Un deficiente comportamiento direccionado hacia una meta en pacientes con esquizofrenia

Proyecto de investigación para la obtención del título de Master en Ciencias del Cerebro y de la Mente

Laboratorio de Neurociencias del Comportamiento de la Facultad de Medicina
Instituto de Investigación del Cerebro y de la Mente, Universidad de Sídney

El presente proyecto de investigación se realizó bajo la supervisión del Dr. Richard Morris, investigador afiliado del Laboratorio de Neurociencias del Comportamiento de la Facultad de Medicina, Universidad de Sidney.

El modelo computarizado de la tarea de aprendizaje instrumental utilizado para los fines de la presente investigación fue desarrollado por el Dr. Morris y otros (2014). Todos los participantes fueron voluntarios y reclutados de acuerdo al criterio de selección establecido.

El presente proyecto de investigación se realizó en las instalaciones del Laboratorio de Neurociencias del Comportamiento, Instituto de Investigación del Cerebro y de la Mente, Camperdown, Sidney – Australia.
POOR GOAL-DIRECTED BEHAVIOUR IN PATIENTS WITH SCHIZOPHRENIA

RESEARCH PROJECT

MASTER OF BRAIN AND MIND SCIENCES

DANIELA ZIRITT

SUPERVISOR: RICHARD MORRIS

BEHAVIOURAL NEUROSCIENCE LABORATORY
FACULTY OF MEDICINE
BRAIN AND MIND RESEARCH INSTITUTE
THE UNIVERSITY OF SYDNEY

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Poor goal-directed behaviour in patients with schizophrenia

Abstract

Goal-directed behaviour depends on two systems: 1) the acquired knowledge of the association between an action and its consequences; and 2) the value given to those consequences (Griffiths, Morris and Balleine 2014; Dolan and Dayan 2013; Balleine and Dickinson, 1998; Dickinson and Balleine. 1994). Poor goal-directed behaviour in schizophrenia may be related to a deficiency in one of the systems or furthermore it may rely in an inability to integrate both systems correctly. The present study tested twenty one healthy adults (HA) with no personal or familial history of psychosis, and 14 people with schizophrenia (SZ) or schizoaffective disorder and no other disorder with age between 26 and 65 years old, using a computerized model of an instrumental learning task. The aim of the study was to determine SZ capacity of learning the reward contingencies of each action (Contingency test), and their ability to learn the causal relationship between the action and outcome (A-O) (Degradation test). The different results obtained between the contingency and degradation tests in SZ suggest a possible impairment in learning A-O associations when random outcomes -an outcome delivered in the absence of its associated action- were included. Furthermore, this impairment of goal-directed behaviour in SZ correlated with self-reported disability (WHODAS) \( r = -0.39, p = 0.03 \).

Introduction

Goals play an important part in how we model our behavior (Dayan 2009). Goal-directed behaviour is flexible, allowing us to succeed in the adaptation to a changing environment
and to make the best choices for our course of actions, controlling the environment according to our desires and needs (Griffiths, Morris and Balleine 2014; Dickinson and Balleine 1994). Important decisions of our life are goal-directed. Goal-directed actions are those actions taken in pursuit of desired consequences, and they depend on two systems: 1) the acquired knowledge of the association between an action and its consequences; and 2) the value given to those consequences (Griffiths, Morris and Balleine 2014; Dolan and Dayan 2013; Balleine and Dickinson 1998; Dickinson and Balleine 1994).

Poor goal-directed actions may show a deficiency in understanding the causal consequences of actions or in the formation of reward value; or furthermore it may rely in an inability to integrate both systems correctly (Griffiths, Morris and Balleine 2014; Balleine and O’Doherty 2010; Balleine and Dickinson 1998). Impairment in this type of behaviour results in incapacity to choose the best course of action and meet goals, and is implicated in the symptomatology of schizophrenia, showing significant functional disability as, for example the inability to gain or maintain employment or education (Griffiths, Morris and Balleine 2014).

Studies using the reward system through instrumental learning tasks (e.g., reversal learning) have shown that schizophrenia’ symptomatology does not compromise all aspects of the reward processing (Waltz and Gold 2007; Murray et al. 2008; Gold et al. 2008). Patients with schizophrenia (SZ) are capable of learning about reward contingency; but when new information is provided they demonstrated an inability to use it to guide their behaviour (Waltz and Gold 2007; Shanks 1993; Shanks and Dickinson 1991). This shows patients can learn the reward contingency of their actions; however they are slow or unable to update this learning under the new contingencies, consistent with a deficit in understanding the causal relationship between their action and consequences. To determine if an impairment exists in their capacity to learn the causal consequences of their actions, the present study tested SZ ability to form and use action-outcome (A-O) associations using contingency degradation tests, in which an outcome is delivered in the absence of its associated action, degrading that particular A-O association (and the causal status of that action). Manipulating the causal relationship between action and outcome in this particular way
allows us to degrade the contingency without modifying the reward contingency of each action (i.e., probability of occurrence of the paired reward) (Balleine and Dickinson 1998).

Instrumental learning in human and animal models have demonstrated that both are sensitive to the causal relationship between actions and outcomes (i.e., learning A-O associations), and have the ability to increase or minimize their actions accordingly to this causal learning (Colwill and Rescorla 1985; Balleine and Dickinson 1998; Dayan and Balleine 2002; Dolan and Dayan 2013). Balleine and Dickinson (1998) trained rats in two instrumental responses, lever pressing and chain pulling, each one reinforced with a different reward, starch solution or food pellets; both delivered with the same probability. Then one of the rewards was delivered under a non-contingent schedule (i.e. for free) which degraded the causal status of the action. Consequently, this resulted in a diminished performance of the degraded action. Shanks and Dickinson (1991) found similar results in healthy humans, when measuring causal ratings and number of responses performed in a contingency test. The non-contingent A-O association produced lower ratings of causal judgment in comparison with the contingent action.

We hypothesize that SZ would be capable of learning the different reward contingencies of each action (Contingency test), but would be insensitive to the causal relation between action and outcome, resulting in impaired causal learning in an instrumental contingency degradation test. Furthermore, this impairment of goal-directed behaviour in SZ could be correlated with symptoms of the disease such as avolition, and with real world functions assessed by self-reported measures of health and disability. Determining if the impairment of goal-directed behaviour in SZ is related to the understanding of the causal association between action and outcome, may help predict the neurobiological pathology underpinning this process and improve possible therapeutic treatments like Cognitive Behaviour Therapy (CBT).

Subjects & Methods

Participants
Twenty one healthy adults (HA) with no personal or familial history of psychosis, and 14 people with schizophrenia (SZ) or schizoaffective disorder and no other disorder with age between 26 and 65 years old were included after meeting the inclusion criteria (Table 1). In HA there was no personal and family history of mental disorders, no substance abuse, and they received no psychiatric medications.

**Materials**

Analogous to the method applied by Morris et al. (2014), we used a computerized model of an instrumental learning task, a two-button response box, and three different food rewards: chocolate cookies, chocolate candies, and BBQ flavoured crackers.

**Procedures**

All participants provided a written consent form after reading and being briefed with the aims and procedures of the study. They also completed a pre-testing questionnaire which included health and disability self-evaluation (WHODAS), and the depression, anxiety and stress scale (DASS). Using a 7-point Likert scale, participants were asked to rate how hungry they were at the moment of the test with one denoting not hungry at all and 7 as very hungry. Participants were then provided with the three food rewards (chocolate cookies, chocolate candies, and BBQ flavored crackers) and were asked to rate how pleasant they found each reward. According to the desirability ratings, two of the food rewards were selected for the contingency degradation tests.

**Contingency Test**

To test the ability of participants in learning the reward contingency, a pilot study was performed using variations in the contingencies between actions and rewards. Participants could perform two actions, tilting the vending machine to the right or the left using the two bottom response box, and each action was paired with a particular food reward (Figure 1A). Six trials of spanning 1-minute each were completed. In each trial one of the actions had a higher probability of releasing the reward. This action needed to be identified as the best action before moving to the next stage (degradation testing). Participants were asked in all the trials to rate in a 7-point Likert scale how causal they found each of the actions (tilting...
the vending machine to the right or to the left to obtain the food reward), considering one as a non-causal relationship and 7 as very causal. The best action changed from trial to trial, which tested the participant’s capacity to adapt.

Figure 1. Example of trials for A) Contingency Test: tilting the vending machine to the left is paired with the BBQ flavoured crackers as the food reward, and to the right is paired with the chocolate candies; and B) Degradation Test: both actions (tilting the vending machine to the right and left) keep the same food outcomes as learned during Contingency Test but a free food outcome is introduced in the absence of its associated action, in this case the BBQ flavoured crackers.

After the pilot study, a second test was carried out to determine the participants’ capacity to learn each A-O contingency when one A-O contingency was degraded with free outcomes.

*Degradation Test*

After the pilot study, a second test was carried out to determine the participants’ capacity to learn each A-O contingency when one A-O contingency was degraded with free outcomes.
As in the previous test, six trials of 1-minute each were performed and after each trial participants were asked to rate how causal their actions were. However in this case both actions had the same probability of releasing the food outcomes and one of the food outcomes was selected to appear also at random. Participants were given the following instructions: “The vending machine is now delivering one of the outcomes at random, whether you press the button or not. In the next test, you need to figure out which outcome you still have control over and which one is random. Use this information to choose the best action and consider waiting as a good strategy to help you determining which action is more effective.” (Figure 1B)

Additional Assessment

Participants completed a working memory task: number-letter sequencing and a test of pre-morbid IQ: the Wechsler Test of Adult Reading (WTAR). Severity of positive and negative symptoms in SZ were assessed by a trained psychologist using the Scales for the Assessment of Positive and Negative Symptoms (SAPS/SANS).
Table 1. Clinical and neuropsychological results for patients with schizophrenia (SZ) and healthy adults (HA), Mean (SEM)

<table>
<thead>
<tr>
<th></th>
<th>SZ (n= 14)</th>
<th>HA (n= 24)</th>
<th>t Value (df = 36)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>45.6 (2.5)</td>
<td>49.2 (1.7)</td>
<td>1.25</td>
<td>.22</td>
</tr>
<tr>
<td>Female Subjects</td>
<td>3</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edinburg Handedness Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years of Education</td>
<td>14.1 (.4)</td>
<td>14.7 (.4)</td>
<td>.94</td>
<td>.35</td>
</tr>
<tr>
<td>WTAR IQ</td>
<td>104.2 (4.6)</td>
<td>105.8 (2.2)</td>
<td>.24</td>
<td>.81</td>
</tr>
<tr>
<td>DASS-21 Scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>12.6 (2.9)</td>
<td>5.2 (1.3)</td>
<td>2.64</td>
<td>.01</td>
</tr>
<tr>
<td>Anxiety</td>
<td>8.9 (1.9)</td>
<td>3.3 (.9)</td>
<td>2.97</td>
<td>.01</td>
</tr>
<tr>
<td>Stress</td>
<td>13.6 (2.6)</td>
<td>8.4 (1.6)</td>
<td>1.81</td>
<td>.08</td>
</tr>
<tr>
<td>BIS/BAS Scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIS</td>
<td>21.5 (.9)</td>
<td>19.0 (.8)</td>
<td>1.94</td>
<td>.06</td>
</tr>
<tr>
<td>BAS-reward subscale</td>
<td>16.4 (.6)</td>
<td>16.0 (.5)</td>
<td>.54</td>
<td>.59</td>
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<tr>
<td>BAS-drive subscale</td>
<td>10.8 (1)</td>
<td>10.5 (.6)</td>
<td>.31</td>
<td>.76</td>
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<tr>
<td>BAS-fun-seeking-subscale</td>
<td>10.1 (.7)</td>
<td>10.8 (.5)</td>
<td>.77</td>
<td>.45</td>
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<tr>
<td>SAPS</td>
<td>34.36 (5.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SANS</td>
<td>38.14 (4.7)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

BAS, Behavioural Approach System; BIS, Behavioural Inhibition System; DASS-21, Depression Anxiety Stress Scale-21; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; WTAR, Wechsler Test of Adult Reading.

Antipsychotic drug treatment of SZ includes: olanzapine n = 3; clozapine n = 5; paliperidone n = 1; aripiprazole n = 3; fluphenazine n = 1; risperidone n = 1.

Results

Figure 2 exhibits the mean causal rating results of each group for each action in the Contingency Test. Both groups were sensitive to the difference in reward contingency between actions, and rated the action with the highest contingency more than the action with the lowest contingency (p < 0.05). No group differences were significant, p < .05. The
mean (SEM) causal ratings in HA for the high contingency action (Hi) was 4.98 (±.20) and for the low contingency action (Lo) 2.83 (±.12), t(22) = 7.60, p < 0.001. In SZ causal ratings for Hi and Lo contingency actions were 4.64 (±.23) and 3.50 (±.26) respectively, t(12)= 3.13, p = 0.008.

![Contingency test](image)

**Fig. 2**: Results of the contingency tests. Both HA and SZ rated higher the high contingency action (Hi) in comparison with the low contingency action (Lo). Mean (SEM) ratings in HA for Hi is 4.98 (±.20) and Lo is 2.83 (±.12), t(22) = 7.60, p < 0.001; mean (SEM) ratings in SZ for Hi is 4.64 (±.23) and Lo is 3.50 (±.26), t(12)= 3.13, p = 0.008. No group differences were significant, p < 0.05.

The focus of our study was the degradation test to determine whether participants could learn the causal relation between their actions and outcomes when the reward contingencies were equal. HA were able to identify the outcome that was random and to rate as more causal the causal action (p < 0.05). Among HA, the mean (SEM) causal ratings for the non-
degraded and degraded actions were 4.28 (±.23) and 2.93 (±.25) respectively, $t(21) = 3.68$, $p = 0.001$. In the case of SZ, results show some level of impairment in differentiating the random food outcome and in identifying the more causal action. Among SZ, the mean (SEM) ratings for the non-degraded outcome was 4.15 (±.40) and for the degraded 3.55 (±.40), $t(12) = 0.82$, $p = 0.43$ (Fig. 3).

Fig. 3: Results of the degradation test. In HA degrading one A-O contingency selectively reduced that action and its causal status ($p < 0.05$). Mean (SEM) ratings in HA for non-degraded is 4.28 (±.23) and for degraded 2.93 (±.25), $t(21) = 3.68$, $p = 0.001$. In the case of SZ there is no difference in ratings, mean (SEM) for the non-degraded 4.15 (±.40) and for the degraded 3.55 (±.40), $t(12) = 0.82$, $p = 0.43$.

The different results obtained between the contingency and degradation tests in SZ suggest a possible inability to identify A-O associations when variables as random outcomes -an outcome introduced in the absence of its associated action- is included. SZ received a mean
(SEM) of 3.37 (±.32) free food outcomes during the test. This showed that even when the outcomes were given randomly, SZ were unable to use the information and identify the best action. These results suggest the reward contingency rather than the causal relationship between action and outcome determines the causal status in SZ.

An important observation among the SZ group is the fact that five of the fourteen patients rated correctly as more causal the non-degraded outcome and one rated both non-degraded and degraded as equal. The rest rated the degraded outcome as more causal. This heterogeneity could provide significant information for the understanding of the impact of poor motivational learning in real-world features as reported by Morris et al. (2014). Considering all the participants that completed the World Health Disability Assessment (WHODAS), (HA = 16, SZ = 14), our preliminary results show a correlation between the ratings reported among all volunteers (n = 30) during degradation test and the self-reported scores for the WHODAS’ ‘Participation in society’ domain, \( r = -0.39, p = 0.03 \). Ratings deltas for the degradation test were calculated considering the contingent action minus the degraded outcome.

**Discussion**

The contingency degradation test performed in the present study has shown that deficits in goal-directed behaviour in SZ could be related to an inability to integrate new information, such as outcomes that appear at random, with the acquired knowledge of causal relationship between actions and consequences in order to guide choice for the best course of action. As we hypothesized, both SZ and HA groups, were sensitive to reward contingency, and were accurate in discriminating and identifying the action with the higher probability of delivering the paired reward from trial to trial, and rating it as more causal. Waltz and Gold (2007) reported similar results using reinforcement and reversal learning tasks. During the initial discrimination learning task participants learned to select the stimuli more-frequently reinforced (one stimuli was reinforced 80% of the time and the other one only 20%), and with both controls and patients with schizophrenia groups found to achieve initial discrimination (Waltz and Gold 2007). Considering this and other previous studies (e.g.
Starks and Dickinson 1991; Balleine and Dickinson 1998; Murray et al. 2008) our results for the Contingency Test support the statement that SZ as well as HA are capable of learning reward contingency and able to adapt the causal ratings to the changes in contingencies.

In the case of the Degradation Test, the early stage of our study meant that the significant differences between groups (HA and SZ) could not be reported. However, results for the causal ratings suggest that SZ were unable to update the causal status of the A-O associations when an outcome was introduced in the absence of its associated action. HA were more accurate in their causal ratings demonstrating their capacity to identify the outcome provided randomly and use this information to update the causal knowledge already acquired.

Liljeholm et al (2011) found that during a degradation test performed with healthy participants, the causal judgments remained constant and high when the conditional probability of the reward following the performed action was higher than the probability of the reward without the action. Similarly, Shanks and Dickinson (1991) reported that the non-contingent A-O association produced lower ratings of causal judgment in healthy participants. These findings demonstrate that causal judgment is influenced by the probability that the reward will occur in the absence of the action. These results from human models akin the ones obtained by Balleine and Dickinson (1998) in their animal model of instrumental learning. By keeping constant the reward contingency and increasing the reward delivered in a non-contingent schedule, the performance of the non-contingent action was selectively decreased (Balleine and Dickinson 1998).

The ability displayed during the Degradation Test of our study by HA (n = 24) and five of the fourteen SZ (n = 5) in updating the causal status of the A-O associations when the reward contingencies were kept equal and an outcome was delivered in the absence of its associated action, suggests that the causal status of the action is determined by the causal relationship rather than by the reward contingency. This provides important evidence that the formation and use of causal associations between action and outcome model goal-directed behaviour.
However, the inability demonstrated by the majority of SZ subjects (n = 9) in identifying the causal outcome and consequently rating as more causal the non-degraded outcome seems to be related with an incapacity of using feedback to update the causal status of the actions. During the Degradation Test all SZ received free food outcomes in each of the six trials, corroborating that feedback was provided. As demonstrated by Murray et al. (2008) during the performance of reversal learning tasks, in which feedback was given to the participants to teach them that the previous correct response became incorrect, patients with schizophrenia showed more reversal errors that healthy participants. Waltz and Gold (2007) also reported significant group differences among controls and patients with schizophrenia when the probability of a reinforce stimuli was reversed after participants learned and identified the stimuli reinforced with 80% frequency during the discrimination learning task. This result from Waltz and Gold (2007)’ study demonstrated that patients with schizophrenia found difficult to update and change their actions according to the new information given. Furthermore, this inability to use feedback could be an important part of the impairment of goal-directed behaviour of SZ that we suspect could be correlated with real world functions assessed by self-reported measures of health and disability. A larger sample size would allow us to verify these early results and corroborate the correlation found at the moment between the ratings obtained during Degradation Test by HA and SZ and the self-reported scores for the WHODAS’ ‘Participation in society’ domain.

This possible deficit in causal learning exhibited by SZ provides valuable evidence for the improvement of psychosis’ treatment. Treatments such as CBT are support by the client’s capacity to understand that changing a particular action identified as the trigger for some of the symptoms experienced will change the outcome associated with it. CBT targets symptoms by changing cognitive and behavioural patterns. If the client is incapable of understanding the causal status of his actions, such as in the case of SZ, this type of treatment would not produce the expected results or may take longer periods of time.

Additionally, degradation test performed in animal models has identified a dorsomedial cortico-striatal circuit as the neurobiological system underpinning goal-directed behaviour (Balleine and O’Doherty 2010). For example lesions in the prelimbic cortex (PC) of the rat’s brain made them insensitive to changes in the action-outcome association (Balleine
and Dickinson 1998). In humans, Liljeholm et al. (2011) reported the ventral medial Prefrontal Cortex (vmPFC) and the right anterior Caudate Nucleus (aCN) were activated when the action was causal with respect to the outcome. These neurobiological findings point to important potential targets for identifying the neuropathology underlying goal-directed deficits in schizophrenia.

**Limitations**

All SZ were taking antipsychotic medication during the time of this study, which is a potential confound in our results. Reliable conversion factors for many of the antipsychotic treatments do not exist (e.g., for clozapine, aripiprazole and palliperdone the mechanism of action is unclear), so we could not convert drug doses to standard units for an ANCOVA to remove this confound. Further studies using a younger sample of first-episode patients (without medication) or even healthy participants with high schizotypy scores may provide important evidence for the possible influences of antipsychotic on goal-directed learning.

**References**


Morris RW, Quail S, Griffiths K, Green M & Balleine BW 2014, ‘Corticostriatal control of goal-directed action is impaired in schizophrenia’, Biol Psychiatry.


