Brain-imaging studies of treatment-resistant schizophrenia: a systematic review

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Around 30% of patients with schizophrenia show an inadequate response to antipsychotics—ie, treatment resistance. Neuroimaging studies can help to uncover the underlying neurobiological reasons for such resistance and identify these patients earlier. Additionally, studies examining the effect of clozapine on the brain can help to identify aspects of clozapine that make it uniquely effective in patients with treatment resistance. We did a systematic search of PubMed between Jan 1, 1980, and April 13, 2015, to identify all neuroimaging studies that examined treatment-resistant patients or longitudinally assessed the effects of clozapine treatment. We identified 330 articles, of which 61 met the inclusion criteria. Replicated differences between treatment-resistant and treatment-responsive patients include reductions in grey matter and perfusion of frontotemporal regions, and increases in white matter and basal ganglia perfusion, with effect sizes ranging from 0·4 to greater than 1. Clozapine treatment led to reductions in caudate nucleus volume in three separate studies. The available evidence supports the hypothesis that some of the neurobiological changes seen in treatment-resistant schizophrenia lie along a continuum with treatment-responsive schizophrenia, whereas other differences are categorical in nature and have potential to be used as biomarkers. However, further replication is needed, and for neuroimaging findings to be clinically translatable, future studies need to focus on a-priori hypotheses and be adequately powered.

Lancet Psychiatry 2016

Published Online
March 3, 2016
http://dx.doi.org/10.1016/S2215-0366(15)00540-4

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Introduction

Schizophrenia is a severe mental illness characterised by psychotic (positive), negative, and cognitive symptoms, and has a prevalence of about 1%.[1] Antipsychotic medication has revolutionised treatment,[2] but 20–30% of patients show little or no response to such drugs.[3] Because of persistent symptoms, these patients stay longer in hospital care and have higher treatment costs than do patients who are responsive to antipsychotics.[4] Furthermore, the longer the duration that symptoms do not show improvement, the worse the prognosis.[5]

Careful studies in the late 1980s and early 1990s showed that fewer than 5% of patients who had not responded to two different first-line antipsychotics showed a response to a further antipsychotic, with the exception of clozapine.[6] This finding has been confirmed in further clinical trials and naturalistic studies.[7] Clearly, there is a group of patients whose illness does not respond to first-line treatment, and this has been termed treatment-resistant schizophrenia.[8] Studies of drug occupancy at dopamine D2/3 receptors reported similar levels of D2 receptor occupancy in responders and non-responders, showing that a failure to obtain adequate drug levels in the brain does not explain the absence of response.[9]

These findings raise two questions. First, what is different about the underlying neurobiology in these patients that causes antipsychotic drugs, other than clozapine, to have little benefit? Second, what features of clozapine make it uniquely effective in these patients? Answering these questions is crucial to the development of new treatments for refractory schizophrenia. A further clinical need is the early identification of patients with treatment-resistant schizophrenia so that they can start appropriate treatment without delay.[10] Treatment guidelines recommend that patients should receive clozapine if they have not responded to adequate trials of at least two antipsychotics.[11] However, in clinical practice, patients generally start clozapine after a long delay.[12] A biomarker that enables early identification of treatment resistance, potentially at first presentation, could obviate the existing requirement for empirical trials of different antipsychotics. In this systematic review, we assess the neuroimaging evidence regarding treatment-resistant schizophrenia, and consider the implications for discovery of biomarkers and development of new treatments.

Methods

We searched PubMed for studies published between Jan 1, 1980, to April 13, 2015. Reference lists of reviews and research papers from the search were also reviewed to identify additional studies. The following keywords were used in our search strategy: ("treatment resistant" OR "treatment refractory" OR "drug resistant"), AND ("schizophrenia" OR "psychosis"), AND ("magnetic resonance imaging" OR "MRI" OR "functional magnetic resonance imaging" OR "fMRI" OR "positron emission tomography" OR "PET" OR "magnetic resonance spectroscopy" OR "MRS" OR "EEG" OR "electro-encephalography" OR "magnetoencephalography" OR "MEG" OR "event related potential" OR "ERP" OR "voxel based morphometry" OR "VBM" OR "diffusor tensor imaging" OR "DTI" OR "SPECT" or "SPECT" or "CT").

Articles were independently selected by EM and RM. The inclusion criteria specified original research articles in English that were published in peer-reviewed journals. We included all studies that recruited treatment-resistant patients and used in-vivo brain-imaging modalities. We also included longitudinal studies reporting neuro-imaging findings before and after clozapine treatment

in patients with resistant schizophrenia; studies examining solely receptor occupancy of clozapine were not included.

The data extracted from each article were sample size, criteria for definition of treatment resistance, brain-imaging modality, medication status, and diagnostic criteria for schizophrenia (appendix). Where possible, effect sizes (Cohen's d for differences between means) for the comparisons were calculated.

See Online for appendix

Results

We identified 330 reports, of which 61 met the inclusion criteria after the full texts were assessed (figure).[13–73] 14 studies defined treatment resistance according to the criteria of Kane and colleagues,[74] 39 used a range of definitions, and eight studies did not specify any criteria (appendix).

Treatment-resistant patients versus healthy controls

In 30 studies, covering 680 patients and 714 controls, treatment-resistant patients were compared with healthy volunteers (table 1). 11 studies used structural MRI, of which five reported decreases in overall grey matter volumes,[14–18] and the reductions were significant in all but one study.[17] Four studies reported grey matter reduction in specific brain regions in treatment-resistant patients:[15,16,19,20] more than 25 distinct areas of reduction were identified, with the left middle frontal, right precentral, and right middle temporal gyri being the most consistently implicated. Regarding white matter volumes, a study of treatment-resistant patients who were receiving haloperidol at the time of the scan reported overall increases,[14] whereas reductions were reported in a study of patients given clozapine[15] and a study in which medication status was not specified.[18] One study showed that resistant patients had enlargement in posterior sections of the corpus callosum, particularly the splenium.[21] Complementing this finding, a diffusion tensor imaging study[22] showed widespread disruptions to white matter tract integrity in patients with treatment-resistant schizophrenia. The disruptions were especially apparent in the corpus callosum, and illness duration was negatively related to fractional anisotropy in the splenium.

Five studies used functional MRI (fMRI). Although the results from three resting-state MRI studies[23–25] and a study using a word-generation task[26] are not necessarily incompatible, they do not give rise to coherent conclusions as a whole. Arterial spin labelling in individuals with resistant auditory hallucinations showed increased cerebral blood flow in areas involved in speech processing.[27]

Seven studies used PET or single-photon emission CT (SPECT). Six of these used radiotracers that allow the measurement of cerebral metabolic rate (eg, ^{18}F-fluorodeoxyglucose [^{18}F-FDG]) or blood flow (technetium-99m-exametazime [^{99m}Tc-HMPAO], oxygen-15 (^{15}O), and technetium-99m-ethyl cysteinate diethylester [^{99m}Tc-ECD]), and all but one[28] showed some degree of hypofrontality in treatment-resistant schizophrenia. Three studies using ^{99m}Tc-HMPAO SPECT showed reduced perfusion of frontal areas.[29–31] In one of these studies,[29] treatment-resistant patients also showed increased perfusion ratios in the basal ganglia, a finding that was replicated in a second study,[30] whereas reduced perfusion of the right dorsolateral prefrontal cortex was associated with severity of negative symptoms. Another study used ^{99m}Tc-ECD SPECT while participants did the Wisconsin Card Sorting Test;[32] individuals with treatment-resistant schizophrenia had reduced cerebral blood flow in frontotemporal regions at rest and a reduced percentage increase during the task.[32] A ^{18}F-FDG PET study[33] showed reduced activity in cortical and subcortical regions in treatment-resistant patients. Another ^{18}F-FDG PET study looking specifically at treatment-resistant hallucinations[28] reported an increase in metabolic activity in many language-related areas.

One of the two studies in which ^{1}H-magnetic resonance spectroscopy was used showed increased glutamate concentrations in the anterior cingulate cortex of individuals with treatment-resistant schizophrenia.[34] The other study showed increased glutamate and glutamine concentrations in the putamen.[35]

The P300 is an event-related component of EEG that is seen when a stimulus deviates from a preceding sequence of standard stimuli and is thought to index information-processing efficiency. Of the six EEG studies, two showed significant decreases in

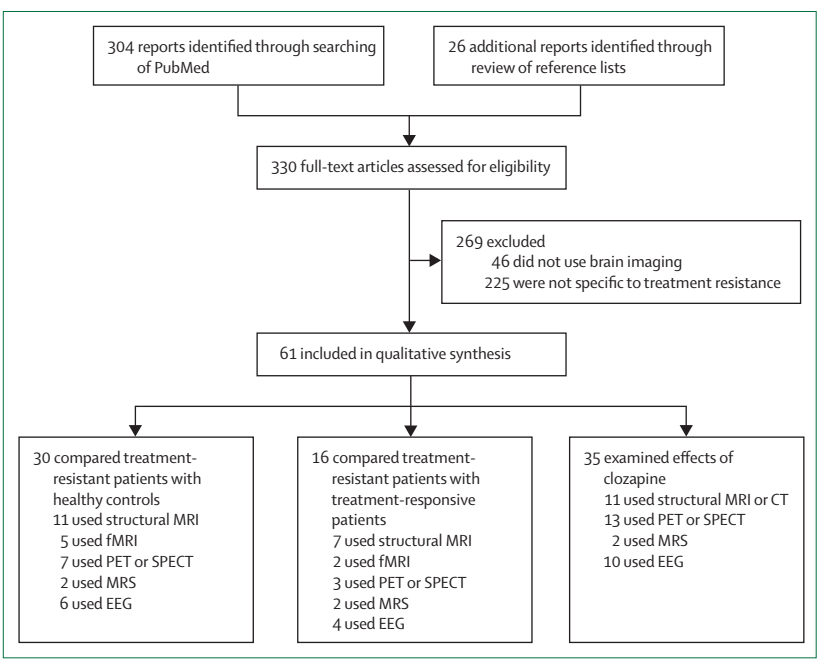

Figure: **Study selection**
Some studies used more than one imaging techniques and examined several populations, and are thus represented more than once. fMRI=functional MRI. MRS=magnetic resonance spectroscopy. SPECT=single-photon emission CT.

	Modality	Main findings
Ahmed et al, 2015[17]	Structural MRI	Raw brain volumes were compared; patients had reduced grey matter (d=0·33 [NS]) and white matter (d=0·32 [NS]) volumes, and increased CSF volume (d=0·19 [NS])
Anderson et al, 2015[15]	Structural MRI	Normalised brain volumes were compared; treatment-resistant patients had decreased grey matter (d=1·23) and white matter (d=0·63) volumes, and increased CSF volume (d=0·23 [NS]); grey matter volume was reduced in the right central operculum and right inferior temporal gyrus Clozapine non-responders had decreased grey matter (d=1·90) and white matter (d=0·99) volumes, and increased CSF volume (d=0·80); grey matter volume was reduced bilaterally across the superior and middle temporal, Heschl's, and post-central gyri, central and parietal opercula, insula, ventromedial prefrontal cortex, and anterior cingulate cortex
Cachia et al, 2008[60]	Structural MRI	Patients had reduced cortical folding in the left frontal middle (d=0·75), left temporal superior (d=0·61), left Sylvius (diagonal branch; d=0·56), and right temporal superior (d=0·83) regions
Hoptman et al, 2005[72]	Structural MRI	Larger grey matter volume in the left orbitofrontal cortex and white matter volume in the bilateral orbitofrontal cortex were associated with aggression
Kubera et al, 2014[19]	Structural MRI	Patients had reduced grey matter volumes, predominantly in the lateral prefrontal, temporal, and parietal regions
Maller et al, 2012[18]	Structural MRI	Raw brain volumes were compared; patients had decreased grey matter (d=0·56), white matter (d=0·66), and CSF (d=0·39) volumes, and reduced hippocampus tail (normalised by intracranial volume; right tail d=1·71; left tail d=1·20)
Molina et al, 2008[14]	Structural MRI	In patients, normalised grey matter volume was decreased (frontal d=1·59; parietal d=0·87 [NS]; occipital d=1·40; temporal d=0·75 [NS]), and normalised white matter volume was increased (frontal d=1·00; parietal d=1·42; occipital d=1·85)
Quaranatelli et al, 2014[16]	Structural MRI	Patients had reduced global grey matter volume (normalised), especially in the left post-central gyrus and dorsolateral superior frontal gyrus; right rolandic operculum, inferior frontal gyrus, insula, and amygdala; and bilateral precentral and middle frontal gyrus
Sun et al, 2009[21]	Structural MRI	Patients had increased total normalised volume of corpus callosum (d=1·9), particularly in CC3 (d=1), CC4 (d=1), and CC5 (d=0·4)
Zugman et al, 2013[20]	Structural MRI	Patients had reduced grey matter volume in the left orbitofrontal, middle temporal, fusiform, caudal middle frontal, and superior temporal gyri, and lingual areas; and in the right precentral, pars triangularis, middle temporal, and lateral occipital areas
Holleran et al, 2014[22]	Structural MRI—diffusion tensor imaging	Patients had reduced fractional anisotropy in the genu, body, and splenium of corpus callosum; temporal inferior and superior longitudinal fasciculus, external capsule, temporal uncinate fasciulus, posterior and left anterior limb of the internal capsule, fornix, cerebellar peduncles, and corticospinal tract; patients also had increased radial diffusivity in voxels in genu, body, and splenium of corpus callosum, right inferior longitudinal fasciculus, posterior limb of the internal capsule, and external capsule
Alonso-Solís et al, 2015[23]	Resting-state MRI	In patients, functional connectivity of the posterior inferior parietal lobule with the occipital fusiform and ligual gyri, and left occipital pole was increased
Vercammen et al, 2010[24]	Resting-state MRI	Patients with treatment-resistant auditory verbal hallucinations had decreased functional connectivity between the left temporoparietal junction and right inferior frontal gyrus; severity of hallucinations was associated with reduced coupling between the left temporoparietal junction and the bilateral anterior cingulate and amygdala
Wolf et al, 2011[25]	Resting-state MRI	In treatment-resistant patients, speech-related network had elevated connectivity in the bilateral temporal lobe and reduced connectivity in the left anterior cingulate cortex; attention network showed increased connectivity in the right middle frontal gyrus; executive function network had decreased connectivity in the left precuneus, right middle frontal gyrus, and superior frontal gyrus
Wolf et al, 2012[27]	MRI—arterial spin labelling	Patients had increased regional cerebral blood flow in the left inferior frontal gyrus, left anterior cingulate cortex, the supplementary motor area in a cluster including the left middle and superior temporal gyri, the left insula, and the right middle temporal and right supramarginal gyri, extending to the right temporoparietal cortex
Fitzgerald et al, 2007[26]	Functional MRI—word generation	Patients had reduced activation in medial frontal regions and enhanced activation in the left caudal precentral gyrus
Demjaha et al, 2012[43]	^{18}F-DOPA PET	Healthy volunteers and treatment-resistant patients showed no differences in striatal dopamine synthesis capacity
Klirova et al, 2013[28]	^{18}F-FDG PET	Patients with treatment-resistant hallucinations had increased perfusion in the lentiform nucleus, thalamus, and postcentral, left parahippocampal, and right superior frontal gyri; in the left acoustic–linguistic cortex, increased perfusion was seen in the middle temporal gyrus and temporoparietal junction
Molina et al, 1997[29]	^{99m}Tc-HMPAO SPECT	Patients had reduced perfusion in the right posterior temporal (d=1·52), left ventral prefrontal (d=0·63), and left dorsolateral (d=1·56) regions; and increased perfusion in the right basal ganglia (d=–1·22)
Molina et al, 1997[30]	^{99m}Tc-HMPAO SPECT	Right basal ganglia perfusion decreased in healthy controls, increased in clozapine non-responders, and substantially increased in treatment-resistant patients who responded to clozapine; perfusion in the thalamus and left basal ganglia was similar between treatment-resistant patients and healthy controls, but was decreased in clozapine non-responders; perfusion in the left lower prefrontal dorsolateral cortex was lower in treatment-resistant patients and clozapine non-responders than in healthy controls; perfusion in the upper dorsolateral cortex was higher in treatment-resistant patients than in healthy controls and clozapine non-responders
Molina et al, 2007[33]	^{18}F-FDG PET	Treatment-resistant patients who were given clozapine showed reduced activity in the dorsolateral, orbitofrontal, anterior cingulate, and insular cortices, and head of caudate nuclei

(Table 1 continues on next page)

	Modality	Main findings
(Continued from previous page)		
Molina et al, 2008[31]	^{99m}Tc-HMPAO SPECT	Treatment-resistant patients who were given risperidone showed decreased activity in the medial prefrontal and middle cingulate cortices, and insula; these patients showed increased perfusion in the brainstem and hippocampus, and a small part of the left posterior occipital and temporal region
Zhao et al, 2006[32]	^{99m}Tc-ECD SPECT	Patients had decreased regional cerebral blood flow at rest and reduced percentage increase during Wisconsin Card Sorting Test in the left (d=1·48) and right (d=1·40) frontal lobes, and the left (d=1·31) and right (d=1·48) temporal lobes (effect sizes shown are for blood flow at rest)
Demjaha et al, 2014[34]	^{1}H-MRS	Patients showed increased glutamate concentrations in the anterior cingulate cortex (d=1·45) compared with healthy controls
Goldstein et al, 2015[35]	^{1}H-MRS	Treatment-resistant patients who responded to clozapine had a higher glutamate–glutamine to creatinine ratio in the putamen (d=3·68) than had healthy controls, although this finding did not stand after correction for multiple comparisons
Galletly et al, 2005[36]	EEG	Treatment-resistant patients (before clozapine treatment) had lower midline N1, P300, and parietal slow-wave activity than had healthy controls
Horton et al, 2011[37]	EEG	In frequency-deviant conditions, patients had decreased latencies (d=0·93) and amplitude (d=1·19) of mismatch negativity; in duration-deviant conditions, no difference in latency was seen (d=0·59), and patients had decreased amplitude of mismatch negativity (d=3·14)
Milovan et al, 2004[39]	EEG	Patients had increased amplitude of mismatch negativity (midline electrode d=0·98; lateral electrode d=0·89)
Molina et al, 2008[14]	EEG	Patients had reduced P300 amplitude (d=2·94)
Ravan et al, 2015[45]	EEG	Machine-learning investigation of EEG responses to auditory odd ball task was able to classify healthy controls and treatment-resistant patients with a 81·4% accuracy
Umbricht et al, 1998[38]	EEG	Patients had decreased amplitudes of mismatch negativity (d=0·99)

Effect sizes (Cohen's d for differences between means) are shown where the calculation was possible. NS=not significant. CSF=cerebrospinal fluid. ^{18}F-FDG=^{18}F-fluorodeoxyglucose. ^{99m}Tc-HMPAO=technetium-99m-exametazime. SPECT=single-photon emission CT. ^{99m}Tc-ECD=technetium-99m-ethyl cysteinate diethylester. MRS=magnetic resonance spectroscopy.

Table 1: **Summary of findings of studies comparing treatment-resistant patients with healthy controls**

P300 amplitude in patients compared with controls.[14,36] In two studies, the mismatch negativity component, which is thought to index the integrity of the pre-attentive sensory network, decreased in amplitude in treatment-resistant patients.[37,38] One study of 13 patients was not in agreement with the above findings, both in terms of mismatch negativity and P300 components;[39] however, medication status of patients was not specified in this study, raising the possibility that different medication status could explain the discrepancy.

Treatment-resistant patients versus treatment-responsive patients

We identified 16 studies that compared treatment-resistant patients (n=298) with treatment-responsive patients (n=264; table 2). All seven studies that used structural MRI[14–16,19,20,40,41] showed reduced grey matter in frontal areas in resistant patients compared with responsive patients, although the reduction was not significant in two studies.[14,40] Two studies[14,15] reported enlarged white matter volumes in resistant patients, but the increase was significant in only one of them.[14]

A resting-state MRI study showed that treatment-resistant patients had greater functional connectivity between the dorsomedial prefrontal cortex and other frontotemporal areas, but reduced connectivity between the ventromedial prefrontal cortex and areas of the cingulate cortex.[23] The other fMRI study, which used arterial spin labelling,[27] showed increased regional cerebral blood flow in the left superior temporal gyrus, right supramarginal gyrus, and temporal polar cortex in patients with treatment-resistant auditory hallucinations.

Three studies used PET or SPECT. By contrast with the arterial spin labelling MRI study,[27] no differences in perfusion between resistant and responsive groups were reported in a ^{99m}Tc-HMPAO SPECT study.[40] In an ^{18}F-FDG PET study,[42] haloperidol challenge caused widespread decreases in metabolic activity in resistant patients but not in treatment-responsive patients. Demjaha and colleagues[43] used F-DOPA PET to show increased striatal dopamine synthesis capacity in responsive patients compared with resistant patients.

A subsample of Demjaha and colleagues' study[43] was investigated with ^{1}H-magnetic resonance spectroscopy.[34] Treatment-resistant patients had significantly higher glutamate concentrations in the anterior cingulate cortex than had healthy controls,[34] whereas responsive patients had similar levels to healthy controls. Goldstein and colleagues[35] showed that in treatment-resistant patients who responded to clozapine, concentrations of glutamate and glutamine were increased in the putamen and reduced in the dorsolateral prefrontal cortex, compared with individuals who responded to first-line antipsychotics.

One of the four EEG studies reported that treatment-resistant patients showed non-significant P300 decreases compared with responsive patients.[14] Another study

	Modality	Main findings
Anderson et al, 2015[15]	Structural MRI	Grey matter volume was reduced globally in treatment-resistant patients who responded to clozapine and clozapine non-responders (d=0·84 for clozapine responders *vs* antipsychotic responders); compared with antipsychotic responders, treatment-resistant patients had decreased grey matter volume in the temporal, post-central, middle and superior frontal, and supramarginal gyri, and the lateral occipital cortex; compared with antipsychotic responders, clozapine non-responders had reduced grey matter volume in the right parietal operculum and left cerebellum; no significant differences in grey matter volume were seen between treatment-resistant patients and clozapine non-responders; white matter volumes were slightly increased (NS) in treatment-resistant patients who responded to clozapine
Kubera et al, 2014[19]	Structural MRI	Compared with individuals who did not have auditory verbal hallucinations, those who have treatment-resistant hallucinations had decreased grey matter volume across a structural network involving predominantly the medial frontal, orbitofrontal, and superior temporal regions
Lawrie et al, 1995[40]	Structural MRI	Treatment-resistant patients had decreased whole brain volume (d=0·41 [NS]) and decreased right temporal lobe volume (d=0·46 [NS])
Mitelman et al, 2005[41]	Structural MRI	Treatment-resistant patients had decreased grey matter volume in the posterior cingulate and retrosplenial cortices
Molina et al, 2008[14]	Structural MRI and EEG	Treatment-resistant patients had reduced grey matter volume (frontal d=0·87 [NS]; occipital d=0·81 [NS]) and increased white matter volume (frontal d=1·13 [NS]; parietal d=1·35 [NS]; occipital d=1·43 [NS]) at baseline; compared with antipsychotic responders, treatment-resistant patients had increased grey matter volume longitudinally (frontal d=1·95; parietal d=2·11; occipital d=1·81) and decreased white matter volume longitudinally (frontal d=1·18; parietal d=1·65; occipital d=1·22)
Quaranatelli et al, 2014[16]	Structural MRI	Treatment-resistant patients had decreased grey matter volume in the left post-central and superior frontal gyri (dorsolateral), and bilateral middle frontal gyrus
Zugman et al, 2013[20]	Structural MRI	In treatment-resistant patients, grey matter volume was reduced in the dorsolateral prefrontal cortex
Alonso-Solís et al, 2015[23]	Resting-state MRI	In treatment-resistant patients, functional connectivity was increased between the dorsomedial prefrontal cortex and the central opercular cortex, insular cortex, precentral gyrus, and superior temporal gyrus, and between the temporal pole and the cerebellum; functional connectivity was decreased between the ventromedial prefrontal cortex and the paracingulate, anterior cingulate, and subcallosal cortices, and between hippocampal formation and the posterior cingulate cortex and precuneus complex
Wolf et al, 2012[27]	MRI—arterial spin labelling	Compared with patients who did not have auditory verbal hallucinations, those who had treatment-resistant hallucinations had increased cerebral blood flow in the left superior temporal gyrus, right supramarginal gyrus, and temporoparietal cortex
Bartlett et al, 1998[42]	^{18}F-FDG PET—haloperidol challenge	In treatment-resistant patients, metabolic rate was decreased in the whole brain (d=1·2), left (d=1·05) and right (d=0·87) dorsolateral prefrontal cortex, and left temporal cortex (d=1·19); in treatment-responsive patients, metabolic rates were not affected
Demjaha et al, 2012[43]	F-DOPA PET	Treatment-resistant patients had reduced dopamine synthesis capacity in the whole striatum (d=1·11), decreased associative (d=1·31) and limbic (d=1·04) subdivision dopamine synthesis capacity, and sensorimotor subdivision (NS)
Lawrie et al, 1995[40]	^{99m}Tc-HMPAO SPECT	No significant differences in perfusion were seen between treatment-resistant patients and antipsychotic responders
Goldstein et al, 2015[35]	^{1}H-MRS	Glutamate–glutamine to creatinine ratio in the dorsolateral prefrontal cortex was decreased in treatment-resistant patients who responded to clozapine (d=2·17) and substantially decreased in clozapine non-responders (d=3·99) compared with antipsychotic responders; treatment-resistant patients who responded to clozapine had increased glutamate–glutamine to creatinine ratio in the putamen compared with antipsychotic responders (d=3·31) and clozapine non-responders (d=4·00)
Demjaha et al, 2014[34]	^{1}H-MRS	Compared with antipsychotic responders, treatment-resistant patients had increased glutamate concentrations in the anterior cingulate cortex (d=0·70 [NS])
Lee et al, 2006[46]	EEG	Treatment-resistant patients had increased frequencies of gamma–beta1 (d=0·61) and gamma–beta2 (d=0·69); a correlation between frequencies of gamma–beta2 and gamma–beta3 (range of *r*=0·42–0·61) in posterior and anterior electrodes was seen in treatment-resistant patients but not in antipsychotic responders
Lee et al, 2008[47]	EEG	In treatment-resistant patients, gamma frequency at D2 was increased (ie, more chaotic) in the right frontal electrode Fp2 (d=0·58) and beta frequency at D2 was increased (ie, less chaotic) in the left parietal electrode P3 (d=0·7)
Molina et al, 2008[14]	EEG	P300 amplitude was decreased in treatment-resistant patients (d=0·53 [NS])
Ramos et al, 2001[44]	EEG	Treatment-resistant patients had decreased alpha2, beta1, and beta2 frequencies in the temporal region, and increased beta2 frequency in the occipital region; increased intrahemispheric correlation in Fp2–F4; and decreased intrahemispheric correlation between F8 and T4

Effect sizes (Cohen's d for differences between means) are shown where the calculation was possible. NS=non-significant. ^{18}F-FDG=^{18}F-fluorodeoxyglucose. ^{99m}Tc-HMPAO=technetium-99m-exametazime. SPECT=single-photon emission CT. MRS=magnetic resonance spectroscopy.

Table 2: **Summary of findings of studies comparing treatment-resistant patients with responders to antipsychotics**

showed that treatment-resistant patients had a different connectivity pattern from that of treatment responders, with a higher interhemispheric correlation between frontal electrodes.[44] Gamma–beta correlations index a response to novel auditory stimuli.[75] One study reported significant increases in gamma and beta frequencies in speech-related areas, and a significant gamma–beta correlation in resistant patients but not in responsive

	Modality	Main findings
Ahmed et al, 2015[17]	Structural MRI	Decrease in grey matter volume over 6–12 months was greater in treatment-resistant patients given clozapine than in healthy controls (right prefrontal cortex d=1·06 [NS]; left prefrontal cortex d=1·02 [NS]; periventricular area d=1·85 [NS]); cortical thickness of the left medial frontal cortex and right medial temporal cortex was lower in clozapine non-responders than in responders (d=1·07)
Anderson et al, 2015[15]	Structural MRI	No significant structural differences were seen between treatment-resistant patients who responded to clozapine and clozapine non-responders
Arango et al, 2003[51]	Structural MRI	Increased grey matter volume in the right prefrontal cortex before treatment was associated with good response in patients given clozapine, but with poor response in patients given haloperidol
Chakos et al, 1995[54]	Structural MRI	Patients were scanned at baseline and then at 55 weeks after clozapine treatment; caudate nucleus volume was decreased by 10% in those given clozapine (d=0·94) but increased by 8% in those remaining on typical antipsychotics
Honer et al, 1995[48]	CT	Cortical sulcal spaces were smaller in clozapine responders than in non-responders
Friedman et al, 1991[50]	CT	Patients who had good responses to clozapine had smaller prefrontal sulcal spaces than those who had moderate responses, who in turn had smaller prefrontal sulcal spaces than non-responders
Konicki et al, 2001[49]	CT	Prefrontal sulcal spaces were smaller in clozapine responders than in poor responders (d=3·80)
Lauriello et al, 1998[53]	Structural MRI	No correlation was seen between change in brief psychiatric rating scale and sulcal CSF or grey matter volumes in the prefrontal and frontal cortices; increased sulcal CSF volumes in the anterior superior temporal lobe were associated with clinical improvement
Molina et al, 2003[52]	Structural MRI	Improvement in positive symptoms was related to increased temporal grey matter volume at baseline; improvement in negative symptoms was related to increased baseline dorsolateral prefrontal cortex volumes; improvement in disorganised symptoms was related to reduced baseline intracranial and hippocampal volumes
Molina et al, 2008[14]	Structural MRI	Treatment-resistant patients showed longitudinal changes compared with healthy controls over about 28 months, including increases in grey matter volume in the frontal (d=1·24), parietal (d=1·68), and occipital (d=1·99) regions; and decreases in white matter volume in the frontal (d=1·36), parietal (d=1·53), and occipital (d=1·63) regions
Scheepers et al, 2001[55,56]	Structural MRI	Clozapine use led to a significant decrease in caudate nucleus volume over 24 weeks (d=0·23); this decrease was not related to clinical response at 24 weeks, but when patients were followed up for 52 weeks the decrease in left caudate nucleus volume was significantly greater in responders than in non-responders (d=0·56)
Buchsbaum et al, 1992[57]	^{18}F-FDG PET	Metabolic rates in the basal ganglia were increased after clozapine treatment and decreased after thioxene treatment, and the effects were most pronounced on right side; baseline metabolic rates predicted clinical medication response, and clozapine and thioxene responders could be differentiated by their right inferior caudate metabolic rates
Ergün et al, 2010[62]	^{99m}Tc-HMPAO SPECT	After 8 weeks of clozapine treatment, changes in blood flow were seen in 12 of 20 patients, mostly in the basal ganglia or frontal cortex
Ertugrul et al, 2009[61]	^{99m}Tc-HMPAO SPECT	In clozapine responders, right and left (superior and medial) frontal to caudate perfusion ratio increased with treatment, whereas this change was not seen in non-responders; change in perfusion ratio was associated with improvements in cognitive testing; response to clozapine was predicted by baseline right frontal:thalamus perfusion (d=0·56)
Lahti et al, 2003,[63] 2004[13]	^{15}O-PET	Regional cerebral blood flow in the striatum was increased after clozapine treatment and substantially increased after haloperidol treatment; blood flow to the anterior cingulate, dorsolateral frontal, and occipital cortices was increased more after clozapine than haloperidol treatment; both drugs led to reduced blood flow in the hippocampus, ventrolateral frontal cortex, and right middle temporal cortex
Molina et al, 2003[52]	^{18}F-FDG PET	Improvement of negative symptoms was predicted by baseline activity in the dorsolateral prefrontal cortex
Molina et al, 2005[71]	^{18}F-FDG PET	6 months of clozapine treatment led to a decrease in metabolic activity in the dorsolateral and medial prefrontal cortices, basal ganglia, and left inferior temporal cortex, and an increase in metabolic activity in the occipital cortex; decreased basal ganglia activity was associated with a reduction in negative symptoms; decreased activity in motor areas was related to increased disorganisation symptoms; increased activity in the primary visual area was associated with increased positive symptoms
Molina et al, 1996,[59] 1997[30]	^{99m}Tc-HMPAO SPECT	Before clozapine treatment, responders had increased perfusion in the thalamus, basal ganglia, and left lower and right upper dorsolateral prefrontal cortex; after clozapine treatment, responders showed decreased perfusion in the thalamus, basal ganglia, and upper dorsolateral cortex, whereas non-responders did not show significant changes in any perfusion values
Molina et al, 2008[31]	^{99m}Tc-HMPAO SPECT	After 1 month of clozapine treatment, patients no longer showed decrease in activity in cingulate or insular regions, although perfusion still decreased in the medial prefrontal cortex; hyperactivity in the brainstem, temporolateral, and occipital areas was still present; the increase in perfusion in the medial occipital cortex and caudate head, and decrease in the posterior cingulate cortex and hippocampus were greater in clozapine responders than in non-responders
Potkin et al, 1994[58]	^{18}F-FDG PET	Compared with baseline scans while receiving placebo, after 39 days of clozapine treatment patients showed increased perfusion in the striatum and decreased perfusion in the frontal and occipital cortices
Potkin et al, 2003[64]	^{18}F-FDG PET	Patients with the homozygous *DRD1 2,2* genotype showed widespread metabolic decreases after clozapine treatment and good clinical response, but this was not reported for heterozygous individuals with the *DRD1 1,2* genotype; heterozygotes showed worsening of symptoms that was associated with metabolic decreases in the left prefrontal and bilateral temporal cortices, and an increase in the right inferior temporal cortex

(Table 3 continues on next page)

	Modality	Main findings
(Continued from previous page)		
Zhao et al, 2006[32]	^{99m}Tc-ECD SPECT	Clozapine had no effect on regional cerebral blood flow either during resting state or during Wisconsin Card Sorting Test, although improvement in behavioural performance on the task was reported
Ertugrul et al, 2009[61]	^{1}H-MRS	An almost significant (p=0·05) increase in N-acetylaspartic acid to creatinine ratio was seen in the left dorsolateral prefrontal cortex after clozapine treatment
Goldstein et al, 2015[35]	^{1}H-MRS	Glutamate–glutamine to creatinine ratio in the putamen was higher in clozapine responders than in non-responders (d=4·00)
Galletly et al, 2005[36]	EEG	Clozapine treatment was associated with normalisation of P300 and late slow waves, and partial normalisation of N1 amplitude
Gross et al, 2004[67]	EEG	Clozapine treatment was associated with an increase in theta power in midline, which was related to clinical improvement
Kikuchi et al, 2014[70]	EEG	10 (38%) of 26 patients given clozapine developed EEG abnormalities; individuals who developed abnormalities were more likely to be younger and had a shorter duration of illness
Knott et al, 2001[68]	EEG	Clozapine treatment decreased relative alpha power, and mean beta and total spectrum frequencies; and increased absolute total, delta, and theta power
Knott et al, 2002[66]	EEG	Clozapine treatment normalised some of the interhemispheric and intrahemispheric coherence abnormalities present at baseline
Lacroix et al, 1995[65]	EEG	Clozapine treatment led to increases in theta and alpha bands; low responders showed a greater increase in beta1 bands than did high responders; high responders showed increased coherence between many regions (centred on the right anterior-medial temporal region and in the theta band) that was not seen in low responders
MacCrimmon et al, 2012[69]	EEG	Baseline EEG was compared with second EEG, taken on average 1·4 years after starting clozapine treatment; clozapine augmented power in delta and theta bands globally (particularly in the frontal areas) and reduced beta3 power; power of alpha band showed a frontal increase and posterior decrease
Ravan et al, 2014[45]	EEG	After clozapine treatment, EEG of responders became indistinguishable from that of healthy controls, whereas the EEG of non-responders remained substantially different
Tsekou et al, 2015[73]	EEG	Clozapine treatment was associated with increased stage 2 sleep, reduced slow-wave sleep, and increased random eye movements
Umbricht et al, 1998[38]	EEG	Clozapine partly normalised P300 decreases but did not affect mismatch negativity

Effect sizes (Cohen's d for differences between means) are shown where the calculation was possible. NS=not significant. CSF=cerebrospinal fluid. ^{18}F-FDG=^{18}F-fluorodeoxyglucose. ^{99m}Tc-HMPAO=technetium-99m-exametazime. SPECT=single-photon emission CT. ^{99m}Tc-ECD=technetium-99m-ethyl cysteinate diethylester. MRS=magnetic resonance spectroscopy.

Table 3: **Summary of findings of longitudinal studies of treatment-resistant patients before and after clozapine, and studies predicting clozapine response**

patients.[46] A second study by the same group examined this effect in terms of dimensional complexity and showed reduced neuronal synchronisation in the prefrontal cortex of resistant patients.[47]

Predictors of clozapine response and effects of clozapine in treatment-resistant patients

We identified 35 papers, covering 844 patients and 322 controls, that examined the effects of clozapine (table 3). 11 studies used structural neuroimaging, of which three early studies used CT scans in an attempt to identify predictors of clozapine response.[48–50] In these studies, a consistent finding was that prefrontal sulcal spaces were smaller in responders to clozapine than in poor responders, which is in agreement with later findings that large prefrontal[51,52] and temporal[52] grey matter volumes are associated with a good response to clozapine. Some conflicting findings have been reported; one MRI study[53] showed almost diametrically opposed results in that response was associated with larger sulcal spaces in the anterior superior temporal lobe. However, this study included both treatment-intolerant and treatment-resistant patients, and this difference in patient population might account for the discrepancy. Another study[15] did not find any direct significant contrasts between individuals who had responded well to clozapine and those who did not respond.

Regarding the effects of clozapine treatment, a longitudinal study[54] showed that, over the course of 1 year, patients started on clozapine showed a 10% reduction in caudate nucleus volume, whereas those remaining on typical antipsychotics had an 8% increase. These findings were replicated by two studies showing that clozapine use led to caudate nucleus reductions over 24 weeks[55] and 52 weeks.[56] Furthermore, greater reductions in left caudate volume were seen in clozapine responders than in non-responders. Molina and colleagues[14] reported widespread reductions in grey matter volume and increases in white matter volume in treatment-resistant patients compared with healthy controls, and these changes were, to some extent, reversed during clozapine treatment. By contrast, another study[17] showed that grey matter losses in the prefrontal cortex were (non-significantly) greater in patients given clozapine than in healthy volunteers, although clozapine

responders had less cortical thinning over the left medial frontal and right middle cortices than had clozapine non-responders during this period.

13 studies used PET or SPECT. Two early ^{18}F-FDG PET studies showed increased metabolic rates in the basal ganglia[57,58] and reduced rates in the frontal cortex[58] after clozapine treatment. However, two ^{99m}Tc-HMPAO studies[30,59] suggested that increased basal ganglia and frontal cortex perfusion before treatment was associated with clozapine response, and that treatment reduced perfusion. These differences might be accounted for by the fact that, at the time of imaging, individuals in the ^{18}F-FDG PET studies had stopped taking antipsychotics for at least 14 days, whereas in the ^{99m}Tc-HMPAO studies individuals were taking antipsychotics, which have been shown to alter brain metabolism.[76] A later study using ^{99m}Tc-HMPAO SPECT[61] showed that clozapine treatment led to increased perfusion of the frontal cortex, and that such an increase predicted response; again, imaging was done after a 1-week wash-out period as opposed to during antipsychotic treatment.

Some of the discrepancies between study findings might be accounted for by differences in the medication status of patients. However, the likelihood that some of this heterogeneity is intrinsic to the question under examination is well illustrated by two studies. In a study that reported individual patient findings after clozapine treatment (n=20),[62] six patients had increases and four had reductions in basal ganglia perfusion, whereas four patients had increases and one had a reduction in frontal cortex perfusion. A ^{15}O-PET study[63] showed that clozapine treatment led to increases in perfusion in the dorsolateral part of the frontal cortex but decreases in the ventrolateral part.

An ^{18}F-FDG PET study[64] suggested that response to clozapine is modulated by different alleles of *DRD1*, which codes for D1 receptors. Cortical metabolic decreases were associated with clinical improvement for patients with the *DRD1 2,2* genotype but not for patients with the heterozygous *DRD1 1,2* genotype.

One study[61] used ^{1}H-magnetic resonance spectroscopy to measure concentrations of N-acetylaspartic acid, a marker of neuronal integrity. Low concentrations in the dorsolateral prefrontal cortex were associated with clinical improvement, whereas 8 weeks of clozapine treatment led to increased concentrations, although no correlation with clinical improvement was reported. Another study[35] suggested that individuals on clozapine who show a good response have higher concentrations of glutamate and glutamine in the putamen than have those with a poor response.

Among the ten EEG studies identified, one reported that clozapine normalised P300 and slow-wave components,[36] and another study showed that clozapine partly normalised P300 decreases but did not have any effect on mismatch negativity.[38] These findings suggest that clozapine possibly affects attentive but not pre-attentive processing. Five studies used spectral analysis to assess effects of clozapine.[65–69] Two early studies[65,66] measured coherence and showed that resistant patients have interhemispheric and intrahemispheric dysconnectivity in anterior brain regions that was partly normalised by clozapine treatment. These changes in coherence were also related to improvement in negative symptoms. Three studies showed the widespread effects of clozapine on spectral power, suggesting increases in both fast-wave and slow-wave power.[67–69]

Discussion

The neurobiology of treatment resistance

Two main schools of thought exist regarding the neurobiology of treatment-resistant schizophrenia. One of these, which can be characterised as the continuum hypothesis, posits that the same pathophysiological processes underlie symptoms in both responsive and resistant patients, but that these processes occur to a greater degree in resistant patients and treatment is therefore less effective. The other hypothesis, which can be regarded as a categorical one, is that resistant schizophrenia has a fundamentally different pathophysiology from that of responsive schizophrenia, and existing treatments are ineffective because they target the wrong processes.[77]

The panel summarises the findings that have support from more than one study. Structural studies uniformly show grey matter reductions in treatment-resistant patients relative to healthy controls, which is consistent with findings seen in schizophrenia in general.[78] However, such volume reductions might not be universally detrimental, with one study showing an association between symptom severity and large orbitofrontal cortex volumes.[72] Functional changes were also similar to those reported in schizophrenia in general.[26,27]

When resistant patients were compared with responsive patients, the most replicated finding was a greater reduction in grey matter in resistant patients, predominantly in frontal areas. Studies using fMRI[27] and EEG[14] also suggested a continuum of pathology: neurobiological differences exist between healthy controls and antipsychotic responders but were even more pronounced in resistant patients.

In terms of neurochemistry, two PET studies are consistent in suggesting that resistant patients might have different dopaminergic functioning compared with responsive patients.[42,43] One F-DOPA PET study[43] showed raised dopamine synthesis capacity in patients with schizophrenia in general but no evidence of increased capacity in resistant patients. A ^{18}F-FDG PET study[42] of the effect of a haloperidol challenge showed substantial decreases in metabolic activity in resistant patients but not in responsive patients. Such decreases can be interpreted as being secondary to responsive patients having elevated presynaptic dopamine reserves, and thus being able to accommodate the antidopaminergic

 Published online March 3, 2016 http://dx.doi.org/10.1016/S2215-0366(15)00540-4

effects of haloperidol; by contrast, treatment-resistant patients do not have the same elevated presynaptic dopamine reserves, resulting in decreased metabolism. If resistant patients do indeed have a dopaminergic system with normal function, this raises the question of what neurochemical abnormalities underlie treatment resistance. Glutamatergic dysfunction has been implicated in the development of schizophrenia, in relation to both positive and negative symptoms.[79–87] The two ^{1}H-magnetic resonance spectroscopy studies were consistent in showing glutamatergic elevations in treatment-resistant patients compared with responsive patients.[34,35] Since high glutamate concentrations have been associated with excitotoxicity and structural brain changes,[88] such elevations in resistant patients could account for the relative grey matter reductions reported in some studies. Although this finding supports the idea that glutamatergic dysfunction underlies resistance, the hypothesis needs to be further tested.

Apart from neuroimaging, other evidence also supports both continuum and categorical hypotheses. Results from one study[89] suggested a potential genetic framework on which categorically different schizophrenia subtypes could be placed, and categorical differences in dopaminergic and glutamatergic function might be able to account for differences in treatment response.[77] Conversely, other studies provide support for the continuum hypothesis, showing that patients with increased exposure to both environmental[90] and genetic[91] risk factors are more likely to be treatment resistant.

Researchers have begun to use multimodal imaging techniques to more precisely delineate the neurobiological processes underlying psychotic disorders.[92–94] An expansion of this approach to include both thorough phenotypic characterisation and measurement of environmental and genetic factors might be needed to gain a fuller understanding of the causative factors leading to treatment resistance.

Treatment-resistant patients will, by definition, have greater symptom severity than responsive patients, but they might also have longer illness duration and greater cumulative exposure to antipsychotics. Long-term exposure to antipsychotics has been shown to cause both increases in basal ganglia volume[95] and atrophy of cortical grey matter.[96,97] Therefore, the neuroimaging differences reported could be confounded by such an exposure, rather than represent underlying differences in pathophysiology.

The effects of clozapine on brain structure and function, and predictors of clozapine response

Two studies showed an association between clozapine treatment and reductions in caudate volume, whereas other antipsychotics were associated with enlargement.[54–56] Reductions in caudate volume were also associated with a good clinical response. Furthermore, two SPECT studies[30,59] showed that response to clozapine is predicted by increased pretreatment perfusion of the basal ganglia, which decreases with successful treatment.

These findings suggest that clozapine's superior effectiveness might be related to its normalising effect on striatal structure and function, which is consistent with its reduced affinity for the D2 receptor.[98] Some patients seem to show a good response to antipsychotics initially and then develop resistance after several years of treatment.[8,99] Such secondary treatment resistance has been suggested to be a result of D2/3 receptor supersensitivity caused by receptor upregulation or other changes. Antipsychotic exposure is associated with dopamine D2/3 receptor upregulation in rodents;[100] although the degree to which this event happens in human beings is unclear, antipsychotic treatment is associated with changes in striatal volume and functional indices in patients.[95] Clozapine has a relatively low affinity for and fast dissociation from the D2/3 receptor.[98] Thus, putatively, these actions at the D2/3 receptor could allow D2/3 supersensitivity to resolve, and underlie clozapine's effectiveness for individuals who have developed secondary treatment resistance after sustained antipsychotic treatment. Although this hypothesis is consistent with the normalisation of the striatal functional and structural changes seen with clozapine treatment, further testing in patients is necessary. Moreover, this explanation alone is unlikely to account for all of clozapine's clinical effectiveness, not least

Panel: **Neuroimaging features of treatment-resistant schizophrenia**

Compared with healthy controls

- Grey matter reduction, particularly in frontal and temporal regions[14–16,18]
- Decreased metabolism[33] and perfusion in frontal areas[28–32]
- Enlargement of the posterior corpus callosum[21]
- Disruption to white matter tracts, particularly in the corpus callosum[22]
- Increased perfusion in the basal ganglia[29,30]

Compared with treatment-responsive patients

- Grey matter reduction, particularly in frontal regions[15,16,20,40,41]
- Increased white matter volume[14,15]
- Reduced striatal dopamine synthesis[42,43]
- Elevated glutamate concentration in the anterior cingulate cortex[34]
- Glutamate and glutamine concentrations are increased in the putamen and decreased in the dorsolateral prefrontal cortex in clozapine responders[35]

Effects of clozapine

- Reduced prefrontal atrophy in clozapine responders compared with non-responders[48–52]
- Clozapine leads to reduction in caudate nucleus volume[54–56]

because enhanced effectiveness in treatment-resistant patients is not seen with quetiapine, which also has relatively low affinity for D2/3 receptors.[101]

Clozapine affects a large number of other neurotransmitter systems, including the glutamatergic system.[102] In view of the glutamatergic abnormalities that have been associated with resistant schizophrenia,[34,35] the effects of clozapine on this system might contribute to its superior effectiveness.

The apparent inconsistency between the two studies that showed increased perfusion after clozapine treatment[57,58] and the others can potentially be explained by differences in participants' medication status at the time of imaging. Lahti and colleagues' findings[13] neatly illustrate the fact that striatal perfusion increases with elevated D2 antagonism. Therefore, if a scan is done at baseline when participants are receiving non-clozapine antipsychotics and again when they are receiving clozapine, a reduction in perfusion might be expected because of a relative reduction in D2 antagonism. However, if the baseline scan is done when participants are receiving no antipsychotic treatment, the scan after clozapine treatment might be expected to show increased perfusion, as a result of the relative increase in D2 antagonism.

In terms of predicting response, early studies suggested that individuals with the most noticeable frontal atrophy were the least likely to benefit from clozapine treatment,[14,48–51] but later studies have produced conflicting results.[15,53] The findings regarding clozapine's longitudinal effects on global grey matter volume are too inconsistent for any conclusions to be drawn. Electrophysiological studies showed that clozapine has widespread effects on spectral power[66–68] and connectivity.[65,66] A good clinical response to clozapine seems to be accompanied by normalisation of various EEG measures towards the values seen in healthy controls;[36,38,45] however, no consistent findings show markers that can predict treatment response at baseline.

Research limitations and future directions

Our systematic review highlights the heterogeneity that permeates neuroimaging research into treatment resistance. Some of this heterogeneity might be inherent to the problem under examination. There might be many ways for an illness to be treatment resistant, but only one route to treatment response. In particular, individuals with similar clinical presentations might show treatment resistance because of different pharmacokinetic and pharmacodynamic factors, or because their underlying disease aetiology varies substantially. However, some of this heterogeneity is a result of the methods used. The cohorts studied vary widely in illness duration, previous drug treatment, and treatment at time of scan, and the studies used different sample sizes, imaging techniques, and analysis methods. A further issue contributing to heterogeneity is that many studies were underpowered to detect even moderate effect sizes (eg, Cohen's d=0·5). Another limitation is the variable definition of treatment resistance among studies. Therefore, the use of standardised, quantifiable criteria to define resistance is important for research purposes, since the use of such criteria would allow for more direct comparisons across studies, which are particularly important in the identification of biomarkers.

Cross-sectional comparisons of treatment-resistant and responsive patients can potentially pinpoint differences that might underlie treatment resistance, but they cannot determine causality. Furthermore, some confounders are difficult to exclude in cross-sectional studies—eg, the finding that high clozapine doses correlate with more grey matter loss is confounded by the association of high doses with disease severity.[17] In view of such confounding, the possibility that differences are secondary to other factors cannot be excluded. We did not identify any studies that prospectively investigated brain structure or function from illness onset to the development of treatment resistance. A logical strategy is to start with cross-sectional studies to identify brain differences between responders and resistant patients but, ultimately, prospective studies from illness onset are needed to identify the biological factors that underlie treatment resistance. Furthermore, prospective studies will be needed to assess whether any neurobiological markers have the potential for clinically relevant prediction of treatment resistance.

The available imaging evidence provides some support for both continuum and categorical hypotheses. This finding suggests that a hybrid of both hypotheses might best describe the neurobiology of resistant schizophrenia: some aspects such as structural changes might occur on a continuum, whereas other aspects, such as presynaptic dopamine function, might be categorically different. Although 61 imaging studies of resistant schizophrenia have been identified, few of these have attempted to replicate previous findings. Well controlled, ideally prospective, studies from illness onset are needed to definitively determine the key aspects of the neurobiology underlying treatment resistance and to identify reliable biomarkers.

Contributors

ODH and EM conceived the study and designed the literature search. RM and EM reviewed abstracts, selected studies for inclusion, and extracted data. EM, RM, and ODH wrote the Review.

Declaration of interests

ODH has received investigator-initiated research funding from and/or participated in advisory or speaker meetings organised by AstraZeneca, Autifony, BMS, Eli Lilly, Jansenn, Lundbeck, Lyden-Delta, Otsuka, Servier, Sunovion, and Roche. Neither ODH nor his family members have been employed by or have holdings or a financial stake in any biomedical company. EM and RM declare no competing interests.

Acknowledgments

This study was funded by Medical Research Council UK (MC-A656–5QD30; to ODH), Maudsley Charity (number 666; to ODH), the Wellcome Trust (094849/Z/10/Z; to ODH), the UK National Institute for Health Research Biomedical Research Centre at South London, Maudsley National Health Service Foundation Trust, and King's College London.

References

1 Howes OD, Murray RM. Schizophrenia: an integrated sociodevelopmental-cognitive model. *Lancet* 2014; **383:** 1677–87.

2 Howes OD, Egerton A, Allan V, McGuire P, Stokes P, Kapur S. Mechanisms underlying psychosis and antipsychotic treatment response in schizophrenia: insights from PET and SPECT imaging. *Curr Pharm Des* 2009; **15:** 2550–59.

3 Kane JM. Addressing nonresponse in schizophrenia. *J Clin Psychiatry* 2012; **73:** e07.

4 Kennedy JL, Altar CA, Taylor DL, Degtiar I, Hornberger JC. The social and economic burden of treatment-resistant schizophrenia: a systematic literature review. *Int Clin Psychopharmacol* 2014; **29:** 63–76.

5 Black K, Peters L, Rui Q, Milliken H, Whitehorn D, Kopala LC. Duration of untreated psychosis predicts treatment outcome in an early psychosis program. *Schizophr Res* 2001; **47:** 215–22.

6 Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988; **45:** 789–96.

7 Agid O, Foussias G, Singh S, Remington G. Where to position clozapine: re-examining the evidence. *Can J Psychiatry* 2010; **55:** 677–84.

8 Beck K, McCutcheon R, Bloomfield MA, et al. The practical management of refractory schizophrenia—the Maudsley Treatment Review and Assessment Team service approach. *Acta Psychiatr Scand* 2014; **130:** 427–38.

9 Howes ODO, Kambeitz J, Kim E, et al. The nature of dopamine dysfunction in schizophrenia and what this means for treatment. *Arch Gen Psychiatry* 2012; **69:** 776–86.

10 Howes OD, Vergunst F, Gee S, McGuire P, Kapur S, Taylor D. Adherence to treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation. *Br J Psychiatry* 2012; **201:** 481–85.

11 NICE guidelines [CG178]. Psychosis and schizophrenia in adults: prevention and management. London: National Institute For Clinical Excellence, 2014. http://www.nice.org.uk/guidance/cg178 (accessed Jan 7, 2016).

12 Howes OD, Vergunst F, Gee S, McGuire P, Kapur S, Taylor D. Adherence to treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation. *Br J Psychiatry J Ment Sci* 2012; **201:** 481–85.

13 Lahti AC, Holcomb HH, Weiler MA, et al. Clozapine but not haloperidol Re-establishes normal task-activated rCBF patterns in schizophrenia within the anterior cingulate cortex. *Neuropsychopharmacology* 2004; **29:** 171–78.

14 Molina V, Reig S, Sanz J, et al. Differential clinical, structural and P300 parameters in schizophrenia patients resistant to conventional neuroleptics. *Prog Neuropsychopharmacol Biol Psychiatry* 2008; **32:** 257–66.

15 Anderson VM, Goldstein ME, Kydd RR, Russell BR. Extensive gray matter volume reduction in treatment-resistant schizophrenia. *Int J Neuropsychopharmacol* 2015; published online Feb 25. DOI:10.1093/ijnp/pyv016.

16 Quarantelli M, Palladino O, Prinster A, et al. Patients with poor response to antipsychotics have a more severe pattern of frontal atrophy: a voxel-based morphometry study of treatment resistance in schizophrenia. *Biomed Res Int* 2014; **2014:** 325052.

17 Ahmed M, Cannon DM, Scanlon C, et al. Progressive brain atrophy and cortical thinning in schizophrenia after commencing clozapine treatment. *Neuropsychopharmacology* 2015; **40:** 2409–17.

18 Maller JJ, Daskalakis ZJ, Thomson RHS, Daigle M, Barr MS, Fitzgerald PB. Hippocampal volumetrics in treatment-resistant depression and schizophrenia: the devil's in de-tail. *Hippocampus* 2012; **22:** 9–16.

19 Kubera KM, Sambataro F, Vasic N, et al. Source-based morphometry of gray matter volume in patients with schizophrenia who have persistent auditory verbal hallucinations. *Prog Neuropsychopharmacol Biol Psychiatry* 2014; **50:** 102–09.

20 Zugman A, Gadelha A, Assunção I, et al. Reduced dorso-lateral prefrontal cortex in treatment resistant schizophrenia. *Schizophr Res* 2013; **148:** 81–86.

21 Sun J, Maller JJ, Daskalakis ZJ, Furtado CC, Fitzgerald PB. Morphology of the corpus callosum in treatment-resistant schizophrenia and major depression. *Acta Psychiatr Scand* 2009; **120:** 265–73.

22 Holleran L, Ahmed M, Anderson-Schmidt H, et al. Altered interhemispheric and temporal lobe white matter microstructural organization in severe chronic schizophrenia. *Neuropsychopharmacology* 2014; **39:** 944–54.

23 Alonso-Solís A, Vives-Gilabert Y, Grasa E, et al. Resting-state functional connectivity alterations in the default network of schizophrenia patients with persistent auditory verbal hallucinations. *Schizophr Res* 2015; **161:** 261–68.

24 Vercammen A, Knegtering H, den Boer JA, Liemburg EJ, Aleman A. Auditory hallucinations in schizophrenia are associated with reduced functional connectivity of the temporo-parietal area. *Biol Psychiatry* 2010; **67:** 912–18.

25 Wolf ND, Sambataro F, Vasic N, et al. Dysconnectivity of multiple resting-state networks in patients with schizophrenia who have persistent auditory verbal hallucinations. *J Psychiatry Neurosci* 2011; **36:** 366–74.

26 Fitzgerald PB, Sritharan A, Benitez J, et al. A preliminary fMRI study of the effects on cortical activation of the treatment of refractory auditory hallucinations with rTMS. *Psychiatry Res* 2007; **155:** 83–88.

27 Wolf ND, Grön G, Sambataro F, et al. Magnetic resonance perfusion imaging of auditory verbal hallucinations in patients with schizophrenia. *Schizophr Res* 2012; **134:** 285–87.

28 Klirova M, Horacek J, Novak T, et al. Individualized rTMS neuronavigated according to regional brain metabolism ((18)FGD PET) has better treatment effects on auditory hallucinations than standard positioning of rTMS: a double-blind, sham-controlled study. *Eur Arch Psychiatry Clin Neurosci* 2013; **263:** 475–84.

29 Molina Rodríguez V, Montz Andrée R, Pérez Castejón MJ, et al. Cerebral perfusion correlates of negative symptomatology and parkinsonism in a sample of treatment-refractory schizophrenics: an exploratory 99mTc-HMPAO SPET study. *Schizophr Res* 1997; **25:** 11–20.

30 Molina Rodríguez V, Andrée RM, Castejón MJ, et al. Fronto-striato-thalamic perfusion and clozapine response in treatment-refractory schizophrenic patients. A 99mTc-HMPAO study. *Psychiatry Res* 1997; **76:** 51–61.

31 Molina V, Tamayo P, Montes C, et al. Clozapine may partially compensate for task-related brain perfusion abnormalities in risperidone-resistant schizophrenia patients. *Prog Neuropsychopharmacol Biol Psychiatry* 2008; **32:** 948–54.

32 Zhao J, He X, Liu Z, Yang D. The effects of clozapine on cognitive function and regional cerebral blood flow in the negative symptom profile schizophrenia. *Int J Psychiatry Med* 2006; **36:** 171–81.

33 Molina V, Sanz J, Sarramea F, Palomo T. Marked hypofrontality in clozapine-responsive patients. *Pharmacopsychiatry* 2007; **40:** 157–62.

34 Demjaha A, Egerton A, Murray RM, et al. Antipsychotic treatment resistance in schizophrenia associated with elevated glutamate levels but normal dopamine function. *Biol Psychiatry* 2014; **75:** e11–13.

35 Goldstein ME, Anderson VM, Pillai A, Kydd RR, Russell BR. Glutamatergic neurometabolites in clozapine-responsive and -resistant schizophrenia. *Int J Neuropsychopharmacol* 2015; **18:** pyu117.

36 Galletly CA, Clark CR, McFarlane AC. Clozapine improves working memory updating in schizophrenia. *Eur Neuropsychopharmacol* 2005; **15:** 601–08.

37 Horton J, Millar A, Labelle A, Knott VJ. MMN responsivity to manipulations of frequency and duration deviants in chronic, clozapine-treated schizophrenia patients. *Schizophr Res* 2011; **126:** 202–11.

38 Umbricht D, Javitt D, Novak G, et al. Effects of clozapine on auditory event-related potentials in schizophrenia. *Biol Psychiatry* 1998; **44:** 716–25.

39 Milovan DL, Baribeau J, Roth RM, Stip E. ERP study of pre-attentive auditory processing in treatment-refractory schizophrenia. *Brain Cogn* 2004; **55:** 355–57.

40 Lawrie SM, Ingle GT, Santosh CG, et al. Magnetic resonance imaging and single photon emission tomography in treatment-responsive and treatment-resistant schizophrenia. *Br J Psychiatry* 1995; **167:** 202–10.

41 Mitelman SA, Shihabuddin L, Brickman AM, Hazlett EA, Buchsbaum MS. Volume of the cingulate and outcome in schizophrenia. *Schizophr Res* 2005; **72:** 91–108.

42 Bartlett EJ, Brodie JD, Simkowitz P, et al. Effect of a haloperidol challenge on regional brain metabolism in neuroleptic-responsive and nonresponsive schizophrenic patients. *Am J Psychiatry* 1998; **155:** 337–43.

43 Demjaha A, Murray RM, McGuire PK, Kapur S, Howes OD. Dopamine synthesis capacity in patients with treatment-resistant schizophrenia. *Am J Psychiatry* 2012; **169:** 1203–10.

44 Ramos J, Cerdán LF, Guevara MA, Amezcua C, Sanz A. Abnormal EEG patterns in treatment-resistant schizophrenic patients. *Int J Neurosci* 2001; **109:** 47–59.

45 Ravan M, Hasey G, Reilly JP, MacCrimmon D, Khodayari-Rostamabad A. A machine learning approach using auditory odd-ball responses to investigate the effect of clozapine therapy. *Clin Neurophysiol* 2015; **126:** 721–30.

46 Lee S-H, Wynn JK, Green MF, et al. Quantitative EEG and low resolution electromagnetic tomography (LORETA) imaging of patients with persistent auditory hallucinations. *Schizophr Res* 2006; **83:** 111–19.

47 Lee S-H, Choo J-S, Im W-Y, Chae J-H. Nonlinear analysis of electroencephalogram in schizophrenia patients with persistent auditory hallucination. *Psychiatry Investig* 2008; **5:** 115–20.

48 Honer WG, Smith GN, Lapointe JS, MacEwan GW, Kopala L, Altman S. Regional cortical anatomy and clozapine response in refractory schizophrenia. *Neuropsychopharmacology* 1995; **13:** 85–87.

49 Konicki PE, Kwon KY, Steele V, et al. Prefrontal cortical sulcal widening associated with poor treatment response to clozapine. *Schizophr Res* 2001; **48:** 173–76.

50 Friedman L, Knutson L, Shurell M, Meltzer HY. Prefrontal sulcal prominence is inversely related to response to clozapine in schizophrenia. *Biol Psychiatry* 1991; **29:** 865–77.

51 Arango C, Breier A, McMahon R, Carpenter WT Jr, Buchanan RW. The relationship of clozapine and haloperidol treatment response to prefrontal, hippocampal, and caudate brain volumes. *Am J Psychiatry* 2003; **160:** 1421–27.

52 Molina V, Reig S, Sarramea F, et al. Anatomical and functional brain variables associated with clozapine response in treatment-resistant schizophrenia. *Psychiatry Res* 2003; **124:** 153–61.

53 Lauriello J, Mathalon DH, Rosenbloom M, et al. Association between regional brain volumes and clozapine response in schizophrenia. *Biol Psychiatry* 1998; **43:** 879–86.

54 Chakos MH, Lieberman JA, Alvir J, Bilder R, Ashtari M. Caudate nuclei volumes in schizophrenic patients treated with typical antipsychotics or clozapine. *Lancet* 1995; **345:** 456–57.

55 Scheepers FE, de Wied CCG, Hulshoff Pol HE, van de Flier W, van der Linden JA, Kahn RS. The effect of clozapine on caudate nucleus volume in schizophrenic patients previously treated with typical antipsychotics. *Neuropsychopharmacology* 2001; **24:** 47–54.

56 Scheepers FE, Gispen de Wied CC, Hulshoff Pol HE, Kahn RS. Effect of clozapine on caudate nucleus volume in relation to symptoms of schizophrenia. *Am J Psychiatry* 2001; **158:** 644–46.

57 Buchsbaum MS, Potkin SG, Marshall JF, et al. Effects of clozapine and thiothixene on glucose metabolic rate in schizophrenia. *Neuropsychopharmacology* 1992; **6:** 155–63.

58 Potkin SG, Buchsbaum MS, Jin Y, et al. Clozapine effects on glucose metabolic rate in striatum and frontal cortex. *J Clin Psychiatry* 1994; **55** (suppl B)**:** 63–66.

59 Molina Rodríguez V, Montz Andreé R, Pérez Castejón MJ, Capdevila García E, Carreras Delgado JL, Rubia Vila FJ. SPECT study of regional cerebral perfusion in neuroleptic-resistant schizophrenic patients who responded or did not respond to clozapine. *Am J Psychiatry* 1996; **153:** 1343–46.

60 Cachia A, Paillère-Martinot ML, Galinowski A, et al. Cortical folding abnormalities in schizophrenia patients with resistant auditory hallucinations. *Neuroimage* 2008; **39:** 927–35.

61 Ertugrul A, Volkan-Salanci B, Basar K, et al. The effect of clozapine on regional cerebral blood flow and brain metabolite ratios in schizophrenia: relationship with treatment response. *Psychiatry Res* 2009; **174:** 121–29.

62 Ergün EL, Volkan-Salanci B, Ertugrul A, Demir B, Erbas B. Evaluation of SISCOM in routine regional cerebral blood flow alterations after clozapine, in schizophrenia. *Hell J Nucl Med* 2010; **13:** 35–39.

63 Lahti AC, Holcomb HH, Weiler MA, Medoff DR, Tamminga CA. Functional effects of antipsychotic drugs: comparing clozapine with haloperidol. *Biol Psychiatry* 2003; **53:** 601–08.

64 Potkin SG, Basile VS, Jin Y, et al. D1 receptor alleles predict PET metabolic correlates of clinical response to clozapine. *Mol Psychiatry* 2003; **8:** 109–13.

65 Lacroix D, Chaput Y, Rodriguez JP, et al. Quantified EEG changes associated with a positive clinical response to clozapine in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 1995; **19:** 861–76.

66 Knott VJ, LaBelle A, Jones B, Mahoney C. EEG coherence following acute and chronic clozapine in treatment-resistant schizophrenics. *Exp Clin Psychopharmacol* 2002; **10:** 435–44.

67 Gross A, Joutsiniemi SL, Rimon R, Appelberg B. Clozapine-induced QEEG changes correlate with clinical response in schizophrenic patients: a prospective, longitudinal study. *Pharmacopsychiatry* 2004; **37:** 119–22.

68 Knott V, Labelle A, Jones B, Mahoney C. Quantitative EEG in schizophrenia and in response to acute and chronic clozapine treatment. *Schizophr Res* 2001; **50:** 41–53.

69 MacCrimmon D, Brunet D, Criollo M, Galin H, Lawson JS. Clozapine augments delta, theta, and right frontal EEG alpha power in schizophrenic patients. *ISRN Psychiatry* 2012; **2012:** 596486.

70 Kikuchi YS, Sato W, Ataka K, et al. Clozapine-induced seizures, electroencephalography abnormalities, and clinical responses in Japanese patients with schizophrenia. *Neuropsychiatr Dis Treat* 2014; **10:** 1973–78.

71 Molina V, Gispert JD, Reig S, et al. Cerebral metabolic changes induced by clozapine in schizophrenia and related to clinical improvement. *Psychopharmacology (Berl)* 2005; **178:** 17–26.

72 Hoptman MJ, Volavka J, Weiss EM, et al. Quantitative MRI measures of orbitofrontal cortex in patients with chronic schizophrenia or schizoaffective disorder. *Psychiatry Res* 2005; **140:** 133–45.

73 Tsekou H, Angelopoulos E, Paparrigopoulos T, et al. Sleep EEG and spindle characteristics after combination treatment with clozapine in drug-resistant schizophrenia: a pilot study. *J Clin Neurophysiol* 2015; **32:** 159–63.

74 Kane JM, Honigfeld G, Singer J, Meltzer H. Clozapine in treatment-resistant schizophrenics. *Psychopharmacol Bull* 1988; **24:** 62–67.

75 Hong LE, Summerfelt A, McMahon RP, Thaker GK, Buchanan RW. Gamma/beta oscillation and sensory gating deficit in schizophrenia. *Neuroreport* 2004; **15:** 155–59.

76 Kim E, Howes OD, Turkheimer FE, et al. The relationship between antipsychotic D2 occupancy and change in frontal metabolism and working memory: a dual [(11)C]raclopride and [(18) F]FDG imaging study with aripiprazole. *Psychopharmacology (Berl)* 2013; **227:** 221–29.

77 Howes OD, Kapur S. A neurobiological hypothesis for the classification of schizophrenia: type A (hyperdopaminergic) and type B (normodopaminergic). *Br J Psychiatry* 2014; **205:** 1–3.

78 Wright IC, Ellison ZR, Sharma T, Friston KJ, Murray RM, McGuire PK. Mapping of grey matter changes in schizophrenia. *Schizophr Res* 1999; **35:** 1–14.

79 Egerton A, Stone JM. The glutamate hypothesis of schizophrenia: neuroimaging and drug development. *Curr Pharm Biotechnol* 2012; **13:** 1500–12.

80 Egerton A, Fusar-Poli P, Stone JM. Glutamate and psychosis risk. *Curr Pharm Des* 2012; **18:** 466–78.

81 Krystal JH, Karper LP, Seibyl JP, et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry* 1994; **51:**199–214.

82 Lisman JE, Coyle JT, Green RW, et al. Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. *Trends Neurosci* 2008; **31:** 234–42.

83 Moghaddam B, Javitt D. From revolution to evolution: the glutamate hypothesis of schizophrenia and its implication for treatment. *Neuropsychopharmacology* 2012; **37:** 4–15.

84 Moghaddam B, Adams B, Verma A, Daly D. Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. *J Neurosci* 1997; **17:** 2921–27.

85 Newcomer JW, Farber NB, Jevtovic-Todorovic V, et al. Ketamine-induced NMDA receptor hypofunction as a model of memory impairment and psychosis. *Neuropsychopharmacology* 1999; **20:** 106–18.

86 Stone JM, Dietrich C, Edden R, et al. Ketamine effects on brain GABA and glutamate levels with 1H-MRS: relationship to ketamine-induced psychopathology. *Mol Psychiatry* 2012; **17:** 664–65.

87 Stone JM, Raffin M, Morrison P, McGuire PK. Review: the biological basis of antipsychotic response in schizophrenia. *J Psychopharmacol* 2010; **24:** 953–64.

88 Olney JW, Farber NB. Glutamate receptor dysfunction and schizophrenia. *Arch Gen Psychiatry* 1995; **52:** 998–1007.

89 Arnedo J, Svrakic DM, Del Val C, et al, and the Molecular Genetics of Schizophrenia Consortium. Uncovering the hidden risk architecture of the schizophrenias: confirmation in three independent genome-wide association studies. *Am J Psychiatry* 2015; **172:** 139–53.

90 Hassan AN, De Luca V. The effect of lifetime adversities on resistance to antipsychotic treatment in schizophrenia patients. *Schizophr Res* 2015; **161:** 496–500.

91 Frank J, Lang M, Witt SH, et al. Identification of increased genetic risk scores for schizophrenia in treatment-resistant patients. *Mol Psychiatry* 2015; **20:** 150–51.

92 Lubeiro A, Rueda C, Hernández JA, Sanz J, Sarramea F, Molina V. Identification of two clusters within schizophrenia with different structural, functional and clinical characteristics. *Prog Neuropsychopharmacol Biol Psychiatry* 2016; **64:** 79–86.

93 Allen P, Chaddock CA, Howes OD, et al. Abnormal relationship between medial temporal lobe and subcortical dopamine function in people with an ultra high risk for psychosis. *Schizophr Bull* 2012; **38:** 1040–49.

94 Fusar-Poli P, Howes OD, Allen P, et al. Abnormal prefrontal activation directly related to pre-synaptic striatal dopamine dysfunction in people at clinical high risk for psychosis. *Mol Psychiatry* 2011; **16:** 67–75.

95 Ebdrup BH, Nørbak H, Borgwardt S, Glenthøj B. Volumetric changes in the basal ganglia after antipsychotic monotherapy: a systematic review. *Curr Med Chem* 2013; **20:** 438–47.

96 Ho BC, Andreasen NC, Ziebell S, Pierson R, Magnotta V. Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. *Arch Gen Psychiatry* 2011; **68:** 128–37.

97 Dorph-Petersen K-A, Pierri JN, Perel JM, Sun Z, Sampson AR, Lewis DA. The influence of chronic exposure to antipsychotic medications on brain size before and after tissue fixation: a comparison of haloperidol and olanzapine in macaque monkeys. *Neuropsychopharmacology* 2005; **30:** 1649–61.

98 Kapur S, McClelland RA, VanderSpek SC, et al. Increasing D2 affinity results in the loss of clozapine's atypical antipsychotic action. *Neuroreport* 2002; **13:** 831–35.

99 Sheitman BB, Lieberman JA. The natural history and pathophysiology of treatment resistant schizophrenia. *J Psychiatr Res* 1998; **32:** 143–50.

100 Samaha AN, Seeman P, Stewart J, Rajabi H, Kapur S. "Breakthrough" dopamine supersensitivity during ongoing antipsychotic treatment leads to treatment failure over time. *J Neurosci* 2007; **27:** 2979–86.

101 McEvoy JP, Lieberman JA, Stroup TS, et al, and the CATIE Investigators. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry* 2006; **163:** 600–10.

102 Goff DC, Coyle JT. The emerging role of glutamate in the pathophysiology and treatment of schizophrenia. *Am J Psychiatry* 2001; **158:** 1367–77.