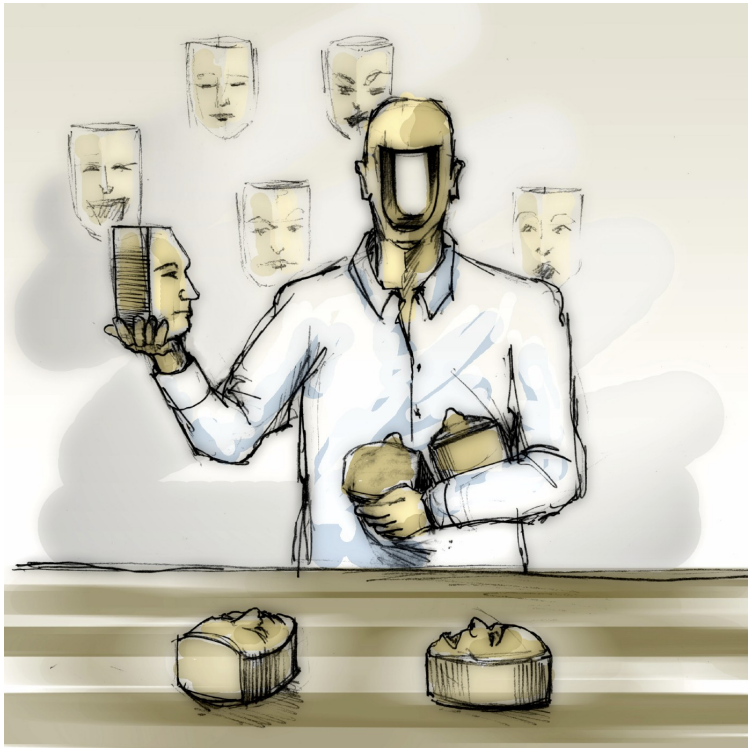
# Impulsivity in bipolar disorder and schizophrenia: a review on functional imaging studies



**Erik Oudman (F.A. Oudman)**

**Supervisors:**

**Florian Bootsman**

**Neeltje E.M. van Haren**

**Koen B. Böcker**

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## Abstract

Pathological impulsivity is one of the most often reported characteristics of bipolar and schizophrenic patients. Besides impulsivity, symptoms of both diseases are seen in schizoaffective disorder and there are many genetic, structural brain and neurocognitive communalities between the two disorders. Therefore, we conducted a PUBMED search on studies investigating impulsivity by means of functional neuroimaging (fMRI and PET) during the Stroop and Continuous Performance Paradigm in schizophrenia and bipolar disorder. A total of 48 articles matching our criteria were identified and used as the basis for this review. Bipolar patients far less often showed decreased performance (1 out of 16 articles) relative to schizophrenia patients (18 out of 32 articles) when compared to controls. Moreover, in schizophrenia, accuracy deficits were found to be both the result of inattention as well as impulsivity related problems. We argue that schizophrenia patients are more hampered on task performance and related brain activation than bipolar patients, since the right middle frontal cortex, right ventrolateral prefrontal cortex and anterior cingulate cortex are reliably found to be hypoactivated in schizophrenia while hypoactivation is often restricted to the right ventrolateral prefrontal cortex in bipolar disorder. However, we suggest that the results of this study merely reflect a general finding on executive functioning in bipolar disorder and schizophrenia, which is supported by correspondence to recent literature on executive functioning and morphological alterations in schizophrenia and bipolar disorder. Besides, this review elaborates on methodological problems such as IQ differences between groups, medication intake and lack of statistical power. We argue these characteristics to be crucial confounders and recommend the application of novel paradigms to further investigate impulsivity in bipolar disorder and schizophrenia.

## Introduction

Impulsivity has been defined as 'behaviour that is performed with little or inadequate forethought (Evenden, 1999). In pathological form, this behaviour is dysfunctional and associated with actions that are criminal and violent, physically harmful, or inappropriate with respect to social standards (Dickman, 1990). Impulsivity is a central feature to a multitude of psychiatric disorders (Moeller et al., 2001). Most common are the reports of impulsivity in Attention Deficit Hyperactivity Disorder (ADHD), drug addiction and psychopathy (Sher and Trull, 1994; Tannock, 1998, Jentsch et al., 1999). Specifically, pathological impulsivity is also one of the most often reported characteristics of bipolar disorder and schizophrenia (Moeller et al., 2001; Swann et al., 2001; Kumari et al., 2008). Moderating pathological impulsivity is of great relevance for all psychiatric disorders since pathological impulsivity is associated with considerable social and job dysfunction, accidents, suicide, aggression, criminality and excessive spending. Additionally, it prevents patients from engaging in, or accomplishing full benefit from treatment (Hollander and Evers, 2001; Hoptman et al., 2004; Roiser et al., 2008).

Historically, impulsivity has been linked to frontal lobe dysfunction, associated with problems in inhibition of dysfunctional behaviour (Damasio et al., 1990; Horn et al., 2003). This underlying neural correlate of pathological impulsivity was replicated as a reduction in prefrontal metabolism (Raine et al., 1997), and later as a dysfunction in dorsolateral prefrontal cortex activation during functional magnetic resonance imaging (Valdes et al., 2006). However, the exact neural network involved in pathological impulsivity is still largely unknown. Therefore, studying impulsivity in vivo by means of functional brain imaging can provide novel insides into the underlying neural disturbance of pathological impulsivity (Rubia, 2001).

Two frequently adopted paradigms intended to give a reflection of impulsivity are the Go No-Go (Continuous Performance) and Stroop paradigm. The Go No-Go paradigm is besides impulsivity often applied to measure selective and sustained attentional processes (Rosvold et al., 1956; Cornblatt and Malhotra, 2001). Here, subjects monitor a sequence of stimuli and are instructed to refrain from responding to one of the stimuli but respond to all the others (CPT-X), respond to identical pairs (CPT-IP), or only respond to one specific stimulus when a contextual cue is presented before the stimulus (CPT-AX) (Bellani & Bramilla, 2008; Perlstein et al., 2003). Studies on healthy subjects suggest the involvement of right ventral frontal and orbitofrontal brain regions to be the most crucial to response inhibition (Konishi et al., 1999; Liddle et al., 2001; Hazeltine et al., 2001;

Horn et al., 2003). Other important brain regions are the anterior cingulate cortex, the supplementary motor area, parietal cortices and basal ganglia (Humberstone et al., 1997; Cohen et al., 1998; Rubia et al.,2001; Liddle et al., 2001; Hazeltine et al., 2001; Watanabe et al., 2002; Honey et al., 2005; Ogg et al., 2008). Stroop interference is the slowing that occurs when a colour word (in letters) conflicts with the required naming of an ink colour (Stroop, 1935; MacLeod, 1991). During fMRI or PET, participants are required to button press for congruent (a red word written in red) or incongruent stimuli (a red word written in green) instead of vocal response. On a neurophysiological level studies on healthy subjects suggest the involvement of the anterior cingulate cortex, the right middle frontal cortex, the left inferior frontal cortex during monitoring in the Stroop task (Zysset et al., 2001, Mitchell, 2007; Derfuss et al., 2005).

To date, impulsivity in schizophrenia and bipolar disorder has never been jointly investigated in studies applying functional neuroimaging. This is remarkable, since the comparison can yield important results in more than one way: First, the comparison of impulsivity in bipolar disorder and schizophrenia is essential to address the specificity of the underlying neurocognitive mechanisms (Walker et al., 2002). Because recent evidence indicates that bipolar disorder and schizophrenia share many elements of pathology, cross-comparison between both disorders is an essential step in novel approaches to classification and the search for common causes (Fischer & Carpenter, 2009; Ellison-Wright & Bullmore, 2010). Second, whereas behavioural, anatomical and genetic studies already investigated communalities between bipolar disorder and schizophrenia, hemodynamic studies never did this systematically. Earlier, both diseases were already found to share a common genetic basis and co-aggregation in families was reported (Williams et al., 2009; Craddock et al., 2006; Moskvina et al., 2009; Lichtenstein et al., 2009; Van Snellenberg & de Candia, 2009). Furthermore, both disorders are often diagnosed co-morbid and schizoaffective disorder forms an important link between both disorders (Taylor, 1992; APA, 2002). Also, structural brain abnormalities show resemblance and neurocognitive profiles are partially shared (McIntosh et al., 2005; Reichenberg et al., 2009). However, whether the underlying brain metabolism and activation is shared remains a question. Third, getting a better understanding of impulsivity in both psychiatric disorders can help to emphasize on the nature of impulsivity in treatment strategies. Recently, self-report scales of impulsivity were found to have a differential relationship to depression and bipolar disorder (Swann et al., 2008). A lack of planning was particularly related to depression whereas motor-

impulsivity related to problems in inhibiting behaviour was more specific to bipolar disorder. By finding specificities in neural functioning and behaviour, future treatment techniques may apply functional imaging as a successful diagnostic tool.

The purpose of this review is therefore to investigate the human neurophysiological correlates underlying impulsivity in schizophrenia and bipolar disorder. We focus on findings from task-related neuroimaging studies that applied hemodynamic brain techniques (fMRI, PET) to investigate impulsivity during the frequently applied rapid decision paradigms which emphasize on the inhibitory and attentional aspects of impulsivity (Dougherty et al., 2003). Besides alterations in brain activations, this review examines the relation between task performance and brain activation or metabolism. By giving an overview of the neurophysiological findings on impulsivity in schizophrenia and bipolar disorder, this review aims to provide evidence for communalities and divergences in the neurophysiological basis for impulsivity in these two illnesses.

## Methods

We conducted a search for English papers published in journals from 1995 onwards using PubMed. Articles that did not use functional Magnetic Resonance Imaging (fMRI) or Positron Emission Tomography (PET) were excluded. Also, reviews of the literature were not included. Therefore, all included articles are between-group design studies on patients with schizophrenia or bipolar patients compared to healthy controls. We decided to focus primarily on the promising and most frequently applied rapid decision paradigms used to measure state-dependent changes in impulsivity (Dougherty et al., 2003). By far the most frequently used paradigms to measure response inhibition and impulsivity in schizophrenia and bipolar disorder are the Go No-Go or Continuous Performance Paradigm (CPT) and the Stroop Paradigm. Both paradigms correspond to specific features of impulsivity: In the Go No-Go paradigm, participants need to respond to some stimuli, but inhibit response to other stimuli. This requires the ability to inhibit 'Go' responses during some of the trials. Two operationalizations of this paradigm are response control and the inhibition of prepotent responses. Often, characteristics of diminished response control are measured as longer reaction times and a higher number of commission errors (false positives), while omission errors (misses) are thought to reflect inattention (Halperin et al., 1991; Swann et al., 2003. In the Stroop Paradigm participants name the color of color-incongruent and congruent words. Naming the color of the word takes longer and is more prone to errors if the color is incongruent as compared to congruent. During incongruent trials, more interference results from the inability to inhibit the word reading. Here, longer reaction times and more errors are observed related to problems on inhibitory control (Levy & Anderson, 2002). Two crucial operationalizations of this paradigm are therefore the inhibition of inappropriate responses and interference.

Since many authors refer to the selected paradigms as being representative of different concepts, we selected the search terms: 'CPT schizophrenia'. 'CPT bipolar', 'CPT-AX schizophrenia', 'CPT-AX bipolar' (CPT-AX is one specific version of the CPT), 'Go No Go schizophrenia', 'Go No Go bipolar'; 'Stroop schizophrenia' and 'Stroop bipolar'. A total of 48 articles matching our criteria were identified and subsequently used as the basis for this review.

# Functional Neuroimaging of impulsivity in Bipolar Disorder

**Table 1.** Studies applying a Go No-Go or Stroop task to investigate differences in brain activation between bipolar disorder and healthy controls.

| Authors | Task | N | Phase | Illness Dur. Y (SD) | Meds | Task Perform. P v.s. C | Brain activity P v.s. C . (Brodmann areas) |
|---|---|---|---|---|---|---|---|
| Altshuler et al., 2005 | CPT-X | C= 13 P= 11 | Manic | | 7 med. / 4 not | Commissions & Omission Errors n.s. | **Hypoactivation** R-orbitofrontal (47), R- hippocampus, L-cingulate (24) |
| Mazzola-Pomietto et al., 2009 | CPT-X | C= 16 P= 16 | Manic | 10.8 (12.9) | All med | Commissions & Omission Errors n.s. RT increased | **Hypoactivation** in L-VLPFC (47) & R-VLPFC (47) |
| Kaladjjan et al., 2009b | CPT-X | C= 10 P= 10 (longit udinal) | Manic & Euthymic | 14.2 (14.6) | All med | Commissions & Omission Errors n.s. RT increased | Euthymic vs Manic: **Hypoactivation** in L-amygdala **Hyperactivation** Posterior cingulate (7/31) |
| Strakowski et al.,2004 | CPT-IP | C= 10 P= 10 | Euthymic | 2,2 (1.9) | Off Med | Commissions & Omission Errors n.s. | **Hypoactivation** in L-MFC (11), L-fusiform (20) **Hyperactivation** limbic, paralimbic (34), L-VPFC (10/47), R-IFC. (13/47), R-Visual association areas (18,19,39) |
| Nelson et al.,2007 | CPT-X | C= 17 P1= 20 , P2=5 | P1 Euthymic, P2:Hypomanic (14y) | | 52% med | Commissions & Omission Errors n.s. Change accuracy decreased | P1 & P2: **Hyperactivation** in L-DLPFC (8), R-DLPFC (6) and M1 (6/4) (for success) |
| Kaladjjan et al., 2009a | CPT-X | C= 20 P= 20 | Euthymic | 12,9 (11) | All -1 med | Commissions & Omission Errors n.s. | **Hypoactivation** in L-frontopolar (10), bilateral amygdala |
| Wessa et al.,2007 | CPT-X (faces) | C= 17 P= 17 | Euthymic | 21.9 (12.7) | 15 med | Commissions & Omission Errors n.s. | No difference for Go No-Go |
| Welander-Vatn et al., 2009 | CPT-X (V) | C= 28 P= 27 | Bipolar disorder 2 | 15.1 | Mix | Commissions & Omission Errors n.s. | No difference for Go No-Go |
| Brooks et al., 2006 | CPT-X | C=27 P =8 | Depressed | . | Off Med | Comissions, & omissions n.s. RT increased | Bilateral subgenual prefrontal cortex (26,27,28) correlates with omissions. In C not. |
| Blumberg et al., 2003a | Stroop | c 10 p 10 | adolescent BD | | 3 unmed | RT incongruent & congruent + errors n.s. | **Hyperactivation** in inferior thalamus and L-putamen during entire task |
| Blumberg et al., 2003b | Stroop | C 20 M 11 D/E 10 | P1 Manic M P2 Depress./Euth. (D/E) | | 13 unmed | RT incongruent & congruent + errors n.s. | **Hypoactivation** in R-VPFC (47) in mania, **Hyperactivation** L-VPFC (47) in depression (vs euthymic), / association R-VLPFC (47) & mood |
| Gruber et al., 2004 | Stroop | C 12 P14 | Euthymic 86% | 15.2 (6.7) | 3 unmed | RT incongruent Slower. congruent + errors n.s. | **Hypoactivation** in R-ACC (24/32), **Hyperactivation** DLPFC (46/10) (during interference) |
| Strakowski et al., 2005 | Stroop | C 16 P 16 | Euthymic | 4.8 (4.4) | 50%med / 50% unmed | P more false alarms. RT n.s. | **Hypoactivation** in R-MFC (10) cerebellum, bilateral temporal cortex (21), L-putamen in euthymic. Medicated patients displayed increases in activation for the ACC and DLPFC vs unmedicated |
| Roth et al., 2006 | Stroop | C 11 P 11 | Mixed | | All med | RT incongruent & congruent + errors n.s. | **Hypoactivation** in R-IFC (13) R-MFC (6), R-Pons, L-cingulate (31), L-parahippoc. (35), L-fusiform (19). |
| Kronhaus et al., 2006 | Stroop | C 11 P 10 | Euthymic & Subsyndr. | 16.8 (4.5) | All med | RT incongruent and congruent Slower. + errors n.s. | **Hypoactivation** in L-VLPFC (8), L-fusiform (10), L-DLPFC (5), Precuneus (3). **Hyperactivation** L-orbitofrontal (10), L-MFC (5). |
| Marchand et al., 2007 | Stroop | C 15 P 14 | Depressed | 27.1 (12.3) | All med | RT incongruent & congruent + errors n.s. | **Hypoactivation** in L- and R-posterior cingulate (24), L-precentral gyrus (3/4), L- and R-striatum |

C = controls , P = patients, RT = Reaction Times, Off Med = Off medication, med = medicated , Mix = mixed medicated/ nonmedicated, unmed = unmedicated. L- = left , R- = Right, SFC = Superior Frontal Cortex, MFC = Middle Frontal Cortex, IFC = Inferior Frontal Cortex, DLPFC = Dorsolateral Prefrontal Cortex, ACC = Anterior Cingulate Cortex, SPG = Superior Parietal Gyrus, IPG = Inferior Parietal Gyrus, PCG = postcentral gyrus, STC = Superior Temporal Cortex, Depress. = Depressed., Euth. = Euthymic , Subsyndr. = Subsyndromal

*Go No-Go findings in bipolar patients*

As far as we know, nine studies employed a Go No-Go paradigm during fMRI or PET in bipolar disorder (table 1, upper part). Three of these focussed on the manic phase of the disorder (Altshuler et al., 2005; Mazzola-Pomietto et al., 2009, Kaladjian et al., 2009a). During this phase patients showed an abnormally elevated or irritable mood, rapid speech, racing thoughts, decreased need for sleep, hyper sexuality, euphoria, impulsiveness, grandiosity, and increased interest in goal-directed activities (APA, 2000). All three studies showed comparable performance characteristics of the patient group and control group without any significant difference on commission (false alarms) or omission errors (misses). However, all three studies also found evidence for small, non significant decreases in performance for the patient group. The accuracy measurements in these three studies were not found to be directly related to differences in brain activation. Two out of three studies on manic patients found evidence for decreased activations in the right ventrolateral prefrontal cortex (VLPFC) or lateral orbitofrontal cortex (both referred to as brodmann area 47) in manic patients as compared to controls (Altshuler et al., 2005; Mazzola-Pomietto et al., 2009). However, both studies showed some complicating factors. Altshuler et al. (2005) included four unmedicated patients, but did not investigate possible differences between the medicated and unmedicated patients. Mazzola-Pomietto et al. (2009) included a consistently medicated patient group, but was hindered by a high drop-out rate (56% of the patient group), which makes it possible that the eventual study group is not entirely representative for the population of manic patients. Besides the finding of decreased activation in the right VLPFC, one study found evidence for attenuated cingulate response (Altshuler et al., 2005).

In addition to the studies on mania, five studies focussed on euthymic bipolar patients (Strakowski et al., 2004; Nelson et al., 2007, Wessa et al., 2007; Kaladjian et al., 2009b). Euthymic bipolar patients are in a neutral mood in absence of a manic or depressed cycle (APA, 2000). None of the studies reported significant differences with respect to measurements of omissions and commissions. However, one study observed that healthy subjects showed increased alertness, measured as enhanced accuracy the trial after the required response changed. This characteristic of preparedness was less likely to occur in the bipolar patient group (Nelson et al., 2007). Furthermore, all studies found evidence for slight, nonsignificant worsening of performance in the patient group compared with the control group. The neurophysiological results of these studies are less consistent than studies on manic patients. Two studies found evidence for

hyperactivations during the inhibition of responses (Strakowski et al., 2004; Nelson et al., 2007). The first measured an increase in brain activation in frontal, limbic, paralimbic, and occipital areas. However, the results might be incomparable with the other studies on euthymic patients since the patient group in this study had a shorter illness duration than the other four studies presented. Furthermore, this is the only study on bipolar patients that found evidence for a direct correlation between performance and activation of the bilateral VLPFC and left inferior frontal cortex. The study by Nelson et al. (2007) found hyperactivation in the left dorsolateral prefrontal cortex and motor cortex. Interestingly, both studies included only unmedicated patients in their patient group. The studies that did not find evidence for hyperactivations seem harder to interpret. For example, Wessa et al. (2007) applied the Go No-Go paradigm as cognitive control task, while the primary focus of this article was on a different paradigm. This makes it possible that differences between the patient and control group remained undetected, because of a different focus. Furthermore, the authors reported little information on the analysis of the Go No-Go data. Also, Welander-Vatn et al. (2009), who recruited a group of twenty-seven bipolar 2 participants, did not find any differences between the patient group and control group on brain activation and performance. In this study however, little information was available about the control subjects included in this study. The hypoactivation in the left frontopolar and bilateral amygdala found in a recent study (Kaladjian et al. 2009), are the first reports on hypoactivations in euthymic patients during this paradigm. This possibly highlights the importance of proper matching criteria to elucidate minor changes in brain activation between bipolar patients and controls.

To date, only one study focussed on depressed bipolar individuals. In this study, Brooks et al. (2006) compared a relatively small patient group of 8 participants to 27 control subjects. No significant differences between the groups were found. However, patient's brain activation in the subgenual prefrontal cortex correlated with accurate task performance, while for healthy controls this was not the case. As this is the first study on bipolar depressed patients applying a Go No-Go paradigm, results are difficult to interpret.

*Stroop Paradigm findings in bipolar disorder*

To date seven studies (table 1, lower part) investigated the neurophysiological correlates of Stroop interference by means of fMRI and PET in bipolar disorder. Four of them found evidence for hypoactivation in the frontal cortex in patients as compared to healthy

controls (Blumberg et al., 2003b, Strakowski et al., 2005; Roth et al., 2006; Kronhaus et al., 2006). Three out of four studies localised the hypoactivation of the frontal cortex, also referred to as hypofrontality, in the right frontal cortex, whereas the exact part of the frontal cortex that is found to be hypoactivated differs between studies. (Blumberg et al., 2003b, Strakowski et al., 2005; Roth et al., 2006). Two of the studies that did not find evidence for hypofrontality showed nevertheless evidence for hypoactivations in the cingulate cortex (Gruber et al., 2004; Marchand et al., 2007).

Initially, these results seem to provide a clear account of hypofrontality and some evidence for diminished response in the cingulate cortex. However, the four studies all used a patient group in a different phase of the disease (manic, euthymic, mixed and euthymic/subsyndromal respectively). Furthermore, five out of seven studies had problems with comorbid psychiatric disorders or substance abuse. For example, the study by Blumberg et al. (2003a) included a group with a total count of eleven additional diagnoses. Moreover, in the study of Marchand et al. (2007) 80% of the participants had been diagnosed with other psychiatric or substance abuse disorders. This relatively high number of supplementary diagnoses can possibly be explained by the fact that they included a specific group of military veterans. Besides, the subjects in Roth et al. (2006) had a total count of four additional psychiatric disorders and Gruber et al. (2004) included two substance abusers.

Besides, three out of seven studies included only medicated and four studies included medicated and unmedicated patients. Moreover, the differences between illness duration in all seven studies are large, ranging from more than a quarter century (Marchand et al. (2007) to less than five years since disease onset (Strakowski et al. (2005). A peculiar phenomenon is the habit of not providing information on illness duration in the subject characteristics. Both studies by Blumberg et al. (2003a; 2003b) and the study by Roth et al. (2006) did not mention this rather crucial characteristic.

**Table 2.** Studies applying a Go No-Go or Stroop paradgim to investigate differences in brain activation between schizophrenic patients and healthy controls.

| Authors | Paradigm | N | Phase | Illness Dur. Y (SD) | Meds | Task Perform. P v.s. C | Brain activity Patients v.s. Controls |
|---|---|---|---|---|---|---|---|
| Siegel et al., 1995 | CPT-X (zero, degraded) | C 20<br>P1 25<br>P2 14 | P1: Schizo<br>P2: Autism | 4 | Off Med | More Comission & Omission Errors | P1: **Hypoactivation** R-MFC, R- IFC, L-angular, R-supramarginal gyrus, R-ACC. R-MFC & R-IFG correlate with performance (overall PET metabolism) |
| Schröder et al., 1996 | CPT-X (zero) | C 47<br>P 79 | Schizo subgroup | 6.7 (5.6) | Off Med | | Delusional: **Hypoactivation** hippocampus Negative: **Hypoactivation** frontal, **Hyperactivation:** left tempo ral Disorganized: parietal and motor area **hyperactivation**, corpus collosum **Hypoactivation** (overall PET metabolism) |
| Cohen et al., 1998 | CPT-X (auditory) | C 41<br>P 19 | Schizo | 13.2 | Off Med | More Comission & Omission Errors | **Hypoactivation** PFC, increased posterior putamen metabolism (overall PET metabolism) |
| Rubia et al., 2001 | CPT-X (airplane) | C 7<br>P 6 | Schizo | 1.25 (0.3) | All | Commission & Omission Errors & RT n.s. | **Hypoactivation** L- ACC (32/24) |
| Laurens et al.,2003 | CPT-X (K) | C 16<br>P 10 | Schizo | 11 | All | More Comission & Omission Errors RT increased. | R-MFC (6/9), R-IPG (40/7/2), L-MOC (17/18/19) **Hyperactivation** during correct inhibition. L-SPG & L-IPG (7,40,2,3) R-precuneus (7/19) **Hyperactivation** during commission errors. |
| Ford et al., 2004 | CPT-X | C 11<br>P11 | Schizo | 17.3 (13.9) | All | Less Commission Errors. More Omission Errors during No-Go. | **Hypoactivation** R-IFG (46,47), R-MFC (8), R-cingulate (32), R-IFG (7/40), R-SPG(7/40), R-precuneus, L-amygdala (34), L-MTG (19/37/39), L-STG (39), L-GP, L-putamen during no-go. **Hypoactivation** R-MFG (6/32), L-MFC (6,8,9, 10,32), R-SFG (6), L-PCG (4,6,13),R-Cingulate (24,32), L-Cingulate (24,31,32), L-Cuneus, R-STG (13/22/43/44) during no-go – go. |
| Honey et al., 2005 | CPT-degraded | C 12<br>P1 11<br>P2 11 | P1: Schizo pos/neg<br>P2: schizo pos | P1: 22.2 (4.2)<br>P2: 24.7 (6.4) | All | P1: More Commission Errors, P2: n.s.<br>P1 &2: RT n.s. | **Hyperactivation** R & L-SFC, R & L-IPG, R & L-cingulate, R-PCG, L-caudate, L & R-thalamus, L-precentral, R & L-STG, R-cerebellum, R-MFC, R-IFG. **Hypoactivation** R & L-angular, L-putamen.<br>P1>P2: R-STG, R-MFC, L-SPG |
| Arce et al., 2006 | CPT-X (circles) | C 17<br>P 17 | Schizo | 13.9 | All | Commission & Omission Errors n.s. RT Increased | ACC (32/, 24), Cingulate (31) & L-MFC (9) **Hypoactivation** during nogo trials |
| Kaladjian et al.,2007 | CPT-X | C 21<br>P 21 | Schizo | 12.8 | All | Commission & Omission Errors n.s. RT increased | R-IFG (45/47) **Hypoactivation** during correct inhibition |
| Joyal et al.,2007 | CPT-X | C 12<br>P1 12<br>P2 12 | P1: Schizo + APD<br>P2: Schizo | 8.7 | All | Commission & Omission Errors & RT n.s. | P2: R-MFC (46/9) **Hypoactivation** during entire task. P1 (Antisocial): R-MFC (45/ 46/9) **Hypoactivation**, **Hyperactivation** L-IFG (10/46/47), R-IFG (44/45) |
| Barkataki et al.,2008 | CPT-X (circles) | C 14<br>P1 12<br>P2 12 | P1: schizo<br>P2: violent schizo | P1: 11 (5.7)<br>P2: 12.3 (7.6) | Mix | P1 & P2: More Comission & Omission Errors | P1 **Hypoactivation** L-caudate during go vs nogo trials P2: **Hypoactivation** L-thalamus in Nogo20% vs nogo40% |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Volz et al., 1999 | CPT-IP | C 20 P14 | Schizo | | Off Med | Commission & Omission Errors n.s. | **Hypoactivation** R-MFC, Cingulate, L-thalamus (entire task) |
| Salgado-Pineda et al., 2004 | CPT-IP | C 14 P 14 | Paranoid (12) | 1.9 (1.6) | All | More Comission & Omission Errors RT increased | **Hypoactivation** R-IFC (44/45), R-MFC (9), Cingulate (32/31/24), L- and R-angular (39), L- and R-MTG (21), R-STG (22/37) bilateral thalamus during entire task |
| Salgado-Pineda et al., 2007 | CPT-IP | C 14 P 14 | Paranoid (12) | 1.9 (1.6) | All | More Comission & Omission Errors RT increased | activation DLPFC (9) did correlate less with other structures |
| Barch et al., 2001 | CPT-AX | C12 P 14 | Schizo | <1 | naive | More Comission Errors RT increased | **Hypoactivation** DLPFC (46/9) during longer processing |
| Carter et al., 2001 | CPT-AX | C 16 P 17 | Schizo | 16 (9.1) | All | No increase in RT after error, which was observed in C | **Hypoactivation** ACC (10/40) (error-related activity) |
| MacDonald et al., 2003 | CPT-AX | C 17 P 17 | Schizo | | All | More Comission & Omission Errors RT increased | **Hypoactivation** L-DLPFC (9) (maintanance of a cue), unrelated to performance |
| Perlstein et al., 2003 | CPT-AX | C 15 P 16 | Schizo | 14.1 (2.2) | All | More Comission & Omission Errors | R-DLPFC (46/9) **Hypoactivation** (maintanance of a cue), related to prepotent response tendecy |
| MacDonald et al., 2005 | CPT-AX | C 28 P1 18 P2 12 | P1: Schizo P2: Psychosis | | none | More Comission Errors | **Hypoactivation** R-MFC(9), L-MFC (10), R-IFC (44/45) during different cue. |
| Carter et al., 1997 | Stroop | C 15 P 14 | schizo | | All | Stronger performance interference, RT increased | **Hypoactivation** in R-ACC (10), left precentral gyrus (6), right hippocampal gyrus (47) during incongruence - error correlates as trend with ACC activity |
| Epstein et al., 1999 | Stroop | C 6 P1: 6 P2: 5 | P1: paranoid P2: schizo | | All | | **Hyperactivation** P1 parahippocampus, **hypoactivation** dorsal ACC & VPFC |
| Nordahl et al, 2001 | Stroop | C 10 P 9 | paranoid schizo | 14.6 (9.3) | off medic | Stronger performance interference, RT increased | **Hyperactivation** R-ACC (trend), correlates positively with errors |
| Yücel et al., 2002 | Stroop | C 6 P 5 | Schizo | 11.5 (8.5) | all except 1 | | **Hypoactivation** in L- and R- ACC, Left ACC most hypoactivation |
| Weiss et al., 2003 | Stroop | c 13 P 13 | Schizo | 6.23 (4.7) | all | Performance & RT n.s. | **Hyperactivation** in L- IFG(9,6), R- IFG (9), ACC (24, 6) , R- precuneus (7) and temporal cortex (22, 44). **Hypoactivation** in L-temporal and L-occipital cortex (37,39,22). negative correlation between L-pfc and accuracy for healthy controls but not schizophrenia patients |
| Jeong et al., 2005 | Stroop | C 10 P 10 | Schizo | 4.3 (4.4) | all | Accuracy declines RT n.s. (when covaried with age, educ) | **Hypoactivation** in L-ACC, L-paracingulate (32), L- and R- STG. **Hyperactivation** R-IFG (47), R-precentral gyrus (6), L-claustrum (10) L-paracingulate, R-PFC and R-precentral gyrus correlate negatively with nr of psychotic episodes |
| Kerns et al., 2005 | Stroop | C 13 P 13 | Schizo | | all | Accuracy declines (trend)<br><br>RT increased (trend) | During conflict: **Hypoactivation** L-ACC (32), R-IPG (7) , L-SPG (40), L-STG (42). **Hyperactivatiion** L-thalamus, R-putamen, L-STG (38).<br><br>During Error: **Hypoactivation** L-ACC (32) R-Cuneus (31,18) , R-caudate, L- |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | MTG (37), R-putamen . **Hyperactivation** L-postcentral (6/7), R-IPG (40) |
| Harrison et al., 2006 | Stroop | C 8 P 8 | Schizo-phreniform | no schizo yet | naive | Performance n.s. RT increased | **Hypoactivation** L-MFG, Cingulate cortex |
| Yücel et al., 2007 | Stroop | C 8 P 8 | Schizo | < 0.5 | naive | Performance n.s. RT slower for specifically incongruent trials | **Hypoactivation** L-paracingulate (32), **Hyperactivation** L-ACC (24) |
| Weiss et al., 2007 | Stroop | C 8 P 8 | Schizo | 2.4 (3.7) | naive and off meds | Accuracy declines (trend), | **Hypoactivation** L-IFG, L-MFG, R-MFG (6,9,10), ACC (24), R-PG (40), hypothalamus. **Hyperactivation** L- and R- temporal (22, 41), L- and R-occipital cortex (17), L-insula, R-lentiformis, R-caudate. ACC and temporal lobe correlate with good performance, R-ACC also with bad performance |
| Brewer et al., 2007 | Stroop | C 8 P 8 | Schizo | < 0.5 | naive/ later all med | Accuracy declines, less errors after treatment RT n.s. | **Hypoactivation** in R-DLPFC and R-VLPFC -> both better after treatment (8 weeks) |
| Krabbendam et al., 2009 | Stroop | C 9 P 11 | Schizo | 12.6 (9.1) | all | Performance n.s. | **Hypoactivation** in L-ACC, L-IFG, R-MTG. Follow-up (6-8 weeks): L-IFG activation increased correlated with decreased positive symptoms. |
| Ungar et al., 2010 | Stroop | C15 P15 | Schizo | 22 | all | n.s. difference in Stroop. No increase in RT after error, which was observed in C | **Hypoactivation** ACC (32), R-MFC (44). **Hyperactivation** precuneus (19). |

C = controls , P = patients, Schizo = Schizophrenic, RT = Reaction Times, Off Med = Off medication, Mix = mixed medicated/ nonmedicated. SST = stop signal task L- = left , R- = Right, SFC = Superior Frontal Cortex, MFC = Middle Frontal Cortex, IFC = Inferior Frontal Cortex, DLPFC = Dorsolateral Prefrontal Cortex, ACC = Anterior Cingulate Cortex, SPG = Superior Parietal Gyrus, IPG = Inferior Parietal Gyrus, PCG = postcentral gyrus, STC = Superior Temporal Cortex, GP = Globus Pallidus,

*Go No-Go paradigm*

Nineteen studies applied the Go No-Go paradigm in fMRI and PET studies in schizophrenia patients (table 2, upper part). Although these studies took place during fifteen years of research under many different circumstances, there seems to be vast consistency in the findings of these studies. A large majority, namely fifteen out of nineteen papers, report hypoactivation of the frontal cortices or anterior cingulate cortices in schizophrenia during performance on the Go No-Go paradigm (Siegel et al., 1995; Schröder et al., 1996 Cohen et al., 1998; Rubia et al., 2001; Ford et al., 2004; Arce et al., 2006; Kaladjian et al., 2007, Joyal et al., 2007; Volz et al., 1999; Salgado-Pineda et al., 2004; Barch et al., 2001; Carter et al., 2001; MacDonald et al., 2003; Perlstein et al., 2003). Five of these studies found more commission and omission errors during performance on the Go No-Go paradigm (Siegel et al., 1995; Cohen et al., 1998; Salgedo-Pineda et al., 2004; MacDonald et al., 2003; Perlstein et al.,2003), two additional studies

found evidence for more commission errors but not omission errors (Barch et al., 2001; MacDonald et al., 2005), whereas one study found more omission errors but less commission errors (Ford et al., 2004). This indicates that a minority of studies that found evidence for alternated processing in schizophrenia also found evidence for performance difficulties. Moreover, more studies found evidence for a global decrease in performance than a decrease limited to commission errors.

Many of the studies that found evidence for hypoactivation in the prefrontal cortex differentiated between left and right hemisphere and between specific subareas within the prefrontal cortex. For example, nine studies reported decreased right middle prefrontal cortex activity (Siegel et al., 1995; Laurens et al., 2003; Joyal et al., 2007; Volz et al., 1999; Salgado-Pineda et al., 2004; MacDonald et al., 2003; Perlstein et al., 2003). A part of this brain area is also referred to as the dorsolateral prefrontal cortex, which was often the focus of hypoactivation (BA 46 and 9). In addition, six studies found evidence for right inferior frontal cortex hypoactivations in schizophrenia patients (Siegel et al., 1995; Salgado-Pineda et al., 2004; Perlstein et al., 2003; MacDonald et al., 2005). Finally, five studies found specifically the anterior cingulate cortex to show hypoactivation during the Go No-Go tasks. (Siegel et al., 1995; Rubia et al., 2001; Arce et al., 2006; Volz et al., 1999; Carter et al., 2001). Of these studies, only one found evidence for decreased accuracy (Siegel et al., 1995).

An important question about neurophysiological findings is how they relate *directly* to behavioural data. To date, the results on this are inconclusive. While some studies find evidence for abnormalities in brain activation unrelated to performance (e.g. Cohen et al., 1998; Barch et al., 2001; MacDonald et al., 2003), others find specific correlations between accuracy or reaction times and brain activation (Siegel et al., 1995; Perlstein et al., 2003; MacDonald et al., 2005;). For example, Perlstein et al. (2003) found a relationship between reaction times (but not accuracy) and R-DLPFC activation for distractors, but not for targets. Siegel et al. (1995) showed a negative correlation between anterior cingulate activation and general task performance. Furthermore, MacDonald et al. (2005) observed a relationship between middle frontal gyrus activity and task demands in healthy subjects, but failed to find this association in patients with schizophrenia. Many studies discuss the relationship between accuracy and brain activation only in general terms. It is often difficult to determine whether observed hypoactivation in schizophrenia is due to information processing deficits or lack of motivation in schizophrenia patients (Schmand et al., 1994; Manoach, 2003). As far as we know, all

studies that applied the Go No-Go paradigm in schizophrenia patients had an average hit rate of 90% or higher. Four studies even report hit rates higher than 95% (Laurens et al., 2003; Barkataki et al., 2008; Kaladjian et al., 2007; Arce et al., 2006). This partially rules out the possibility that the observed hypofrontality is due to a lack of involvement. However, it does not rule out the possibility that in a more difficult Go No-Go paradigm, patients would show a different pattern of neural processing. In this review, two studies on schizophrenia found evidence for hyperactivation instead of hypoactivation. This partially results from the focus of both studies. Laurens et al. (2003) focussed specifically on activations during successful inhibition instead of global activation and Honey et al. (2005) adopted a different version of the Go No-Go task.

Within the past fifteen years major advances are put forward with relation to the applied methods. For example, Ford et al. (2004) used an elegant design by combining ERP and fMRI measurements. While the fMRI data alone was not consistent with other studies, so was the ERP data. They conclude that '.. patients with schizophrenia who had a more normal pattern of P300s did not have a normal fMRI response may reflect their inability to recruit DLPFC, inferior parietal lobe and striatum' (p.124). Regarding the number of included subjects, the PET studies in this review (Schröder et al., 1996; Siegel et al., 1995; Cohen et al., 1998) included more participants than subsequent fMRI studies. The largest study is the one by Schröder et al. (1995) where 79 patients and 47 controls participated. In contrast, Rubia et al. (2001) included only six patients and seven controls. The majority of studies however, included between ten and twenty subjects per group.

Apart from the number of included participants, the diversity in illness duration between patients is remarkable. While only one study included participants with a recent diagnosis of schizophrenia (Barch et al., 2001), ten studies included patients with illness durations of more than five years and four studies did not report on this characteristic (table 2). The study by Honey et al. (2005) included participants with average illness duration of more than twenty years, which is to date the longest illness duration in imaging studies on the Go No-Go paradigm.

Twelve out of nineteen studies included participants that used antipsychotic medication during the time of testing. Strikingly, the three PET studies (Schröder et al., 1996; Siegel et al., 1995; Cohen et al., 1998) all asked participants to stop their antipsychotic medication regime weeks before the day the neuroimaging scans were made. This is most likely related to the fact that antipsychotic medication has been found to have direct effects on metabolism measured with PET (Seeman, 2002).

The studies included in this review use a different way of matching the control sample to the patient sample. For example, two early studies did not match the participant groups (Schröder et al., 1996; Siegel et al., 1995). Three studies solely matched on age (Cohen et al., 1998; Joyal et al., 1998; Volz et al., 1998). Four studies matched on task performance (Cohen et al., 1998; Barch et al, 2001; Arce et al., 2006; Kaladjian et al., 2006). Five studies used a more complicated matching procedure by matching on parental education, education, sex and age (Barch et al., 2001; Carter et al., 2001; MacDonald et al., 2003; Perlstein et al., 2003; MacDonald et al., 2005) which is becoming more common nowadays. Interestingly, a study that found inconsistent results (hyperactivations and hypoactivations throughout the entire cortex), was the only one that controlled for IQ differences (Honey et al., 2005). On the other hand, this study used a different version the paradigm (CPT-degraded items) and the long illness duration (>22 years) may also contribute to this specific findings.

One of the most remarkable aspects of the studies reported here is the lack of clinical differentiation in participants included in the patient group. Only the study by Schröder et al. (1995) differentiated between 'delusional', 'disorganized' and 'negative' schizophrenia, while one other study divided their patient group in 'positive and negative' symptoms (Honey et al., 2005). Because the clinical diversity of schizophrenic patients is enormous, one could argue that studies should try to focus on specific subgroups of patients with schizophrenia and to investigate the diagnostic specificity of findings.

*Stroop Paradigm*

Thirteen studies investigated the Stroop interference related brain areas by means of fMRI and PET. Ten out of thirteen studies found evidence for hypoactivation in the anterior cingulate cortex (ACC) (Carter et al., 1997; Epstein et al., 1999; Yücel et al., 2002; Jeong et al., 2005; Kerns et al., 2005; Harrison et al., 2006; Weiss et al., 2007; Krabbendam et al., 2009; Ungar et al., 2010). One study found significant evidence for hyperactivation in the ACC, but found hypoactivation in the paracingulate cortex (Yücel et al., 2007) and another one showed a trend towards significant hyperactivation in the ACC (Nordahl et al., 2001).

Out of the ten studies that found evidence for declines in activation, five also showed evidence for hampered performance (Carter et al., 1997; Jeong et al., 2005; Kerns et al., 2007; Weiss et al., 2007; Brewer et al., 2007) and three reported a significantly slower response in the patient group (Carter et al., 1997; Kerns et al., 2005; Harrison et al.,

2006). Moreover, overall six studies report decreased performance (Carter et al., 1997; Nordahl et al., 2001; Kerns et al., 2005; Weiss et al., 2007; Brewer et al., 2007; Krabbendam et al., 2009) and three studies found no evidence for significant changes in performance (Weiss et al., 2003; Harrison et al., 2006; Yücel et al., 2007). Important to note is that two studies did not report on accuracy (Epstein et al., 1999; Yücel et al., 2002) and four did not report on reaction times (Epstein et al., 1999; Yücel et al., 2002; Weiss et al., 2007; Krabbendam et al., 2009).

Since the observed hypoactivations of the cingulate cortex might relate to declines in performance and slower response times, it is fruitful to investigate the direct relationship between performance and brain activation. However, at this point it is difficult to interpret the observed relationship. For example, one early study reported that errors show a trend towards a significant correlation with anterior cingulate activity (Carter et al., 1997), another study puts forward that good performance correlates with activation of this brain area (Weiss et al., 2007).

A possible crucial issue while interpreting the findings on the ACC is the medication status of the patient group. While five out of twelve studies included patients that were either off medication or medication naïve, three of them reported hypoactivation in the ACC (Harrison et al., 2006; Weiss et al., 2007; Brewer et al., 2007) and two of them on hyperactivations in this brain region (Nordahl et al., 2001; Yücel et al., 2007). This might indicate that patients on medication show the opposite relative to patients off medication.

Besides the findings on the ACC, four studies report increased activation in either the inferior frontal gyrus or ventrolateral prefrontal gyrus in schizophrenia patients as compared to controls during the Stroop paradigm (Jeong et al., 2005; Kerns et al., 2005; Harrison et al., 2006; Brewer et al., 2007). Furthermore, three found evidence for altered response in the left inferior frontal gyrus (Weiss et al., 2003; Weiss et al., 2007; Krabbendam et al., 2009).

Two recent studies applied a follow-up paradigm (Brewer et al., 2007; Krabbendam et al., 2009) to investigate treatment effects. Brewer et al. (2007) concluded that both the right dorsolateral and ventrolateral activations became less deficient as compared to controls after treatment. In addition, Krabbendam et al. (2009) concluded that the activation in the left inferior frontal gyrus correlated with performance after treatment, but not before. Meanwhile, both studies did not find significant learning effects in the Stroop paradigm. A different approach was taken by Ungar et al. (2010) who focussed on incongruency-

after-effects (negative priming) which are not observed in schizophrenia patients but are found in healthy subjects.

Finally, a number of studies on schizophrenia patients that applied the Stroop paradigm recruited participants that had illness durations of more than 10 years. Since there is convincing evidence for progressive changes in morphological and functional abnormalities (Pantelis et al., 2005; Van Haren et al., 2007; Whalley et al., 2009), this might complicate generalizations of the results of these studies. However, three out of thirteen studies actually did not report illness duration. To model possible treatment related, or illness duration related effects future research should give transparency on this account, which would make it possible to systematically investigate medical treatment effects and illness duration.

## Conclusion

This review investigated the communalities and divergences between performance and neural deficiencies in bipolar and schizophrenic patients as compared to healthy individuals during impulsivity related paradigms in fMRI or PET. We focused on the Go No-Go and Stroop paradigm, which are currently the most frequently adopted paradigms. To date, sixteen studies investigating one of both paradigms during functional neuroimaging have been performed in patients with bipolar disorder and thirty-two studies in patients with schizophrenia. Therefore, making sound inferences regarding deviant processing in bipolar patients are forced to be preliminary. Also, the characteristic of the bipolar patient groups recruited for the reported studies are very heterogeneous which further complicates the implications of the presented papers. With respect to task performance and reaction times one out of sixteen studies reported a decrease in performance and four showed an increase in reaction times in bipolar disorder, which indicates that changes in performance or reaction times are far from a general finding in bipolar disorder (see table 1). The most reliable neurophysiological abnormalities were found in the frontal cortices, but the direction of the changes in neural recruitment is likely to be dependent on the phases of bipolar disorder. Generally speaking, eleven out of sixteen studies found hypoactivations in one or more brain areas, while five studies found evidence for hyperactivations. More specifically, five studies point to hypoactivation of the frontal cortices in bipolar disorder during response inhibition and interference (Blumberg et al., 2003b, Strakowski et al., 2005; Altshuler et al., 2005; Roth et al., 2006; Mazzola-Pomietto et al., 2009), while only one of these studies found significant alterations in task performance (Strakowski et al., 2005) and four studies did not find evidence for significantly more misses or false alarms respectively. When illness phases are viewed separately, three out of four studies that focussed on manic patients found evidence for hypoactivations in the right ventrolateral prefrontal cortex corresponding to Brodmann area 47 and 10, which was not the case when patients were in the euthymic phase. This combination of decreased ventrolateral prefrontal activation and no general changes in performance suggest a small but reliable change in inhibition-related brain functioning.

In schizophrenia, eighteen out of thirty-two studies reported decreases in performance, while ten found no altered performance. In the Go No-Go paradigm, eight out of the twelve studies that found evidence for hampered performance reported both an increase in omission and commission errors, whereas four studies only showed evidence

for an increase in commission errors and five studies reported no significant differences. Moreover, seven studies reported lower reaction times, while three do not. In the Stroop paradigm, six studies reported more errors in schizophrenia, while five studies showed no difference between patients and controls. Also, six studies found stronger reaction time interference in schizophrenia, while four do not. A large majority, namely twenty-seven papers, reported hypoactivation of the frontal cortices or anterior cingulate cortices in schizophrenia during performance on the Go No-Go or Stroop paradigm. In the Go No-Go paradigm, the most robust finding was hypoactivation of the right middle frontal cortex (MFC, a brain region which incorporates the dorsolateral prefrontal cortex). The brain region that was mainly affected during the Stroop paradigm was the anterior cingulate cortex (ACC). Also, six studies on schizophrenia reported right inferior frontal and right ventrolateral prefrontal cortex (VLPFC) hypoactivations. This suggests that paradigms related to impulsivity robustly show hypoactivations in the right MFC, right VLPFC and ACC in schizophrenia patients, accompanied by a generally observed decrease in performance (see figure 1).

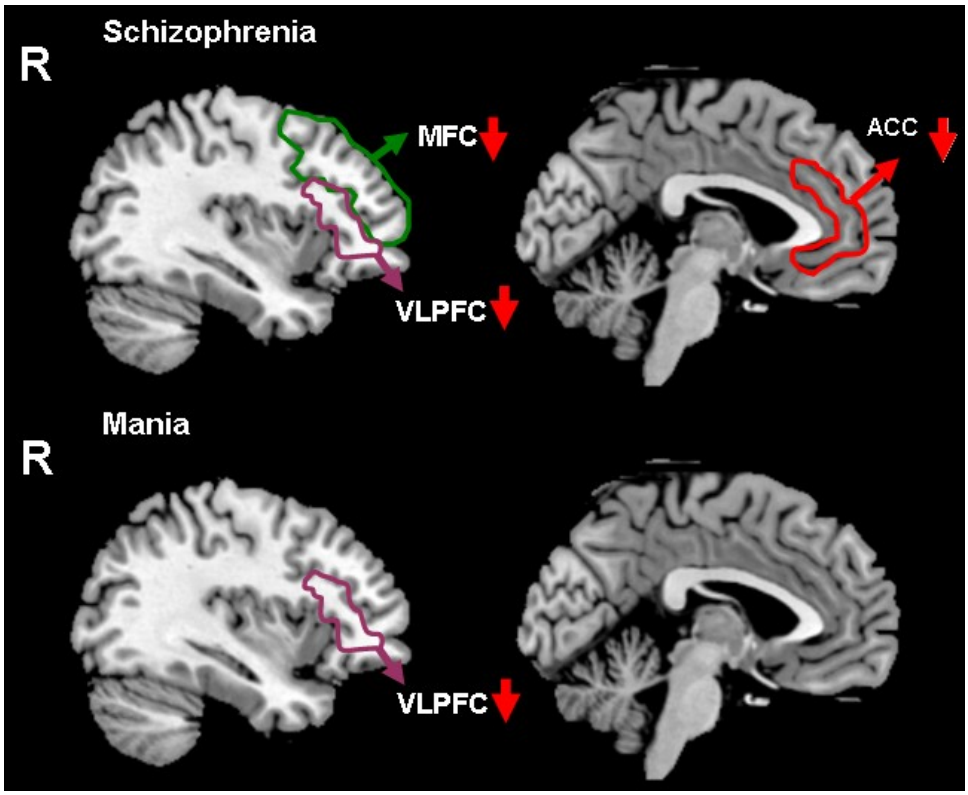


Figure 1 – Brain areas showing differential processing in schizophrenia (top) and bipolar mania (bottom) during impulsivity related paradigms (Go No-Go paradigm, Stroop paradigm) in a majority of studies in this review. R = Right, MFC = Middle Frontal Cortex, VLPFC = Ventrolateral Prefrontal Cortex, ACC = Anterior Cingulate Cortex.

## Discussion

*Primary findings*

With respect to performance, many studies included in this review found evidence for decreased accuracy measured as increases in omission and commission errors in schizophrenia compared to a relative small number of studies in bipolar disorder. On a neural level, both bipolar patients in a manic phase and schizophrenia patients show hypoactivations in the right ventrolateral prefrontal cortex. However, the right middle frontal cortex and anterior cingulate cortex which were most often reported to show hypoactivation in schizophrenia are less reliably found to be hypoactivated in bipolar disorder or mania. Therefore, both on the neural as well as on the performance level patients with schizophrenia seem to show more pronounced effects compared to patients with bipolar disorder during impulsivity related paradigms, whereas evidence for some overlap is evident. This finding is in agreement with the earlier view that both bipolar disorder and schizophrenia show alterations in the prefrontal-network (O'Connell et al., 1995; Strakowski et al., 2005b), however it challenges the idea that both schizophrenia patients and bipolar patients are hampered to the same extent on fast-acting paradigms such as the Go No-Go and Stroop paradigm. As far as we know, this is the first study that examines the relationship between task performance during functional brain imaging on the Go No-Go and Stroop paradigm in patients suffering from schizophrenia or bipolar disorder.

With respect to previous literature, the findings of this review correspond to a recent meta-analysis on morphological changes in 14 studies on bipolar disorder and 42 studies on schizophrenia (Ellison-Wright & Bullmore, 2010). Here, reduced morphological brain volumes were found to show a large overlap, whereas changes in brain volume in patients with bipolar disorder are more restricted than in schizophrenia. Furthermore, it also agrees with one of the few explicit comparisons between schizophrenia and bipolar patients on verbal fluency were both bipolar and schizophrenia patients were found to show differential processing in the frontal cortices, but schizophrenia patients showed a more widespread disturbance (Curtis et al., 2001). For schizophrenia, a recent meta-analysis on forty-one functional neuroimaging studies showed evidence for comparable brain alterations as our review (Minzenberg et al., 2009) and an extensive literature about prefrontal functioning in schizophrenia also highlighted the important nature of dorsolateral prefrontal cortex, ventrolateral prefrontal cortex and anterior cingulated cortex disruption (Ragland et al., 2007). This suggests that impulsivity-related brain

activation for the adopted papers in this review follow a more general trend in decreases of performance and frontal brain activation instead of an impulsivity-domain restricted finding. The finding of increases for commission as well as omission errors also supports this, since it is generally accepted that omission errors merely reflect inattention whereas commission errors are often related to impulsivity (Halperin et al., 1991; Swann et al., 2003).

*Neural processes*

Altered processing in the middle frontal cortex (incorporating the dorsolateral prefrontal cortex), the ventrolateral prefrontal cortex and the anterior cingulate cortex have long been studied in brain research. The middle frontal cortex is at the top of the motor and sensory hierarchy, which makes it likely to be the structure that integrates and evaluates information from diverse sources (Nakata et al., 2008). From the literature it is known that specifically the right frontal areas are involved in many attentional processes (Cabeza & Nyberg, 2000). Specifically, it is crucial for behavioural inhibition, since lesions produce a profile of distractibility, forgetfulness, impulsivity, poor planning, and locomotor hyperactivity related to impulsivity (Brennan et al., 2008). Others argue that right middle frontal cortex or dorsolateral prefrontal cortex activation is inefficient in schizophrenia during working memory tasks (Manaoch et al., 2003). However, this brain area is also activated during motor planning, organization, and regulation (Procyk & Goldman-Rakic, 2006). Second, the ventrolateral prefrontal cortex has been reported to be involved in managing first-order information and monitoring a stream of information (Cabeza & Nyberg, 2000; Picton et al., 2007). Lesion studies suggest that general monitoring processes are disrupted after damage to the ventrolateral prefrontal cortex (Picton et al., 2006). Also, this brain area is one of the most frequently reported areas involved in response inhibition in fMRI experiments (Hazeltine et al., 2001; Horn et al., 2003). More riskful decision-making in manic patients during a gambling task was associated with underactivation of the same brain area, suggesting a diminished function in monitoring and inhibition (Rubinsztein et al., 2001). Third, the anterior cingulate cortex (ACC) is involved in cognitive control. Activity in this brain region reflects detection of response conflict and response regulation (Barch et al., 1997; Yeung et al., 2005, Roelofs et al., 2005).

*Hypofrontality*

The current review indicates that all three brain regions show inefficient processing in schizophrenia, whereas only the ventrolateral part is reliably found to be hypoactivated in mania. This places the results of this review within the long debate on the nature of disruption in the frontal cortices in schizophrenia, which lately also applies to bipolar disorder (Matsuo et al., 2004). On the one hand, hypofrontality (hypoactivation of the frontal cortices) might be a representation of either too heterogeneous or too functionally discrete recruitments of additional neural resources (Kaladjian et al., 2007). However, it has also been suggested that undetected performance abnormalities (Aron et al., 2003) or a larger within-group variation which lowers the average activity, play a major role (MacDonald et al., 2005). Furthermore, it was suggested that task-related head movement inside the scanner can result in confounded hypoactivation during functional MRI (Bullmore et al., 1999). Recent evidence seems to support an inverted U-shaped relation between activation of the frontal cortices and relative demands. Here, initially compensatory mechanisms in schizophrenia such as increased effort after hampered neural recruitment result in hyperactivation during the first, most easy phase of a task (Potkin et al., 2009). After task demands gradually increase, within-group variation increases and some participants either give up or cannot recruit additional resources. This results in observed hypoactivation during the more difficult parts of the executive task (Weinberger, 1996; Manoach et al., 2003; Potkin et al., 2009). Possib,ly decreased performance and decreased activation of the frontal cortices are causally related. As an early sophisticated study by Sax et al. (1999) already indicated, prefrontal anatomical deficits were related to decreased performance on the Go No-Go task. Both in bipolar disorder and schizophrenia incidentally this relationship is supported for functional brain activation (Brooks et al., 2006; Perlstein et al., 2003). But, as the study by Salgado-Pineda et al. (2007) indicates, the one-on-one relationship between performance and brain activation is not as clear as it seems. This study showed that brain structures involved in inhibitory processes showed a lower internal relation in bipolar patients than controls, which indicates that global functioning of a neural network can contribute significantly to performance instead of single brain structures. However, as a recent article concluded, instead of deficiencies in a single brain structure a general reduction of top-down cognitive control is disrupting cognitive functions in schizophrenia (Royer et al., 2009). Since the present review focussed on impulsivity-related processes but found comparable results as both the morphological meta-analysis and a functional MRI study, we argue that the reduction of top-down control observed in schizophrenia to lesser extent may also

relate to impulsivity. However, future research might give more insights by comparing bipolar disorder and schizophrenia directly instead of this indirect approach.

*Methodological issues in neuroimaging of bipolar disorder and schizophrenia*

On a methodological level, both studies on bipolar disorder and schizophrenia suffer from comparable confounders. Throughout the years, many have been tackled, but still several important confounders remain present. Many relate to the composition of the patient groups involved. A major gap in many papers is the lack of information on medication which complicates the interpretation of the findings. Accumulating evidence suggests that medication can explain at least partly the differences in activation between the patients and control subjects. For example, it has been shown that both atypical and typical antipsychotic medication result in a general decrease in blood perfusion (Molina et al., 2008). Furthermore, differential performance on a Go No-Go paradigm after typical compared to atypical antipsychotic treatment has been reported (Ehlis et al., 2007). In bipolar disorder, Strakowski et al. (2004) showed, activations in the frontal brain areas to increase in medicated compared to unmedicated patients. Although it is difficult to recruit medication naive or medication free participants, a more standardized way of reporting medication status could already give benefits in comparing studies and interpreting findings. At the moment, more recent studies on schizophrenia (e.g. Perlstein et al., 2003, Barkataki et al., 2008, Ungar et al. 2010) explicated medication used by conversion into chlorpromazine equivalents. This makes it possible to control statistically for dose of medication.

Another difficulty relates to the matching of participants. While earlier studies did not match, later studies controlled for age, years of education, years of parental education and sometimes socioeconomic status. Still, a major confounder is not controlling for IQ as revealed by Heckers et al. (2004) who matched on subject and parental education, while mean IQ scores differed 13.7 points (113.2 vs. 99.5). A reason not to do so, is because some argue that lower IQ measurements are disease-inherent pathologic markers instead of confounds (Koenen et al., 2009; Urfer-Parnas et al., 2009). Although this might be the case, it hinders the interpretation of neuroimaging data because IQ measurements show a strong psychometric relationship and share overlapping neural regions with many neurocognitive measurements (Burgess et al., 2006). In some studies, IQ differences even show a stronger relation to commission errors than self-report scales of impulsivity (Horn et al, 2003). Therefore, IQ differences might explain more variance than the illness itself.

A different problem relates to the lack of statistical power in many studies. Most studies include groups of approximately 15 participants, which subsequently is regarded as a limitation of the study in the same article. With the current state of knowledge it should be possible to combine efforts in creating a (1) large heterogeneous group to be representative of patient population as a whole or (2) smaller homogeneous groups to represent a single symptom (e.g. manic or euthymic in case of bipolar disorder, paranoid or disorganized in case of schizophrenia). Large sample consortium studies in schizophrenia (e.g. FBIRN; Potkin et al., 2009) are growing while for bipolar disorder and schizophrenia combined recently a new consortium (B-SNIP) started. In addition, a virtue of large studies beyond better statistical power is the focus on one specific paradigm instead of dozens nearly identical paradigms used in different labs (Pearlson, 2009). Finally, only a few studies looked into a combination of functional and structural differences between patients and controls (e.g. Salgado-Pineda et al., 2003). The combination of structural and functional MRI can contribute to a common model of impulsivity in schizophrenia and bipolar disorder (Rubia, 2001).

*Future orientations*

Whereas the accumulation of evidence on measures of impulsivity has been assessed by means of the Go No-Go and Stroop Paradigm, other paradigms are adopted to measure functional brain abnormalities related to impulsivity in schizophrenia and bipolar disorder. One of these paradigms is the Stop Signal Paradigm. As far as we know, only few papers in schizophrenic and bipolar patients adopted this paradigm in the MRI scanner. Here, participants are required to respond as soon as possible after the presentation of a stimulus by pressing one or two buttons. The main outcome measure is the assessment when participants are required to withhold response (Stop trials) within a variable delay before the stop signal (Vink et al., 2006). A major issue in comparing data from different studies on this paradigm is the difference between a more conservative or a more progressive strategy in responding to the stimuli. In some studies, participants are asked to respond as frequently as possible while other studies ask their participants to withhold responses, which ultimately results in a different composition of the errors (Strakowski et al. 2008). However, in the next decade this paradigm is likely to become widely used because of its event-related nature. Another paradigm that is extensively used outside the scanner is the delay discounting paradigm. In these paradigms a decreased subjective value of a reinforcing stimulus (money) as a function of time to the

delivery is observed. Impulsive participants prefer a somewhat smaller immediate reinforcer over a higher delayed reinforcer. A recent study on abstinent drug-abusers found evidence for hypoactivation in the dorsolateral prefrontal cortex and the anterior cingulate cortex using an fMRI version of a delay discounting paradigm (Hoffman et al., 2008), which makes this paradigm a good candidate to further investigate impulsivity in the scanner environment. Also, the Iowa Gambling Task recently has been adopted in the MRI scanner. In this task, four decks of cards are presented, of which the subjects need to choose one of the decks. Every deck represents a win to loss ratio differing from the other decks. The goal of the game is to win as much money as possible (Bechara et al., 1994). A reason this paradigm has not been adopted many times yet is because of its high-demanding nature. Moreover, an extensive and complicated brain network is activated (Li et al., 2009).

*Conclusion*

This review is conducted to elucidate possible common and diverging underlying neurophysiological mechanisms of impulsive behaviour in schizophrenia and bipolar disorder. The studies included in this review focussed on the Go No-Go and the Stroop paradigm during functional imaging by means of fMRI and PET. We argue that schizophrenia patients are more hampered on task performance and related brain activation than bipolar patients, since the right middle frontal cortex, right ventrolateral prefrontal cortex and anterior cingulate cortex are reliably found to be hypoactivated in schizophrenia while hypoactivation is often restricted to the right ventrolateral prefrontal cortex in bipolar disorder. However, we suggest that instead of a domain-specific trend for impulsivity, the results of this study merely reflect a domain-general finding which is supported by correspondence to recent literature on executive functioning and morphological alterations in schizophrenia and bipolar disorder. Although impulsivity often has been related to inhibitory functions, both commission errors and omission errors were reliably found to be increased in schizophrenia, while being largely unhampered in bipolar disorder. However, it is important to note that functional neuroimaging research on both schizophrenia and bipolar disorder is in a preliminary and therefore still suffers from methodological problems such as IQ differences between groups, medication intake and lack of statistical power. We argue these characteristics to be crucial confounders and recommend the application of novel paradigms to further investigate impulsivity in bipolar disorder and schizophrenia.

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"While acknowledgements have been largely neglected in the EAP literature, they are almost universal in dissertation writing, where they offer students a unique rhetorical space to convey their genuine gratitude for assistance and to promote a favourable social and scholarly character... The analysis also shows that students, particularly those in the "soft" sciences, tended to construct generically more complex acknowledgements with a greater variety of patterns" (Hyland & Tse, 2004).

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