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Treatment effects in schizophrenia: evidence from neuroimaging

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Cognitive deficits as well as difficulties in emotion recognition in schizophrenic patients have shown to be related to dysfunctions, especially in frontal, striatal and parietal areas as well as the amygdala. In the present review the effect of various treatment strategies and trainings on these processes will be addressed. Cognitive improvements along with functional alterations, especially in the anterior cingulate cortex, the dorsolateral prefrontal cortex, the inferior frontal gyrus, the inferior parietal gyrus as well as striatal regions seem to be associated with medication of atypical neuroleptics. Functional adaptations in frontal areas were also demonstrated after emotion training, cognitive behavioural training, repetitive TMS and real time fMRI neurofeedback. Apart from this, predominantly parietal and occipital regions appear to be of importance. These findings support the hypothesis that improvements in the symptomatology are related to neurobiological modifications.

Key words: **Schizophrenia - Neuroimaging - Mental disorders, therapy.**

Neurobiological dysfunctions as well as structural alterations in various brain regions including the anterior cingulate cortex (ACC), medial frontal areas, the dorsolateral prefrontal cortex (DLPFC), temporal lobes, the hippocampus, the amygdala, the thalamus and the insula have often been demonstrated in patients with schizophrenia.[1, 2] The reduction in grey matter may be magnified over time.[1] Apart from this, a dysbalance in cortical and subcortical dopaminergic transmissions has been suggested:[3] subcortical mesolimbic dopaminergic (DA) projections are supposed to be hyperactive, resulting in hyperstimulation of D2 receptors. By contrast, a hypostimulation of D1 receptors is thought to be related to dysfunctions in mesocortical DA projections to the prefrontal cortex. The classical dopamine hypothesis implies an association between dopaminergic hyperactivity and positive symptoms, and has indirectly been supported by the efficacy of dopamine antagonists in psychotic states or inversely by the notion that dopamimetic agents might induce exogenous psychosis.[4] Consequently, positive symptoms such as hallucinations or delusions are reported to be more susceptible to a treatment with dopamine receptor blockers as compared to negative symptoms, such as affective flattening, anhedonia, loss of motivation, which often do not respond adequately to (typical)

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neuroleptic treatment.[5-7] Anhedonia, the inability to experience pleasure, and other affective negative symptoms are related to a dysfunction of dopaminergic neurons in the ventral striatum:[8-10] ventral striatal activation has been associated with pleasant anticipatory emotions, whereas ventral striatal dysfunction has been linked to anhedonia and loss of motivation.[11-13] Apart from dopaminergic dysfunctions, altered neurotransmissions at glutamatergic, GABAergic and cholinergic synapses are suggested in schizophrenic patients.[14]

The pharmacological profile of typical and atypical neuroleptics is different with a relatively high D2 dopamine receptor blockade in typical neuroleptics [15, 16] which may contribute to secondary negative symptoms, such as apathy or anhedonia.[10, 17, 18] In atypical neuroleptics there is evidence that the D2 affinity is modified with preferential effects on mesolimbic pathways. Furthermore interactions with other neurotransmitter systems, *e.g.*, the serotonergic system have been taken into consideration and play an important role.[15, 16, 19] Thus, the pharmacological profile of atypical neuroleptics seemed to be more effective in the treatment of negative symptoms than that of typical neuroleptics.[6, 20]

Antipsychotic medication is assumed to have effects on cognitive processes.[21-23] The effects of atypical antipsychotics seem to be superior to those of typical neuroleptics.[24, 25] However, several studies reported that the magnitude of improvement did not differ between treatment with haloperidol and treatment with second-generation antipsychotics.[22]

An examination of immediate effects of the administration of first- and second-generation neuroleptics in schizophrenic patients with 15 (O) water PET revealed increased activations in the dorsal and ventral striatum, the thalamus, the caudate nucleus and the ACC as well as reduced responses in frontal, temporal and cerebellar regions with haloperidol. The administration of olanzapine led to increases in the ventral striatum, the caudate nucleus, the ACC and temporal cortices as well as decreases in the thalamus and lingual cortex.[26] In addition, haloperidol induced greater activation of the dorsal striatum than olanzapine.[26] Overall the study indicated differences in the effect of typical and atypical drugs, especially in the basal ganglia.[26]

Reward processing in schizophrenia and the influence of antipsychotic medication on the related processes

Prefrontal-striatal-thalamic brain regions, including the ventral striatum, the nucleus accumbens (NAcc), the medial amygdala, the orbitofrontal cortex (OFC) as well as the medial prefrontal cortex (MPFC), are innervated by dopaminergic projections and were activated during the presentation of primary and secondary rewarding stimuli.[27-36] These brain regions are central to the so-called "reward system". Reward-related information processing focuses on those stimuli that an organism will try to gain.[29] In brain imaging studies it has been shown that anticipation of increasing rewards is associated with selective and proportional ventral striatum/NAcc activation, whereas punishments do not elicit similar activities.[30, 37-39] Both rewards and punishments lead to activation in the medial caudate regions. The encoding of reward and punishment is fundamental to adaptive behaviour.[40-42] The reward processes can be influenced by drugs like cocaine [8, 43] as well as dopamine agonists like amphetamine.[39] In addition, animal studies indicated that increased firing of dopamine enhances BOLD responses in the dorsomedial and ventrolateral striatum, the NAcc and the dorsal thalamus.[44] Thus, the observed activation of the NAcc through reward anticipation, the activation of the MPFC through reward outcomes, and the deactivation of both through non-reward could partly be a result of the changing dynamics of its dopamine release.

Deficits in reward-associated processes have been shown in various psychiatric diseases, *e.g.*, substance dependence, affective diseases and schizophrenia, suggesting a high significance of the reward system for

psychiatric diseases. Deficits in the processing of reward-related stimuli have been demonstrated in schizophrenic patients. Nielsen *et al.* (2012) demonstrated reward-associated alterations in antipsychotic naïve patients: BOLD responses of patients were decreased during reward anticipation in the ventral tegmentum, the ventral striatum and the ACC. Functional responses in the ventral striatum were related to positive symptoms.[45] Reduced ventral striatum activity was also evident during the presentation of reward-indicating as well as loss-indicating cues in unmedicated schizophrenic patients compared to healthy subjects, together with a negative correlation between negative symptoms and left striatal responses.[38] The striatal dysfunction may contribute to negative symptoms such as anhedonia, apathy, and loss of drive and motivation.[38]

The dissociation of the neurobiological basis of reward expectation and reward receipt or omission of rewards revealed BOLD responses in the ventral tegmental area and the ventral striatum in both groups. Differences between patients and controls were evident in the ACC with only healthy controls showing increasing activation with increasing reward. Responses were decreased in patients and negatively associated with positive symptoms.[46] During reward receipt or omission, responses in the ventral striatum and the mesial prefrontal cortex were demonstrated in both groups. In summary, the results provided support for the suggestion that in schizophrenic patients treated with atypical antipsychotics mesolimbic cortical regions are rather hypoactive during reward processing.[46] Others revealed that the attribution of salience to reward-predicting stimuli and the computation of prediction errors are particularly deficient in schizophrenic patients.[47]

Deficits in the processing of reward-related information in schizophrenic patients seem to be related to a dysregulation in the mesolimbic dopaminergic system.[47] It has been suggested that a chaotic or stress-induced dopamine release in the ventral striatum could interfere with reward anticipation and the occurrence of unexpected rewards or reward-indicating stimuli.[48-51] Apart from dopaminergic neurons the serotonergic system has been particularly associated with the regulation of reward-related behaviours.[52] Thereby different receptor subtypes and the localisation of receptors in the brain probably have differential effects on these processes.[52]

In the last few years, the differential effect of atypical and typical antipsychotics on cognitive functions and their neurobiological basis have attracted more attention. One aspect of these considerations is that atypical neuroleptics have demonstrated to influence the dopamine in the prefrontal cortex, while this effect is less clear for typical neuroleptics.[53, 54] The increased efficacy of atypical antipsychotics in terms of improvement of negative symptoms might be related to positive effects of these drugs on the ventral striatum during reward anticipation.[19] In healthy subjects the administration of a single dose of olanzapine led to increased BOLD responses in reward-associated brain structures, including the ventral striatum, the inferior frontal gyrus and the dorsal ACC.[28]

The direct comparison of medication effects revealed a significant increase in BOLD responses during anticipation of potential monetary gain, compared to the neutral condition (no monetary gain/loss) in the bilateral ventral striatum, including the NAcc in healthy subjects. The results of the schizophrenic patients were influenced by antipsychotic medication, with an increased activation of the right ventral striatum in patients treated with atypical neuroleptics when anticipating a gain compared to anticipating no consequence. In patients receiving typical antipsychotics the comparison of the anticipation of gain and neutral consequences did not change any BOLD responses.[55] The results of patients treated with typical neuroleptics resembled unmedicated schizophrenics with respect to the difficulties in activating the ventral striatum.[55] These difficulties in normalising reward anticipation-related brain responses in the ventral striatum may limit the effectiveness of typical neuroleptics when treating negative symptoms.[55]

In a subsequent study of the same group, patients medicated with typical antipsychotics showed decreased ventral striatum responses compared to healthy subjects and an association between ventral striatal activation and negative symptoms.[56] After a switch to atypical neuroleptics, BOLD responses of patients and healthy subjects did not differ. The authors concluded that a failure to activate the ventral striatum during reward anticipation was pharmacologically state-dependent and only observed in patients treated with typical neuroleptics but not with olanzapine. This could indicate that this drug does not induce secondary negative symptoms through interference with reward anticipation.[56]

Effect of medication on executive functions

Cognitive deficits, *e.g.*, working memory difficulties, rank among the core features of schizophrenic patients and are related to long-term social and occupational impairments.[57, 58] Working memory (WM) deficits are predominantly related to dysfunctions in temporal areas and frontal areas, including the DLPFC:[59-67] frontal BOLD responses of schizophrenic patients were reduced when they performed poorly, whereas unimpaired task performance was related to increased activity in frontal brain regions.[68, 69]

In order to examine the effects of neuroleptics on WM functions, patients were tested before and after monotherapy with quetiapine. The results indicated that after 12 weeks of stable medication with quetiapine WM-related BOLD responses were increased compared to the first examination, *e.g.*, in the ventrolateral prefrontal cortex (VLPFC).[70] Other studies have demonstrated a normalisation of ACC responses and DLPFC responses, respectively, during medication with atypical antipsychotics.[71, 72] In addition, disturbances of the right DLPFC, the right thalamus and the left cerebellum normalised along with an improvement in clinical status, which could represent a state-related phenomenon. By contrast, the dysfunction of the left fronto-thalamo-cerebellar circuitry (left DLPFC, left thalamus, right cerebellum) remained comparatively stable.[71]

Several studies compared the effect of typical and atypical neuroleptics on cognitive functioning: the assessment of WM-related functions revealed deficient behavioural responses in schizophrenic patients compared to healthy subjects irrespective of the actual medication.[73] In addition, patients demonstrated decreased BOLD responses in the DLPFC and the right parietal cortex compared to healthy subjects during the medication with atypical drugs. WM-associate responses did not change after switching to olanzapine. However, neurobiological correlates of attentional processes were influenced by atypical antipsychotics.[73] The switch from conventional antipsychotics to aripiprazole led to an improved task performance and an increased activity in the dorsal ACC.[74] The authors concluded that the increase in BOLD activity during a WM task could reflect a beneficial effect of partial dopamine antagonists on cognitive deficits.[74]

Other studies focusing on cognitive control and cognitive flexibility demonstrated pronounced variations in frontal areas due to pharmacological treatment: first episode patients demonstrated decreased DLPFC and ACC responses compared to healthy controls before treatment.[75] ACC functions improved after four weeks of antipsychotic treatment, whereas the DLPFC activity remained unchanged. These results may indicate that the ACC might be especially sensitive to remedial antipsychotic treatment effects.[75] The prominent role of the ACC was also demonstrated during a flexibility task with an altered task performance and a decreased perfusion in brain regions that are associated with cognitive flexibility in untreated patients. Treatment with atypical antipsychotics for six weeks led to a significant improvement in both task performance and level of perfusion in the ACC.[76]

Effect of cognitive rehabilitation training

One therapeutic approach for the improvement of cognitive functions in schizophrenic patients is a cognitive remediation therapy. In a study of Wexler *et al.* (2000) eight schizophrenic patients participated in four to five sessions of cognitive training per week for ten weeks. After the training, three patients showed significantly increased cognitive functions. In five patients the therapy effect was small. Cognitive improvements were related to increased neural responses in the left inferior frontal gyrus; a kind of "normalisation" of neuronal responses was assessed.[77]

Bor *et al.* (2011) demonstrated functional results associated with cognitive therapy focusing on the dimensions attention/concentration, working memory, logical thinking and executive functions. Functional MRI was used to examine the effect of cognitive training on neural responses after three months. Overall, patients improved their behavioural performance in attention and reasoning capacities after cognitive remediation therapy. Functional differences regarding a verbal task were not significant between groups. However, the therapy group demonstrated over-activations in the left inferior/middle frontal gyrus, the cingulate gyrus and the inferior parietal lobule during the spatial task indicating measurable physiological adaptations after cognitive training.[78]

Effect of psychopharmacological treatment on resting state

In the last few years, the assessment of neurophysiological responses during rest has gained importance (default mode). Resting state MRI measurements are thought to reflect spontaneous neural function.[79] The default mode network includes the ventromedial prefrontal cortex, the posterior cingulate cortex, the precuneus and the lateral parietal cortex.[79] Typically, the default network is more active during rest than during cognitive tasks and is thought to be related to internal thoughts and feelings.[79] Schizophrenic patients showed altered default mode-related brain responses.[80-83] Disruptions of the default mode network have been linked to cognitive deficits in schizophrenic patients.[84]

After short-term treatment with second generation antipsychotic medications, patients showed increased responses in the prefrontal and parietal cortex, the left superior temporal cortex and the right nucleus caudatus.[85] These functional variations were associated with a reduction of clinical symptoms.[85] Other studies demonstrated a reduced connectivity strength within the default mode network in patients with schizophrenia in the posterior cingulate, whereas the connectivity in the precuneus and the inferior parietal lobule seemed to be increased compared to controls.[86] Although reduced connectivity seems to be the predominant finding in schizophrenia, there are resting-state MR imaging studies reporting not only reduced but also increased connectivity between components or subsystems of the DMN.[87, 88] The treatment with olanzapine was related to an increased connectivity in the ventromedial prefrontal cortex; by contrast, activity in posterior brain regions did not change.[86]

Effect of psychopharmacological treatment on the processing of emotional information

Impaired emotion processing, *e.g.*, deficits in the recognition of facial affect [89-91] as well as reduced facial expressions during social interaction [92] are common in schizophrenic patients.[93, 94] Emotion identification deficits are associated with functional impairments, including deficits in social problem solving, social skills and community functioning,[95] and appear to be moderated by demographic and clinical factors, *e.g.*, antipsychotic treatment.[96] The amygdala and an extended network of brain regions, *e.g.*, the VLPFC, the ACC and prefrontal areas, have been linked to emotional processes.[97-100]

Schizophrenic patients demonstrate abnormal neuronal responses in the amygdala and prefrontal brain regions during emotional processing [101-108] with decreased responses in the amygdala especially during negative affect.[102, 103, 108-112] In addition, further limbic and paralimbic structures such as the hippocampus, the PFC, the ACC, the insular cortex, the NAcc and the parahippocampal gyrus are affected.[103, 112-114] Connectivity deficits are prominent between amygdala and brainstem, visual cortex, the dorsal and ventral divisions of the medial PFC, indicating a functional disconnection.[108] The dysfunctions in the amygdala and their connections with the prefrontal cortex are assumed to cause reduced emotional expression (affective flattening) and emotion recognition deficits.[101] In a recent proposal Williamson and Allman suggested that schizophrenia is associated with a failure of the directed effort network, which includes the dorsal and posterior anterior cingulate cortices, the auditory cortex, and the hippocampus to synchronise with the representational network. Mood disorders seem to be associated with a failure of the emotional encoding network, including the orbital prefrontal cortex, the ventral ACC and the amygdala, in order to synchronise with the representational network.[115]

The assessment of treatment effects on emotional processing showed increased responses in the left amygdala in patients compared to controls after four weeks of treatment with olanzapine during the presentation of threatening pictures. These responses decreased after eight weeks compared to four weeks treatment. In addition, the VLPFC activation during implicit processing of emotions decreased between four and eight weeks of treatment.[116] Long term treatment (six months) with quetiapine led to BOLD responses in prefrontal areas, that are commonly associated with emotion processing, during the presentation of sad films; these responses were absent in the same patients without any medication.[117] In addition, symptoms were improved after medication. The authors suggested that the activation of prefrontal brain regions could be effective in improving blunted affect related symptoms (*e.g.*, emotional withdrawal, social avoidance).[117] Increased prefrontal responses, *e.g.*, in the right DLPFC and the right ACC as well as the amygdala and the putamen were also demonstrated after 22 weeks of treatment with quetiapine during passive viewing of negative stimuli.[118]

Training of affect recognition

In the past, behavioural emotion training programmes have led to positive effects.[119-122] Habel *et al.* (2010) compared behavioural data and functional MRI results of schizophrenic patients who underwent a specific training in order to identify the main facial signs of six basic emotions. The results of these patients were compared to those of schizophrenic patients without training and to healthy subjects. Before training, the identification of emotional facial expressions was impaired. The behavioural results were improved after the training. In addition, increased activation was noted in the left middle and the superior occipital lobe, the right inferior and the superior parietal cortex, and the inferior frontal cortex bilaterally. The authors suggest that specific training effects seem to correspond with cerebral effects, probably reflecting a more efficient use of attentional, perceptual or cognitive strategies.[123]

Prediction of treatment response

An important therapeutic issue is the prediction of treatment response at the beginning of a therapeutic process. Van Veelen *et al.* (2011) examined whether the treatment with atypical antipsychotics influences BOLD responses in the DLPFC. In addition, the relation between treatment response and DLPFC function was addressed.[124] The investigation of the effect of practice (comparison of novel working memory task and practiced working memory task) revealed that patients who responded to treatment did not differ from controls regarding BOLD responses. By

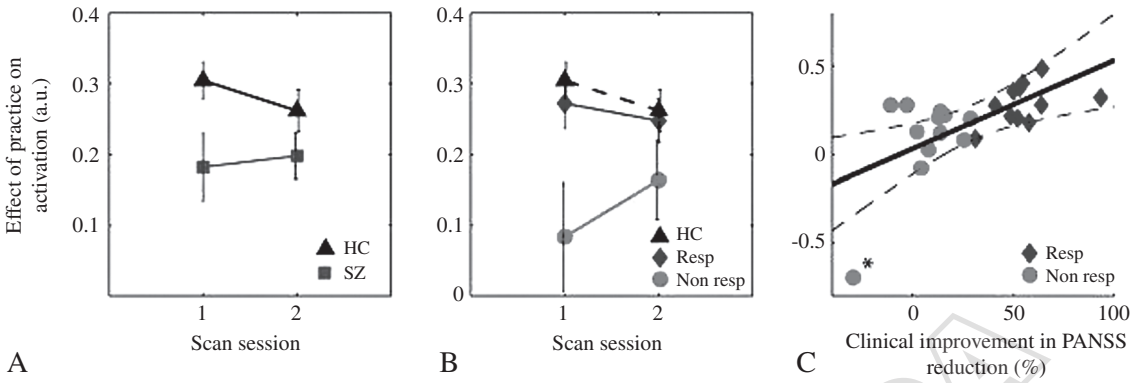

Figure 1.—A) The effect of practice on brain activity in the left DLPFC in healthy controls (HC) and schizophrenia patients (SZ) at baseline and the second scan; B) the effect of practice was smaller for non-responders (NonResp) than for responders (Resp) and healthy controls; C) the effect of practice on activation in the left DLPFC was predictive of clinical outcome (van Veelen *et al.* 2011 with kind permission of Elsevier©).

contrast, non-responders demonstrated a reduced practice effect in the DLPFC that was presented already at baseline. The authors suggested that this effect might be predictive for treatment response [124] (Figure 1).

Investigation of non-invasive brain stimulation methods with functional MRI

Repetitive transcranial magnetic stimulation (rTMS) has proved to be effective as clinical intervention for the reduction of auditory hallucinations.[125, 126] However, rTMS does not work equally well for all patients and at least some studies present conflicting results.[127] The investigation of the influence of rTMS on functional brain responses in healthy subjects revealed an increased connectivity between the right temporoparietal cortex and the DLPFC and the angular gyrus in subjects who had received rTMS. These findings are interpreted as indicator for a normalisation of functional connectivity between these regions, which might underlie the therapeutic effects of rTMS, *e.g.*, for schizophrenic patients.[128]

Transcranial direct current stimulation (tDCS) has found promising results for schizophrenic patients with medication-refractory auditory verbal hallucinations [129] and showed increased improvement in probalistic association learning.[130] In a first pilot single case study Homan *et al.* found improvements in clinical symptoms accompanied by a decrease in regional cerebral blood flow in the frontal and temporal lobes indicating that tDCS had a specific neurobiological effect.[131] An initial pilot study with real time fMRI neurofeedback (rtfMRI) found that two weeks of rtfMRI are able to change activity and connectivity in bilateral insular cortices and can change the perception of emotions in schizophrenic patients.[132]

Neurobiological aspects of cognitive behavioural therapy

Cognitive behavioural therapy (CBT) can be reasonable to schizophrenic patients when combined with antipsychotic medication. Its beneficial effect is a reduction in persistent positive symptoms, *e.g.*, delusions and secondary disturbances, including depressive symptoms.[133, 134] In a study by Kumari *et al.* (2009), patients on stable antipsychotic medication were divided into two groups: 26 patients received treatment as usual (TAU) plus CBT for psychosis for six to eight months, another 26 patients received TAU alone. The results indicated increased performance during a WM task in patients with CBT plus TAU compared to patients with TAU alone. In addition, stronger activity in the DLPFC and the connectivity to the cerebellum in the first ex-

amination was associated with post-CBT clinical improvement.[135]

Another large longitudinal study assessing the effect of CBT plus TAU after six to eight months of treatment demonstrated decreased activation in the inferior frontal gyrus, the insula, the thalamus, the putamen and occipital areas in response to fearful and angry stimuli after therapy compared to baseline.[136] Functional variations were related to symptom improvement. The authors assumed that CBT for psychosis may mediate symptom reduction by improving the processing of threats in a less distressing way [136] (Figure 2).

Visually guided saccades

Attention, sensory and sensorimotor processing can be examined using visually guided saccades.[137] The generation of saccades is closely linked to exogenous visual attention mediated by neocortical areas, including the frontal and parietal eye field.[138] In addition, the striatum, the thalamus, the cerebellum and the brainstem contribute to sensorimotor aspects of eye movement control and their regulation by automatic attentional processes.

In schizophrenic patients the activation in the frontal eye field, the parietal eye field and the cerebellum was decreased compared to matched healthy subjects.[137] After four to six weeks of treatment with antipsychotics functional responses these abnormalities were absent or less prominent, suggesting an improved function in attentional and sensorimotor systems. Other functional alterations were demonstrated in the sensory and the ventromedial prefrontal cortex, the dorsal prefrontal cortex, the dorsal striatum and the thalamus demonstrating profound effects of treatment on various brain areas, including the frontostriatal system.[137]

FMRI effects of nicotinic agonists and nicotine

An important brain structure for schizophrenic patients is the hippocampus: hippocampal hyperactivity was observed in SPECT imaging during various motoric and cognitive tasks in schizophrenic patients.[139, 140] Therefore, the effect of a nicotine agonist on functional responses in the hippocampus was examined during a phase two test using a double-blind crossover design. It was shown that the administration of a nicotinic agonist diminished the activity of the hippocampus during pursuit eye movements. The authors indicated that these results are in line with the function of nicotine receptors on inhibitory interneurons in the hippocampus.[141] The importance of the nicotinic cholinergic system in schizophrenia was also demonstrated in another study: the administration of an alpha 7-nicotinic agonist to schizophrenic patients led to alterations in the default network, especially the posterior cingulate, the inferior parietal cortex and the medial frontal gyrus.[142] The results implicate nicotinic cholinergic dysfunction in schizophrenia.[142]

Deficits in various cognitive domains can transiently be reduced by nicotine.[143] A positive effect of nicotine on functional brain responses was also demonstrated in a working memory task: nicotine improved the performance of schizophrenic patients during a comparatively difficult working memory task and worsened the results of healthy subjects.[144] Apart from behavioural improvements, BOLD responses of schizophrenic patients were enhanced in the ACC and the bilateral thalamus.[144]

Conclusions

Improvements in cognitive functioning in schizophrenic patients are associated with increased BOLD responses especially in frontal areas, the ventral striatum and the amygdale.[46, 75, 116, 117, 145-148] Antipsychotics can lead to acute variations in functional MRI responses with differential effects for atypical and typical neuroleptics, especially in the basal ganglia:[26] functional improvements are smaller during medication with typical neuroleptics compared to atypical neuroleptics.[147] Increased BOLD responses

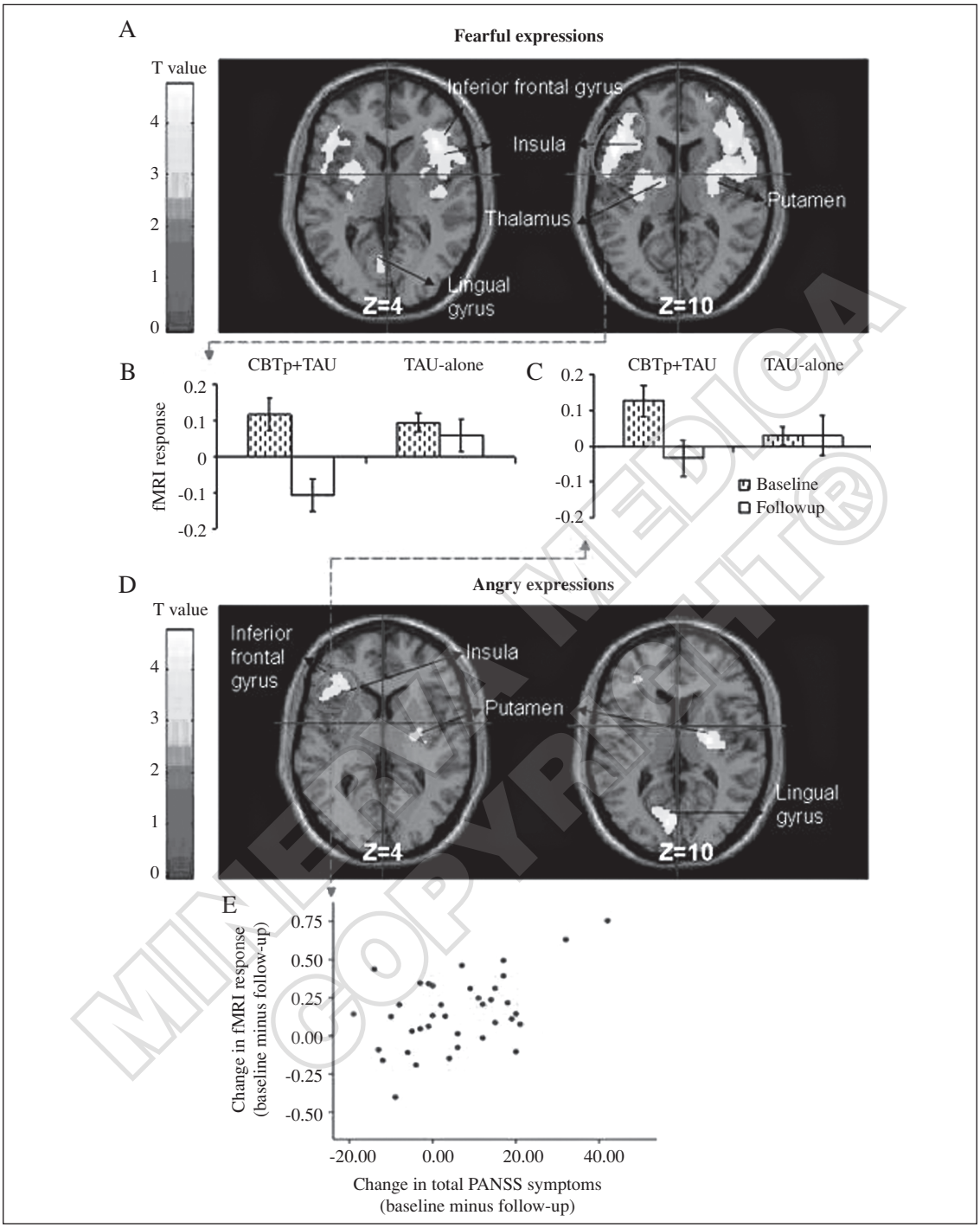

Figure 2.—A and D) Areas of reduced brain activity following CBT for psychosis + TAU (but not following TAU alone) to fearful and angry facial expressions (voxel threshold P<0.005 uncorrected); B) mean functional MRI response in the left inferior frontal insula cluster in each group at baseline and follow-up to fearful expressions; C) mean functional MRI response in the left inferior frontal cluster in each group at baseline and follow-up to angry expressions; E) scatter plot of decreases in activity from baseline to follow-up in the left inferior frontal region during angry expressions against change in symptoms from baseline to follow-up across the whole sample (Kumari *et al.* 2012 with kind permission of Oxford University Press).

(especially in frontal and striatal areas) and improved cognitive functions can also be seen when patients switch from typical to atypical neuroleptics.[56, 73, 145]

Apart from medication effects, various other treatment strategies and trainings seem to be effective and can lead to functional variations: emotion recognition training, for example, resulted in functional variations in the occipital lobe, inferior and superior parietal areas and the inferior frontal gyrus.[123] Repetitive TMS led to an increased connectivity between temporo-parietal areas and the inferior frontal gyrus.[128] Cognitive behavioural training was related to greater activity in the DLPFC [135] as well as a reduced reactivity to fearful stimuli in the frontal, thalamic and occipital brain regions.[136] TDCS showed promising results on hallucinations and may have a specific neurobiological effect demonstrated with the aid of MRI techniques.[131] Real time fMRI neurofeedback changed activity and connectivity in bilateral insular cortices and changed the perception of emotions in schizophrenic patients.[132] Altogether, the importance of a network of frontal, parietal, thalamic and occipital areas was highlighted for a better assessment of treatment effects in schizophrenic patients. In addition, DLPFC activity is also suggested to be important for the prediction of treatment response.[124]

Riassunto

Effetti del trattamento nella schizofrenia: evidenze dal neuroimaging

È stato dimostrato come i deficit cognitivi e le difficoltà nel riconoscimento emotivo in pazienti schizofrenici siano associati a disfunzioni, soprattutto nelle aree frontali, striatali, parietali e nell'amigdala. Nella presente review affrontiamo gli effetti di diversi interventi educativi e strategie terapeutiche su tali processi. I miglioramenti cognitivi, unitamente alle alterazioni funzionali, soprattutto nella corteccia cingolata anteriore, nella corteccia prefrontale dorsolaterale, nel giro frontale inferiore, nel giro parietale inferiore e nelle regioni striatali, sembrano essere associati al trattamento con antipsicotici atipici. Adattamenti funzionali nelle aree frontali sono stati dimostrati anche dopo l'educazione emotiva, l'educazione cognitivo-comportamentale, la TMS ripetitiva e il neurofeedback fMRI in tempo reale. Oltre a ciò, le regioni parietale e occipitale sembrano rivestire una particolare importanza. Tali risultati supportano l'ipotesi che i miglioramenti nella sintomatologia siano associati ad alterazioni neurobiologiche.

Parole chiave: Schizofrenia - Neuroimaging - Cervello, malattie, terapia.

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