Author's response to reviews

Title: Incentive Motivation Processing in First-Episode Psychosis: a Behavioural Study

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Author's response to reviews: see over
Dear Editor

We thank you and the reviewers for commenting on our manuscript. We have revised the manuscript accordingly and we detail our responses to the comments below. We hope that you will reconsider our paper, one of the first to demonstrate deficits in an objective, laboratory based, measure of incentive motivation in psychosis, for publication in BMC Psychiatry. I can confirm that all authors have seen and approved the revised manuscript.

Yours sincerely

Dr Graham Murray on behalf of all the authors.

REVIEWER 1

COMMENT 1. It would be useful to provide more descriptive information about the participants. Were the patients tested near the time of entry into the CAMEO program or at some later time point? Was the medication-free group neuroleptic naïve, or off medications for a certain time period prior to study entry – were they off all medications or just antipsychotics? Were any patients in an episode of depression at the time of assessment? Were patients and controls matched on characteristics other than age and sex? How were controls screened?

AUTHOR RESPONSE: We have now expanded the section on participants. 11 of the 18 patients were taking antipsychotic medication; all of these 11 were
taking “atypical” antipsychotic agents with a mean chlorpromazine equivalent dose of 264mg. Of these, 3 were taking olanzapine (10mg daily) 2 risperidone (1mg daily and 3 mg daily), 2 quetiapine (500mg daily and 400mg daily), 2 aripiprazole (10mg daily and 15mg daily), 1 amisulpride (200mg daily) and 1 clozapine (400mg daily). Of the 7 antipsychotic-free patients, 5 were taking no medication, 1 was taking sertraline and 1 was taking sodium valproate. Only 1 of the 6 antipsychotic free patients had briefly previously taken neuroleptics, but had stopped 2 weeks before cognitive assessment. Patients were not tested immediately upon referral, but were, in general, tested as soon as possible after their clinical condition stabilised and permitted cognitive assessment, which resulted in over 75% of the sample being assessed within 5 months of referral. The remaining patients were all tested within 12 months of referral. When controls responded to the advertisement for the study, they were screened using a locally devised telephone interview where they were asked if they had ever suffered from any mental illness or alcohol or drug addiction; controls were excluded from this study if any pathology was identified. If they met the inclusion criteria on telephone interview and entered the study, then, prior to the cognitive assessment, an unstructured medical history was taken by a psychiatrist (LP), who also rated current psychopathology in controls using the BPRS. Again, any psychiatric illness identified here resulted in exclusion.

**COMMENT 2. There is a discrepancy in the number of patients reported – were there 18 or 19?**
AUTHOR RESPONSE: The sample size is 18 patients. The comment of “12 of the 19 patients were taking antipsychotic medication” is a typographic error, for which we apologize and which we have now corrected. It should read “11 of the 18 patients were taking antipsychotic medication”.

 COMMENT 3. More information should be provided about the CRRT – there is no description of the number of trials or the parameters of the task (e.g., where equal number of 10, 50, and 90% trials administered; responses made with dominant hand?)

AUTHOR RESPONSE: We have now expanded the description of the CRRT. Responses were indeed made with the dominant hand. 40 trials were administered in practice, and 96 trials were administered in the test, with 32 trials of each cue-type. Thus, equal numbers of 10%, 50% and 90% trials were indeed included.

 COMMENT 4. The Methods section would flow better if the Data analysis section was moved after the description of the neuropsych tests.

AUTHOR RESPONSE: We have now changed the order in accordance with this suggestion.

 COMMENT 5. It is not clear exactly how subjects were classified as showing a reaction time effect on the CRRT – does this simply mean RT’s on 90% trials
were lower than on 10% trials by any amount, or was a specific cut-off score used to infer that there was a meaningful effect?

AUTHOR RESPONSE: We defined a categorical reward related speeding effect as meaning that mean RT on the 90% trials was lower than mean RT on 10% trials (by any amount). Additionally, we also analyse the test using continuous measures, in order to examine the degree or extent of reward related speeding.

COMMENT 6. The authors indicate that spatial working memory scores did not relate to CRRT performance and conclude that these tests measure independent constructs. Although the correlation was non-significant within the small patient sample, it was in the medium range (.35) – this non-trivial relationship does not support an interpretation of independence. This association appears broadly consistent with the recent study by Heery & Gold (2007).

AUTHOR RESPONSE: this is an interesting comparison, and we now comment on this is the discussion.

COMMENT 7. It would be interesting to know whether CCRT performance correlates with different types of clinical symptoms within the patient group.

AUTHOR RESPONSE: There was no correlation between CRRT performance and either positive or negative symptoms. We now include this in the results section.
COMMENT 8. The patient sample includes a mix of schizophrenia/schizoaffective patients and patients with other psychotic disorders (bipolar, delusional, NOS). The conceptual link between the incentive motivational process captured by the CRRT and certain negative symptoms of schizophrenia is clear. Do the authors believe this paradigm can also shed light on other clinical phenomena – e.g., psychotic symptoms that patients with bipolar or delusional disorder (who often do not have negative symptoms) may experience? If so, some discussion would be helpful.

AUTHOR RESPONSE: As we very briefly alluded to in the introduction, previous theorists have argued that reinforcement learning and incentive motivation deficits could predispose to, or underlie, psychotic symptoms, and therefore could be common to both affective and non-affective psychosis (eg Miller et al 1993: “Striatal dopamine in reward and attention: a system for understanding the symptomatology of acute schizophrenia and mania”). However, as both reviewers ask us to expand on the rationale for examining motivational processing abnormalities in non-schizophrenic psychoses, we have extended the introduction to clarify this issue.

REVIEWER 2
COMMENT: Sample size and selection: The authors explored their hypothesis in a sample of 18 patients (although in the text (page 5) is say that 12 of the 19 patients). It is definitively a small sample for cognitive studies. May the author provide the statistical power of this sample to detect small differences between groups?

AUTHOR RESPONSE: The sample size is 18 patients. The comment of “12 of the 19 patients were taking antipsychotic medication” is a typographic error, for which we apologize and which we have now corrected. It should read “11 of the 18 patients were taking antipsychotic medication”.

The reviewer is correct in that it is a comparatively small sample, which we acknowledge in our discussion. However, the modest sample size did not preclude demonstrating a significant difference between patients and controls. In view of the long history of speculation of motivational and reinforcement learning abnormalities in psychosis despite the comparative absence of empirical evidence, we argue that our work does nevertheless make a contribution to the field. We agree that given the small sample size, it is important for us to clarify the degree of statistical power in our analyses. We now provide a power calculation, which, as it is a retrospective analysis, we include in the additional material:

In order to determine the proportion of patients showing reinforcement related speeding in a Chi-square test, given that 90% of controls show this effect, there
is 80% power to detect the alternative hypothesis, with a Type 1 error probability of 0.05, that 50% of patients or less show reinforcement related speeding. As the data show, in fact only 22% of patients showed reinforcement related speeding, thus our sample of 18 patients provided over 95% power.


COMMENT: It is unclear why the authors included affective and non-affective psychosis. It is widely accepted nowadays that bipolar and schizophrenia differs in the profile of cognitive deficits.

AUTHOR RESPONSE: In our study there was no significant difference on any test between patients ultimately diagnosed with schizophrenia and those ultimately diagnosed with bipolar disorder: we now comment on this in the text. The justification for studying first-episode psychosis, as opposed to schizophrenia or bipolar disorder etc, is partly pragmatic and partly theoretical. In early psychosis, it is often not possible to make DSM-IV diagnoses such as schizophrenia, as patients have not been unwell long enough to assign a diagnosis of schizophrenia, which requires a duration of illness of 6 months or more (see Barnett et al 2005). For these pragmatic reasons, we assessed patients as soon as possible after their clinical condition stabilised and permitted cognitive assessment, and then followed up the patients, gathering all available
clinical information, in order to assign diagnoses 12 months after the initial assessment.

For the theoretical arguments, as regards reinforcement learning and incentive motivation, as we briefly allude to in the introduction, previous theorists have argued that deficits here could predispose to, or underlie, psychotic symptoms, and therefore could be common to both affective and non-affective psychosis (Miller et al 1993). As reviewer 1 also asked us to expand on the rationale for examining motivational processing abnormalities in non schizophrenic psychoses, we have now extended the introduction to clarify why reward processing dysfunction may be common to affective and non-affective psychosis.

In a more general sense, we note that the classic Kraepelinian dichotomy between schizophrenia and bipolar disorder continues to be debated, and whilst it is true that a number psychiatrists and researchers do believe it is valid, a number of other authors argue against the validity of this distinction (Craddock and Owen 2007: Rethinking psychosis: the disadvantages of a dichotomous classification now outweigh the advantages World Psychiatry. 2007 June; 6(2): 20–27.). Although reviewer 2 argues that it is accepted that there are different cognitive deficits in bipolar disorder and schizophrenia, some of the studies that have led to this dichotomy focus on chronic samples, and in some studies of bipolar cognition, patients with bipolar psychosis are not distinguished from patients without psychosis. Perhaps there are different views in the field of early
psychosis, where many clinical research services and research studies (although not all) investigate psychosis per se rather than 1st episode schizophrenia. We follow the recommendation of McGorry et al 1998: “Our recommendation, one which is supported by these data as well as other arguments (McGorry et al. 1990a, 1996), is that, in early psychosis in particular, the focus should be on psychosis rather than schizophrenia if progress in both basic research and clinical care is to progress.” P.D. McGorry, R.C. Bell, P.L. Dudgeon and H.J. Jackson The dimensional structure of first episode psychosis: an exploratory factor analysis. Psychol. Med. 28 (1998), pp. 935–947.

To set the context, we list here, a selection of recent studies that have followed McGorry 1998 and examined cognition, or brain structure/function, in first episode psychosis (as opposed to studying specific Kraepelinian diagnoses). For example, Ayres et al 2007, one of the largest studies of cognition in first episode psychosis to date, and which included patients with affective and non-affective psychosis, and did not find any significant differences between schizophrenia and bipolar disorder. Other examples include Cuesta et al 2002, Wood et al 2003, Sanders et al 2004, Barnett et al 2005, Schaufelberger et al 2005, Dazzan et al 2005, Lappin et al 2006, Vermissen et al 2007.


Paola Dazzan, Kevin D Morgan, Ken Orr, Gerard Hutchinson, Xavier Chitnis, John Suckling, Paul Fearon, Philip K McGuire, Rosemarie M Mallett, Peter B
COMMENT:

*Another relevant confounder may be the fact that 12 patients were taking antipsychotics. Due to the differential effects of antipsychotics in cognition, a detailed description of concomitant medications, types and doses of...*
antipsychotic is warranted. It is unclear that the rest of patients (N=6) were
drug-naïve or drug free. This issue is relevant owing by the fact that these are
acutely ill patients. It has been stated that valid and reliable cognitive evaluation
in first episode would not be conducted before week 12. I also suggest including
some additional information regarding the comparison between treated and
untreated patients.

AUTHOR RESPONSE:
It is true that a limitation of the study, as in most psychosis studies, is that some
patients were taking medication, which we do acknowledge as a limitation in the
discussion. We have now included the exact doses of medications used. “11 of
the 18 patients were taking antipsychotic medication; all of these 11 were taking
“atypical” antipsychotic agents with a mean chlorpromazine equivalent dose of
264mg. Of these, 3 were taking olanzapine (10mg daily) 2 risperidone (1mg
daily and 3 mg daily), 2 quetiapine (500mg daily and 400mg daily), 1 clozapine
(400mg daily), 2 aripiprazole (10mg daily and 15mg daily), and 1 amisulpride
(200mg daily). Of the other 7 antipsychotic-free patients, 5 were taking no
medication, 1 was taking sertraline and 1 sodium valproate. Only 1 of the
antipsychotic free patients had previously taken antipsychotics. We note, that the
groups with and without antipsychotic medication both showed deficits – so it is
unlikely that these results are driven by the differential effects of antipsychotic
drugs. We did state that most patients had mild symptoms, but we should have
made it clearer that patients were allowed to stabilize before cognitive assessment, and we now do so.

COMMENT:

*It is unclear whether the authors present their results as the proportion of participant in each group with cognitive impairments. The authors should make clear their rationale for using this statistical approach.*

AUTHOR RESPONSE: We presume the comment is intended to read “it is unclear why the authors present their results as the proportion of participants in each group with cognitive impairments.” It is standard practice, when analysing the ID-ED attentional set-shifting task, to examine the proportion of patients passing all stages of the test. Regarding the CRRT, we were interested in the *presence* of reinforcement related speeding (thus a dichotomous variable which necessitates using a Chi-Squared test), and the *degree* of reinforcement related speeding (a continuous variable which necessitates using appropriate tests, in this case, Analysis of Variance).

COMMENT: Do the authors assess drug history or drug (caffeine, alcohol, cannabis, ….) consumption during the day of evaluation? Would they expect that differences between female and male in this cognitive test?

AUTHOR RESPONSE: Given that, to date, rather few studies in humans have examined reinforcement learning and motivational processing, (in spite of the
clear relevance of these processes for psychiatric research) it is difficult to comment on whether we should expect sex differences. We hope our article will encourage other groups to investigate this area in more detail in both healthy and psychiatric populations. No patients had taken alcohol or illicit drugs on the day of the assessment. We did not assess caffeine use on the day of the assessment.

COMMENT: The fact that first-episode psychotic patients did not show cognitive deterioration in attention, executive and spatial working memory is unexpected. The authors may discussed why they did not find cognitive deficits in contrast to previous literature describing moderate-marked (1.5-2 SD below) deficits.

RESPONSE: As we state in the results section, patients did show impairments in spatial working memory, and as we state in the discussion, there is previous evidence from Pantelis and McGorry’s group that this measurement may be a particularly sensitive measure in early psychosis. Our patients showed intact attentional set-shifting; this finding converges with other studies such as the West London Study of First Episode Schizophrenia, which demonstrated that attentional set-shifting function may be comparatively unaffected early in the course of psychotic illness also (Joyce et al 2005, Hutton et al 1998). As far as we are aware, no previous study has examined the RVIP test in first episode psychosis.