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Review

Neuroimaging findings in treatment-resistant schizophrenia: A systematic review
Lack of neuroimaging correlates of treatment-resistant schizophrenia

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ABSTRACT

Background: Recent developments in neuroimaging have advanced the understanding of 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 that 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.

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"

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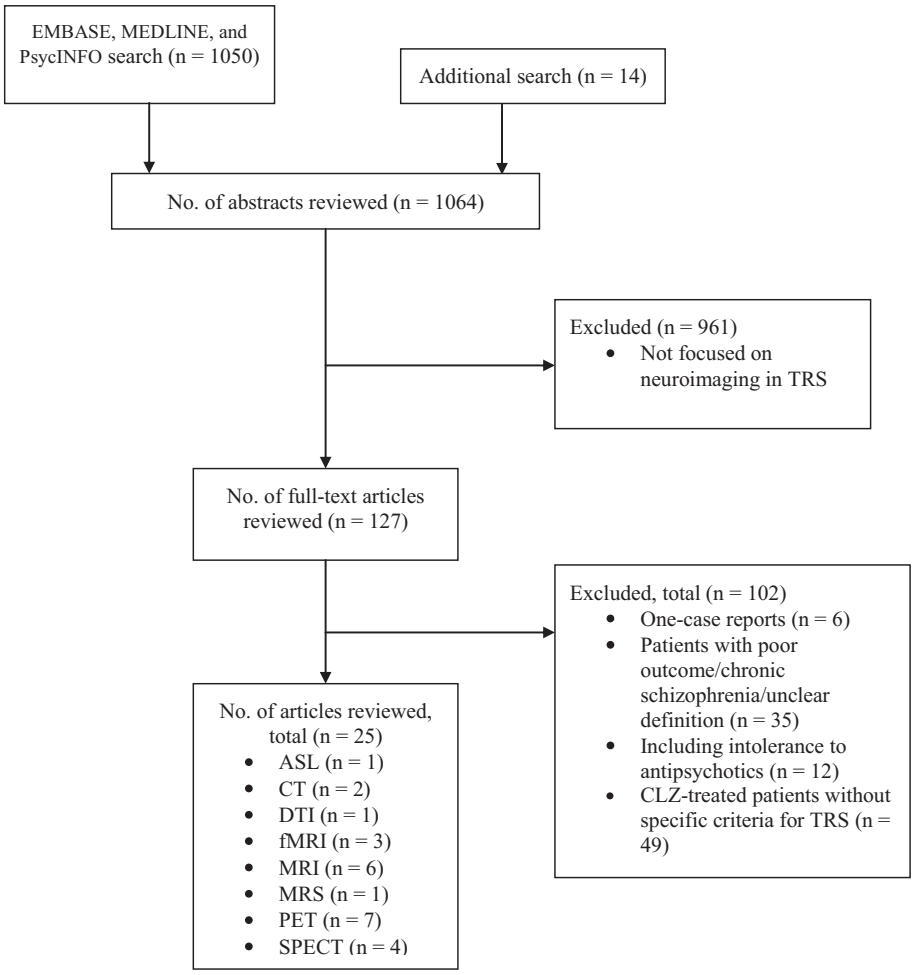
schizophrenia (URS), there are no treatments to date that have proven consistently effective (Cipriani et al., 2009; Sommer et al., 2012). (See Fig. 1.)

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, 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.,



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.

Fig. 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.