Conflict adaptation in patients diagnosed with schizophrenia

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1. Introduction

The brain is believed to constantly monitor its performance in order to maintain goal-directed behavior. Along the way, it faces conflicts that arise from information that is irrelevant to current goals. Conflict monitoring theory holds that the anterior cingulate cortex (ACC) detects such conflicts and upon detection triggers the dorsolateral prefrontal cortex (DLPFC) to regulate behavior (e.g., Botvinick et al., 2001; Carter and Van Veen, 2007; Holroyd and Coles, 2002) – for example by increasing attention to relevant information (e.g., Egner and Hirsch, 2005). This process is typically referred to as conflict adaptation. Despite the existence of various other conceptual and/or computational models on ACC-DLPFC functioning (e.g., Alexander and Brown, 2011; Silvetti et al., 2011), conflict monitoring theory has been highly influential over the last decades and it has been used as a framework also to understand cognitive impairments in various patient groups such as schizophrenia.

Neuro-imaging work indicates that patients diagnosed with schizophrenia show structural and functional abnormalities in both ACC (e.g., Carter et al., 1997; Kerns et al., 2005; Minzenberg et al., 2014) and DLPFC (e.g., Lesh et al., 2011, 2013). This has been reviewed elsewhere (e.g., Barch et al., 2009; Keshavan et al., 2008) and we here do not reiterate this literature; yet, as noted, these areas are core constituents of the network underlying conflict adaptation as proposed by conflict monitoring theory (e.g., Mansouri et al., 2017; Carter and Van Veen, 2007). A prediction, then, would be that conflict adaptation is impaired in patients diagnosed with schizophrenia. Critically, however, behavioral studies on core conflict adaptation indices do not yet allow for a clear evaluation of this prediction (Abrahamse et al., 2016a; Carter et al., 2012), and more empirical work is required. In the current study we focus on one of the core indices of conflict adaptation – the congruency sequence effect or CSE.

The CSE builds on conflict tasks such as the Stroop task (Stroop, 1935). In this task, the goal to name the ink-color (e.g., blue) of a specific color word (e.g., ‘blue’ or ‘red’) is rendered more or less
effortful by presenting either incongruent and thus cognitively conflicting items (e.g., the word ‘red’ in blue ink) or congruent items (e.g., the word ‘blue’ in blue ink), respectively. The performance difference between congruent and incongruent items – the so-called Stroop effect – provides an index for the amount of conflict experienced. The Stroop effect on the current trial has been shown to be sensitive to the previous trial context: A smaller current trial Stroop effect is observed after an incongruent as compared to a congruent previous trial. This is referred to as the CSE. The CSE is most typically interpreted in terms of conflict adaptation: After an incongruent trial the brain increases the processing of task-relevant information – or decreases the processing of task-irrelevant information – in order to better manage upcoming conflict (Botvinick et al., 2001).

In schizophrenia, the CSE has been explored only sparsely, and with equivocal outcomes that are difficult to interpret (Abrahamse et al., 2016a; Carter et al., 2012). Specifically, McNeely et al. (2003) showed similar CSEs between patients diagnosed with schizophrenia and healthy controls, whereas Kerns et al. (2005) observed an absence of the CSE in patients. Additionally, the interpretation of the CSE in terms of conflict-related adjustments in the brain has been challenged by episodic memory accounts (Schmidt et al., 2016; but see Abrahamse et al., 2016b). In terms of feature binding, for example, the CSE data pattern can be fully explained from the costs of partial repetitions of stimulus and/or response features between successive trials – which are more frequent for congruency alternations than congruency repetitions (Mayr et al., 2003; Hommel et al., 2004). Additionally, the CSE data pattern may be explained from stimulus-response contingency learning (Mordkoff, 2012; Schmidt, 2013; Schmidt and De Houwer, 2011). Specifically, when using all possible incongruent items in a typical Stroop design, congruent trials contain higher contingency between the word feature and the correct response than incongruent trials, and current trial and previous trial contingency have been shown to interact to produce a similar data pattern as the congruency sequence effect (Schmidt and De Houwer, 2011). In a design that does not control for feature binding and contingency learning, it is not clear whether (and to what extent) conflict adaptation is at work. Fortunately, various methodological adjustments have been proposed in
recent years to achieve less confounding (Duthoo et al., 2014; Jiménez and Méndez, 2013; Kim and Cho, 2014; Schmidt & Weismann, 2014). Critically, however, the two previous studies on the CSE in schizophrenia (Kerns et al., 2005; McNeely et al., 2003) did not apply such adjustments. The latter is important especially when considering that patients diagnosed with schizophrenia have been related to impaired learning (e.g., Collins et al., 2014; Rushe et al., 1999).

Overall, the main aim of the current study was to explore the CSE in patients diagnosed with schizophrenia – in a design that was validated in a sample of matched healthy controls. As will be elaborated on in the Method section, we controlled for design confounds related to feature binding and stimulus-response contingency learning. Besides providing an additional empirical test on the absence/presence of the CSE in schizophrenia, the current study thus implemented an improved design as compared to the previous studies by Kerns et al. (2005) and McNeely et al. (2003). We hypothesized that if abnormal ACC and DLPFC functioning in schizophrenia results in impaired conflict adaptation, we would find a reliable CSE for healthy controls but not for patients diagnosed with schizophrenia.

2. Method

2.1. Participants

Sixteen patients diagnosed with schizophrenia were recruited from psychiatric centers. Their demographic and clinical information are presented in Table 1. Sixteen healthy controls were matched to the patient group in terms of age, gender, and years of education (Table 1). All patients were diagnosed with schizophrenia by an interdisciplinary team or the attending physician, and were treated for this condition on an outpatient or semi-permanent basis in the respective institutions.
Patients with a history of neurological disorders (e.g. traumatic brain injury), other psychiatric disorders, brain damage, serious head injury, drug use (excluding marijuana and alcohol), or addiction were excluded. Moreover, systematic users of benzodiazepines were excluded because of the known long-term detrimental effects of this kind of medication on cognitive functioning (Barker et al., 2004). Patients were free of psychotic symptoms (i.e., hallucinations or delusions) at the moment of testing. In terms of their medication scheme, all patients were on atypical antipsychotic medication (varying between 1-3 kinds), while two patients additionally were on typical antipsychotic medication; two patients received benzodiazepines occasionally upon agitation. Participants were not colorblind and had normal or corrected-to-normal vision. The study protocol was approved by all relevant ethics committees. Written informed consent was obtained from all participants prior to their enrolment in the study and participants received a monetary compensation of 35 euro upon finishing the study.

2.2. Apparatus

The experiment was performed on laptops (refresh rate of 60Hz, 12.1 inch screens). Stimulus presentation, timing, and data collection were controlled using the E-Prime experimental software package (Version 2.0; Psychology Software Tools, Inc., Sharpsburg, PA). Responses were collected with custom-made voice-keys connected to a headset microphone.

2.3. Stimuli, tasks and procedure

The Stroop experiment that is reported here was part of a larger study that overall covered two (for healthy controls) or three (for the patient group) half-day sessions (morning or afternoon) which were all scheduled over the course of a single week. Specifically, in one session participants first performed the Stroop experiment for the exploration of the CSE, and afterwards another Stroop experiment with a so-called context-specific proportion congruency manipulation (cf. Crump et al., 2006). However, since no context-specific proportion congruency effect was observed for either patients or healthy controls, we decided to not report on that experiment in the current paper. In a
second session participants completed an unrelated task to explore motor sequence skill in schizophrenia. Finally, patients participated in a third session in which they were interviewed for the positive and negative syndrome scale (PANSS). In the current paper we thus restrict ourselves to the Stroop experiment that was intended to explore the CSE.

Upon entering the testing room (i.e., either the lab or an empty room at home for the healthy controls, and an empty room at one of the centers for patients), participants were seated in front of the laptop. Viewing distance was approximately 50cm, though this was not strictly controlled. Instructions for the task to be performed were provided on the screen, but the experimenter was available for additional explanation if needed. Participants performed a vocal Stroop task in which they were instructed to name the ink color (i.e., black, purple, green, yellow, blue, or red) of a color-word (i.e., one of the Dutch words ‘zwart’, ‘paars’, ‘groen’, ‘geel’, ‘blauw’, and ‘rood’; for ‘black’, ‘purple’, ‘green’, ‘yellow’, ‘blue’, and ‘red’, respectively) that was presented in bold (Courier New font) on a light-grey background. Following 12 practice trials, participants performed a total of 192 experimental trials, distributed across two equal-sized blocks (each approximately taking 12 minutes to finalize) that were separated by a self-paced pause (i.e., between trials 96 and 97). Stroop items were presented until a response was registered, or until 1800ms had passed without a response. After the response registration or passing of the response deadline a 1000ms inter-trial interval preceded the presentation of the next item. Stroop items were presented centrally on the screen and the proportion of congruent and incongruent items was equal throughout the task. No response feedback was provided.

A critical aspect of the current study related to the pairwise coupling of colors to tackle feature binding and stimulus-response contingency learning confounds. That is, two specific colors were paired (i.e., blue-red, black-purple, and yellow-green) and all congruent and incongruent items were construed from these pairs (for example, an incongruent item with the ink-color red was always formed from the color-word BLUE). This pairwise construction of items ensured that color-words
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were not predictive of a specific response (i.e., each color-word was equally associated with each of the two responses), thus weakening the stimulus-response contingency learning confound. Moreover, the trial design was implemented under the restriction that items across subsequent trials could not derive from the same color pair, thus preventing typical feature binding effects from occurring (i.e., there were no stimulus and response repetitions across subsequent trials). The use of six different colors (and thus responses) was the main reason for using a voice-key instead of manual responses on the keyboard – preventing the need for learning a demanding set of color-key mappings.

After the Stroop task, participants completed a number of brief questionnaires to test their general cognitive abilities (i.e., a translation of the Montreal Cognitive Assessment; Nasreddine et al., 2005) and their Dutch reading proficiency (Schmand et al., 1992). The duration of the session was approximately 1 hour. In a different session, the patients additionally completed the PANSS, the Brief Psychiatric Rating Scale, and the Simpson-Angus Scale.

2.4. Data preprocessing

On average on 15% of the trials (range across participants: 2-40%) the voice-key was either not triggered, or triggered by an improper stimulus (e.g., a cough or background noise)¹. These misrecorded trials were excluded together with the first trial of each of the two blocks. Additionally, we excluded trials on which an incorrect response was properly registered. Next, trials with reaction times that fell outside the range of mean reaction time plus/minus two standard deviations (calculated per participant, per cell of our design) were excluded (< 5% outliers). Finally, because of our interest in the CSE we excluded trials immediately following incorrect, misrecorded, and outlier trials.

3. Results

¹ Background noise could not be controlled as well as in a typical lab study due to the fact that matched, healthy controls mostly performed the experiment at home, and patients performed the experiment at the center that they were recruited from.
As a result of the design choices and the data preprocessing described above, the number of trials appropriate for analyses differed greatly between participants, with for some participants only a limited amount of trials left (range: 33-149 trials across all four cells of the design). We fitted a linear mixed-effects model (LME) on individual-trial reaction times using the lmer function of the R package lme4 (R Development Core Team, 2011). In an LME the contribution of each participant to the overall analyses is weighted by cell counts. The model fitted on reaction times involved Current Trial Congruency (2; congruent versus incongruent), Previous Trial Congruency (2; congruent versus incongruent), and Group (2; patient group versus healthy controls) in a full factorial fixed effects design. Participants were considered as a random effect factor. Also, for each of the fixed effect factors it was tested whether by-participant random slopes were needed (inclusion of interaction effects in the random effect structure resulted in an over-parameterized model that failed to converge; cf. Bates et al., 2015). This resulted in a model with random slopes for Current Trial Congruency and Group. The reported p-values for the fixed effects are based on a Type-III ANOVA using a $\chi^2$-distribution as implemented in the R package ‘car’ (Fox and Weisberg, 2011).

The LME showed main effects of Current Trial Congruency, $\chi^2 (1) = 82.0$, $p < 0.001$, and Previous Trial Congruency, $\chi^2 (1) = 12.4$, $p < 0.001$, whereas Group showed a near-significant main effect, $\chi^2 (1) = 3.4$, $p = 0.06$. More importantly, there was a significant interaction between Current Trial Congruency and Previous Trial Congruency, $\chi^2 (1) = 16.4$, $p < 0.001$, that was not further modulated by Group ($p = 0.78$). After a congruent previous trial, the mean reaction times for Current Trial Congruency were 629ms (congruent trials) and 768ms (incongruent trials); after an incongruent previous trial these values were 666ms and 766ms, respectively. This interaction indicates the CSE. Results did not show any other reliable effects ($ps > 0.40$). Despite the fact that the CSE was not modulated by Group, we explored CSE contrasts per group, and these showed the CSE for both healthy controls, $\chi^2 (1, N = 16) = 7.9$, $p = 0.005$, and patients, $\chi^2 (1, N = 16) = 8.6$, $p = 0.003$. Similar analyses on error percentages (using the glmer function) only revealed a reliable impact of Current Trial Congruency, $\chi^2 (1) = 25.2$, $p < 0.001$ (i.e., a typical congruency effect).
4. Discussion

In the current study we assessed the CSE for both patients diagnosed with schizophrenia and healthy, matched controls. Previous efforts in this respect by Kerns et al. (2005) and McNeely et al. (2003) showed equivocal results, and, moreover, were plagued by feature binding and stimulus-response contingency learning confounds that can account for the CSE data pattern without any reference to conflict-based adaptation. In the current study we explored the CSE in a design in which three color pairs were constructed, and in which i) congruent and incongruent Stroop items were always formed from within color pairs while ii) alternating pairs between successive trials. This allowed us to control for both stimulus-response contingency and feature binding confounds (see above). A reliable CSE was observed for both patients and healthy controls, which did not statistically differ from each other. As such, the current findings are compatible with those of McNeely et al. (2003) – but in an improved design – while they contrast those from Kerns et al. (2005) who did not find a reliable CSE in patients diagnosed with schizophrenia.

The current study provides a relatively confound-free (but see below) confirmation of the CSE in patients diagnosed with schizophrenia. This strengthens the challenge of dealing with the apparent contradiction between abnormal functioning associated with schizophrenia in brain regions strongly implied in conflict adaptation (e.g., ACC and DLPFC) on the one hand, and mixed results in behavioral work on conflict adaptation in this patient group on the other hand. This challenge is important to address, however, since the behavioral work allows for a window into the interpretation of the neuro-imaging findings. The following considerations are noteworthy in this respect: First, the current study comprises a relatively limited sample (comprising mostly male participants), which cautions any claims about generalizability of our findings as well as about the absence of differences in CSE between patients and controls. Second, on a related issue, it has to be noted that in the current study we opted for a group of matched healthy controls. As a consequence, the patient group consisted of relatively well-functioning patients with no recent substance
abuse/dependence. On the one hand, this leads to the possibility that a group of patients that would be more representative of the entire schizophrenia population (and thus with additional challenges) may not show the CSE. Indeed, this may explain why Kerns et al. (2005) did not find the CSE in their sample. On the other hand, if indeed more representative patients would not demonstrate a CSE, then it would hint at a critical impact of comorbid psychiatric problems – and thus that the absence of the CSE is not conditional on schizophrenia per se. Third, it has been argued that in the general domain of working memory and/or executive control, the brain of patients diagnosed with schizophrenia may engage spared regions to compensate for regions that are compromised (e.g., Tan et al., 2006). Future studies may explore such potential compensation within the context of conflict adaptation. Fourth, exposing performance differences between patients diagnosed with schizophrenia and healthy controls may be sensitive to specific choices in design. For example, with regard to the typical finding of an enlarged Stroop effect in patients diagnosed with schizophrenia (something that we did not observe in the current study), Westerhausen et al. (2011) noted on the basis of a meta-analysis that card-based and computerized versions of the Stroop task may differ in their consistency to capture such an enlarged Stroop effect. It is currently unknown how specific parameters of the design may impact the CSE results.

While most studies on conflict adaptation employed manual responses, in the current study we opted for a vocal Stroop task for two reasons. First, the Stroop effect is typically larger with vocal than with manual responses, and we reasoned that this scaling up of effects may work in favor of observing any potential CSE (though it must be noted that the CSE and the size of the Stroop effect do not typically correlate across-subject; Weissman et al., 2014). Second, and more importantly, we required at least six different response options and we did not have the opportunity to go through extensive training of six stimulus-response mappings. The downside of the choice for vocal responses is that we lost a large portion of trials due to voice-key problems – a problem which was amplified by the administration of the experiment away from the sound-controlled lab, and the impact of which
was amplified by our restriction to only analyze trials for which also the previous trial was correctly recorded (and responded to).

Finally, it has to be noted that controlling for feature binding and stimulus-response contingency learning confounds goes a long way in defending a conflict adaptation interpretation of the CSE – but it does not provide a definite conclusion. For example, additional alternatives to conflict adaptation have recently been proposed. Schmidt and Weismann (2016) proposed that – besides learning which response to perform (i.e., the stimulus-response contingency learning account) – the typical CSE pattern may also be related to learning about when to respond. A critical feature in this temporal learning account is that the response threshold on the current trial may be temporarily lowered around the moment that a response was generated on the previous trial. A model taking into account both such temporal learning and other simple cognitive processes (e.g., attentional wandering) demonstrated the plausibility of a temporal learning mechanism to account for the CSE. Despite a lack of strong empirical support for such alternatives at present, we believe that patient studies should follow up closely on novel insights emerging from this line of research.

In summary, the current study observed a CSE in patients diagnosed with schizophrenia while controlling for feature binding and stimulus-response contingency confounds. Given that previous work was not consistent in this respect, this is an important empirical contribution. Within the context of conflict monitoring theory, these findings prompt further exploration of the apparent contradiction between abnormal ACC and DLPFC functioning in schizophrenia on the one hand, and a reliable CSE as observed at the behavioral level on the other hand.

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References


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Table 1. Demographic and clinical characteristics and cognitive measures of all subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Schizophrenic patients [mean (S.D.)]</th>
<th>Control subjects [mean (S.D.)]</th>
<th>Statistics</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>37.06 (8.62)</td>
<td>36.38 (9.00)</td>
<td>t(30) = -0.22</td>
<td>0.83</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>13/3</td>
<td>13/3</td>
<td></td>
<td></td>
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<tr>
<td>Handedness (left/right)</td>
<td>3/13</td>
<td>2/14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education (in years)</td>
<td>12.5 (3.63)</td>
<td>12.56 (2.00)</td>
<td>t(30) = -0.06</td>
<td>0.95</td>
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<tr>
<td>PANSS total score</td>
<td>53.25 (10.43)</td>
<td></td>
<td></td>
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<tr>
<td>Positive symptoms</td>
<td>13.31 (4.14)</td>
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<tr>
<td>Negative symptoms</td>
<td>11.56 (3.20)</td>
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<tr>
<td>General psychopathology</td>
<td>28.38 (7.52)</td>
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<tr>
<td>MoCa total score</td>
<td>25.19 (2.34)</td>
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<tr>
<td>Intellectual performance (IQ)</td>
<td>99.67 (10.97)</td>
<td>104.25 (6.62)</td>
<td>t(29) = -1.42</td>
<td>0.17</td>
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