Chapter 4

Set-shifting ability and clinical variation in psychotic disorders

Claudia J.P. Simons
Piotr J. Quee
GROUP Investigators

Journal of the International Neuropsychology Society (submitted)
ABSTRACT

Introduction Although patients with psychotic disorders display altered performance on set-shifting tasks, it remains unclear whether this is attributable to implicit or explicit task requirements. The present study investigated i) whether set-shifting performance differs between patients with a psychotic disorder and controls and ii) associations with clinical variables. Methods Patients (N=951) were compared with healthy controls (N=527) on a task requiring alternation between two rules of responding based on trial-by-trial feedback (explicit set-shifting). Part of the sample (n=259 patients, n=222 controls) was administered a second task with a switch in the pattern of responding (implicit set-shifting). Results Patients showed significantly larger switching cost than controls on the explicit task, but not on the implicit task. Increased cost for explicit set-shifting was already apparent in recent-onset first-episode patients and was not associated with number of psychotic episodes. Effects of age of onset and duration of illness on switching cost disappeared when adjusting for age. Explicit set-shifting was associated with all dimensions of psychopathology. Discussion Patients with psychotic disorders do not show diminished flexibility when shifts in task rules are procedural, but are less flexible when explicit rules for responding change. This diminished flexibility in explicit shifting does not appear to deteriorate over time.
1. INTRODUCTION

Executive functioning refers to a constellation of higher level cognitive abilities involved in planning, self-monitoring and behavioural flexibility, which are held responsible for independent functioning (e.g. Miyake et al., 2000). One of the most consistent findings in patients with a psychotic disorder is the presence of altered performance on tasks assessing set-shifting ability (Heinrichs and Zakzanis, 1998). Set-shifting tasks such as the Wisconsin Card Sorting Test (WCST) and Competing Programs Task (Bilder et al., 1992) consist of a series of rule changes and require both cognitive stability to establish and maintain an appropriate response set and cognitive flexibility for the switching to different response rules. Despite robust performance differences in patients, with relatively large effect sizes compared with several other domains of cognitive functioning, set-shifting ability may not be a robust intermediate phenotype. Studies on set-shifting ability in unaffected siblings of patients with psychotic disorder have produced mixed results (Goldberg et al., 1990; Keefe et al., 1994; Meijer et al., 2012; Sitskoorn et al., 2004; Snitz et al., 2006) and suggest that it may not co-segregate with psychotic disorder (Ceaser et al., 2008). Thus, set-shifting may represent a marker of disease rather than of underlying familial vulnerability. Altered set-shifting performance may be a particularly relevant clinical phenotype, given that the ability to learn to change responses by experience is crucial for everyday functioning where task demands and context change continuously. This is supported by findings that set-shifting performance is associated with functional outcome (Green, 1996) and that improvements in cognitive flexibility may be associated with improvement in functional outcome (Wykes et al., 1999). Identification of the contribution of alterations in set-shifting ability to clinical variation and course of psychotic disorder may help elucidate pathophysiological processes. It has been suggested that dissociations in performance may exist between tasks relying on procedural learning mechanisms and tasks relying on explicit/declarative mechanisms (e.g., a shift to a new response rule when the previous one is no longer appropriate) (Gold et al., 2008; Waltz et al., 2011). It has been suggested that patients with psychosis, may especially impaired on tasks on learning tasks in which explicit hypotheses are tested, such as the WCST, in which patients have to deduct the response rule from trial-to-trial feedback, rather more gradual (procedural) forms of learning, although there is also evidence that patients may show diminished performance on some types of implicit learning tasks (Horan et al., 2008). Thus, it may be hypothesised that patients may be specifically impaired on set-shifting tasks involving explicit shifts in response rules, whereas patients may not show set-shifting problems on tasks that involve shifting from an implicitly learned set of response sequences to a new set with a different pattern but same response rule. However, implicit and explicit mechanisms of set-shifting have never been studied concurrently. In addition, many studies have used traditional tasks to study the explicit mechanisms, such as the WCST, which may involve other cognitive mechanisms such as rule deduction and working memory. It therefore
remains unclear whether set-shifting impairments are attributable to implicit or explicit mechanisms. A number of studies have suggested that (explicit) set-shifting ability may be intact in the earliest stages of illness (Elliott and Sahakian, 1995; Hutton et al., 1998; Pantelis et al., 2009) and may only be apparent in established schizophrenia (Elliot et al., Pantelis et al. 1999; Wood et al., 2002). However, there are some reports of altered performance in first-episode patients (Murray et al., 2008). Set-shifting ability has been associated with negative and disorganization symptoms (Leeson et al., 2009; Nieuwenstein et al., 2001; Pantelis et al., 1999). This is in accordance with findings for the majority of neurocognitive domains, although subtle differential patterns between symptom dimensions and different cognitive alterations have been suggested (de Gracia Domínguez et al., 2009; Nieuwenstein et al., 2001).

The aim of the present study was to investigate the nature and the clinical relevance of set-shifting impairment in patients with a psychotic disorder. First, patients were compared with healthy controls on performance on two different set-shifting tasks: a response shifting task requiring alternation between two rules of responding to be deduced from feedback (explicit set-shifting) and a set shifting task in which the implicit pattern of responding shifts during the task (implicit set-shifting). It was hypothesized that performance on the explicit set-shifting task would be diminished in patients with a psychotic disorder compared to healthy control subjects, but that set-shifting performance on the implicit set-shifting task may not be altered. Second, it was explored whether set-shifting ability is already significantly diminished in recent-onset first-episode patients or is associated with course of illness and only diminished in established disorder as suggested by previous literature. It was investigated whether set-shifting was associated with illness characteristics and whether set-shifting may be a state-marker. With respect to illness characteristics, it was hypothesized that set-shifting ability was associated with negative and disorganization symptoms. Finally, the present study analysed to what degree any associations between clinical variables and set-shifting were reducible to associations with generalized cognitive functioning.

2. METHODS

2.1 Participants

The full GROUP sample consisted of 1120 patients with non-affective psychotic disorder and 590 unrelated control subjects (Korver et al., 2012). Inclusion criteria were: (i) age range 16 to 50 years, (ii) diagnosis of non-affective psychotic disorder and (iii) good command of Dutch language. Control subjects had no first or second degree relative with a psychotic disorder as established by the Family Interview for Genetic Studies (NIMH Genetics Initiative, 1992) with the control subject as the informant. Diagnosis was based on the Diagnostic and Statistical Manual of Mental Disorder-IV (DSM-IV) criteria (American Psychiatric Association, 2000), assessed with the Comprehensive Assessment of Symptoms and History (CASH)
SET-SHIFTING ABILITY

interview (Andreasen et al., 1992) or Schedules for Clinical Assessment for Neuropsychiatry (SCAN 2.1) (Wing et al., 1990). DSM-IV diagnoses of the patients were: schizophrenia and related disorders (DSM-IV 295.x; n=945, 84%), other psychotic disorders (DSM-IV 297/298; n=149, 13%) and psychotic illness in the context of substance-abuse or somatic illness (n=9; 1%) (Genetic Risk and Outcome in Psychosis (GROUP) Investigators, 2011). General intellectual ability was measured using IQ scores derived from the four-subtest version (Information, Block Design, Digit Symbol Coding and Arithmetic) (Blyler et al., 2000) of the Dutch version of the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1997). See Table 1 for demographics and clinical characteristics.

The study protocol was approved centrally by the Ethical Review Board of the University Medical Centre Utrecht and subsequently by local review boards of each participating institute.

| Table 1. Demographic and clinical characteristics of patients and control subjectsa |
|-----------------|-----------------|-----------------|-----------------|
|                  | Patients (N=951)| Controls (N=527)| Between-group comparisons |
| Age              | 27.7 ± 8.2       | 30.4 ± 10.7     | t=5.4            | <.001 |
| Sex (% male)     | 76.2             | 47.1            | χ²=128.3         | <.001 |
| IQ               | 94.7 ± 16.2      | 109.6 ± 15.3    | t=17.1           | <.001 |
| Age at onset of psychosis | 22.4 ± 6.9       | 18.9            |                 |
| Duration of illness in years | 4.4 ± 4.1        | 1.7 ± 1.2       |                 |
| Recent onset psychosis (< 1 year), % | 13.9 ± 6.5       | 15.2 ± 6.7      |                 |
| Number of psychotic episodes | 16.8 ± 6.3       | 15.7 ± 5.6      |                 |
| PANSSb positive  | 12.0 ± 3.9       |                 |                 |
| PANSS negative   | 15.2 ± 6.7       |                 |                 |
| PANSS disorganization | 16.8 ± 6.3       |                 |                 |
| PANSS emotional distress | 15.7 ± 5.6       |                 |                 |
| PANSS excitement | 56.2 ± 15.9      |                 |                 |
| PANSS symptoms   | 54.9 ± 16.0      |                 |                 |
| PANSS disability | 86.8             |                 |                 |
| Current antipsychotics, % | 12.0 ± 3.9       |                 |                 |
| Mean dosec       | 8.1 ± 63.2       |                 |                 |

aTable presents means ± SD, or numbers (in %); bPANSS=Positive and Negative Syndrome Scale; cGAF=Global Assessment of Functioning; dDose of current antipsychotics, haloperidol equivalent.

After full verbal and written information about the study, written informed consent was obtained from all participants before the start of the first assessment.

2.2 Set-shifting tasks

One set-shifting task (response shifting task) was administered to the whole GROUP sample. Part of the sample (the part of the sample that was collected in selected representative
geographical areas in the southern part of the Netherlands and the Dutch-speaking part of Belgium by the Maastricht centre of the GROUP project) was administered a second task assessing set-shifting ability (set-shifting task).

2.2.1 Explicit set-shifting task
The response shifting task (RST), a modified version of the Competing Programs Task (Bilder et al., 1992; Nolan et al., 2004), was administered in order to assess set-shifting ability from an imitation response rule to a reversal response rule. Subjects are presented with the stimulus word “left” or “right” in the middle of the screen and must respond by pressing a key on either the left or right side of the keyboard. Stimuli are presented for 3000 ms, followed by feedback (“correct” or “wrong”) for 1000 ms. During blocks 1 and 3 (imitation), subjects must press the key congruent with the stimulus, e.g. the left key when presented with the stimulus “left”. During blocks 2 and 4 (reversal), subjects must press the key incongruent with the stimulus, e.g. the right key when presented with the stimulus “left”. Each block ends (and the rule changes) after either a maximum of 20 trials or the criterion of eight consecutive correct responses is reached. Subjects must deduce the response rules from trial-by-trial feedback, without explicit instruction.

Outcome variables were accuracy cost (proportion correct in the imitation condition – proportion correct in the reversal condition) and reaction time cost (reaction time in the reversal condition – reaction time in the imitation condition). The first response in each block and responses that were preceded by errors were excluded from analyses (Meiran et al., 2000). In addition, only reaction times for correct responses were used and trials with a reaction time shorter than 150 ms were eliminated from the analyses.

2.2.2 Implicit set-shifting task
In the Set Shifting Task (Cogtest plc, London) (Bilder et al., 1992), subjects are asked to respond as fast as possible to the direction in which a square appears on the computer screen by pressing the corresponding key on the keyboard. In the first phase (30 stimuli), the square appears randomly on either the left or the right side of the screen, in order to establish baseline reaction time. Subsequently, the participant (implicitly) learns the first ‘response set’, which is a simple right-right-left sequence. After some experience with this rule, reaction time usually decreases from the baseline reaction time as subjects learn to anticipate the next stimulus in the sequence. If the participant makes an error or does not respond, a new triad is commenced. Subjects need to perform correctly on 8 sequences (or triads) consecutively for initial set acquisition to be presumed. They are allowed up to 60 individual stimuli to learn the set rule.

Following the initial acquisition phase, without prior warning, the stimulus sequence is reversed (to left-right-right). This shift in response set is usually associated with an increase
in reaction time, slower than the baseline reaction time, the set shifting effect. Again the subject is given up to 60 stimuli to learn this rule. When he or she has performed correctly on 8 sequences of left-left-right presses, the set is deemed acquired and this phase terminates. The initial acquisition phase is then presented again in exactly the same manner, followed by a further change of set, with identical parameters. The subject thus goes through 3 reversals altogether to obtain reliable measures.

Set shifting cost was calculated by subtracting the mean reaction time at the end of the initial ‘response sets’ (last 7 stimuli) from the mean reaction time at the beginning (first 7 stimuli) of the ‘reversal sets’. A shifting cost for accuracy was calculated as well, by subtracting the total errors made during the ‘response sets’ from the total errors made during the ‘reversal sets’.

2.3 Clinical assessment
Recent onset psychosis was defined as ‘no more than 1 psychotic episode with onset in the year prior to the assessment’. The non-recent onset patients had an illness duration of longer than 1 year, or had experienced multiple psychotic episodes. Age at onset was defined as age at first contact with mental health services and was assessed retrospectively using combined information from patients and clinicians. Duration of illness was defined as the onset the period of the first psychotic episode until date of testing, calculated in years. Dose of current daily antipsychotic medication was converted to milligram haloperidol equivalents (Andreasen et al., 2010), excluding extreme outliers of > 3 SD.

Current severity of clinical symptoms was measured with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), which consists of 30 items. Each item is scored on a scale ranging from 1 (absent) to 7 (extreme), with rating incorporating the behavioural effect of symptoms as well as their severity. Originally, the PANSS consisted of 3 domains: a positive and negative syndrome scale and a general psychopathology scale. Later, a more fine-grained, 5-factor structure was developed (van der Gaag et al., 2006a; van der Gaag et al., 2006b), incorporating the factors positive symptoms, negative symptoms, emotional distress, excitement and disorganization. In the current study, we used the 5-factor structure. In addition, current symptoms and functioning were measured with the Global Assessment of Functioning (GAF) scale, adapted from the DSM-IV (American Psychiatric Association, 2000); GAF scores were split into their separate symptom and disability component scores to improve psychometric properties.

2.4 Statistical analyses
First, performance on the implicit and explicit set-shifting task in patients with psychotic disorder was compared to performance in healthy controls. Analyses were run separately for the implicit set-shifting task (SST) and the explicit task (RST), and were conducted for
accuracy cost and reaction time cost scores. Given the fact that some families contributed more than one subject, hierarchical clustering of data was taken into account by including a family random effect in the model, using the multilevel random regression XTREG routine in STATA, version 11 (StataCorp, 2009). Subsequently, if results showed a significant difference in cost in patients compared to controls, clinical correlates of set-shifting cost were explored in patients with psychotic disorder. All analyses were adjusted \textit{a priori} for age and sex. IQ and dose of antipsychotic medication were also investigated to explore independence of effects.

3. RESULTS

3.1 Participants
Response Shifting Task scores were available for 951 patients (84.9%) and 527 controls (89.5%). Set shifting task scores were available for 259 patients and 222 controls. Mean reaction time cost (i.e. increase in reaction time in reversal compared to initial imitation condition) for explicit set-shifting was $M=206.4$ ($SD=234.7$) in patients and $M=195.4$ ($SD=178.2$) in controls. Mean accuracy cost for explicit set-shifting (drop in proportion correct) was $M=.26$ ($SD=.27$) for patients and $M=.22$ ($SD=.25$) in controls. Mean reaction time cost for implicit set-shifting was $M=-65.4$ ($SD=64.4$) in patients and $M=-62.1$ ($SD=49.9$) in controls, mean accuracy cost for implicit set-shifting was $M=.02$ ($SD=.34$) in patients and $M=-.001$ ($SD=.24$) in controls. The subgroup that was administered the implicit set-shifting task did not differ on explicit set-shifting scores compared to the whole sample.

3.2 Implicit and explicit set-shifting ability in patients versus controls
Although patients had significantly more errors ($b=1.34$, 95% CI 1.34-2.34, $p=.008$) and longer reaction times ($b=18.05$, 95% CI 10.31-25.80, $p<.001$) compared to control subjects for the reversal set of the implicit set-shifting task, patients did not show evidence for significant increases in cost for implicit shifting from initial to reversal set (reaction time cost: $b=-4.28$, 95% CI -16.29-7.73, $p=.45$; accuracy cost: $b=.04$, 95% CI -.03-.10), $p=.26$) compared to control subjects. In contrast, patients did show an increased accuracy cost for the explicit set-shifting task ($b=.06$, 95% CI .03-.09, $p<.001$) compared to control subjects. There was no difference between the patient and control group for reaction time cost on the explicit set-shifting task ($b=6.75$, 95% CI -17.89-31.38, $p=.59$).

3.3 Associations between set-shifting and stage of illness
Given that the Response Shifting Task requiring explicit set-shifting showed significant differences between patients and control subjects in accuracy cost of switching, associations between accuracy cost on the RST and clinical variables were explored.

There were no significant differences between recent onset and non-recent onset
patients on accuracy switching cost ($b=.03$, $95\% \text{ CI} -.02-.07$, $p=.26$), both groups performing worse than healthy controls subject in terms of greater reduction in accuracy when shifting to reversal condition ($\text{recent onset}: b=.06$, $95\% \text{ CI} .03-.09$, $p<.001$; $\text{non-recent onset}: b=.04$, $95\% \text{ CI} .03-.13$, $p=.001$). No significant effects were found for number of psychotic episodes ($b=.01$, $95\% \text{ CI} -.01-.02$, $p=.51$).

Although age of onset ($b=.01$, $95\% \text{ CI} .003-.01$, $p<.001$) and duration of illness ($b=.01$, $95\% \text{ CI} .002-.01$, $p=.006$) were both significantly associated with accuracy cost, both variables showed correlation with age ($r>.80$ and $r>.40$, respectively), and the effects disappeared when adjusting for the covariates age and sex ($b=-.001$, $95\% \text{ CI} -.01-.003$, $p=.50$ and $b=.002$, $95\% \text{ CI} -.003-.01$, $p=.45$, respectively), suggesting mediation by age.

### 3.4 Associations with symptoms

Accuracy cost was associated with all five symptom dimensions (positive: $b=.003$, $95\% \text{ CI} .001-.01$, $p=.02$, negative: $b=.003$, $95\% \text{ CI} -.00001-.01$, $p=.052$, disorganization: $b=.007$, $95\% \text{ CI} .004-.010$, $p<.001$, emotional distress: $b=.005$, $95\% \text{ CI} .002-.008$, $p=.001$, excitement: $b=.007$, $95\% \text{ CI} .002-.011$, $p=.004$). Neither current antipsychotic medication status (yes/no) nor dose of antipsychotic medication were related to accuracy cost ($b=.04$, $95\% \text{ CI} -.01-.09$, $p=.15$, $b=.003$, $95\% \text{ CI} -.001-.006$, $p=.13$) and could therefore not explain associations between symptoms and accuracy cost. IQ, however, was significantly associated with accuracy cost ($b=-.003$, $95\% \text{ CI} -.005-.003$, $p<.001$). In a regression model with symptom dimension as dependent variable and set-shifting and IQ as independent variables, set-shifting remained significantly associated with disorganisation and emotional distress ($b=2.17$, $95\% \text{ CI} 60-3.73$, $p=.007$ and $b=2.02$, $95\% \text{ CI} 56-3.48$, $p=.007$, respectively), with IQ also having a significant independent effect on both symptom dimensions (disorganisation: $b=-.11$, $95\% \text{ CI} -.14-.009$, $p<.001$; emotional distress: $b=-.03$, $95\% \text{ CI} -.05-.002$, $p=.03$). In contrast, accuracy cost was no longer significantly associated with the other three symptom dimensions after adjusting for IQ, although there were trend associations for the positive and excitement dimension (positive: $b=1.53$, $95\% \text{ CI} -1.19-3.25$, $p=.08$; negative: $b=.40$, $95\% \text{ CI} 1.32-2.11$, $p=.65$; excitement: $b=.93$, $95\% \text{ CI} -.06-1.93$, $p=.07$). Both GAF symptoms and GAF disability were also significantly associated with accuracy cost ($b=-.001$, $95\% \text{ CI} -.002-.0001$, $p=.03$; $b=-.001$, $95\% \text{ CI} -.002-.0001$, $p=.03$, respectively), but these effects were eliminated when adjusting for IQ ($b=-.001$, $95\% \text{ CI} -.002-.001$, $p=.29$, $b=-.0003$, $95\% \text{ CI} -.001-.001$, $p=.58$, respectively).

### 4. DISCUSSION

The present study investigated set-shifting performance in patients with non-affective psychotic disorder using two different set-shifting tasks. The first aim of the study was to investigate whether altered set-shifting performance in patients was specific to explicit
shifting of response rules or whether implicit shifting of response set would also be altered. The results suggested that patients show evidence for diminished set-shifting ability in terms of relative decrease in response accuracy from imitation to reversal trials compared with control subjects for the explicit, but not for the implicit set-shifting task. These findings are in line with previous suggestions that patients may be more impaired on tasks relying on explicit/declarative mechanisms but not on tasks relying on procedural learning mechanisms (Gold et al., 2008; Waltz et al., 2011). The response shifting task requires negative feedback-based switching of response to a competing response and the additional inhibition of the more natural response (left=press left button), whereas the implicit set-shifting task only requires subjects to abandon a previous successfully learned response sequence. Thus, patients have seemingly no more (relative) difficulty compared to control subjects with adapting to sudden changes in the implicit pattern of responding, but do experience more difficulty when they have to adapt their response rules based on trial-to-trial feedback.

In contrast to previous studies (Elliott and Sahakian, 1995; Hutton et al., 1998; Pantelis et al., 2009), the present findings suggest that explicit set-shifting performance differs already from healthy control performance in recent-onset first-episode patients. Furthermore, set-shifting performance was not associated with number of psychotic episodes; and although duration of illness and age of onset were both associated with RST accuracy cost, these associations disappeared when adjusting for age. Because particularly age of onset showed evidence of collinearity with age ($r > .80$), it is difficult to tease apart the effects of these clinical variables from the effect of age. However, the effect of age on RST accuracy cost was very similar in healthy controls and patients ($b = .005$ and $b = .006$, respectively). Thus, explicit set-shifting ability appears to be already diminished in the early stages of illness and this does not appear to deteriorate with time.

In contrast to previous studies that have linked set-shifting ability specifically to current severity of negative and disorganization symptoms (Leeson et al., 2009; Nieuwenstein et al., 2001; Pantelis et al., 1999), the alteration in set-shifting performance (larger accuracy cost) was associated with all five symptom dimensions of the PANSS, although the association with negative symptoms just missed significance at alpha=.05. However, the association negative symptoms may be more related to general cognitive functioning rather than to set-shifting ability per se, given that the effect was eliminated when adjusting for IQ. Similarly, global assessment of symptoms and disability was also associated with set-shifting ability, but this association also appeared to be more related to general cognitive functioning. In contrast, adjusting for IQ reduced the associations between positive and excitement symptoms to a trend level, but the associations with disorganisation and emotional distress symptoms remained significant. The findings that response shifting performance – a task with simple contingencies (left/right stimulus-response) in contrast to the multicomponential WCST that involves more complex hypothesis testing (Bilder et al., 1992) - showed only modest
correlation ($r = -.21$) with general cognitive ability (IQ), having independent associations with clinical symptoms, suggests that it may measure fairly discrete cognitive processes.

Some limitations should be taken into consideration when interpreting the results. Not all subjects had set-shifting task scores. This was predominantly due to problems related to computerized assessment and data storage, which form a challenge in multi-centre studies (Keefe et al., 2006). However, patient status also affected the number of missing test results. Therefore, it cannot be ruled out that patients with more cognitive alterations were more likely to have missing data, resulting in attenuated effect sizes.

Alterations in set-shifting ability in patients were small (drop in proportion correct from imitation to reversal trials was -27% in patients compared to -21% in controls) and may not be of clinical relevance (expressed in standardized effect sizes: $\beta's < .20$). However, set-shifting ability was associated with disorganization symptoms and emotional distress and these associations, as well as the difference between and patients and controls, remained significant (all $p's < .02$ remain significant) when applying the Simes modification of the Bonferroni correction (Simes, 1986) to control for the risk of type 1 error in the multiple non-independent tests.

In conclusion, the present findings suggest that patients with psychotic disorder, from the first-episode onwards, show a significant, albeit small, decrement in flexibility compared to healthy controls when task demands require the explicit switching of response rules, in contrast to implicit, procedural shifts in response rules for which patients show equivalent flexibility compared to controls. Diminished flexibility in switching between explicit response rules is associated with increased all five dimensions of psychopathology and does not appear to deteriorate over time.