HCs and NTRS responders (Alonso-Solis et al., 2015; McNabb et al., 2018), and increased striatal rs-FC with these areas was generally associated with worse treatment response (Sarpal et al., 2016). On the other hand, rs-FC was *reduced* in these areas when clozapine was administered (Ganella et al., 2017; Ganella et al., 2018; White et al., 2016). Given that these regions were disrupted in contrasts between TRS patients and both HCs and NTRS responders, this cluster could be an informative and clinically useful rs-FC marker of treatment resistance. Additionally, a recent study reported that increased connectivity between the default mode network and sensorimotor network predicted lesser positive symptom severity in a generalized schizophrenia population (Lee et al., 2018). Nonetheless, these findings provide a prima facie rationale for more formal and intensive investigation of the sensorimotor network in TRS with respect to developing a neuroimaging marker of treatment resistance.

From the perspective of using rs-FC to investigate underlying mechanisms of schizophrenia, a cluster of regions including the precuneus, cuneus, intracalcarine cortex, lingual gyrus, and fusiform gyrus was commonly disrupted across NTRS and TRS. One interpretation of this clustering might be a disruption of the "what/where pathways". Also known as the two-stream hypothesis, the pathways describe visual and auditory information processing from the occipital cortex to the temporal lobe (the "what" pathway) and parietal lobe (the "where" pathway) (Goodale and Milner, 1992). A rather poignant observation is the interaction between the what/where pathways and the sensorimotor network. While beyond the scope of this review, feedback mechanisms involved in speech recognition are thought to integrate the networks, especially for predictive coding of speech and subsequent speech generation (Hickok, 2012); thus, it is conceivable that dysconnectivity between these networks could be associated with auditory hallucinations and other positive symptoms experienced by patients with schizophrenia. In a manner potentially unifying the themes discussed in this section, one study noted a link between the sensorimotor network and the precuneus in the default mode network (Kaufmann et al., 2015), whereas a recent review on rs-FC in schizophrenia identified abnormal connectivity primarily in task-positive regions (including the insula and anterior cingulate cortex, i.e. the salience network) and the default mode network (including the precuneus, posterior cingulate cortex, and medial frontal gyrus) (Sheffield and Barch, 2016). The relationship is evidently complex, though the frequency of common and related findings in these regions is encouraging for developing more comprehensive theories that may explain mechanisms of schizophrenia.

Given that seven of the ten studies in this review were published after the last comprehensive review of neuroimaging studies in TRS (Mouchlianitis et al., 2016), it is clear that there is a growing interest toward using functional connectivity to better understand treatment response and resistance in schizophrenia. Overall, however, and despite great interest, the comparability of findings was limited due to differences in patient group characteristics and methodological approaches. These sources of heterogeneity are barriers toward the convergence of functional connectivity findings for a hypothesis of FC in schizophrenia and are discussed further in the next sections.

5. Limitations

The conclusions derived in this review ought to be qualified by several limitations. With regard to the methods and procedures of this review, including only studies that explicitly *categorized* patients with schizophrenia by treatment response precluded the consideration of studies that examined treatment response across a general schizophrenia cohort. Such studies could provide insight for functional connectivity differences associated with treatment response, but a potential functional connectivity difference that contrasts responders from nonresponders could be occluded in analyses across a general schizophrenia cohort, leading to confounding effects. Furthermore, some evidence suggests that TRS may be categorically different from treatment-responsive schizophrenia (Demjaha et al., 2014; Demjaha et al., 2012). For this reason, this review adopted the more stringent approach.

With regard to the comparability of results between studies, several factors related to patient group characteristics limit both direct and

indirect comparisons. First, while diagnostic criteria for TRS were similar across studies, the differences were nontrivial and could lead to incompatible comparisons. For example, all studies regarding TRS specified that patients in the TRS group must have failed at least two trials of first-line antipsychotics; however, minimum dose equivalents, the assessment of "failed" treatment response, and minimum trial durations were inconsistent or unspecified. While criteria for the diagnosis of TRS have previously been described (Kane et al., 1988), the use of such criteria was hardly standardized (Mouchlianitis et al., 2016) until the recent development of the Treatment Response and Resistance in Psychosis (TRRIP) consensus guidelines (Howes et al., 2017). As many studies included in this review had already finished or were underway when the TRRIP guidelines were being developed, limiting this review to only TRRIP-compliant studies would have been premature. Second, information on prior or current adherence to prescribed pharmaceutical treatments was seldom collected. Whereas "treatment resistance" is usually understood in context of inefficacy of antipsychotics, a patient that refuses or fails to adhere to prescribed antipsychotic regimens may be "treatment-resistant" by virtue of nonadherence rather than inefficacy of antipsychotic treatment. Previous research suggests that some patients with TRS have subtherapeutic antipsychotic serum levels by way of nonadherence, and that this nonadherence may contribute to heterogeneity in TRS patient groups (McCutcheon et al., 2015). In light of this issue, the TRRIP guidelines recommend several minimum criteria for current adherence in TRS, including that >80% of prescribed doses are taken, that the assessment of adherence be from two different sources, and that antipsychotic plasma levels be measured at least once (Howes et al., 2017). Third, given both the known efficacy of clozapine over other antipsychotics for TRS (Kane et al., 1988) and the likelihood that clozapine exerts its effects through a pharmacologically distinct mechanism (Kane and Correll, 2016), failing to distinguish clozapine from other antipsychotics could introduce unpredictable and confounding effects. However, studies where all patients with TRS are treated with clozapine may not be well equipped to distinguish effects of clozapine from TRS. Only one study in this review resolved this conflict by comparing "clozapine-eligible" TRS patients and NTRS responders to distinguish the confounding effects of clozapine from TRS (McNabb et al., 2018).

Differences in the application of rs-FC analysis methods also largely precluded reasonable comparisons between studies and may be an inherent challenge for any review of functional connectivity findings occurring over the timespan of the studies reviewed. While the nature of a research question should inform the selection of a particular analytical approach, the degree of comparability between different rs-FC analyses is highly dependent on the analytical approach used. At the same time, over the past decade, advances in computational neuroimaging have led to increasingly complex methods that have fundamentally changed the way researchers conceptualize and measure functional connectivity. For example, the earliest study included in this review measured the specific functional connectivity of two a priori ROIs with eight other a priori ROIs (Vercammen et al., 2010). Later studies measured functional connectivity as the co-activation of individual a priori seed ROIs with the rest of the brain (Alonso-Solis et al., 2015; Sarpal et al., 2016; Sarpal et al., 2017; White et al., 2016) or as the co-activation between brain networks (identified a posteriori and represented as maximally independent statistical components) and the rest of the brain (Ganella et al., 2018; Wolf et al., 2011). More recently, functional connectivity has been assessed by graph analysis, which examines pairwise co-activations between all ROIs defined by parcellations from a brain atlas (Ganella et al., 2017; Ganella et al., 2018; McNabb et al., 2017). Although these methods appear to be superficially similar, different approaches may measure different underlying phenomena (Chen and Glover, 2015; van den Heuvel and Pol, 2010). Such considerations similarly prohibit sensible meta-analysis of summary measures of functional connectivity between studies that use highly divergent methods. Fortunately, certain approaches such as seed-based ROI analysis and independent components analysis have been shown to produce similar results, and their similarities may be described qualitatively (Van Dijk et al., 2010). Quantitative comparisons between such methods are also theoretically possible but may require the original data (Joel et al., 2011).

6. Future directions

Functional connectivity is one of many tools available to researchers and clinicians. The construction of a comprehensive theory for treatment response and resistance will require incorporating of findings from other neuroimaging and research modalities. Diffusion tensor imaging could provide an anatomical substrate for linking distal areas of activation in rs-FC (Skudlarski et al., 2010), whereas magnetic resonance spectroscopy may uncover underlying biochemical changes in neuroimaging foci associated with treatment response or resistance (Iwata et al., 2018). In context of brain connectivity, findings from functional connectivity studies are often difficult to interpret (Buckner et al., 2013), but complementary analyses measuring effective connectivity may assist with clarifying causational interactions within and between networks (Friston, 2011; Goldenberg and Galvan, 2015).

Nonetheless, the findings in this review provide a strong basis for the clinical and scientific potential of functional connectivity in elucidating markers and mechanisms of treatment resistance and response in schizophrenia. With growing research interest on the topic, a coordinated research strategy would greatly advance knowledge regarding treatment response and resistance. This sentiment has been expressed amongst researchers studying TRS in the TRRIP consensus guidelines, which detail minimum and optimum criteria for various domains of TRS (Howes et al., 2017). Full operationalization of TRRIP guidelines in future studies will ensure a greater level of consistency between studies, especially to facilitate comparisons and to reconcile findings.

On the other hand, whereas the fast-paced development of rs-FC analysis methods has provided important perspectives on the relationship between functional connectivity and treatment resistance, it has limited the comparability between studies, the replication of findings, and the ability to draw conclusions from meta-analytic approaches. The publication of deidentified raw data with along with original analyses allows both the innovation from novel analytic techniques in addition to enabling comparison between studies for replication and improved statistical power. Data sharing is increasingly feasible with platforms such as OpenNeuro (https://openneuro.org) and multimodal imaging data standards such as the Brain Imaging Data Structure (BIDS) (Gorgolewski et al., 2017), which is compatible with validated preprocessing pipelines like *fmriprep* (Esteban et al., 2019).

It should be noted that methodological heterogeneity amongst the studies reviewed was mostly amongst the preprocessing of fMRI data and the analysis of rs-FC rather than in the fMRI acquisition methods, so incomparability between studies could potentially be resolved by making the raw data available. If the publishing of interoperable datasets becomes common practice, testing competing hypotheses as specified by particular rs-FC methods will also become more feasible and could facilitate the identification of consistent, replicatable group rs-FC differences.

Contributors

N.K.C. conceived the idea, performed the literature search, extracted findings, and drafted the manuscript. J.K. performed the literature search, reviewed the draft manuscript, and contributed to the writing of the manuscript. P.S., E.B., E.P., F.C., and Y.I. all reviewed the draft manuscript and contributed to the writing of the manuscript. P.G. and A.G.G. supervised the writing process of this manuscript and provided critical feedback on the interpretation of findings. All authors contributed to and have approved the final draft of the manuscript.

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Appendix A. Supplementary data

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