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Current Neuropharmacology, **2015**, *13*, **435-444**

Brain Functional Effects of Psychopharmacological Treatments in Schizophrenia: A Network-based Functional Perspective Beyond Neurotransmitter Systems

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Abstract: Psychopharmacological treatments for schizophrenia have always been a matter of debate and a very important issue in public health given the chronic, relapsing and disabling nature of the disorder. A thorough understanding of the pros and cons of currently available pharmacological treatments for schizophrenia is critical to better capture the features of treatment-refractory clinical pictures and plan the developing of new treatment strategies. This review focuses on brain functional changes induced by antipsychotic drugs as assessed by modern functional neuroimaging techniques (i.e. fMRI, PET, SPECT, MRI spectroscopy). The most important papers on this topic are reviewed in order to draw an ideal map of the main functional changes occurring in the brain during antipsychotic treatment. This supports the hypothesis that a network-based perspective and a functional connectivity approach are needed to fill the currently existing gap of knowledge in the field of psychotropic drugs and their mechanisms of action beyond neurotransmitter systems.

Keywords: Antipsychotic drugs, functional neuroimaging, network, psychopharmacology, schizophrenia, treatment.

MECHANISMS OF ACTION OF ANTIPSYCHOTIC DRUGS: THE NEED FOR A PARADIGM SHIFT

Schizophrenia (SZ) is a chronic and highly disabling disorder with a lifetime prevalence of about 0.7% [1]. Despite some advances of pharmacology in the treatment of this mental disorder, dimensions such as negative symptoms and cognitive dysfunction very often seem to respond poorly [2]. Thus, exploring the effects on the brain of the most used psychotropic drugs (i.e. antipsychotic drugs) is pivotal in order to understand the strength and limitations of current treatment strategies and develop new compounds potentially able to "fill the gap" of the incomplete response to treatment frequently observed by clinicians. This is a critical point as lingering psychotic and cognitive symptoms prevent a satisfactory recovery in terms of global and social functioning. Furthermore, an incomplete treatment response perpetuates a significant distress in patients and caregivers.

All currently approved treatments for SZ are basically D2-type dopamine receptors blockers, although the "binding spectrum" and kind of antidopaminergic effect of antipsychotic drugs become more complex with second generation antipsychotics (SGA), molecules showing significant affinity profiles for 5-HT2A serotonin-receptors and influencing a number of neurotransmitters [3].

Modern pathophysiological theories of brain dysfunction in SZ focus on glutamatergic pathways [4, 5]. Novel experimental therapeutic approaches stemming from these theories aim at normalizing or modulating brain glutamatergic function by targeting N-methyl-D-aspartate type glutamate receptors [6, 7] or type 5 metabotropic glutamate receptors, although the evidence in this regard is still at a preclinical level [8, 9]. Furthermore, specific pharmacological treatments for cognitive dysfunctions taken from Alzheimer's disease research are under clinical investigation in SZ. These treatments selectively target the alpha-7 subunit of the nicotinic receptor for acetylcholine [10-12].

However, these novel approaches risk to suffer from the same limitations that made our understanding of antipsychotic mechanisms of action incomplete in the "dopaminergic theory era" if they don't tend to a comprehensive description of the very complex action of therapeutic agents on the brain as a whole.

During the last two decades, several studies have investigated brain functional effects of psychotropic drugs in SZ. Indeed, the vast majority of these studies focused on antipsychotic drugs and employed the following techniques: i. functional Magnetic Resonance Imaging (fMRI); ii. Single Photon Emission Computerized Tomography (SPECT); iii. Positron Emission Tomography (PET); and iiii. Magnetic Resonance Imaging (MRI) Spectroscopy.

In this review we discuss the most important neuroimaging papers describing the *in vivo* effects of psychopharmacological treatments within the human brain in clinical samples of patients affected by SZ and healthy controls (HC) in order to conceptually support the need for a paradigm shift from a neurotransmitter-centred or a brain-localization-centred approach to a network-based approach in the study

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1570-159X/15 $58.00+.00

of brain functional effects of pharmacological treatments. This will possibly inform future research and the development of novel therapeutic agents.

BRAIN FUNCTIONAL EFFECTS OF PSYCHO-PHARMACOLOGICAL TREATMENT

Three recent systematic review papers summarized longitudinal fMRI, SPECT/PET dopaminergic occupancy and resting cerebral blood flow (rCBF) studies addressing the issue of the effects of antipsychotic drugs in SZ [13-15].

Abbott and colleagues provided a thorough systematic review of eight longitudinal fMRI studies focusing on pharamcological treatment effects in schizophrenia over a mean treatment period of 45 days [13]. Their choice to select longitudinal investigations is warranted as cross-sectional studies are not capable of distinguishing treatment effects from brain functional changes due to SZ pathophysiology. Results of seven out of eight studies indicate a normalization of the Blood-Oxygen-Level-Dependent (BOLD) fMRI signal, basically reflecting a reversal of the anomalous fMRI signal documented at baseline assessment [16-23]. Furthermore, five investigations reported a concurrent denormalization of BOLD fMRI signal associated with antipsychotic treatment from baseline brain functional assessment [16, 19-22]. In particular, normalization was observed in the right cerebellum, primary motor and sensory cortices, anterior cingulate, intraparietal sulci, the insula, superior temporal gyri, ventral medial prefrontal cortex, the default mode network and fronto-parietal and temporal networks. On the contrary, denormalization was observed in the left cerebellum, the cingulate motor area, the caudate and putamen, supramarginal gyri, dorso-lateral prefrontal cortex, dorsal medial thalamus and the right ventral lateral prefrontal cortex. Notably, only one study found a significant association between changes in brain activity and symptomatic improvement [22]. Furthermore, in one study brain functional parameters at baseline were predictive of clinical outcome [23]. Regrettably, no study found a significant relationship between cognitive performance and changes in fMRI BOLD signal with one exception. In fact, Sambataro and colleagues found that working memory performance was related to ventral medial prefrontal cortex connectivity after 28 days of antipsychotic treatment [21]. The authors interpret this lack of clinical/brain functional association results across studies as depending on the fact that the usual trajectory of early symptomatic severity decrease, after the beginning of an antipsychotic treatment, has a pronounced downward slope within the first week of treatment and a subsequent more gradual further improvement. These smaller changes in clinical rating scores have possibly obscured, in the authors' opinion, any potentially existing relationships between psychotic symptoms and fMRI correlates [13]. However, in this regard it should also be noted that the only investigation demonstrating a relationship between brain functional changes and psychopathological improvement and the only investigation reporting a relationship between brain functional changes and a measure of cognitive performance adopted a complex network-based approach. This will be discussed in detail within the next section.

Another approach to the description of antipsychotic drug *in vivo* mechanisms of action and its link to clinical response is through SPECT/PET dopaminergic occupancy with specific ligands. Howes and colleagues critically reviewed the existing literature in this field in order to describe the nature of dopaminergic abnormalities in SZ and how anti-dopaminergic activity of antipsychotic drugs impacts on their mechanism of action, treatment response and side effects [14]. Basically, the authors propose a model of psychosis which relies on a dopamine-mediated aberrant salience, arguing that antipsychotic drug efficacy against psychotic symptoms may be due to an anti-dopaminergic inhibition of this aberrant salience. From SPECT/PET studies now we are aware that a rather precise D2-blockade threshold is crucial for treatment response. In fact, studies using low doses of antipsychotic drugs showed little clinical response when D2 receptor occupancy was less than 50% [24]. The results of a double blind study on subjects at their first psychotic episode indicate that a 65% D2 receptor occupancy threshold was the best cut-off between responders and non-responders, with receptor occupancy above this threshold associated with higher incidence of adverse effects rather than further clinical improvement [25]. Furthermore, a significant clinical improvement occurs over the first two weeks of treatment. Also, a high D2 occupancy 48 hours after starting a new antipsychotic treatment predicts a greater clinical response two weeks later [26]. Finally, PET studies have demonstrated that in some cases there is little or no response to antipsychotic drugs even when D2 occupancy is above the therapeutic threshold [27]. The latter consideration clarifies that a threshold of D2 receptor blockade is necessary but not sufficient to achieve an antipsychotic response. It is clear that other neurotransmitter systems and their reciprocal interactions are pivotal in the patho-physiology of SZ and in determining the "whole brain response", probably accounting for a successful antipsychotic treatment.

For these reasons, a recent systematic meta-analytic review focused on rCBF, a measure correlated with neuronal metabolism [28], in order to propose this neuroimaging marker as a potential predictor of symptomatic improvement following antipsychotic treatments [15]. Investigations on SZ employed heterogeneous methodologies such as PET, SPECT and labelled-Xenon inhalation and adopted both cross-sectional and longitudinal designs. Results showed that antipsychotic medications induce significant rCBF changes in the striatum, frontal, temporal and, to a lesser extent, thalamic and cerebellar regions, all areas known to undergo structural changes after antipsychotic treatment [29-31]. Intriguingly, different antipsychotic drugs may have differential effects on regional rCBF. In fact first generation antipsychotics (FGA) have greater rCBF subcortical effects (especially within the basal ganglia) while SGA have greater cortical effects. This is in line with the differential pharma-codynamics of FGA and SGA, with the latter showing an affinity for 5-HT2A serotonergic receptors counterbalancing D2 receptor occupancy [32]. Therefore, increased FGA D2 affinity possibly accounts for greater subcortical rCBF changes. Indeed, subcortical areas, particularly the basal ganglia, are more densely populated with D2 receptors than cortical areas. Notably, some longitudinal studies reviewed in the meta-analytic paper summarized above provide evidence that several psychopathological dimensions display

a significant association with brain activity at follow-up scans after antipsychotic treatment in specific areas [33-36] (see Table **1** for details).

Fig. **1** provides a graphical synthesis of the areas frequently showing significant changes with antipsychotic treatments in studies already reviewed by papers discussed in this section and studies that will be reviewed in the following sections.

THE IMPORTANCE OF A NETWORK-BASED PERSPECTIVE

The only fMRI study which reported significant correlations between changes in brain activity and symptomatic improvement used a "resting state" paradigm carried out in drug naive first episode SZ patients [22]. Lui and colleagues provided evidence for widespread brain functional changes following a 36-day administration of several SGA and clozapine. The main strengths of this design rely on a longitudinal assessment of drug naive patients through fMRI techniques aimed at capturing amplitude of low frequency fluctuations (ALFF) and functional network connectivity. Specifically, the normalization produced by antipsychotic treatment consisted in increased ALFF in the ventral medial cortex and reduced functional network connectivity between fronto-parietal and temporal networks. Denormalization patterns were reported as well, with increased ALFF within the striatum (i.e. caudate and putamen), decreased functional connectivity in multiple cortical and subcortical regions and reduced functional connectivity between two cortical-subcortical networks and one cortical-cortical network. In synthesis, functional network connectivity normalizes with antipsychotic treatment between frontal-parietal and temporal networks and denormalizes between precuneus/basal ganglia, occipital/basal ganglia and parietal/temporal networks. Despite sophisticated measures such as ALFF are generally thought to reflect spontaneous neural activity [37], their underpinnings need to be better characterized. For example, from a network perspective antipsychotic treatment may result in a reduced integration of brain synchronous activity, with attenuated functional connectivity, but the impact of medication in

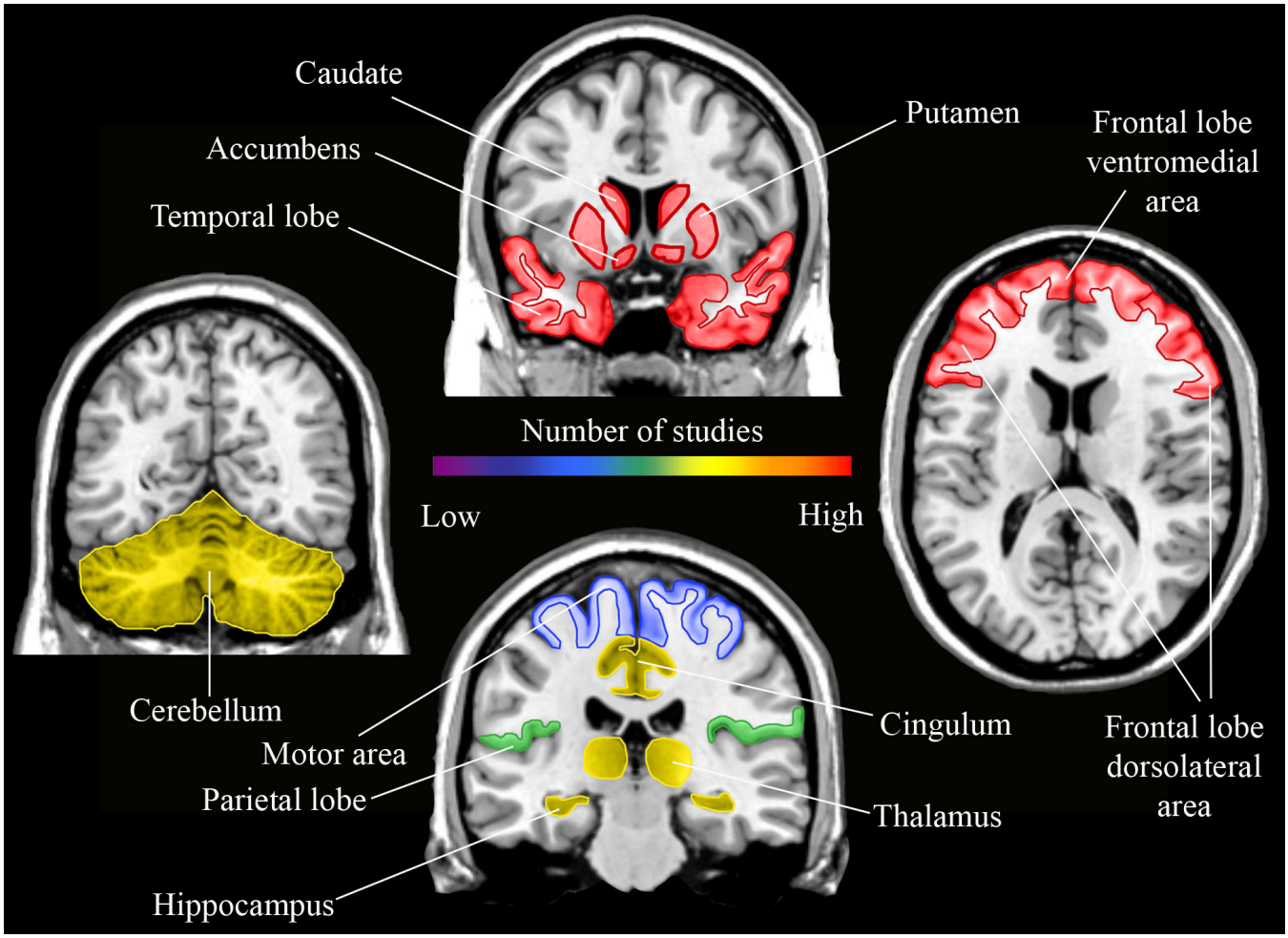

Fig. (1). Graphical synthesis of brain areas found to display significant changes in activity associated with psychopharmacological treatments in functional neuroimaging studies on Schizophrenia. LEGEND: Areas are colour-coded on the base of the frequency of their significant functional change across studies reviewed in the present paper. Maximum frequencies have to be considered for areas painted in colours at the yellow-red end of the chromatic spectrum. Yellow-red areas also represent brain regions whose drug-induced activity changes are more frequently associated with clinical variables at follow-up in longitudinal studies (see Table **1**).

reducing neural network integration is probably nonspecific. In fact, if aberrant fronto-parietal and temporal activity was normalized by treatment, in fronto-striatal and thalamo-cortical networks an aberrant neural network activity was induced by treatment compared to baseline measures in these areas. Thus, normalization and denormalization patterns observed in the study may represent the neurophysiological bases of therapeutic and adverse effects of SGA. Indeed, reducing functional connectivity in fronto-striatal and the thalamo-cortical circuits may underlie effects like secondary negative symptoms, problems in planned volitional behaviour and cognitive functions [38-40]. On the other hand, increased ALFF in cortical rather than subcortical regions is significantly associated with improvement in the positive symptoms subscale scores of the Positive and Negative Syndrome Scale (PANSS) in SZ.

Another method allowing to determine functional connectivity is H215O PET, a technique which is able to capture changes in rCBF through PET scanning after the injection of a specific tracer [41]. Bolding and colleagues designed a H215O PET study to evaluate changes in functional connectivity as a result of treatment with antipsychotic drugs in SZ [42]. Patients were blindly randomized to receive haloperidol or olanzapine and were scanned at three different time points after a 2 weeks washout from previous treatments, and after 1 and 6 weeks of treatment. The authors focused on an "a priori" selected network encompassing the nucleus accumbens, the hippocampus and the medial frontal cortex. This network had previously been found to be implicated in antipsychotic drug action [43-45] and it is known to be modulated by dopamine [46]. This is indeed a good example of how to conceive drug action on specific neurotransmitter systems as reverberating on more complex functional networks. The authors found that functional connectivity between the medial frontal cortex and the nucleus accumbens significantly increases after one week of treatment and gradually decreases over the next five weeks. Differently, functional connectivity between the medial frontal cortex and the hippocampus significantly decreases over the whole six-week treatment period. Furthermore, the strength of functional connectivity between the medial prefrontal cortex and the hippocampus after one week of treatment seems to predict treatment response. The significant changes in functional connectivity occurred at rest and during sensory-motor and decision tasks. The authors concluded that antipsychotic drugs (both FGAs and SGAs) rapidly regulate the balance between prefrontal and limbic regions, thus playing a crucial role in restoring adaptive behaviours. Notably, these changes cannot be entirely accounted for by D2-receptor blockade. In fact, in order to explain these functional changes an interaction among at least three different neurotransmitters systems (namely the dopaminergic, the glutamatergic and the GABA-ergic) must be hypothesized, especially in terms of induced neuroplasticity [47, 48].

D2-receptor blocking compounds are not the only molecules that have been shown to exert a modifying action on network-based brain functional measures. A recent study by Tregellas and colleagues showed that DMXB-A, an alpha-7 nicotinic receptor agonist, produces at both high and low dosages a decrease in default network activity as measured by resting-state fMRI in the posterior cingulate, inferior parietal cortex and medial frontal gyrus and an increased activity in the precuneus [49]. In addition, brain functional response is related to a polymorphism in the alpha-7 nicotinic receptor gene CHRNA7. The same agent produces significant effects on task-specific hippocampal responses only at high dosages. The findings of this important study provide additional hints that network-based, rather those specific-region-based, functional measures have high sensitivity in detecting brain functional changes following psychopharmacological treatment of SZ, likely moderated by genetic variability. This phenomenon was already described for the antipsychotic drug olanzapine in an fMRI investigation by Bertolino and colleagues, showing that the (Val(108/158)Met) polymorphism in the catechol O-methyltransferase (COMT) gene predicts improvement in working memory performance and prefrontal physiology after 8 weeks of treatment [50].

This genetic influence might explain the heterogeneity of functional neuroimaging studies on drug treatment effects in SZ as well. Therefore, future studies putting together brain network complexity and genetic influences are warranted in order to better clarify brain functional treatment effects in SZ and how they are related to clinical response. Such studies should be longitudinal, multiple-dose, using functional-connectivity/network-based/whole-brain approaches. To date 22 published studies fit, at least partially, this ideal description [16, 19-22, 33-36, 42]. Seven of them found a significant relationship between the longitudinally observed change in brain activity and clinical/neuropsychological parameters and they are briefly summarized in Table **1**.

MRI SPECTROSCOPY STUDIES

MRI spectroscopy studies addressing the role of several brain metabolites in the pathophysiology of SZ and their significance from a neurobiological point of view are numerous. These studies mainly focused on N-acetylaspartate (NAA), glutamate and glutamine concentrations in multiple pivotal brain areas and were comprehensively reviewed in two meta-analytic papers [51, 52]. NAA is considered a marker of neuronal integrity and predicts severity of illness in several neurodegenerative disorders, while a low glutamate to glutamine ratio is generally consistent with increased synaptic glutamatergic activity and enhanced neurotoxicity [53-55]. A meta-analysis of these studies confirmed that there is enough evidence to support the hypothesis that NAA levels are reduced in a broad range of brain areas in SZ patients, particularly within the hippocampus and frontal gray and white matter. In addition, authors described no evidence that NAA levels are differentially reduced in gray matter and white matter, no evidence for a difference in NAA levels between at onset and chronic patients, and compelling evidence of medial frontal region glutamate decrease and glutamine increase in SZ compared to HC.

Unfortunately, MRI spectroscopy studies addressing brain functional effects of antipsychotic treatments in terms

Table 1. Longitudinal, multiple-dose, functional-connectivity/network-based/whole-brain studies on brain functional effects of antipsychotic drugs in schizophrenia finding a significant association between brain activity changes and clinical/ neuropsychological variables at follow-up after antipsychotic treatment.

Study (Year) [Ref]	Sample Size	Method	Drug(s) (mean dose, mg/day)	Results
Bolding (2012) [42]	37 SZ	Functional connectivity analysis through H215O PET-determined rCBF at rest and during sensory-motor and decision tasks. Scans were obtained at baseline, after the washout, at 6 days of treatment and at 6 weeks.	Participants were blindly randomized to haloperidol 10-20 mg for 6 weeks, Olanzapine 12.5-25 mg for 6 weeks, Placebo for one week followed by haloperidol 10-20 mg for 5 weeks, Placebo for one week followed by Olanzapine 12.5-25 mg for 5 weeks	Functional connectivity between the medial frontal cortex and the nucleus accumbens significantly increased after one week of treatment and gradually decreased over the next five weeks. Functional connectivity between the medial frontal cortex and the hippocampus significantly decreases over the whole six-week treatment period. The strength of functional connectivity between the medial prefrontal cortex and the hippocampus after one week of treatment predicted treatment response defined as the change in BPRS Psychosis Subscale score from baseline.
Sambataro (2010) [21]	17 SZ, 19 HC	fMRI spatial ICA (Independent Component Analysis) functional connectivity during N-back working memory task	28-56 days olanzapine (20 mg/day)	Reduced negative modulation in the default mode network during the working memory task after 56 days of treatment; increased default mode connectivity with the ventral medial prefrontal cortex. Working memory performance was related to ventral medial prefrontal cortex connectivity after 28 days of antipsychotic treatment.
Lui (2010) [22]	34 SZ, 34 HC	Resting state fMRI with amplitude of low frequency fluctuations (ALFF), functional connectivity and functional network connectivity	36 days aripiprazole (20 mg/ day), clozapine (52.5 mg/day), olanzapine (16.9 mg/day), quetiapine (495 mg/ day), risperidone (4.2 mg/day), and sulpiride (800 mg/day)	Increased ALFF in the ventral medial cortex, caudate and putamen; reduced functional network connectivity between fronto- parietal and temporal networks and decreased functional connectivity in multiple cortical and subcortical seeds; reduced functional connectivity between two pairs of cortical-subcortical and one cortical- cortical network. Increased ALFF was associated with reduced scores at the PANSS positive symptoms subscale.
Sharafi (2005) [33]	20 SZ	SPECT-determined rCBF after a 3 months washout and after a new antipsychotic treatment.	Clozapine or other "classical" antipsychotic drugs at a mean dosage of 300 mg/day and 600 mg/day respectively (Chlorpromazine equivalent doses, duration of treatment not specified).	Reduced rCBF in superior frontal, inferior frontal, posterior parietal and right anterior parietal regions at follow-up. The PANSS Anergia factor severity was associated with Posterior parietal rCBF at follow-up. PANSS Thought disturbance factor was associated with left superior frontal rCBF and left thalamic/basal ganglia rCBF. Paranoia was associated with left superior frontal rCBF and Depression with right superior temporal rCBF.
Vaiva (2002) [34]	19 SZ	SPECT-determined rCBF after a 6 week-washout and 4 weeks of antipsychotic treatment (10 SZ were antipsychotic-naïve).	Amisulpride (100 mg/day) for 4 weeks.	Increase in rCBF within the dorso-lateral prefrontal cortex and right posterior frontal cortex following treatment. Improvements in affective withdrawal and anhedonia were associated with rCBF in posterior frontal regions, temporo-parietal junction and anterior frontal regions respectively.
Erkwoh (1997) [35]	24 SZ, 20 HC	SPECT-determined rCBF	Various non-specified antipsychotics at a mean dose of 616 mg/day in Chlorpromazine equivalents. Duration of treatment not specified.	Reduced rCBF in left inferior frontal regions following treatment. At follow up blunted affect was associated with left thalamic rCBF, emotional withdrawal with left basal ganglia rCBF, difficulties in abstract thinking with anterior cingulate rCBF, right basal ganglia rCBF and right thalamic rCBF. Lack of spontaneity was associated with left mesial temporal rCBF, stereotyped thoughts with inferior temporal rCBF and left mesial temporal rCBF.

Table 1. contd….

Study (Year) [Ref]	Sample Size	Method	Drug(s) (mean dose, mg/day)	Results
Sabri (1997) [36]	24 SZ Drug-naïve), 20 HC (scanned at baseline only)	SPECT-determined rCBF	Bromperidol, Clozapine, Haloperidol, Levomepromazine, sulpiride or thioridazine at a mean dose of 848.7 mg/day in Chlorpromazine equivalents for 96.8 days.	The paranoid subgroup showed a rCBF reduction in left inferior frontal regions after treatment. At follow up PANSS negative score was associated with frontal, cingulate, temporal, basal ganglia and thalamic rCBF Affective flattening and emotional withdrawal were associated with frontal, temporal, basal ganglia and thalamic rCBF. Difficulties in abstract thinking was associated with right frontal, cingulate, basal ganglia and thalamic rCBF. Decreased spontaneity and stereotyped thinking were associated with bitemporal rCBF ratios.

of brain metabolites concentration changes in specific areas are relatively scarce.

Choe and colleagues found no changes in NAA with treatment in their sample of patients with chronic SZ [56]. On the other hand, a study by Bertolino and colleagues used MRI spectroscopy to assess the dependence of NAA levels in multiple brain areas on medication status in SZ patients through a within-patient design [57]. Patients were studied after a period of stable antipsychotic treatment of at least four weeks and then after a two-week washout period and the main finding indicated that patients displayed higher levels of NAA while on antipsychotics electively within the dorsolateral prefrontal cortex. Furthermore, Fannon and colleagues found that treatment with SGAs was associated with an increase in NAA hippocampal levels in a sample of drug naïve patients early in the course of their illness [58]. A more recent longitudinal study on an analogous sample of patients with minimal previous antipsychotic exposure determined NAA concentrations in the frontal and occipital lobes, caudate nucleus and cerebellum before and after a two-year treatment with either haloperidol of quetiapine [59]. The study reported no significant NAA levels changes in any of the anatomical regions studied, although SZ patients displayed reduced NAA levels even in a very early phase of their illness. Finally, the more recent report on this topic found NAA levels restored in adolescents diagnosed with early onset SZ after a six-month treatment with SGAs within the prefrontal cortex and thalamus [60].

Indeed, the marked inconsistencies between these studies may be explained by sample characteristics, especially with respect to duration of illness and antipsychotic treatment, small sample sizes and variations in MRI spectroscopy techniques (e.g. using NAA to choline ratios or NAA absolute concentrations, single-voxel imaging vs chemical shift etc.). As regards duration of illness and the potential impact of long-term antipsychotic treatments it should be noted that the largest MRI spectroscopy study conducted so far showed increased levels of glutamine, consistent with increased glutamatergic synaptic release and thus enhanced neurotoxicity, within the anterior dorsal cingulate cortex of chronic SZ patients with a history of long term antipsychotic treatment, along with a significant reduction of NAA levels [61].

More importantly, it should be kept in mind that the spectroscopic approach is limited by its inadequacy in assessing functional interconnections among different brain areas. Thus the inconsistency of results observed in MRI spectroscopy studies confirm that the more a neuroimaging functional technique relies on a network-based conception, the more it will be sensitive to changes induced by pharmacological treatments and their eventual relationships with clinical dimensions.

FOCUS ON CLOZAPINE

About one third of patients do not respond to standard antipsychotic treatments [62]. The only antipsychotic drug effective so far in these forms of the disorder is clozapine [62-64] that is also particularly effective on the cognitive component of the disorder [65]. These clozapine-related phenomena significantly challenged the D2-receptor blockade paradigm on which pharmacological treatment of SZ had always been based. In fact, clozapine has perhaps the broadest affinity spectrum in psychopharmacology, with actions at a wide range of neurotransmitters receptors.

Theories on efficacy of clozapine in treatment resistant schizophrenia mainly focused on the “limbic selectivity” of this drug and on its very high affinity for 5-HT2A serotonergic receptors. However, the limbic selectivity theory data, from PET and SPECT D2 occupancy studies, are inconsistent [66-68]. Furthermore, other antipsychotic drugs share similar patterns of D2 binding [67, 69, 70]. On the contrary, results on the 5-HT2A selectivity theory are more consistent and are indeed supported by PET imaging studies [71, 72]. Despite this positive outcome, the fact that other SGA such as risperidone, olanzapine and quetiapine are characterized by this pharmacodynamics as well [73-77] but are less efficacious in SZ patients resistant to treatment makes again uncertain this theory. In reality, the peculiar antipsychotic action of clozapine does not clearly rely on factors simply related to single neurotransmitters systems or single brain areas. Thus, the study of its pharmacodynamics may serve as a very helpful paradigm in order to make

inferences on the whole-brain functional change occurring with antipsychotic treatments in SZ.

Despite these premises, there are no functional neuroimaging studies providing final evidence for significant differences between clozapine and other SGAs in terms of induced brain functional changes as observable by currently available techniques. However, an important fludeoxyglucose F18 PET rCBF study by Cohen and colleagues showed important differences in changes of rCBF between clozapine-treated patients and patients taking the FGA fluphenazine [78, 79]. In particular, both medications lowered metabolic rates in the superior prefrontal cortex and increased metabolic rates within the limbic cortex, but fluphenazine only increased metabolic rates in subcortical regions and lateral temporal regions while clozapine only decreased inferior prefrontal cortex activity. This suggests that both drugs are capable of inducing a shift to limbic cortex activity but also display metabolic specificities potentially impacting on their efficacy and safety profiles. However, it should be noted that in this case clozapine was compared to a FGA with a very different pharmacodynamics, especially in terms of D2-receptor blocking properties.

Therefore, the neurobiological underpinnings of the unique effects of clozapine on treatment-refractory SZ remain puzzling, especially as regards what makes it different from other SGAs.

As for the effects on the cognitive component of SZ observed during treatment with clozapine, further considerations are needed. Disruption of information processing with decreased signal- to-noise ratio in the PFC, allowing irrelevant input processing, has been implicated in schizophrenia [80-82]. On the base of studies of clozapine administration in animal models it can be hypothesized that clozapine facilitates long term potentiation (LTP) in the hippocampus-prefrontal cortex pathway [83, 84], thus increasing the signal-to-noise ratio within the prefrontal cortex by changing synaptic plasticity. This possibly results in shifting to a more balanced pattern of facilitating and attenuating of specific synaptic inputs through a complex interplay of dopaminergic, noradrenergic and serotonergic activity modulation [85-87]. Unfortunately, there is currently no evidence from *in vivo* functional brain imaging studies supporting the validity of this hypothesis in humans.

Longitudinal studies based on functional connectivity detecting techniques are warranted in order to disentangle these issues (i.e. the effects of clozapine on treatment-refractory schizophrenia and the cognitive component of the disorder) and plan the development of new compounds or treatment strategies sharing clozapine therapeutic properties with a better safety profile.

CONCLUSIONS

We have reviewed the most important functional neuroimaging studies addressing changes in brain activity associated with psychopharmacological treatments in SZ including previously published review papers on the topic.

According to the results of fMRI, PET, SPECT and MRI spectroscopy studies a global picture emerges clearly showing effects of antipsychotic drugs on the activity of dorsolateral and medial prefrontal regions, striatal regions including the nucleus accumbens, the cingulate cortex, the cerebellum, thalamus, parietal regions and cortical sensory-motor areas (see Fig. **1**). Among these, the regions most frequently involved in brain functional changes induced by antipsychotics are definitely prefrontal and striatal regions. No difference emerges between FGAs and SGAs in terms of brain functional changes with the exception of a more pronounced subcortical activity for FGAs and a more pronounced cortical activity for SGAs. This difference is emphasized by rCBF studies. Despite its well-known efficacy in treatment-resistant patients, clozapine does not seem to induce a peculiar and specific pattern of brain activity change, especially when compared to other SGAs.

Also, among the studies we have reviewed, a significant relationship between pharmaco-induced brain functional changes and improvement in clinical measures has rarely been reported. Importantly, studies that succeeded in showing such a relationship mainly relied on network-based and functional connectivity techniques. Thus, further studies should be focused on functional connectivity with longitudinal designs, and they are warranted in order to clarify whether the action of the currently available pharmacological treatments for SZ, in terms of whole brain activity change, and their limits in patients who do not respond to standard treatments are better explained by a network-based functional perspective beyond neurotransmitter systems.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

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Received: November 04, 2014 Revised: December 10, 2014 Accepted: January 01, 2015