

# Cognitive-behavioral therapy for schizophrenia: an overview on efficacy, recent trends and neurobiological findings

Maristela Candida<sup>1</sup>, Carlos Campos<sup>1,II</sup>, Bárbara Monteiro<sup>1</sup>, Nuno Barbosa F. Rocha<sup>II</sup>, Flávia Paes<sup>1</sup>, António Egídio Nardi<sup>I</sup>, Sérgio Machado<sup>I,III</sup>

<sup>I</sup> Universidade Federal do Rio de Janeiro, Instituto de Psiquiatria, Laboratório de Pânico e Respiração, Rio de Janeiro, RJ, Brasil.

<sup>II</sup> Instituto Politécnico do Porto, Escola Superior de Tecnologia da Saúde, Porto, Portugal

<sup>III</sup> Universidade Salgado de Oliveira, Programa de Pós-graduação em Ciências da Atividade Física, Laboratório de Neurociência da Atividade Física, Rio de Janeiro, Niterói, Brasil

**OBJECTIVE:** Cognitive Behavioral Therapy (CBT) has been recommended by several international guidelines as the gold-standard treatment to address the needs of patients with schizophrenia. This review provides an overview on recent advances regarding CBT for schizophrenia.

**METHODS:** An electronic search was performed on PubMed/MEDLINE, Web of Science and Cochrane Database, using the key-words: "schizophrenia", "psychosis", "cognitive-behavioral therapy", "CBT" and "psychotherapy".

**RESULTS:** Numerous systematic reviews support the immediate and long-term efficacy of Cognitive Behavioral Therapy to reduce positive and negative symptoms in patients with schizophrenia. In the last decade, CBT for schizophrenia has been applied to clinical high-risk subjects and delivered using innovative approaches (low intensity, web-based and self-guided). Brain regions and networks which support high-level cognitive functions have been associated with CBT responsiveness. There is preliminary evidence indicating that CBT induces a prefrontal dependent increase in the top-down modulation of social threat activation.

**CONCLUSION:** In the last decade, CBT for schizophrenia has explored new treatment outcomes, targeted acute and pre-clinical populations and provided alternative methods to reach more patients and reduce intervention costs. The patients' neurocognitive profile seems to play a critical role in treatment response and combining CBT with cognitive remediation may allow to enhance therapeutic effects. Although CBT for schizophrenia is widely established as a gold-standard practice, future studies using innovative CBT protocols, exploring brain-related predictors and treatment outcomes may allow this intervention to be more effective, personalized and to reach a wider number of patients.

**KEYWORDS:** Cognitive-behavioral therapy; Schizophrenia; Psychosis; Neurobiological; Neuroplasticity.

Candida M, Campos C, Monteiro B, Rocha NBF, Paes F, Nardi AE, Machado S. Cognitive-behavioral therapy for schizophrenia: an overview on efficacy, recent trends and neurobiological findings. *MedicalExpress* (São Paulo, online). 2016;3(5):M160501.

Received for Publication on April 27, 2016; First review on May 4, 2016; Accepted for publication on July 17, 2016; Online on September 20, 2016

E-mail: maristelacandida@gmail.com

## ■ INTRODUCTION

Numerous meta-analyses have highlighted cognitive behavioral therapy (CBT) as one of the most effective psychological interventions for a wide range of psychiatric disorders including depression, bipolar disorder, obsessive-compulsive disorder, anxiety disorders, among others.<sup>1-7</sup> The core assumption of CBT

is that feelings, behaviors and physiological responses are mainly influenced by the way an individual perceives daily life situations.<sup>1,9</sup> Patients with psychiatric disorders commonly display cognitive distortions as they perceive and process information in a way that does not match reality.<sup>10-14</sup> The main goal of CBT is to change dysfunctional thoughts into more adapted and realistic alternative thoughts, allowing improvements in the emotional and behavioral state of the patient.<sup>8,9</sup> To achieve these changes, therapists combine a wide-range of cognitive

DOI: 10.5935/MedicalExpress.2016.05.01

and behavioral techniques such as cognitive restructuring, gradual exposure, systematic desensitization, breathing and relaxation techniques, among others.

CBT has been a valuable resource to address the needs of patients with schizophrenia: it was first introduced in the early 1990s, when there were several concerns on targeting delusions directly as they qualitatively differ from normal experiences.<sup>15</sup> It was originally applied for patients with psychosis in order to address positive symptoms, by recruiting the client's ability to think about and question delusional or self-evaluative beliefs.<sup>16-19</sup> Using a collaborative approach to understand distressing psychotic experiences, therapist target and question beliefs that hinder individuals' life goals, allowing the patients to reappraise their experiences and establish alternative ways to deal with them.<sup>20,21</sup>

### How does CBT for schizophrenia work?

CBT for schizophrenia is based on the cognitive model of the disease which together with neurobiological evidence provides a rationale for the psychopathology of schizophrenia.<sup>22</sup> Thereby, positive symptoms (delusions and hallucinations) are associated with impaired cognitive processing induced by dopamine hyper-regulation, leading to several processing biases (e.g. jumping to conclusions, confirmation bias and externalization).<sup>23-25</sup> Conversely, negative symptoms are related to hypo-disregulation of dopamine signals related to reward stimuli, which leads to reduced motivational drive and the gradual appearance of negative symptoms (e.g. social withdrawal, lack of interests).<sup>23</sup>

Within this framework, CBT for schizophrenia relies on a number of techniques to effectively target cognitive processing biases and the underlying positive and negative symptoms.<sup>26</sup> When addressing hallucinations, therapists must consider several characteristics of the voice hearing experience (frequency, loudness, number of voices, source location, potential triggers).<sup>26-29</sup> After careful assessment of the patients' experience, therapists may recommend a wide range of approaches to reduce distress: distracting patients from their voices, enhancing effective coping skills, using rational responding techniques (e.g. examining the evidence), metacognitive approaches, modified dysfunctional thought record, and normalization techniques to reduce negative emotions associated with voices.

Delusions are a very challenging target of CBT because it is hard to determine whether any specific belief is a delusion or not. The therapist needs to understand the patients' flexibility and conviction as well as the context, plausibility and persistence of beliefs.<sup>20,22</sup> Patients with schizophrenia usually have some resistance to disclose their psychotic experiences within the therapeutic context. Thus, a strong and trustful therapeutic relationship must be established so that the therapist can effectively comprehend

the psychotic experience.<sup>26</sup> When targeting delusions, therapists must engage in a complex process to compensate for reasoning bias, starting with the identification of the causes and consequences of the delusional beliefs. Therapists must also examine paranoid thoughts to find alternative explanations and use decentering techniques. Finally, when delusional beliefs are resistant to change there should be an increasing focus on the stress/fear associated with those beliefs.<sup>26-29</sup>

In the last years, clinicians have also adapted CBT to target negative symptoms, using simple behavioral activation concepts (e.g. activity schedule, gradual task assignments) and cognitive methods to address the maladaptive schema underlying negative symptoms.<sup>21,30</sup> Understanding the onset of illness is also an important component of CBT for schizophrenia, because it allows therapists to educate patients about the stress vulnerability model, to reduce catastrophic appraisals about their illness, to identify risk factors to prevent future relapses and to develop an individualized case formulation regarding onset and maintenance of the problems.<sup>26</sup>

### Guidelines on CBT for schizophrenia

The evidence supporting the efficacy of CBT for patients with schizophrenia has widely increased all around the world. International guidelines from several countries have endorsed CBT for schizophrenia, including the United Kingdom<sup>31-33</sup>, the United States<sup>34-36</sup>, Australia and New Zealand<sup>37</sup>, Sweden<sup>38</sup> and Scotland<sup>39</sup>, among others. The National Institute for Health and Care Excellence (NICE) has recommended this intervention for every patient with schizophrenia (acute, chronic, in remission), even suggesting CBT as a first-line treatment for at-risk populations.<sup>33</sup> Most guidelines also stress that CBT should be delivered by a qualified staff through a minimum of 16 individual sessions. However, as CBT for schizophrenia has clearly proved to be an effective treatment strategy, researchers and therapist have recently begun to explore alternative CBT procedures, such as low-intensity interventions and self-guided or internet-based protocols, which may reduce intervention costs and reach a wider number of patients.

Finally, in the last decade there has been a great interest in the neurobiological effects of CBT, as increased awareness regarding neuroplasticity and learning has led researchers and clinicians to wonder how this intervention changes the brain.<sup>40,41</sup> Better understanding of the brain mechanisms which underlie CBT can play a crucial role to further understand the neural correlates of symptom reduction, to improve the efficacy and accuracy of intervention programs and to choose the most effective treatment for each patient. However, evidence regarding the brain mechanisms which support or underlie CBT effectiveness for patients with schizophrenia have been scarcely explored.

CBT for schizophrenia has been widely accepted as a valuable intervention but several questions still linger among researchers and clinicians. Which are the main outcomes of CBT for schizophrenia? How can we make this intervention more effective and personalized to patients' needs? Does CBT for schizophrenia plays a role in brain-related outcomes? And which are the hot research topics for the next decade? This reviews aims to guide the reader through these questions by providing an overview on recent advances regarding CBT for patients with schizophrenia.

## ■ METHOD

This study is a narrative review as it provides a comprehensive narrative synthesis of previously published information regarding CBT for schizophrenia, including books, electronic or paper-based journal articles, expert commentaries and personal experience in the field from the authors. It also aims to critically discuss the state of the art on CBT for schizophrenia from a theoretical and contextual point of view. An electronic search was performed between January and March 2016, in the databases of PubMed/MEDLINE, Web of Science (Web of Science Core Collection) and Cochrane Database (Central Register of Controlled Trials). The search was completed using the key-words: "schizophrenia", "psychosis", "cognitive-behavioral therapy", "CBT" and "psychotherapy". Included papers and important reviews regarding CBT for schizophrenia were also manually screened for additional relevant studies. Main textbooks regarding CBT for schizophrenia as well as the work of the leading authors on the field were also screened.

Throughout this review, Cohen's *d* statistics (abbreviated *d*) shall be used to indicate the standardized difference between means (mean difference/standard deviation).

## ■ RESULTS AND DISCUSSION

Based on the retrieved information our findings were organized into three subsections: (a) efficacy of CBT for schizophrenia in several different outcomes (delusions, hallucinations, negative symptoms); (b) recent advances on CBT protocols (e.g. low-intensity, self-guided, at-risk patients); (c) neurobiological findings regarding CBT for schizophrenia.

### Efficacy of CBT for schizophrenia: evidence from systematic-review and meta-analysis

A wide range of systematic reviews and meta-analyses highlight the effectiveness of CBT for schizophrenia, whereas we only found two meta-analyses that reported no benefits from this intervention.<sup>41,43</sup> CBT for schizophrenia was initially created to help patients to reappraise the

meaning and purpose of hallucinations and delusions.<sup>44</sup> Thereby, the first systematic reviews focused exclusively on the effectiveness of CBT on positive symptoms.

Bouchard et al.<sup>45</sup> were to first to complete a review suggesting the positive effects of CBT to target delusions and hallucinations. Since then, several effect size analyses and meta-analyses have reported small to moderate treatment effects of CBT on positive symptoms ( $d = 0.29-0.65$ ).<sup>46-50</sup> Gould et al.<sup>49</sup> found significant treatment effects in 5 controlled trials using cognitive therapy aiming to modify patients' distorted beliefs about delusions and hallucinations ( $d = 0.65$ ). Another meta-analysis actually reported CBT had larger effects in acute psychotic patients ( $d = 0.57$ ) in comparison to chronic patients with persistent positive symptoms ( $d = 0.27$ ).<sup>50</sup>

Researchers have also explored the effectiveness of CBT to specifically address hallucinations or delusions. Van der Gaag et al.<sup>51</sup> reported that individually tailored case-formulation CBT had significant treatment effects on delusions ( $d = 0.24$ ) and hallucinations ( $d = 0.46$ ), even after controlling for unblinded studies. Another recent meta-analysis on the effects of CBT on delusions actually found significant small to moderate effects in comparison to treatment-as-usual ( $d = 0.27$ ), although there were no significant differences in comparison to other interventions.<sup>15</sup>

In the last decade, there have also been reviews exploring several secondary outcomes of CBT for schizophrenia, especially negative symptoms. Rector and Beck<sup>52</sup> completed an effect size analysis which found moderate to large pre-post treatment improvements on negative symptoms ( $d = 0.91$ ). Wykes et al.<sup>47</sup> reported small significant treatment effects of CBT for schizophrenia even after excluding low quality studies ( $d = 0.206$ ). However, a recent meta-analysis found no treatment effects of CBT on negative symptoms, although positive effects have been reported regarding global functioning ( $d = 0.378$ ) and mood ( $d = 0.363$ ).<sup>53</sup> Interestingly, individualized protocols and older trials seem to be associated with negative symptom improvement.

Long term effects are crucial outcomes of CBT for schizophrenia in that they aim to help patients to develop adaptive strategies that should allow them to cope with symptoms after the intervention ends.<sup>4</sup> Interestingly, a meta-analysis by Sarin et al.<sup>46</sup> found no effects immediately after treatment, but reported significant follow-up improvements on positive, negative and general symptoms ( $d = 1.01, 0.2$  and  $0.21$ , respectively). The authors argued that the immediate treatment effects of CBT may be non-specific (e.g. therapeutic relationship) and that specific long-term effects are achieved as the patients become gradually more comfortable to cope with strong dysfunctional beliefs.

Several meta-analyses have also reported small to large follow-up effects on numerous outcomes relevant to

psychosis including (a) frequency and distress associated with positive and negative symptoms ( $d = 1.48$  and  $0.88$ , respectively);<sup>52</sup> (b) positive and general symptom severity ( $d = 0.41$  and  $0.40$ , respectively);<sup>48</sup> (c) delusion related outcomes ( $d = 0.25$ ).<sup>15</sup> Gould et al.<sup>49</sup> actually reported that the follow-up effects on positive symptoms were either maintained or even increased in magnitude after cognitive therapy ( $d = 0.93$ ). Zimmerman et al.<sup>50</sup> also found small to moderate early (3-12 months) and late ( $> 12$  months) follow up effects of CBT in positive symptoms ( $d = 0.40$ ;  $d = 0.33$ , respectively).

There also several systematic reviews and meta-analyses comparing CBT to other psychological interventions. Pilling et al.<sup>54</sup> actually reviewed randomized controlled trials using CBT, family intervention, social skills training and cognitive remediation; they highlighted the increased efficacy of CBT in mental state improvements, including after follow-up. A recent meta-analysis by Turner et al.<sup>50</sup> compared the effectiveness of several psychological and psychosocial treatments for psychosis, including CBT, befriending, cognitive remediation, psychoeducation, social skills training and supportive counseling. When analyzing the studies with a low risk of bias, they found significant treatment effects of CBT (vs. the other interventions pooled together) in reducing positive symptoms, although the reported effect size was small ( $d = 0.16$ ). There is also evidence that the combination of family interventions with individual CBT can be strongly effective in extending the time-to-relapse in young people with psychosis.<sup>56</sup>

It has also been argued that CBT may be effective in the treatment of schizophrenia but that it may not outperform other therapy alternatives when addressing several outcomes such as adverse effects, relapse, re-hospitalization, global mental state and social functioning.<sup>57</sup> Orfanos et al.<sup>58</sup> found no specific effects of CBT group interventions on the negative symptoms and social functioning of patients with schizophrenia. Newton-Howes et al.<sup>59</sup> performed a meta-analysis comparing CBT to supportive therapy and found no significant between-group differences after treatment; however it should be noted that this work has been harshly criticized on account of several methodological inaccuracies (effect sizes miscalculations, non-inclusion of relevant studies, no consideration for intervention dosage).<sup>60</sup>

### Recent trends on CBT for schizophrenia

CBT for schizophrenia was originally developed to address positive symptoms of treatment-resistant patients with schizophrenia; the last 20 years have witnessed innovations and a widening the targets for this intervention. Low intensity CBT for schizophrenia has also been further explored in the past few years as an effort to increase cost effectiveness. A meta-analysis by Hazell et al.<sup>61</sup> found significant treatment effects of low intensity CBT (with an

average of 9.5 hours of contact) on psychotic symptoms post-intervention ( $d = 0.46$ ) and follow-up ( $d = 0.40$ ) as well as follow-up effects on depression ( $d = 0.56$ ) and functioning ( $d = 0.57$ ). Currently, there are not enough trials to compare brief vs. standard CBT for people with schizophrenia; nonetheless it does appear that a reduction of intervention dosage may allow CBT to reach an increased number of patients in need.<sup>62</sup>

Web-based interventions are yet another alternative to enhance patients' access to CBT for schizophrenia and there is evidence regarding its feasibility and preliminary efficacy.<sup>63</sup> More recently, Naeem et al.<sup>64</sup> developed a feasibility study protocol using a self-guided CBT program: this is an intervention which is predominately designed to be conducted without contact with health professionals and which could provide a cheap, flexible and easy tool for CBT implementation. Although their sample included mainly patients with moderate symptomatology and low disability levels, the authors reported a high retention rate and acceptability as well as improved scores regarding disability and positive, negative and general psychopathology.

Several recently published meta-analyses have reported the effects of CBT in preventing first episode psychosis in high risk individuals who started experiencing symptoms. Meta-analytic studies have increasingly included more trials and have reported pooled relative risks (RR) ranging from 0.34 to 0.52, which indicates that CBT successfully and significantly reduced the risk of psychotic transition between 66% and 48%.<sup>65-69</sup> More recently, Van der Gaag et al.<sup>68</sup> findings suggested that CBT intervention can effectively reduce transition to psychosis in clinical high risk patients (RR = 0.52). A meta-analysis by Hutton and Taylor<sup>67</sup> examined the effectiveness of CBT intervention to prevent psychosis in drug-free subjects at risk for psychosis. The pooled relative risk to develop psychosis was significantly reduced by more than 50% in the CBT patients at every time point, including 6 months (RR = 0.47), 12 months (RR = 0.45) and 18-24 months (RR = 0.41) after the intervention.

There have also been several efforts to maximize and explore the treatment effects of CBT in patients with schizophrenia by combining it with other treatments such as motivational interviewing<sup>70</sup>, cognitive remediation<sup>71</sup>, metacognitive techniques<sup>72</sup> and even with protected employment.<sup>73</sup> Drake et al.<sup>71</sup> reported that using cognitive remediation before CBT reduced the number of sessions needed to achieve significant outcomes for psychotic symptoms.

### CBT for schizophrenia and neurobiological findings

There are two main approaches to explore brain-related psychotherapeutic outcomes: (a) the use of imaging methods before and after the intervention in order to identify changes in brain function and/or

structure; (b) the identification of brain-based predictors of psychotherapy response, investigating correlations between pretreatment brain measurements and post-treatment clinical outcomes.<sup>74</sup>

Most studies regarding CBT for schizophrenia have actually explored how neuroimaging measurements can predict CBT efficacy for these patients.<sup>75-80</sup> Premkumar et al.<sup>78</sup> examined structural MRI predictors of symptom changes observed after CBT in psychotic patients. In the CBT plus standard care group, they looked at increases in gray matter volume: they claim that (a) improved positive symptoms were associated with increased gray matter volume in the right cerebellum ( $r = 0.581$ ;  $p = 0.003$ ); (b) improvement in negative symptoms were associated with volume increases in the left precentral gyrus ( $r = 0.653$ ;  $p = 0.001$ ) and right inferior parietal lobe ( $r = 0.628$ ;  $p = 0.001$ ); (c) improvements related to general psychopathology were associated with volume increases in the right superior temporal gyrus ( $r = 0.676$ ;  $p < 0.001$ ), the cuneus ( $r = 0.700$   $p < 0.001$ ) and the cerebellum ( $r = 0.627$ ;  $p = 0.001$ ). Increased cuneal gray matter volume could imply a more effective recall of learned strategies. Enlarged cerebellar gray matter volume may allow effective reasoning and relational processing, while findings on the posterior superior temporal gyrus may enhance cognitive flexibility and insight. Thereby, Premkumar et al.<sup>78</sup> postulated that an increase in gray matter volume within high-level cognitive processing areas may facilitate and enhance responses to CBT in patients with schizophrenia.

Interestingly, no significant predictors have been described for the frontal regions, which led Premkumar and associates to explore the association between the orbitofrontal cortex and CBT responsiveness in patients with schizophrenia.<sup>80</sup> There was a significant correlation between pre-treatment orbitofrontal cortex gray matter volume and positive symptom improvement ( $r = 0.530$ ;  $p = 0.01$ ) after a CBT protocol. The authors also found an association between rightward orbitofrontal cortex asymmetry and reduction of negative ( $r = 0.542$ ;  $p = 0.01$ ) and general psychopathology ( $r = 0.482$ ;  $p = 0.02$ ). The orbitofrontal cortex plays an important role on emotional decision-making and cognitive flexibility which may enhance CBT responsiveness for schizophrenia.

Kumari et al.<sup>75,76</sup> also analyzed fMRI predictors of responsiveness to CBT for schizophrenia using different neuroimaging experimental tasks. First, the authors reported findings regarding the association between baseline brain activity on an n-back task and the response of patients with schizophrenia to CBT.<sup>75</sup> There were significant associations between inferior-middle frontal gyrus and CBT responsiveness regarding total, positive and general psychopathology ( $p = 0.015$ ,  $0.021$  and  $0.025$  respectively). There was also a significant relationship between left dorsolateral prefrontal cortex/cerebellum

connectivity and post-CBT clinical improvement ( $p = 0.04$ ). CBT responsiveness may have been facilitated by the executive processing mediated by the dorsolateral prefrontal cortex and the prefrontal/cerebellum circuits, allowing participants to be more effective in reasoning their beliefs and generalize their acquisitions to several situations.

In their second report Kumari et al.<sup>76</sup> addressed how CBT responses could be predicted by a modified verbal monitoring task, where patients had to monitor self- and externally-generated speech. Findings were somewhat similar because activation of the left inferior frontal gyrus was associated with an increased response to CBT across several conditions ( $p = 0.004$  to  $0.047$ ); this most likely implicates language processing on treatment responses. There was also an association between CBT responsiveness and inferior parietal deactivation with own-voice vs. non-own voice monitoring. This suggests that patients with schizophrenia capable of processing self-relevant information more efficiently may exhibit better treatment responses.

Using proton magnetic resonance spectroscopy, Premkumar et al.<sup>79</sup> were the first to explore the predictive roles of several metabolites important for neuronal integrity on the responsiveness to CBT for schizophrenia. None of the metabolites' concentration at baseline (n-acetyl aspartate, choline, creatine/phosphocreatine) had a significant relationship with post-treatment CBT outcomes. However, n-acetyl aspartate concentration tended to increase in the CBT plus standard care group, concomitantly with a significant amelioration of symptoms. Finally, another report assessed the predictive value of the sensorimotor gating function using pre-pulse inhibition:<sup>77</sup> they describe a significant positive relationship between 120 msec pre-pulse-to-pulse intervals and post-CBT symptom improvement. Pre-pulse inhibition acts as a pre-attentive mechanism, and the reported findings suggest that brain areas involved in top-down processing of information may be associated with CBT responsiveness.<sup>77</sup>

To our knowledge, there are only two studies addressing the effects of CBT for schizophrenia on brain-related outcomes.<sup>81,82</sup> Kumari et al.<sup>81</sup> completed a functional MRI (fMRI) assessment using an implicit facial affect task to examine functional brain changes following a 6-8 months CBT protocol for 22 patients with schizophrenia. After cluster-correction, there were significant findings regarding fearful expression processing, as the CBT group showed greater activity decrease in several brain regions including the bilateral inferior frontal gyrus, right insula, bilateral putamen, left thalamus and left occipital areas; however, none of the regions was correlated with symptom improvements. Ultimately, the main conclusion from this trial is that CBT can decrease the brain responses of patients with schizophrenia to threatening socially relevant stimuli.

Mason et al.<sup>82</sup> explored the functional connectivity changes in high-order cognitive systems which underlie the previously reported CBT induced brain activation improvements regarding processing of social threats. There was a reorganization of brain networks involved in social threats processing because CBT participants displayed increased amygdala connectivity to the right dorsolateral prefrontal cortex, inferior parietal lobe and posterior cingulate gyrus as well as to the left superior temporal lobe, postcentral gyrus and thalamus. The connectivity changes between the amygdala and the dorsolateral prefrontal cortex may suggest that CBT reduced aberrant threat network activation as there is a greater top-down regulation from prefrontal regions. There was also an association between changes in inferior parietal lobe connectivity and improvements in perceived persecutory beliefs.

## ■ GENERAL CONSIDERATIONS

CBT has been used to treat different pathologies with variable success.<sup>83-85</sup> As far as schizophrenia is concerned, it has been widely proved that CBT can reduce symptomatology and promote overall functioning, improving the well-being and quality of life of patients with schizophrenia. Since the first trials targeting positive symptoms in treatment resistant patients, CBT for schizophrenia has clearly advanced. In spite of keeping to its core principles, CBT for schizophrenia has widened the range of targeted patients and symptoms (acute psychosis, clinical high-risk subjects, negative symptoms) and developed alternatives to provide help to a maximum number of patients (low intensity, web-based and self-guided), becoming a more versatile psychotherapeutic tool that can better suit the individual needs of each patient. Thereby, CBT cannot be regarded as one global brand because treatment protocols are very heterogeneous, differing in terms of models, settings, targets, types of individuals (e.g. acute vs chronic) and dosage.<sup>86</sup> Future trials regarding CBT efficacy on behavioral and neurobiological outcomes must take into account the diversity inherent to this intervention modality and define outcomes which accurately assess the postulated changes within the proposed intervention protocols.

Furthermore, the combination of CBT with other psychological interventions seems to be a valuable resource when addressing the needs of patients with schizophrenia. Several systematic reviews regarding cognitive remediation have proven it to be as widely effective in reducing executive and attentional deficits<sup>87-89</sup> as it is in producing neuroplastic changes in the brain of patients with schizophrenia.<sup>90-93</sup> Taking these findings together, one can postulate that cognitive remediation may serve as a valuable tool to produce neuropsychological and neural improvements that can enhance the following effects of CBT, possibly by allowing patients more effective top-down regulation mechanisms. Every patient with schizophrenia generally

displays some kind of neurocognitive deficit but their neuropsychological profile varies widely and may be another factor which hinders the magnitude of findings of meta-analytical studies on CBT.

Evidence from neurobiological predictor studies of CBT for schizophrenia also suggest the importance of neurocognitive variables in CBT response. Currently available evidence suggests a particularly important role of the areas enrolled in high-level cognitive functions, with reports emphasizing the predictive power of brain regions which support language and effective executive functions such as decision making, cognitive flexibility, reasoning and relational processing.<sup>75,78,80</sup> There were also several associations between CBT response and several regions related to maintain or switch attention/focus.<sup>75,76</sup> Some of the areas that predicted CBT response are not known to be impaired in schizophrenia, suggesting that patients with specific neurophysiological and/or neurophysiological functions intact may achieve greater benefits from CBT. Future trials should explore how neural predictors can be related to behavioral neuropsychological measures which can aid researchers and clinicians to develop treatment protocols which better suits each patient's cognitive needs.

Evidence addressing brain-related outcomes seem to be the next step for the use of CBT for schizophrenia, at a point in time where the first reports regarding structural and functional measures as predictors of CBT response on several psychopathology domains begin to appear. There is evidence suggesting that patients with psychiatric disorders are more likely to consider psychotherapy treatment whenever treatment is selected based on neuroimaging scans.<sup>94</sup> The identification of CBT specific biomarkers can have significant clinical usefulness, allowing researchers and therapists to select personalized and individualized treatment which guarantee maximum effectiveness.<sup>74</sup> The population of patients within the spectrum of schizophrenic disorders is hugely heterogeneous and the magnitude of CBT treatment effects may vary widely in different patient subgroups, probably explaining why several meta-analysis regarding CBT efficacy on schizophrenia only reported small to moderate effects. Future studies may explore how neurostructural, neurofunctional and neuromolecular predictors relate with the clinical characteristics and backgrounds of patients (e.g. clinical status, illness duration, genetic and heritability factors) in order to pin point which characteristics support or hinder CBT effectiveness. Furthermore, researchers should not exclusively focus on group results, as predictions about individual subjects may be more clinically relevant.

Finally, evidence is still very scarce as only two trials from the same cohort assessed CBT effects on brain functioning. The reported findings are promising because CBT seems to reduce brain activity in several brain regions in response to social threatening stimuli. Furthermore, the reported functional connectivity study suggests these

changes are related to improved top-down regulation mechanisms between prefrontal regions and structures related to emotional processing. A critical review by Weingarten et al.<sup>74</sup> states that there is a significant amount of evidence suggesting that psychotherapy effects include modulation of brain connectivity networks. Thereby, these first findings regarding CBT induced changes in brain connectivity provide valuable evidence which can complement the typical measured behavioral or brain regions outcomes. Furthermore, CBT brain effects on schizophrenia may resemble the findings from other psychiatric disorders, as there is evidence suggesting that it induces brain activity normalization in impaired regions but also achieves brain changes in regions without pretreatment abnormalities by activating compensatory neural mechanisms.<sup>95,96</sup>

## ■ CONCLUSION

Over the last 20 years, CBT has been proved through numerous meta-analyses to be a useful and effective alternative to address the needs of patients with schizophrenia. Throughout these years, CBT for schizophrenia has reinvented itself, developing from its roots in medication-resistant positive symptoms to reach new treatment outcomes; it can now be provided using alternative methods and appears to be useful to prevent psychosis in high-risk subjects. The neurocognitive profile of patients seems to play a critical role in treatment response; the combination of CBT with cognitive remediation may lead to an enhancement of therapeutic effects; furthermore, recent trials have made critical contributions to the understanding of how brain functioning can be predicted and/or be changed by CBT. The road to the biological validation of CBT for schizophrenia seems to be next step and there is a need to develop larger randomized controlled trials that can compare CBT to other psychotherapies in order to identify specific neurobiological predictors and outcomes. Although CBT for schizophrenia is widely established as a gold-standard practice, new evidence form innovative CBT protocols and neurobiological studies may allow this intervention to be more effective, personalized and to reach a wider number of patients.

## ■ CONFLICT OF INTEREST

Authors report no conflict of interest regarding this study.

## ■ AUTHOR PARTICIPATION

Candida M, Campos C, Monteiro B, Paes F and Machado S developed the project, discussed the data, wrote the first draft of the article, and reviewed its final form;

Rocha NBF, Nardi AE, discussed the data and reviewed the final form of the article.

## TERAPIA COGNITIVO-COMPORTAMENTAL PARA ESQUIZOFRENIA: UMA REVISÃO SOBRE EFICÁCIA, AVANÇOS RECENTES E ACHADOS NEUROBIOLÓGICOS

**INTRODUÇÃO:** A terapia cognitivo-comportamental (TCC) tem sido recomendada em diversas *guidelines* internacionais como a intervenção psicoterapêutica padrão de ouro para pacientes com esquizofrenia. Esta revisão tem como objetivo fornecer uma visão global sobre os avanços recentes da TCC na esquizofrenia.

**MÉTODOS:** Para esta revisão narrativa foi realizada uma busca eletrônica na PubMed/MEDLINE, Web of Science e Cochrane Database utilizando as palavras-chave: “schizophrenia”, “psychosis”, “cognitive-behavioral therapy”, “CBT” e “psychotherapy”.

**RESULTADOS:** Várias revisões sistemáticas suportam a eficácia da TCC na redução a curto e longo prazo dos sintomas positivos e negativos da esquizofrenia. Na última década, a TCC tem sido aplicada a indivíduos com alto risco de psicose, sendo também exploradas abordagens inovadoras na sua utilização (curta duração, *web-based*, autogestão). Redes neurais responsáveis por funções cognitivas de nível superior têm sido associadas a respostas positivas após TCC para esquizofrenia. Existe ainda evidência preliminar que a TCC promove a ativação de zonas pré-frontais responsáveis pela modulação *top-down* face a ameaças sociais.

**CONCLUSÃO:** Na última década, a TCC para esquizofrenia tem explorado novos desfechos, intervindo em populações agudas e pré-clínicas e utilizado métodos alternativos para alcançar mais pacientes e reduzir custos. O perfil neurocognitivo dos pacientes aparenta ter um papel crítico na resposta ao tratamento, pelo que combinar a TCC com reabilitação cognitiva poderá potencializar os seus efeitos terapêuticos. Apesar da TCC ser uma prática recomendada para a esquizofrenia, estudos futuros usando protocolos inovadores e explorando preditores e desfechos relacionados com o cérebro poderão possibilitar que esta intervenção seja mais eficaz, personalizável e alcance o máximo número de pacientes possível.

**PALAVRAS-CHAVE:** terapia cognitivo-comportamental; esquizofrenia; psicose; neuroplasticidade

## ■ REFERENCES

1. Hofmann SG, Wu JQ, Boettcher H. Effect of cognitive-behavioral therapy for anxiety disorders on quality of life: a meta-analysis. *J Consult Clin Psychol.* 2014;82(3):375-91. <http://dx.doi.org/10.1037/a0035491>.
2. Hofmann SG, Smits JA. Cognitive-behavioral therapy for adult anxiety disorders: a meta-analysis of randomized placebo-controlled trials. *J Clin Psychiatry.* 2008;69(4):621-32.

3. Olatunji BO, Davis ML, Powers MB, Smits JA. Cognitive-behavioral therapy for obsessive-compulsive disorder: a meta-analysis of treatment outcome and moderators. *J Psychiatr Res.* 2013;47(1):33-41. <http://dx.doi.org/10.1016/j.jpsychires.2012.08.020>
4. Butler AC, Chapman JE, Forman EM, Beck AT. The empirical status of cognitive-behavioral therapy: a review of meta-analyses. *Clin Psychol Rev.* 2006;26(1):17-31. <http://dx.doi.org/10.1016/j.cpr.2005.07.003>
5. Twomey C, O'Reilly G, Byrne M. Effectiveness of cognitive behavioural therapy for anxiety and depression in primary care: a meta-analysis. *Fam Pract.* 2015;32(1):3-15. <http://dx.doi.org/10.1093/fampra/cmu060>
6. Kornør H, Winje D, Ekeberg Ø, Weisaeth L, Kirkehei I, Johansen K, et al. Early trauma-focused cognitive-behavioural therapy to prevent chronic post-traumatic stress disorder and related symptoms: a systematic review and meta-analysis. *BMC Psychiatry.* 2008;8:81. <http://dx.doi.org/10.1186/1471-244X-8-81>
7. Szentagotai A, David D. The efficacy of cognitive-behavioral therapy in bipolar disorder: a quantitative meta-analysis. *J Clin Psychiatry.* 2010;71(1):66-72. <http://dx.doi.org/10.4088/JCP.08r04559yel>
8. Beck JS. *Cognitive Therapy: Basics and Beyond.* UK: Guilford Press; 1995.
9. Beck AT, Rush A, Shaw B. *Cognitive Therapy for Depression.* NY, USA: Guilford Press; 1979.
10. Rector NA, Beck AT. Cognitive therapy for schizophrenia: from conceptualization to intervention. *Can J Psychiatry.* 2002;47(1):39-48. <http://dx.doi.org/10.1177/070674370204700107>
11. Muran EM, Motta RW. Cognitive distortions and irrational beliefs in post-traumatic stress, anxiety, and depressive disorders. *J Clin Psychol.* 1993;49(2):166-76. [http://dx.doi.org/10.1002/1097-4679\(199303\)49:2<166::AID-JCLP2270490207>3.0.CO;2-6](http://dx.doi.org/10.1002/1097-4679(199303)49:2<166::AID-JCLP2270490207>3.0.CO;2-6)
12. Beck AT. Thinking and Depression: Idiosyncratic Content and Cognitive Distortions. *Arch Gen Psychiatry.* 1963;9:324-33.
13. Bartczak M, Bokus B. Cognitive representations (Metaphorical Conceptualizations) of past, future, joy, sadness and happiness in depressive and non-depressive subjects: cognitive distortions in depression at the level of notion. *J Psycholinguist Res.* 2015;44(2):159-85. <http://dx.doi.org/10.1007/s10936-014-9286-6>
14. Sears S, Kraus S. I think therefore I am: cognitive distortions and coping style as mediators for the effects of mindfulness meditation on anxiety, positive and negative affect, and hope. *J Clin Psychol.* 2009;65(6):561-73. <http://dx.doi.org/10.1002/jclp.20543>
15. Mehl S, Werner D, Lincoln TM. Does Cognitive Behavior Therapy for psychosis (CBTp) show a sustainable effect on delusions? A meta-analysis. *Front Psychol.* 2015;6:1450. <http://dx.doi.org/10.3389/fpsyg.2015.01450>
16. Garety PA, Kuipers L, Fowler D, Chamberlain F, Dunn G. Cognitive behavioural therapy for drug-resistant psychosis. *Br J Med Psychol.* 1994;67 ( Pt 3):259-71.
17. Haddock G, Tarrrier N, Spaulding W, Yusupoff L, Kinney C, McCarthy E. Individual cognitive-behavior therapy in the treatment of hallucinations and delusions: a review. *Clin Psychol Rev.* 1998;18(7):821-38. [http://dx.doi.org/10.1016/S0272-7358\(98\)00007-5](http://dx.doi.org/10.1016/S0272-7358(98)00007-5)
18. Haddock G, Morrison AP, Hopkins R, Lewis S, Tarrrier N. Individual cognitive-behavioural interventions in early psychosis. *Br J Psychiatry.* 1998;172(Suppl 33):101-6.
19. Kuipers E, Garety P, Fowler D, Dunn G, Bebbington P, Freeman D, et al. London-East Anglia randomised controlled trial of cognitive-behavioural therapy for psychosis. 1: effects of the treatment phase. *Br J Psychiatry.* 1997;171:319-27. <http://dx.doi.org/10.1192/bjp.171.4.319>
20. Moorhead S, Turkington D. The CBT of delusional disorder: the relationship between schema vulnerability and psychotic content. *Br J Med Psychol.* 2001;74(Pt 4):419-30. <http://dx.doi.org/10.1348/0007112011161073>
21. Beck AT, Rector NA, Stolar N, Grant PM. *Schizophrenia - Cognitive theory, research and therapy.* New York: Guilford Publications; 2008.
22. Sarin F, Wallin L. Cognitive model and cognitive behavior therapy for schizophrenia: an overview. *Nord J Psychiatry.* 2014;68(3):145-53. <http://dx.doi.org/10.3109/08039488.2013.789074>
23. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III--the final common pathway. *Schizophr Bull.* 2009;35(3):549-62. <http://dx.doi.org/10.1093/schbul/sbp006>
24. Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry.* 2003;160(1):13-23. <http://dx.doi.org/10.1176/appi.ajp.160.1.13>
25. Kapur S, Mizrahi R, Li M. From dopamine to salience to psychosis-linking biology, pharmacology and phenomenology of psychosis. *Schizophr Res.* 2005;79(1):59-68. <http://dx.doi.org/10.1016/j.schres.2005.01.003>
26. Turkington D, Dudley R. Cognitive behavioral therapy in the treatment of schizophrenia. *Expert Rev Neurother.* 2004;4(5):861-8. <http://dx.doi.org/10.1586/14737175.4.5.861>
27. Chadwick P, Birchwood MJ, Trower P. *Cognitive behavior therapy for severe mental illness - An illustrated guide* Chichester, UK: Wiley; 1996.
28. Chadwick O, Birchwood M, Trower P. *Cognitive Therapy for Delusions, Voices and Paranoia.* Chichester, UK: Wiley; 1996.
29. Fowler D, Garety P, Kulpers E. *Cognitive Behavior Therapy for People with Psychosis: a Clinical Handbook.* Chichester, UK: Wiley; 1995.
30. Wright JH, Turkington D, Kingdon DG, Basco MR. *Cognitive behavior therapy for severe mental illness - An illustrated guide* Washington: American Psychiatric Publishing Inc; 2009.
31. National Institute for Health and Care Excellence (NICE). *Schizophrenia: Full National Clinical Guideline on Core Interventions in Primary and Secondary Care.* In: Royal College of Psychiatrists and the British Psychological Society, London: NICE; 2003.
32. National Institute for Health and Care Excellence (NICE). *Schizophrenia: Core Interventions in the Treatment and Management of Schizophrenia in Adults in Primary and Secondary Care.* London: NICE; 2009.
33. National Institute for Health and Care Excellence (NICE). *Psychosis and schizophrenia in adults: treatment and management.* London: NICE; 2014.
34. Lehman A, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, et al. *American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia.* EUA: American Psychiatric Association; 2004.
35. Dixon LB, Dickerson F, Bellack AS, Bennett M, Dickinson D, Goldberg RW, et al. The 2009 schizophrenia PORT psychosocial treatment recommendations and summary statements. *Schizophr Bull.* 2010;36(1):48-70. <http://dx.doi.org/10.1093/schbul/sbp115>
36. Kreyenbuhl J, Buchanan RW, Dickerson FB, Dixon LB, Schizophrenia PORT. The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2009. *Schizophr Bull.* 2010;36(1):94-103. <http://dx.doi.org/10.1093/schbul/sbp130>
37. Royal Australian and New Zealand College of Psychiatrists (RANZCP). *Clinical practice guidelines for the treatment of schizophrenia and related disorders.* New Zealand. RANZCP; 2004.
38. Öjehagen A, Hansson L, Sandlund M, Gustafsson C, Cruce G, Nyström M, et al. [Effects of psychosocial interventions for people with schizophrenia or bipolar disorder. An overview of systematic reviews. *Socialstyrelsen, Sweden, 2006.*
39. Scottish Intercollegiate Guidelines Network (SIGN). *Management of schizophrenia.* Edinburgh: SIGN; 2013.
40. Etkin A, Pittenger C, Polan HJ, Kandel ER. Toward a neurobiology of psychotherapy: basic science and clinical applications. *J Neuropsychiatry Clin Neurosci.* 2005;17(2):145-58. <http://dx.doi.org/10.1176/jnp.17.2.145>
41. Collerton D. Psychotherapy and brain plasticity. *Front Psychol.* 2013;4:548. <http://dx.doi.org/10.3389/fpsyg.2013.00548>
42. Lynch D, Laws KR, McKenna PJ. Cognitive behavioural therapy for major psychiatric disorder: does it really work? A meta-analytical review of well-controlled trials. *Psychol Med.* 2010;40(1):9-24. <http://dx.doi.org/10.1017/S003329170900590X>
43. Jauhar S, McKenna PJ, Radua J, Fung E, Salvador R, Laws KR. Cognitive-behavioural therapy for the symptoms of schizophrenia: systematic review and meta-analysis with examination of potential bias. *Br J Psychiatry.* 2014;204(1):20-9. <http://dx.doi.org/10.1192/bjp.bp.112.116285>



44. Birchwood M, Michail M, Meaden A, Tarrrier N, Lewis S, Wykes T, et al. Cognitive behaviour therapy to prevent harmful compliance with command hallucinations (COMMAND): a randomised controlled trial. *Lancet Psychiatry*. 2014;1(1):23-33. [http://dx.doi.org/10.1016/S2215-0366\(14\)70247-0](http://dx.doi.org/10.1016/S2215-0366(14)70247-0)
45. Bouchard S, Vallières A, Roy M-A, Maziade M. Cognitive Restructuring in the Treatment of Psychotic Symptoms in Schizophrenia: A Critical Analysis. *Behavior Therapy*. 1996;27(2):257-77. [http://dx.doi.org/10.1016/S0005-7894\(96\)80017-7](http://dx.doi.org/10.1016/S0005-7894(96)80017-7)
46. Sarin F, Wallin L, Widerlöv B. Cognitive behavior therapy for schizophrenia: a meta-analytical review of randomized controlled trials. *Nord J Psychiatry*. 2011;65(3):162-74. <http://dx.doi.org/10.3109/08039488.2011.577188>.
47. Wykes T, Steel C, Everitt B, Tarrrier N. Cognitive behavior therapy for schizophrenia: effect sizes, clinical models, and methodological rigor. *Schizophr Bull*. 2008;34(3):523-37. <http://dx.doi.org/10.1093/schbul/sbm114>
48. Burns AM, Erickson DH, Brenner CA. Cognitive-behavioral therapy for medication-resistant psychosis: a meta-analytic review. *Psychiatr Serv*. 2014;65(7):874-80. <http://dx.doi.org/10.1176/appi.ps.201300213>.
49. Gould RA, Mueser KT, Bolton E, Mays V, Goff D. Cognitive therapy for psychosis in schizophrenia: an effect size analysis. *Schizophr Res*. 2001;48(2-3):335-42. [http://dx.doi.org/10.1016/S0920-9964\(00\)00145-6](http://dx.doi.org/10.1016/S0920-9964(00)00145-6)
50. Zimmermann G, Favrod J, Trieu VH, Pomini V. The effect of cognitive behavioral treatment on the positive symptoms of schizophrenia spectrum disorders: a meta-analysis. *Schizophr Res*. 2005;77(1):1-9. <http://dx.doi.org/10.1016/j.schres.2005.02.018>
51. van der Gaag M, Valmaggia LR, Smit F. The effects of individually tailored formulation-based cognitive behavioural therapy in auditory hallucinations and delusions: a meta-analysis. *Schizophr Res*. 2014;156(1):30-7. <http://dx.doi.org/10.1016/j.schres.2014.03.016>
52. Rector NA, Beck AT. Cognitive behavioral therapy for schizophrenia: an empirical review. *J Nerv Ment Dis*. 2001;189(5):278-87. <http://dx.doi.org/10.1097/00005053-200105000-00002>
53. Velthorst E, Koeter M, van der Gaag M, Nieman DH, Fett AK, Smit F, et al. Adapted cognitive-behavioural therapy required for targeting negative symptoms in schizophrenia: meta-analysis and meta-regression. *Psychol Med*. 2015;45(3):453-65. <http://dx.doi.org/10.1017/S0033291714001147>.
54. Pilling S, Bebbington P, Kuipers E, Garety P, Geddes J, Orbach G, et al. Psychological treatments in schizophrenia: I. Meta-analysis of family intervention and cognitive behaviour therapy. *Psychol Med*. 2002;32(5):763-82. <http://dx.doi.org/10.1017/S0033291702005895>
55. Turner DT, van der Gaag M, Karyotaki E, Cuijpers P. Psychological interventions for psychosis: a meta-analysis of comparative outcome studies. *Am J Psychiatry*. 2014;171(5):523-38. <http://dx.doi.org/10.1176/appi.ajp.2013.13081159>.
56. Stafford MR, Mayo-Wilson E, Loucas CE, James A, Hollis C, Birchwood M, et al. Efficacy and safety of pharmacological and psychological interventions for the treatment of psychosis and schizophrenia in children, adolescents and young adults: a systematic review and meta-analysis. *PLoS One*. 2015;10(2):e0117166. <http://dx.doi.org/10.1371/journal.pone.0117166>
57. Jones C, Hacker D, Cormac I, Meaden A, Irving CB. Cognitive behaviour therapy versus other psychosocial treatments for schizophrenia. *Cochrane Database Syst Rev*. 2012;4:CD008712. <http://dx.doi.org/10.1002/14651858.CD008712.pub2>
58. Orfanos S, Banks C, Priebe S. Are Group Psychotherapeutic Treatments Effective for Patients with Schizophrenia? A Systematic Review and Meta-Analysis. *Psychother Psychosom*. 2015;84(4):241-9. <http://dx.doi.org/10.1159/000377705>
59. Newton-Howes G, Wood R. Cognitive behavioural therapy and the psychopathology of schizophrenia: systematic review and meta-analysis. *Psychol Psychother*. 2013;86(2):127-38. <http://dx.doi.org/10.1111/j.2044-8341.2011.02048.x>
60. Hutton P. Cognitive-behavioural therapy for schizophrenia: a critical commentary on the Newton-Howes and Wood meta-analysis. *Psychol Psychother*. 2013;86(2):139-45. <http://dx.doi.org/10.1111/papt.12009>
61. Hazell CM, Hayward M, Cavanagh K, Strauss C. A systematic review and meta-analysis of low intensity CBT for psychosis. *Clin Psychol Rev*. 2016;45(April):183-92. <http://dx.doi.org/10.1016/j.cpr.2016.03.004>.
62. Naeem F, Farooq S, Kingdon D. Cognitive behavioral therapy (brief vs standard duration) for schizophrenia. *Schizophr Bull*. 2014;40(5):958-9. <http://dx.doi.org/10.1093/schbul/sbu113>.
63. Gottlieb JD, Romeo KH, Penn DL, Mueser KT, Chiko BP. Web-based cognitive-behavioral therapy for auditory hallucinations in persons with psychosis: a pilot study. *Schizophr Res*. 2013;145(1-3):82-7. <http://dx.doi.org/10.1016/j.schres.2013.01.002>.
64. Naeem F, Johal R, McKenna C, Rathod S, Ayub M, Lecomte T, et al. Cognitive Behavior Therapy for psychosis based Guided Self-help (CBTp-GSH) delivered by frontline mental health professionals: Results of a feasibility study. *Schizophr Res*. 2016;173(1-2):69-74. <http://dx.doi.org/10.1016/j.schres.2016.03.003>.
65. Marshall M, Rathbone J. Early intervention for psychosis. *Cochrane Database Syst Rev*. 2006(4):CD004718. <http://dx.doi.org/10.1002/14651858.CD004718.pub2>
66. Fuser-Poli P, Borgwardt S, Bechdolf A, Addington J, Riecher-Rössler A, Schultze-Lutter F, et al. The psychosis high-risk state: a comprehensive state-of-the-art review. *JAMA Psychiatry*. 2013;70(1):107-20. <http://dx.doi.org/10.1001/jamapsychiatry.2013.269>
67. Hutton P, Taylor PJ. Cognitive behavioural therapy for psychosis prevention: a systematic review and meta-analysis. *Psychol Med*. 2014;44(3):449-68. <http://dx.doi.org/10.1017/S0033291713000354>.
68. van der Gaag M, Smit F, Bechdolf A, French P, Linszen DH, Yung AR, et al. Preventing a first episode of psychosis: meta-analysis of randomized controlled prevention trials of 12 month and longer-term follow-ups. *Schizophr Res*. 2013;149(1-3):56-62. <http://dx.doi.org/10.1016/j.schres.2013.07.004>.
69. Preti A, Cella M. Randomized-controlled trials in people at ultra high risk of psychosis: a review of treatment effectiveness. *Schizophr Res*. 2010;123(1):30-6. <http://dx.doi.org/10.1016/j.schres.2010.07.026>.
70. Barrowclough C, Haddock G, Wykes T, Beardmore R, Conrod P, Craig T, et al. Integrated motivational interviewing and cognitive behavioural therapy for people with psychosis and comorbid substance misuse: randomised controlled trial. *BMJ*. 2010;341:c6325. <http://dx.doi.org/10.1136/bmj.c6325>.
71. Drake RJ, Day CJ, Picucci R, Warburton J, Larkin W, Husain N, et al. A naturalistic, randomized, controlled trial combining cognitive remediation with cognitive-behavioural therapy after first-episode non-affective psychosis. *Psychol Med*. 2014;44(9):1889-99. <http://dx.doi.org/10.1017/S0033291713002559>
72. Morrison AP, Pyle M, Chapman N, French P, Parker SK, Wells A. Metacognitive therapy in people with a schizophrenia spectrum diagnosis and medication resistant symptoms: a feasibility study. *J Behav Ther Exp Psychiatry*. 2014;45(2):280-4. <http://dx.doi.org/10.1016/j.jbtep.2013.11.003>
73. Kukla M, Davis LW, Lysaker PH. Cognitive behavioral therapy and work outcomes: correlates of treatment engagement and full and partial success in schizophrenia. *Behav Cogn Psychother*. 2014;42(5):577-92. <http://dx.doi.org/10.1017/S1352465813000428>
74. Weingarten CP, Strauman TJ. Neuroimaging for psychotherapy research: current trends. *Psychother Res*. 2015;25(2):185-213. <http://dx.doi.org/10.1080/10503307.2014.883088>
75. Kumari V, Peters ER, Fannon D, Antonova E, Premkumar P, Anilkumar AP, et al. Dorsolateral prefrontal cortex activity predicts responsiveness to cognitive-behavioral therapy in schizophrenia. *Biol Psychiatry*. 2009;66(6):594-602. <http://dx.doi.org/10.1016/j.biopsych.2009.04.036>
76. Kumari V, Antonova E, Fannon D, Peters ER, Ffytche DH, Premkumar P, et al. Beyond dopamine: functional MRI predictors of responsiveness to cognitive behaviour therapy for psychosis. *Front Behav Neurosci*. 2010;4:4. <http://dx.doi.org/10.3389/neuro.08.004.2010>

77. Kumari V, Premkumar P, Fannon D, Aasen I, Raghuvanshi S, Anilkumar AP, et al. Sensorimotor gating and clinical outcome following cognitive behaviour therapy for psychosis. *Schizophr Res.* 2012;134(2-3):232-8. <http://dx.doi.org/10.1016/j.schres.2011.11.020>.
78. Premkumar P, Fannon D, Kuipers E, Peters ER, Anilkumar AP, Simmons A, et al. Structural magnetic resonance imaging predictors of responsiveness to cognitive behaviour therapy in psychosis. *Schizophr Res.* 2009;115(2-3):146-55. <http://dx.doi.org/10.1016/j.schres.2009.08.007>.
79. Premkumar P, Parbhakar VA, Fannon D, Lythgoe D, Williams SC, Kuipers E, et al. N-acetyl aspartate concentration in the anterior cingulate cortex in patients with schizophrenia: a study of clinical and neuropsychological correlates and preliminary exploration of cognitive behaviour therapy effects. *Psychiatry Res.* 2010;182(3):251-60. <http://dx.doi.org/10.1016/j.pscychres.2010.02.008>.
80. Premkumar P, Fannon D, Sapara A, Peters ER, Anilkumar AP, Simmons A, et al. Orbitofrontal cortex, emotional decision-making and response to cognitive behavioural therapy for psychosis. *Psychiatry Res.* 2015;231(3):298-307. <http://dx.doi.org/10.1016/j.pscychres.2015.01.013>.
81. Kumari V, Fannon D, Peters ER, Ffytche DH, Sumich AL, Premkumar P, et al. Neural changes following cognitive behaviour therapy for psychosis: a longitudinal study. *Brain.* 2011;134(Pt 8):2396-407. <http://dx.doi.org/10.1093/brain/awr154>.
82. Mason L, Peters ER, Dima D, Williams SC, Kumari V. Cognitive Behavioral Therapy Normalizes Functional Connectivity for Social Threat in Psychosis. *Schizophr Bull.* 2016;42(3):684-92. <http://dx.doi.org/10.1093/schbul/sbv153>.
83. de Souza Moura AM, Lamego MK, Paes F, Ferreira Rocha NB, Simoes-Silva V, Rocha SA, et al. Effects of Aerobic Exercise on Anxiety Disorders: A Systematic Review. *CNS Neurol Disord Drug Targets.* 2015;14(9):1184-93. <http://dx.doi.org/10.2174/187152731566615111121259>
84. Freire RC, Machado S, Arias-Carrión O, Nardi AE. Current pharmacological interventions in panic disorder. *CNS Neurol Disord Drug Targets.* 2014;13(6):1057-65.
85. Guimarães FMCL, Nardi AE, Cardoso A, Valença AM, da Conceição EG, King ALS. Cognitive behavioral therapy treatment for smoking alcoholics in outpatients. *MedicalExpress.* 2014;1(6):336-340. <http://dx.doi.org/10.5935/MedicalExpress.2014.06.08>
86. Wykes T. Cognitive-behaviour therapy and schizophrenia. *Evidence Based Mental Health.* 2014;17(3):67-8. <http://dx.doi.org/10.1136/eb-2014-101887>.
87. Kurtz MM, Gagen E, Rocha NB, Machado S, Penn DL. Comprehensive treatments for social cognitive deficits in schizophrenia: A critical review and effect-size analysis of controlled studies. *Clin Psychol Rev.* 2016;43:80-9. <http://dx.doi.org/10.1016/j.cpr.2015.09.003>.
88. Kurtz MM, Moberg PJ, Gur RC, Gur RE. Approaches to cognitive remediation of neuropsychological deficits in schizophrenia: a review and meta-analysis. *Neuropsychol Rev.* 2001;11(4):197-210. <http://dx.doi.org/10.1023/A:1012953108158>
89. Grynspan O, Perbal S, Pelissolo A, Fossati P, Jouvent R, Dubal S, et al. Efficacy and specificity of computer-assisted cognitive remediation in schizophrenia: a meta-analytical study. *Psychol Med.* 2011;41(1):163-73. <http://dx.doi.org/10.1017/S0033291710000607>
90. Thorsen AL, Johansson K, Løberg EM. Neurobiology of cognitive remediation therapy for schizophrenia: a systematic review. *Front Psychiatry.* 2014;5:103. <http://dx.doi.org/10.3389/fpsy.2014.00103>.
91. Isaac C, Januel D. Neural correlates of cognitive improvements following cognitive remediation in schizophrenia: a systematic review of randomized trials. *Socioaffect Neurosci Psychol.* 2016;6:30054. <http://dx.doi.org/10.3402/snp.v6.30054>.
92. Wei YY, Wang JJ, Yan C, Li ZQ, Pan X, Cui Y, et al. Correlation Between Brain Activation Changes and Cognitive Improvement Following Cognitive Remediation Therapy in Schizophrenia: An Activation Likelihood Estimation Meta-analysis. *Chin Med J (Engl).* 2016;129(5):578-85. <http://dx.doi.org/10.4103/0366-6999.176983>
93. Kurtz MM. Cognitive remediation for schizophrenia: current status, biological correlates and predictors of response. *Expert Rev Neurother.* 2012;12(7):813-21. <http://dx.doi.org/10.1586/ern.12.71>.
94. Illes J, Lombera S, Rosenberg J, Arnow B. In the mind's eye: provider and patient attitudes on functional brain imaging. *J Psychiatr Res.* 2008;43(2):107-14. <http://dx.doi.org/10.1016/j.jpsychires.2008.02.008>.
95. Mayberg HS. Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. *Br Med Bull.* 2003;65:193-207. <http://dx.doi.org/10.1093/bmb/65.1.193>
96. Hauner KK, Mineka S, Voss JL, Paller KA. Exposure therapy triggers lasting reorganization of neural fear processing. *Proc Natl Acad Sci U S A.* 2012;109(23):9203-8. <http://dx.doi.org/10.1073/pnas.1205242109>.