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Neuroimaging findings in treatment-resistant schizophrenia: a systematic review:

Lack of neuroimaging correlates of treatment-resistant schizophrenia

Shinichiro Nakajima, M.D., Ph.D.[1,2,3,4], **Hiroyoshi Takeuchi, M.D., Ph.D.**[3,4,5], **Eric Plitman, B.Sc.**[1,6], **Gagan Fervaha, B.Sc.**[5,6], **Philip Gerretsen, M.D., M.S.W.**[1,2,3,6], **Fernando Caravaggio, B.Sc.**[1,6], **Jun Ku Chung, B.Sc.**[1,6], **Yusuke Iwata, M.D.**[1,3,4], **Gary Remington, M.D., Ph.D.**[3,5,7], and **Ariel Graff-Guerrero, M.D., Ph.D.**[1,2,3,7]

[1] Multimodal Imaging Group - Research Imaging Centre, Centre for Addiction and Mental Health, Toronto, Canada

[2] Geriatric Mental Health Division, Centre for Addiction and Mental Health, Toronto, Canada

[3] Department of Psychiatry, University of Toronto, Toronto, Canada

[4] Department of Neuropsychiatry, School of Medicine, Keio University, Tokyo, Japan

[5] Schizophrenia Division, Complex Mental Illness Program, Centre for Addiction and Mental Health, Toronto, Canada

Corresponding Author Ariel Graff-Guerrero, M.D., Ph.D. Multimodal Imaging Group – Research Imaging Centre, Centre for Addiction and Mental Health. 250 College Street, Toronto, Ontario, M5T 1R8 Phone: (416) 535-8501 Ext. 4834 Fax: (416) 583-1284 ariel_graff@yahoo.com.mx.
Shinichiro Nakajima, shinichiro_nakajima@hotmail.com
Hiroyoshi Takeuchi, hirotak@dk9.so-net.ne.jp
Eric Plitman, plitmaneric@gmail.com
Gagan Fervaha, gagan.fervaha@camh.ca
Fernando Caravaggio, fernando.caravaggio@gmail.com
Philip Gerretsen, philgerretsen@yahoo.com
Jun Ku Chung, junku.chung@mail.utoronto.ca
Yusuke Iwata, yusuke.iwata2010@gmail.com
Gary Remington, gary.remington@camh.ca

Contributors:
S. Nakajima, H. Takeuchi, G. Fervaha and A. Graff-Guerrero lead study design, literature review and interpretation and manuscript preparation. E. Plitman, P. Gerretsen, F. Caravaggio, JK Chung, Y Iwata , and G Remington contributed to the interpretation of the results. All authors contributed to and have approved the final manuscript.

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[6] Institute of Medical Science, University of Toronto, Toronto, Canada

[7] Campbell Research Institute, Centre for Addiction and Mental Health, Toronto, Canada

Abstract

Background—Recent developments in neuroimaging have advanced understanding biological mechanisms underlying schizophrenia. However, neuroimaging correlates of treatment-resistant schizophrenia (TRS) and superior effects of clozapine on TRS remain unclear.

Methods—Systematic search was performed to identify neuroimaging characteristics unique to TRS and ultra-resistant schizophrenia (i.e. clozapine-resistant [URS]), and clozapine's efficacy in TRS using Embase, Medline, and PsychInfo. Search terms included (schizophreni*) and (resistan* OR refractory OR clozapine) and (ASL OR CT OR DTI OR FMRI OR MRI OR MRS OR NIRS OR PET OR SPECT).

Results—25 neuroimaging studies have investigated TRS and effects of clozapine. Only 5 studies have compared TRS and non-TRS, collectively providing no replicated neuroimaging finding specific to TRS. Studies comparing TRS and healthy controls suggest hypometabolism in the prefrontal cortex, hypermetabolism in the basal ganglia, and structural anomalies in the corpus callosum contribute to TRS. Clozapine may increase prefrontal hypoactivation in TRS although this was not related to clinical improvement; in contrast, evidence has suggested a link between clozapine efficacy and decreased metabolism in the basal ganglia and thalamus.

Conclusion—Existing literature does not elucidate neuroimaging correlates specific to TRS or URS, which, if present, might also shed light on clozapine's efficacy in TRS. This said, leads from other lines of investigation, including the glutamatergic system can prove useful in guiding future neuroimaging studies focused on, in particular, the frontocortical-basal ganglia-thalamic circuits. Critical to the success of this work will be precise subtyping of study subjects based on treatment response/nonresponse and the use of multimodal neuroimaging.

Keywords

schizophrenia; treatment-resistance; clozapine; neuroimaging; glutamate

1. Introduction

All currently available antipsychotics for schizophrenia are, to varying degrees, antagonists of the dopamine D_2 receptor (D_2R) (Kapur et al., 2000; Mamo et al., 2007; Seeman and Kapur, 2000). The efficacy of D_2R antagonism is premised on the dopamine hypothesis of schizophrenia (Howes and Kapur, 2009), which proposes that aberrant dopaminergic functioning is critical in schizophrenia (Abi-Dargham et al., 1998; Hietala et al., 1999; Kapur, 2003; Laruelle et al., 1996; Sato et al., 1992). While the dopamine hypothesis remains central to our current understanding of schizophrenia, approximately 20% to 35% of patients show partial or no response to standard antipsychotic treatment (i.e. conventional or atypical antipsychotics, excepting clozapine [CLZ]) (Lindenmayer, 2000). Individuals in this sample, termed treatment-resistant schizophrenia (TRS), are candidates for CLZ, the one antipsychotic with established efficacy in TRS (Chung and Remington, 2005). However, response to CLZ is limited, in the range of 30-70% (Buchanan et al., 1998;

Chakos et al., 2001; Conley and Kelly, 2001; Kane et al., 1988), and for those who are not responsive to CLZ, “ultra-resistant” schizophrenia (URS), there are no treatments to date that have proven consistently effective (Cipriani et al., 2009; Sommer et al., 2012).

Recent developments in neuroimaging techniques have substantially advanced our understanding of the biological mechanisms underlying schizophrenia, in particular from the standpoint of dopamine, with studies demonstrating that dopamine synthesis capacity, dopamine release and baseline dopamine levels are elevated in the striatum of patients with schizophrenia (Abi-Dargham et al., 2000; Fusar-Poli and Meyer-Lindenberg, 2013; Howes et al., 2012; Howes et al., 2007; Laruelle et al., 1996). With respect to TRS specifically, Demjaha et al. (2012) compared presynaptic dopaminergic dysfunction among patients with TRS, patients with non-TRS, and healthy controls (HC) using ^{18}[F]-DOPA PET (Demjaha et al., 2012). Dopamine synthesis capacity was lower in patients with TRS than in patients with non-TRS, but not different between TRS and healthy controls (HC). Coppens et al. (1991) reported greater than 95% blockade of D_2Rs in the striatum of patients with TRS, concluding that lack of therapeutic response cannot be attributed to insufficient blockade of D_2Rs in this population (Coppens et al., 1991). Focusing presynaptically, it has also been reported that augmentation with tetrabenazine, a presynaptic vesicular monoamine transporter inhibitor, is not effective in patients with TRS (Remington et al., 2012). Taken together, these data indicate that patients meeting criteria for TRS have a form (or forms) of the illness that are mediated beyond dopamine neurotransmission.

To this last point, it has been proposed that TRS represents at least several distinct forms from the standpoint of pathophysiology (Farooq et al., 2013). One form is responsive to CLZ, an atypical antipsychotic with superior efficacy in 30% to 70% of patients with TRS (Agid et al., 2011; Chakos et al., 2001; Kane et al., 1988; Lieberman et al., 1994; Meltzer et al., 1990). Whether part of its efficacy in this group is related to D_2R binding is not entirely clear; CLZ occupies less than 50% of D_2Rs 2-hours following administration and has a very transient effect on D_2Rs (Kapur and Seeman, 2001; Tauscher et al., 1999). Regardless, it must at least in part emerge its response through other mechanisms as individuals meeting criteria for TRS have already demonstrated suboptimal response to standard antipsychotic therapy. This calls into question the role of other receptors and systems, which in the case of clozapine has been postulated to include the glutamatergic system (Abdul-Monim et al., 2006; Abekawa et al., 2006, 2007; Amitai et al., 2012; Amitai et al., 2007; Didriksen et al., 2007; Grayson et al., 2007; Hashimoto et al., 2005; Idris et al., 2005; Lopez-Gil et al., 2007), serotonin 5-HT_{2A} receptors (Nordstrom et al., 1995), and dopamine D_1 (Tauscher et al., 2004) or D_4 receptors (Nord and Farde, 2011; Suzuki et al., 2011; Yilmaz et al., 2012). At present, though, it remains that we do not understand what accounts for the efficacy of clozapine in TRS. In those with TRS who show suboptimal response to clozapine (i.e. URS), our understanding is even less clear since there are no treatments with established efficacy in these individuals (Cipriani et al., 2009; Sommer et al., 2012).

A host of meta-analyses have been conducted on neuroimaging findings in schizophrenia, although not specifically focused on TRS and URS (Brugger et al., 2011; Ellison-Wright et al., 2008; Howes et al., 2012; Leung et al., 2011; Marsman et al., 2013; Steen et al., 2006; Yao et al., 2013). Accordingly, and in light of how important this topic is, the present article

represents a review of the existing literature on treatment resistance (TRS and URS) employing neuroimaging techniques, including arterial spin labeling (ASL), computed tomography (CT), diffusion tensor imaging (DTI), structural magnetic resonance imaging (MRI), functional MRI (fMRI), magnetic resonance spectroscopy (MRS), near infrared spectroscopy, positron emission tomography (PET), and single photon emission tomography (SPECT). The main objective was to elucidate possible neuroimaging characteristics unique to these populations in comparison to those who respond to standard antipsychotic treatment.

2. Experimental/Materials and methods

A systematic computerized literature search of EMBASE, MEDLINE, and PsycINFO was conducted. The following search terms were used: (schizophreni*) AND (resistan* OR refractory OR clozapine) AND ((arterial spin labeling) OR ASL OR (computed tomography) OR (computerized tomography) OR CT OR (magnetic resonance) OR MRI OR fMRI OR MRS OR (positron emission tomography) OR PET OR (diffusion tensor imaging) OR DTI OR (single photon emission computed tomography) OR SPECT OR (near infrared spectroscopy) OR NIRS). Only publications written in English pertaining to the focus of this review were selected and no time span was specified for date of publication. The reference sections of the identified studies and previous reviews (Chung and Remington, 2005; Ebdrup et al., 2013; Howes et al., 2009; Howes and Kapur, 2009; Kuroki et al., 2008; Nord and Farde, 2011; Suzuki et al., 2011; Uchida et al., 2011; Yilmaz et al., 2012) were manually searched for additional studies not identified in the computerized search. We excluded case reports including one subject (Conley et al., 2004; Giesel et al., 2012; Jardri et al., 2009; Langguth et al., 2006; Liao et al., 2012; Schreiber et al., 2002). We selected neuroimaging studies on TRS, defined as schizophrenia with a failure to respond to at least two antipsychotic medications. The literature search was conducted independently by two of the authors (S.N. and H.T.). Their disagreement was resolved by consensus. To enhance the quality of reporting in the present systematic review, we followed standardized guidelines (Moher et al., 2009). The last search was conducted on September 24, 2014, and in total yielded 25 articles which formed the empirical basis of this review.

3. Results

3.1. Structural neuroimaging

Structural neuroimaging studies comparing TRS and response to CLZ are summarized in Table 1. Only a few structural neuroimaging studies have investigated TRS, of which one study compared TRS and non-TRS (Zugman et al., 2013). No study has investigated the effects of CLZ on brain structures in TRS. One investigation specifically compared treatment-resistant auditory verbal hallucinations (TR-AVH) and absence of AVH (Kubera et al., 2014). The available structural neuroimaging literature suggests a link between neuroanatomical abnormalities and TRS, including anomalies in the corpus callosum (CC) compared with HC (Holleran et al., 2014; Sun et al., 2009). It remains unclear whether neuroanatomical changes may be related to CLZ response in TRS.

3.1.1 Comparison between patients with treatment-resistant schizophrenia and healthy controls—Reductions in cortical thickness have been associated with TRS. Zugman et al. (2013) reported that patients with TRS demonstrated a reduction in cortical thickness in the frontal, parietal, temporal and occipital regions versus HC (Zugman et al., 2013). White matter abnormalities have also been linked to TRS; when compared with HC, patients with CLZ-naïve TRS showed reductions in fractional anisotropy and increases in radial diffusivity in the CC and in the temporal lobe areas of cortico-cortical white matter association tracts, which were negatively related to duration of illness (Holleran et al., 2014). These findings raise the possibility that there exist deficits in the microstructural organization of white matter within these areas in TRS. Furthermore, volumetric studies have reported differences between patients with TRS and HC. Sun et al. (2009) demonstrated that the splenium of the CC was larger in those with TRS than in HC, while no difference in the whole CC was found (Sun et al., 2009). Kubera et al. (2014) noted that patients with TR-AVH showed lower lateral prefrontal GM volume than HC (Kubera et al., 2014) while Cachia et al. (2008) reported that those with TR-AVH had lower global sulcal gyrification in both hemispheres and lower local sulcal gyrification in language-related regions than HC (Cachia et al., 2008).

3.1.2 Comparison between patients with treatment-resistant and non-resistant schizophrenia—Zugman et al. (2013) reported that those with TRS demonstrated more widespread reduction in cortical thickness (frontal, parietal, temporal, and occipital regions) than those with non-TRS (frontal regions) regardless of illness severity, in addition to greater reduction in the left dorsolateral prefrontal cortex (DLPFC) (Zugman et al., 2013). Kubera et al. (2014) reported that those with TR-AVH showed lower lateral medial frontal and lateral temporal GM volume than those without AVH (Kubera et al., 2014). Negative correlations were found between medial frontal and lateral temporal GM volume and symptom duration, location, frequency and intensity in those with TR-AVH.

3.1.3. Clozapine response and structural changes in patients with treatment-resistant schizophrenia—We are not aware of any studies examining structural changes following CLZ treatment in TRS, although several investigations have reported on baseline structural predictors of CLZ response. Friedman et al. (1991) found that CLZ response was positively related to a smaller prefrontal sulcal prominence at baseline, reflecting prefrontal atrophy, in those with TRS (Friedman et al., 1991). Konicki et al. (2001) reported that CLZ responders with TRS had less prefrontal sulcal widening at baseline than nonresponders (Konicki et al., 2001). Arango et al. (2003) noted that larger right prefrontal gray matter (GM) volume was associated with better response in terms of whole and negative symptoms to CLZ and smaller sensitivity to akathisia by CLZ in those with TRS (Arango et al., 2003). Molina Rodriguez et al. (2003) found that clozapine-related improvement in positive symptoms was positively related to baseline temporal gray matter volume, improvement in negative symptoms to baseline DLPFC volume, and improvement in disorganization symptoms inversely related to baseline intracranial volume and hippocampal volume (Molina et al., 2003). These findings suggest that symptomatic improvement with CLZ may be associated with less brain atrophy at baseline, particularly in the prefrontal cortex (PFC).

Prospective studies are required, however, to better understand the relationship between concurrent clinical improvement with CLZ and neuroanatomical changes.

3.2. Functional neuroimaging

Functional neuroimaging correlates of TRS and CLZ response are summarized in Tables 2. Once more, few functional neuroimaging studies have examined TRS; two investigations compared TRS and non-TRS (Demjaha et al., 2014; Demjaha et al., 2012), while a further two studies investigated the neurofunctional effects of CLZ on TRS (Molina et al., 2005; Molina et al., 2008). One investigation specifically compared TR-AVH and absence of AVH (Wolf et al., 2012). Few findings have been replicated at this point, but current evidence suggests that a link exists between TRS and neurofunctional abnormalities, particularly, hypometabolism in the PFC (Molina Rodriguez et al., 1997b; Molina et al., 2007) and hypermetabolism in the basal ganglia (BG) (Molina Rodriguez et al., 1997a; Molina Rodriguez et al., 1997b), as compared to HC. CLZ may increase PFC hypoactivation in patients with TRS (Molina et al., 2005; Molina et al., 2008), although this increase is not necessarily related to clinical improvement (Molina et al., 2005; Molina et al., 2008). Whereas, CLZ response has been related to decreased metabolism in the BG (Molina Rodriguez et al., 1997a; Molina Rodriguez et al., 1996; Molina et al., 2005) and thalamus (Molina Rodriguez et al., 1997a; Molina Rodriguez et al., 1996) in TRS.

3.2.1 Comparison between patients with treatment-resistant schizophrenia and healthy controls—Functional neuroimaging studies have investigated TRS versus HC with regard to dopamine synthesis capacity, glutamatergic function, and brain metabolism/perfusion. Demjaha et al. (2012) reported that patients with TRS showed no difference in striatal dopamine synthesis capacity in comparison to HC (Demjaha et al., 2012). In contrast, this group also found that glutamate levels were elevated in the anterior cingulate cortex (ACC) in TRS versus HC while NAA levels were comparable (Demjaha et al., 2014). Since the latter study employed subjects who participated in the former study, these data suggest that those with TRS may have normal dopamine synthesis capacity in the striatum and elevated glutamate levels in the ACC, as compared to HC.

Molina Rodriguez et al. (1997) noted that those with TRS had higher perfusion in the right BG than HC (Molina Rodriguez et al., 1997a), This finding was replicated in a second study by this group, in addition to lower perfusion in the prefrontal and temporal cortices; negative symptoms scores negatively correlated with perfusion in the right DLPFC (Molina Rodriguez et al., 1997b). The same investigators also showed that TRS was associated with decreased perfusion in the medial prefrontal, middle cingulate and insular cortices, as well as increased perfusion in the brain stem and the posterior hippocampus in comparison to HC (Molina et al., 2008). Klirova et al. (2013) reported that those with TR-AVH presented with hypermetabolism in the cluster consisting of bilateral lentiform nucleus and thalamus, left parahippocampal gyrus, bilateral postcentral gyrus, and right superior frontal gyrus, compared with HC (Klirova et al., 2013). Within the left acoustic-linguistic cortex, the hypermetabolism was found in the middle temporal gyrus and temporoparietal junction (TPJ). Wolf et al. (2012) reported that those with TR-AVH showed increased regional

cerebral blood flow (rCBF) in the frontotemporal regions, compared with HC (Wolf et al., 2012).

Wolf et al. (2011) noted that those with TR-AVH showed increased connectivity in the bilateral temporal regions and decreased connectivity in the cingulate cortex within a speech-related network, compared with HC (Wolf et al., 2011). Further, those with TR-AVH exhibited abnormal connectivity in the precuneus within attention-related network and in the right lateral prefrontal areas within executive control network, respectively. Correlations were found between AVH severity and functional connectivity of the left ACC, left superior temporal gyrus (STG), and right lateral PFC. Vercammen et al. (2010) demonstrated that patients with TR-AVH showed reduced functional connectivity between the left STG and right hemispheric homotope of Broca's area, compared with HC (Vercammen et al., 2010). Negative correlations were found between AVH severity and neural coupling between the left TPJ and bilateral ACC as well as bilateral amygdala in those with TR-AVH. Fitzgerald et al. (2007) noted that those with TRAVH presented with word-generation related hypoactivation in the left superior temporal gyrus, bilateral inferior frontal gyrus, ACC, and parietal regions, compared with HC (Fitzgerald et al., 2007).

In relation to the neural correlates of CLZ response, Molina Rodriguez et al. (2007) demonstrated that those with TRS who responded to CLZ had lower perfusion than HC in the PFC, caudate, and thalamus (Molina et al., 2007). Lastly, while one study has reported that patients with URS (i.e. CLZ resistance) showed lower perfusion in the right PFC than HC (Molina Rodriguez et al., 1996), another study by the same group demonstrated lower perfusion in the thalamus and left BG (Molina Rodriguez et al., 1997a). Summarizing, studies indicate that hypometabolism in the PFC and hypermetabolism in the BG may be associated with TRS; in contrast, findings for URS are both limited and inconsistent.

3.2.2 Comparison between patients with treatment-resistant and non-resistant schizophrenia—

Demjaha et al. (2012) noted that patients with TRS showed lower dopamine synthesis capacity in the striatum than those with non-TRS (Demjaha et al., 2012). A subsequent study by this group also found that glutamate levels were comparable in the ACC between those with TRS and those with schizophrenia in remission (numerically higher in TRS), while NAA levels were significantly higher within the ACC in patients with TRS than in those with schizophrenia in remission (Demjaha et al., 2014). Wolf et al. (2012) demonstrated that those with TR-AVH showed increased rCBF in the STG and right supramarginal gyrus/temporoparietal cortex than those without AVH (Wolf et al., 2012). Positive correlations were found between AVH severity and rCBF in the left STG, ACC, and IFG in those with TR-AVH.

3.2.3 Clozapine response and functional imaging in patients with treatment-resistant schizophrenia

3.2.3.1 Change in functional imaging following clozapine treatment: CLZ has been reported to decrease activation in the PFC (Molina et al., 2005; Molina et al., 2008) and BG (Molina et al., 2005), and increase activation of the occipital (Molina et al., 2005), cingulate (Molina et al., 2008), and insular cortices (Molina et al., 2008) in patients with TRS. These

studies imply that CLZ may increase hypoactivation in the PFC in those with TRS; however, this does not appear to be related to clinical improvement (Molina et al., 2005; Molina et al., 2008).

3.2.3.2 Symptom improvement and functional imaging following clozapine treatment: Molina Rodriguez et al. (2008) found that clinical improvement in association with CLZ was related to an increase in activity in the thalamus, but not in association with limbic region perfusion (Molina et al., 2008). Looking at specific symptom domain improvement, the same group reported the following: a decrease in BG activity for negative symptoms, reduced metabolism in the motor area for disorganization, and an increase in visual area activity for positive symptoms (Molina et al., 2005). On the other hand, increased hypoactivation in the PFC in those with TRS was not related to clinical improvement in this population (Molina et al., 2005; Molina et al., 2008).

3.2.3.3 Functional imaging as a baseline predictor of clozapine response: Several studies have reported baseline functional predictors for CLZ response. CLZ responders had a higher perfusion in the PFC, BG and thalamus than nonresponders at baseline (Molina Rodriguez et al., 1996; Molina Rodriguez et al., 1997b). It has also been identified that patients with high metabolic activity in the DLPFC at baseline were more likely to experience improvements in their negative symptoms following CLZ administration (Molina et al., 2003).

3.2.3.4 Difference in functional imaging between clozapine responders and nonresponders: Changes in brain activity with CLZ treatment may classify CLZ responders and nonresponders in those with TRS. More specifically, CLZ responders demonstrated greater increases in perfusion in the medial occipital cortex and caudate head, and greater decreases in perfusion in the posterior cingulate and hippocampus when compared with nonresponders (Molina et al., 2008). Molina Rodriguez et al. (1997) also reported that CLZ responders showed decreased perfusion in the PFC and thalamus (Molina Rodriguez et al., 1997b); and in a second study (1996) identified decreased perfusion in the thalamus and left BG of non-responders (Molina Rodriguez et al., 1996) but in this case no change in PFC perfusion in both responders and nonresponders (Molina Rodriguez et al., 1996).

4. Discussion

Despite the importance of TRS clinically, few neuroimaging studies have specifically focused on this population with solid hypothesis. In the few studies designed to contrast those with TRS versus non-TRS, no clear evidence was found in terms of neuroimaging correlates defining treatment resistance. Of note, no study has compared URS and those with TRS who respond to CLZ. There are several potential reasons for the paucity of neuroimaging studies on TRS and URS, including 1) equivocal definition of TRS and 2) current research interests on those at risk mental state and those with first-episode schizophrenia rather than TRS and URS. On the other hand, compared to HC, replicated findings to date include hypometabolism in the PFC (Molina Rodriguez et al., 1997b; Molina et al., 2007), hypermetabolism in the BG (Molina Rodriguez et al., 1997a; Molina Rodriguez et al., 1997b), and structural anomalies in the CC (Holleran et al., 2014; Sun et al., 2009) of patients with TRS. Only a limited number of investigations examined

alterations in neuroanatomy and/or neurofunction in response to CLZ treatment. Replicated findings indicate that CLZ may increase PFC hypoactivation, although this does not appear related to clinical improvement; furthermore, CLZ-associated clinical improvement may be related to decreased metabolism in the BG and thalamus in TRS. However, very few studies have compared the effects of clozapine and other antipsychotics on brain metabolism. As such, it remains unclear whether these clozapine-induced metabolic changes are specific to this antipsychotic or are also applicable to antipsychotics in general (Buchsbaum et al., 2009); a direct comparison between them on brain activity could contribute to a better understanding of their respective mechanisms of action. To summarize, further research contrasting TRS, non-TRS, and URS is clearly needed, with particular focus on the frontocortical-basal gangliathalamic circuits implicated in treatment resistance.

5. Limitations

This review has to be considered in light of its limitations. First, few studies specifically compared patients with TRS and non-TRS, which limits the conclusions that can be drawn. Comparisons between TRS and HC may not be specific indicators of treatment-resistance, but rather may also reflect abnormalities found in patients with schizophrenia in general (including non-TRS) or persistent effects of antipsychotics on neurofunction and neuroanatomy (Samaha et al., 2008). Second, few studies employed multi-modal imaging, which offers information both about neurofunction and neuroanatomy in the same sample. Third, most studies employed a cross-sectional design to compare TRS and other populations when a longitudinal design is better suited if we are to elucidate whether TRS is a pre-existing condition or what that evolves across time, or whether antipsychotics or illness progression causes/interferes with what is measured in TRS. Fourth, some studies were excluded from this study because they included patients who did not tolerate antipsychotics. This highlights the importance of common agreement regarding criteria for both TRS and URS. TRS has been defined with positive symptoms rather than negative, cognitive or affective symptoms and response to antipsychotics have been derived from a relative change in representative scales. Thus, it is clearly pertinent to assess response/outcome in the context of multiple symptom domains, in addition to functioning (Suzuki et al., 2012). Fifth, only dopamine and glutamate do not necessarily explain biological mechanisms underlying TRS (Selvaraj et al., 2014). For example, serotonergic dysfunction has been implicated for schizophrenia, including increased 5-HT1A receptors and decreased 5-HT2A receptors in the PFC. Further research is needed to examine relationships between the serotonin system and TRS. Sixth, treatment resistance emerges not only in schizophrenia but also other serious mental illnesses such as bipolar disorders (Arnone et al., 2009). It should be useful to conduct neuroimaging studies to compare TRS and other treatment-resistant mental illnesses to elucidate the biological basis of treatment resistance. Finally, we are not aware of any study that has compared patients with TRS responsive to CLZ and URS, a critical question since the differential response to CLZ supports the position that these two populations are mediated by different underlying mechanisms.

6. Future Directions

The paucity of robust evidence supporting a critical role for the dopaminergic system in TRS clearly argues for lines of investigation that take us beyond dopamine (Selvaraj et al., 2014). While dopamine may still be necessary, it is clearly not sufficient in the case of TRS although differences with non-TRS have been identified. In antipsychotic-free patients with schizophrenia, plasma dopamine metabolite levels at baseline have been shown to be associated with treatment response (Yoshimura et al., 2003). With TRS, dopamine synthesis capacity has been reported to be lower versus patients with non-TRS, but similar to HC (Demjaha et al., 2012), while postmortem brain dopamine levels in the caudate were found to be lower when compared with non-TRS (Roberts et al., 2009).

The glutamate hypothesis represents one of a number of alternative models posited that may complement existing thinking regarding dopamine while acknowledging its limitations in TRS (Cadenhead, 2011; Carlsson and Carlsson, 1990; Javitt and Zukin, 1991; Krystal, 2008; Olney and Farber, 1995). The interaction between glutamate and dopamine has been widely documented (Breier et al., 1998; Cepeda and Levine, 1998; David et al., 2005; Grace, 2000; Kegeles et al., 2000; Kulagina et al., 2001; Levine and Cepeda, 1998; West et al., 2003; Yamamoto et al., 1999), with evidence suggesting that dopaminergic dysregulation may be the final common pathway - a result of enhanced cortical glutamate activity in response to hypofunction of N-methyl D-aspartate (NMDA) receptors in patients with schizophrenia (Sharp et al., 2001). The most convincing link between NMDA receptor function and schizophrenia is the ability of NMDA receptor antagonists to induce not only positive symptoms but also negative and cognitive symptoms in healthy volunteers (Krystal et al., 1994; Lieberman et al., 2008; Malhotra et al., 1996) and to exacerbate psychosis in patients with schizophrenia (Malhotra et al., 1997).

While the aforementioned evidence supports a role for glutamate in schizophrenia, its putative role in TRS remains to be elucidated. Proton magnetic resonance spectroscopy (1H-MRS) permits the non-invasive in vivo study of the glutamatergic system (Abbott and Bustillo, 2006; Di Costanzo et al., 2003; Di Costanzo et al., 2007), which is known to play a crucial role in the frontocortical-basal ganglia-thalamic circuits. To date, only one study has explored glutamate levels in patients with TRS (Demjaha et al., 2014), combined with the previous study by the same group, which examined dopamine synthesis capacity in TRS versus non-TRS, and HC (Demjaha et al., 2012). The limited data available suggest that TRS may be associated with higher glutamate levels and normal dopamine synthesis capacity in comparison with non-TRS and controls. Furthermore, we need clearly established criteria that permit accurate classification (i.e. antipsychotic responsive vs. treatment resistant, further subdivided as CLZ responsive or URS).Thus, given that the dopamine hypothesis may not necessarily explain the biological correlates of TRS, further longitudinal 1H-MRS research is required to explore the glutamatergic dysfunction in the frontocortical-basal ganglia-thalamic circuits comparing TRS, URS, and non-TRS in order to elucidate the mechanisms underlying TRS.

7. Conclusion

In conclusion, treatment resistance represents the greatest unmet need in schizophrenia care at present, associated as it is with worse clinical outcomes, social dysfunction, poorer quality of life, increased use of healthcare resources and greater caregiver burden. As many as 30% of patients with schizophrenia meet criteria for TRS, and while a portion of these individuals will respond to CLZ, a substantial number will not. For these individuals we have no treatments at present, giving rise to a trial-and-error clinical approach that is neither systematic nor particularly effective. Neuroimaging is positioned to play a critical role in this regard and while the work to date is limited, findings suggest that: 1) patients with TRS may present with hypometabolism in the PFC, hypermetabolism in the BG, and structural anomalies in the CC, as compared with HC; 2) CLZ may increase PFC hypoactivation in those with TRS; and 3) CLZ efficacy may be related to decreased metabolism in the BG and thalamus in TRS. It remains, though, that this work is in its earliest stages and considerably more research is required; that no work has yet been carried out involving URS speaks to the considerable gaps in our knowledge. In moving forward, we need clearly established criteria of TRS and URS, a multimodal imaging approach, and longitudinal designs that can complement cross-sectional studies. The fact that we have at least three forms of this illness based on treatment response/nonresponse provides the necessary starting point to use strategies like neuroimaging to elucidate the different underlying mechanisms that ultimately contribute to schizophrenia's clinical heterogeneity.

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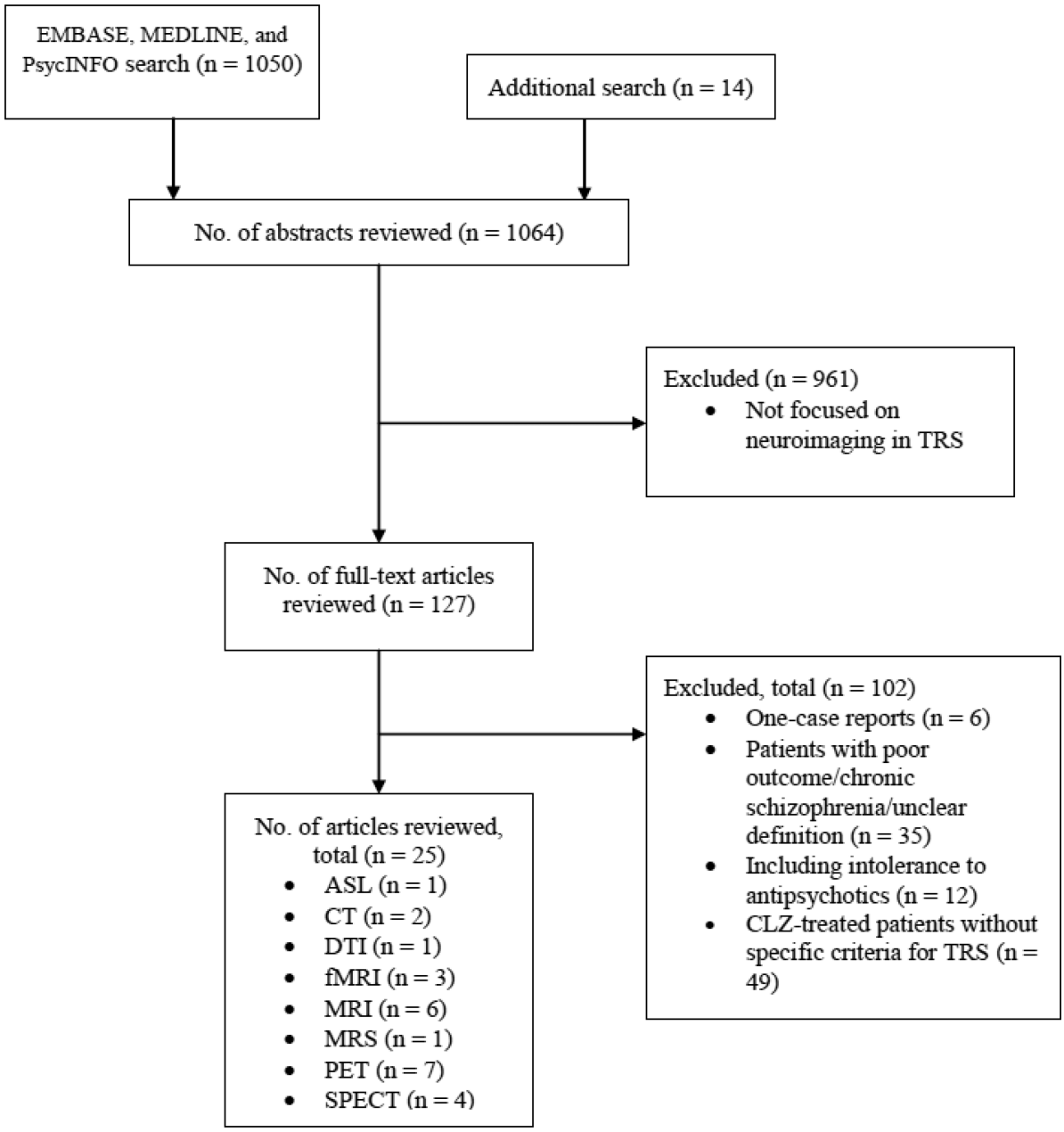

Figure 1.

Flowchart illustrating literature search and exclusion process (PRISMA diagram).

Abbreviations: ASL = arterial spin labeling, AVH = auditory verbal hallucinations, CLZ = clozapine, CT = computed tomography, DTI = diffusion tensor imaging, MRS = magnetic resonance imaging, fMRI = functional MRI, MRS = magnetic resonance spectroscopy, PET = positron emission tomography, SPECT = single photon emission tomography, TRS = treatment resistant schizophrenia.

Table 1

Structural neuroimaging correlates of treatment-resistant schizophrenia and response to clozapine in patients with treatment-resistant schizophrenia

Year	Author	Type of Neuroimaging	Subjects	Definition of TRS	Treatment for groups with TRS	Controls	Findings
TRS and neuroanatomy							
2014	Kubera	MRI	Sz with TR-AVH (n = 10)	Persistent AVH despite ≧2 AP trials (each >6 weeks at adequate dosage of different APs). No pronounced formal thought disorder. Sufficient insight into AVH.	CLZ (monotherapy or combination therapy)	Sz without AVH (n = 10) & HC (n = 14)	Patients with TR-AVH showed lower GM volume in medial and inferior frontal, insular and bilateral temporal regions than those without AVH. Those with TR-AVH showed lower lateral prefrontal GM volume than HC. Negative correlations were found between medial frontal and lateral temporal GMV and symptom duration, location, frequency and intensity in those with TR-AVH.
2014	Holleran	DTI	CLZ - naïve TRS (n = 19)	Prolonged period of ≧moderate positive symptoms + failure to respond to ≧2 APs, including 1 atypical AP.	Atypical APs other than CLZ (cross-sectional)	HC (n = 19)	Patients with CLZ-naïve TRS showed localized reductions in FA with increases in RD in CC and temporal lobe areas of cortico-cortical WM association tracts. Illness duration was negatively related to FA in splenium of CC in those with CLZ-naïve TRS.
2013	Zugman	MRI	TRS (n = 61)	Failure to respond to ≧2 different AP trials (each of 4–6 weeks at a CPZ equivalent dose of ≧400 mg/day or 5 mg/day of RIS) + lack of remission (≧4 on PANSS items of delusions,	72.1% of the patients received CLZ (cross-sectional)	Non-TRS (n = 67) & HC (n = 80)	Patients with TRS presented a more widespread reduction in cortical thickness (frontal, parietal, temporal, and

Year	Author	Type of Neuroimaging	Subjects	Definition of TRS	Treatment for groups with TRS	Controls	Findings
				unusual thought content, hallucinatory behavior, mannerisms/ posturing, blunted affect, social withdrawal, and lack of spontaneity) for 6 months.			occipital regions) than patients with non-TRS (frontal regions) compared with HC. A greater reduction in left DLPFC was found in patients with TRS compared with those with non-TRS.
2009	Sun	MRI	TRS (n = 42)	Little or no symptomatic response to ≥2 different AP trials (each of ≥6 weeks at therapeutic range doses).	CLZ (n = 11), other atypicals (n = 24), typicals (n = 4) (cross-sectional)	TR MDD (n = 45) & HC (n = 30)	Patients with TRS did not differ from HC in the whole CC area. The mean ICV of patients with TRS was smaller than that of HC. After ICV normalization, splenium of CC was identified as larger in patients with TRS than HC.
2008	Cachia	MRI	Sz with TR-AVH (n = 30)	Daily AVH despite ≥2 trials (each ≥6 weeks at usual dosages of APs, including ≥1 atypical APs).	APs (cross-sectional)	HC (n = 28)	Patients with TR-AVH had lower global sulcal gyrification in both hemispheres. Local sulcal gyrification decrease was more significant in language-related regions (superior temporal sulcus bilaterally, left middle frontal sulcus and diagonal branch of left sylvian fissure [Broca's area]).
Structural change after CLZ administration in TRS							
No study							
Prediction of CLZ response in TRS							
2003	Arango	MRI	TRS (n = 22)	Minimum level of positive (≥8 on BPRS items for conceptual disorganization, hallucinations, unusual thought content, and	CLZ (prospective)	TRS (n = 23, HAL, prospective)	Larger right prefrontal GM volume was associated with better response (whole and negative symptoms) to

Year	Author	Type of Neuroimaging	Subjects	Definition of TRS	Treatment for groups with TRS	Controls	Findings
				suspiciousness or ≧4 on ≧1 of the items) and negative (≧20 on SANS total score or ≧2 on ≧1 SANS global item) symptoms at study entry and retrospective history of residual positive or negative symptoms after ≧2 typical AP trials (each of ≧6 weeks). Failure to respond (<30% improvement in positive or negative symptoms) to fluphenazine (10-30 mg/day, open-label, 6 weeks).			CLZ and poorer response to HAL in patients with TRS. Larger right prefrontal GM volume was associated with smaller sensitivity to akathisia by CLZ and greater sensitivity to akathisia by HAL in those with TRS.
2003	Molina Rodriguez	MRI	TRS (n = 25)	Presence of significant positive or disorganization residual symptoms + failure to respond to ≧2 different-class AP trials (each of ≧6 weeks at a CPZ equivalent dose of ≧800 mg/day) in the preceding 12 months.	CLZ (prospective)	No controls	Improvement in positive symptoms with CLZ was related to temporal GM volume, whereas improvement of disorganization symptoms was inversely related to ICV and hippocampal volume. Improvement in negative symptoms with CLZ was related to DLPFC volume.
2001	Konicki	CT	CLZ responders with TRS (n = 26)	≧45 on BPRS-18 total score + ≧4 on BPRS items of conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content + ≧4 on CGI-S + lack of significant symptomatic relief despite 3 AP trials (including 2 different-class AP) trials (each of ≧6 weeks at a CPZ equivalent dose of ≧1000 mg/day) in the	CLZ (prospective)	CLZ nonresponders with TRS (n = 10)	CLZ responders with TRS had less prefrontal sulcal widening than nonresponders. Generalized sulcal prominence did not differentiate between them.

Year	Author	Type of Neuroimaging	Subjects	Definition of TRS	Treatment for groups with TRS	Controls	Findings
				preceding 60 months.			
1991	Friedman	CT	TRS (n = 34)	Failure to respond (≧4 on BPRS items of unusual thought content, conceptual disorganization, suspiciousness, or auditory hallucinations) to ≧2 typical AP trials (each of ≧6 weeks at a CPZ equivalent dose of ≧800 mg/day) in the preceding 12 months.	CLZ (prospective)	No controls	CLZ response was related to a smaller prefrontal sulcal prominence reflecting prefrontal atrophy in patients with TRS.

Abbreviations: AP = antipsychotic, AVH = auditory verbal hallucination, BPRS-18 = the18-items version of the Brief Psychiatric Rating Scale, CC = corpus callosum, CGI-S = the Clinical Global Impression Rating Scales-Severity, CLZ = clozapine, CPZ = chlorpromazine, CT = computed tomography, DLPFC = dorsolateral prefrontal cortex, DTI = diffusion tensor imaging, E-BPRS = the Expanded Brief Psychiatric Rating Scale, FA = fractional anisotropy, GM = gray matter, HC = healthy controls, ICV = intracranial volume, MDD = major depressive disorder, MRI = structural magnetic resonance imaging, PANSS = the Positive and Negative Syndrome Scale, RIS = risperidone, RD = radial diffusivity, SANS = the Scale for the Assessment of Negative Symptoms, Sz = schizophrenia, TR = treatment resistant, TRS = treatment resistant schizophrenia, WM = white matter

Table 2

Functional neuroimaging correlates of treatment-resistant schizophrenia and response to clozapine in patients with treatment-resistant schizophrenia

Year	Author	Type of Neuroimaging	Subjects	Definition of TRS	Treatment for groups with TRS	Controls	Findings
TRS and neurofunction							
2014	Demjaha	(1)H-MRS	TRS (n = 6)	≧4 on ≧1 PANSS positive symptom items + ≧75 on PANSS total score + <59 on GAF despite ≧2 sequential AP trials (each of ≧4 weeks at a CPZ equivalent dose of 400–600 mg/day).	APs (cross-sectional)	Sz in remission (n = 8) & HC (n = 10)	Glu levels were elevated in ACC in patients with TRS compared with HC while Glu levels were comparable between TRS and those with Sz in remission. NAA levels were lower in ACC in those with Sz in remission than TRS and HC, which did not differ.
2013	Klirova	[18F]F DG PET	Sz with TR-AVH (n = 15)	≧5 episodes/day of AH during the past month + nonresponse to ≧1 typical and 1 atypical AP adequate trials	APs (cross-sectional)	HC (n = 10)	Patients with TR-AVH presented with hypermetabolism in the cluster consisting of bilateral lentiform nucleus, thalamus, and postcentral gyrus, left parahippocampal gyrus, and right superior frontal gyrus, compared with HC. Within the left acoustic-linguistic cortex, hypermetabolism was found in the middle temporal gyrus and TPJ.
2012	Demjaha	[18F]D OPA PET	TRS (n = 12)	≧4 on ≧1 PANSS positive symptom items + ≧75 on PANSS total score + <59 on GAF despite ≧2 sequential AP trials (each of ≧4 weeks at a CPZ equivalent dose of 400–600 mg/day).	APs other than CLZ (cross-sectional)	Non-TRS (n = 12) & HC (n = 12)	Patients with TRS showed lower dopamine synthesis capacity in striatum than those with non-TRS. No difference was found in striatal dopamine synthesis capacity between patients with TRS and HC.
2012	Wolf	ASL	Sz with TR-AVH (n = 10)	Persistent AVH despite ≧2 AP trials (each >6 weeks at adequate dosage of different APs). No pronounced	APs (cross-sectional)	Sz without AVH (n = 10) & HC (n = 14)	Patients with TR-AVH showed increased rCBF in left STG and right SMG/TPC than those

Year	Author	Type of Neuroimaging	Subjects	Definition of TRS	Treatment for groups with TRS	Controls	Findings
				formal thought disorder. Sufficient insight into AVH.			without AVH. Those with TR-AVH showed increased rCBF in frontotemporal regions than HC. Those with TR-AVH demonstrated positive correlations between AVH severity and rCBF in left STG, ACC, and IFG.
2011	Wolf	Resting state fMRI	Sz with TR-AVH (n = 10)	Persistent AVH + ≧2 ineffective AP trials (each >6 weeks at adequate dosage of different APs). No pronounced formal thought disorder. Sufficient insight into AVH.	CLZ (monotherapy or combination therapy, cross-sectional)	HC (n = 14)	Within a speech-related network, patients with TR-AVH showed increased connectivity in bilateral temporal regions and decreased connectivity in cingulate cortex compared with HC. Those with TR-AVH exhibited abnormal connectivity in precuneus within attention-related network and right lateral prefrontal areas within executive control network, respectively, compared with HC. Positive correlations were found between AVH severity and functional connectivity of left ACC, left STG, and right lateral PFC.
2010	Vercammen	Resting state fMRI	Sz with TR-AVH (n = 27)	Daily occurrence of AVH despite ≧2 AP adequate trials.	APs (cross-sectional)	HC (n = 27)	Patients with TR-AVH showed reduced functional connectivity between left TPJ and right hemispheric homotope of Broca's area compared with HC. Those with TR-AVH demonstrated negative correlations between AVH severity and neural coupling

Year	Author	Type of Neuroimaging	Subjects	Definition of TRS	Treatment for groups with TRS	Controls	Findings
							between left TPJ and bilateral ACC as well as bilateral amygdala.
2007	Molina Rodriguez	[18F]F DG PET	TRS with good response to CLZ (n = 23)	≥4 on ≥1 SAPS psychotic symptom items + ≥4 on CGI-S despite ≥2 different AP treatments (each of ≥4 weeks at a CPZ equivalent dose of ≥800 mg/day) during the previous year.	CLZ (cross-sectional)	Sz (AP naïve, n = 11) & HC (n = 18)	Patients with TRS showed prefrontal (bilateral orbital, medial frontal, left dorsolateral prefrontal) and caudate hypometabolism compared with both HC and AP naïve patients, and lower thalamic activity than HC.
2007	Fitzgerald	fMRI during word generation task	Sz with TR-AVH (n = 3)	Persistent severe refractory AH + nonresponse to ≥2 adequate AP trials	Atypical APs (CLZ, n = 2, cross-sectional)	HC (n = 4)	Patients with TR-AVH presented with less activation in medial frontal regions (left superior temporal gyrus, left inferior frontal gyrus, right inferior frontal gyrus, anterior cingulate cortex and parietal regions) and greater activation in left caudal precentral gyrus, compared with HC.
2004	Moresco	[18F]F ESP PET	TRS (n = 6)	≥27 on BPRS total score despite ≥2 different-class AP treatments (each of ≥6 weeks at a CPZ equivalent dose of ≥500 mg/day).	CLZ (prospective)	TRS (n = 9, OLZ, prospective)	OLZ showed 4-fold D_2-like receptor occupancy in striatum (43%) but similar cortical 5-HT_2 receptor occupancy (86%) compared with CLZ in patients with TRS, while clinical outcomes were similar.
1997a	Molina Rodriguez	99mTc-HMPAO SPECT	TRS (n = 36)	Active psychosis despite 2 different-class AP treatments (each of ≥8 weeks at a CPZ equivalent dose of ≥1000 mg/day).	Typical APs	HC (n = 28)	Patients with TRS showed bilateral, but predominantly left-sided, decreased perfusion in frontal and temporal cortices, as well as an increased perfusion in right BG compared

Year	Author	Type of Neuroimaging	Subjects	Definition of TRS	Treatment for groups with TRS	Controls	Findings
							with HC. Negative symptoms scores negatively correlated with perfusion in right DLPFC, while parkinsonism positively correlated with activity of primary motor and sensory cortex.
1991	Coppens	[11C]N MSP PET	TRS (n = 6)	No substantial improvement in major symptoms despite 3 different AP treatments (each of ≧8 weeks at an adequate dose with a therapeutic plasma level range of ≧1 APs).	Typical APs	No controls	There was more than 95% blockade of D_2 receptors in the striatum in patients with TRS.
Functional change after CLZ administration in TRS							
2008	Molina Rodriguez	99m Tc-HMPAO SPECT during Stroop test	TRS (RIS, n = 10)	Failure to respond to ≧2 different AP treatments (each of ≧4 weeks at a CPZ equivalent dose of ≧800 mg/day).	CLZ (prospective)	HC (n = 10)	Patients with TRS on RIS showed decreased perfusion in medial prefrontal, middle cingulate and insular regions, as well as increased activity in brain stem and posterior hippocampus compared with HC. CLZ normalized a decreased activation of the cingulate and insular cortices, and increased prefrontal hypoactivation. Clinical improvement with CLZ was related to increased activity in thalamus, not changes in limbic perfusion. CLZ responders showed a higher increase than nonresponders in perfusion in medial occipital cortex and caudate head, and greater decrease in

Year	Author	Type of Neuroimaging	Subjects	Definition of TRS	Treatment for groups with TRS	Controls	Findings
							perfusion in posterior cingulate and hippocampus.
2005	Molina Rodriguez	[18F]F DG PET	TRS (HAL, n = 22)	Failure to respond to treatments with RIS and HAL (each of ≥4 weeks at a CPZ equivalent dose of ≥800 mg/day).	CLZ (prospective)	No controls	CLZ decreased PFC and BG activity and increased occipital metabolism, including primary and association visual areas. Change in negative symptoms was related with decrease in BG activity; improvement in disorganization related to metabolic decrease in motor area, and change in positive symptoms was associated with increased activity in visual area.
2003	Molina Rodriguez	[18F]F DG PET	TRS (n = 25)	Significant positive or disorganization residual symptoms + failure to respond to 2 different-class AP treatments with (each of ≥6 weeks at a CPZ equivalent dose of ≥800 mg/day).	CLZ (prospective)	No controls	Patients with high baseline metabolic activity in DLPFC were more likely to experience improvements in negative symptoms with CLZ.
1997b	Molina Rodriguez	99mTc-HMPAO SPECT	TRS (n = 39)	Failure to respond to 2 different-class AP treatments with (each of ≥8 weeks at a CPZ equivalent dose of ≥800 mg/day).	CLZ (prospective)	No controls	While taking APs before CLZ, patients with TRS had higher perfusion in the right BG than HC.CLZ responders had higher perfusion in right BG and lower perfusion in left DLPFC than HC. Nonresponders showed higher perfusion in right BG and lower perfusion in thalamus and left BG vs. HC. CLZ responders had higher perfusion than nonresponders in thalamus, BG and PFC at

Year	Author	Type of Neuroimaging	Subjects	Definition of TRS	Treatment for groups with TRS	Controls	Findings
							baseline. After receiving CLZ, only CLZ responders showed a decreased perfusion in PFC and thalamus.
1996	Molina Rodriguez	99mTc-HMPAO SPECT	TRS (n = 24)	Paranoid symptoms + failure to respond to 2 different-class AP treatments with (each of ≧8 weeks at a CPZ equivalent dose of ≧800 mg/day).	CLZ (prospective)	No controls	While taking AP before CLZ, CLZ responders showed higher perfusion in thalamus, and left BG than HC. CLZ nonresponders showed lower perfusion in right PFC than HC at baseline. After receiving CLZ, only CLZ responders showed a decrease in thalamus and left BG. No changes in perfusion were found in PFC in both responders and nonresponders.

Abbreviations: ACC = anterior cingulate cortex, AP = antipsychotic, BG = basal ganglia, ASL = arterial spin labeling, AVH = auditory verbal hallucination, BPRS = Brief Psychiatric Rating Scale, CC = corpus callosum, CGI-S = the Clinical Global Impression Rating Scales=Severity, CLZ = clozapine, CPZ = chlorpromazine, DLPFC = dorsolateral prefrontal cortex, FDG = fluoro-deoxyglucose, FESP = fluoro-ethyl-spiperone, fMRI = functional magnetic resonance tomography, GAF = the Global Assessment of Functioning, Glu = glutamate, GM = gray matter, HAL = haloperidol, HC = healthy controls, IFG = inferior frontal gyrus, NAA = N-acetylaspartate, NMSP = 3-N-methylspiperone, OLZ = olanzapine, PANSS = the Positive and Negative Syndrome Scale, PET = positron emission tomography, PFC = prefrontal cortex, rCBF = regional cerebral blood flow, RIS = risperidone, SAPS = the Scale for the Assessment of Positive Symptoms, SMG = supramarginal gyrus, SPECT = single-photon emission computed tomography, STG = superior temporal gyrus, Sz = schizophrenia, 99mTc-HMPAO = echnetium-99m hexamethylpropylene amine oxime, TPC = temporoparietal cortex, TR = treatment-resistant, TRS = treatment resistant schizophrenia