Understanding and translating Working Memory Deficits in schizophrenia into treatment Schizophrenia Research Fund & Mental Health Research UK Joint Award

John Grace QC PhD Scholarship 2014, City University, London, Department of Psychology and Unit for Social and Community Psychiatry

Supervisors: Dr Corinna Haenschel and Professor Stefan Priebe.

Summary:

Even when they are not experiencing acute psychiatric symptoms people living with Schizophrenia have problems in everyday life and social interactions. It is widely accepted that treatments for schizophrenia need to do more to improve everyday life, which requires understanding and targeting of the underlying causes of these problems. Working Memory (WM) is the ability to hold and manipulate information for brief periods of time and is critically important for performing virtually all everyday tasks. Impairment of WM is a common feature of schizophrenia often apparent before the onset of obvious psychiatric symptoms that is linked to problems of daily life. WM is often divided into three stages, encoding (putting things into WM), storage (holding them in WM) and retrieval. Researchers in schizophrenia have generally examined problems in storage and retrieval. However, the project supervisor has shown that many of these problems may start when encoding things into WM. This project will extend the research to identify and treat the causes of encoding difficulties. This will be done by examining the effects of altering the visual properties of items on WM and resulting brain activity. This information will be used to develop a behavioural training programme to improve WM. This should benefit patients' day-to-day life, increase the effectiveness of other treatments and if used in people with high risk reduce the likelihood of onset of the disorder.

Research Student: Cristina Filannino

I am very glad to have been awarded the John Grace QC scholarship to pursue a PhD at City University London and Queen Mary University of London.

I will be supervised by Dr. Corinna Haenschel, Senior Lecturer in Psychology and Cognitive Neurosciences, and Professor Stefan Priebe, Professor for Social and Community Psychiatry.

My project will be about the study of working memory deficits in Schizophrenia and how these can be ameliorated with a cognitive training.

It has been demonstrated that Working Memory, a cognitive ability used widely in everyday life, is severely impaired in Schizophrenia and this has a big impact on patients quality of life. For instance, working memory performance in Schizophrenic patients seems to be a predictor of employment status and poor social functioning. Moreover, cognitive deficits

may also be an obstacle to the success of other pharmacological and behavioural treatments.

The aim of my project is to study the brain mechanism underlying working memory dysfunctions in Schizophrenia by recording activity using electrodes on the scalp. The second aim is to use this knowledge to develop a cognitive training programme that targets the impaired brain system responsible for these deficits. The hope is that this will lead to improve patients' everyday living in terms of occupation and general social skills.

I have already had the chance to study working memory at the University of London in a research project funded by "Placement Abroad" scholarship I was awarded by La Sapienza, University of Rome. Now I am very pleased to have the opportunity to apply this knowledge in a clinical setting.

I am really enthusiastic about this PhD project and I will be very honoured to make a contribution to the understanding of the neural correlates underlying a severe mental illness such as Schizophrenia.

I would like to thank "Mental Health Research UK" for giving me this opportunity and above all for raising funds for research in mental illnesses. Without funding for research it would be hard to expand the knowledge about the topic, preventing the chance to improve patients' quality of life.

Start date: September 2014

Goal: To improve the quality of everyday life and social functioning in people with Schizophrenia by identifying and treating underlying working memory problems.

PhD final report: Cristina Filannino

Department of Psychology – City, University of London, 2014-2018

Title of the thesis: "*Surround Suppression effects on Working Memory performance in the general population and in people with schizophrenia: behavioural and ERPs evidence"*

During my PhD, I have investigated to what extent basic perceptual mechanisms affect visual working memory performance in people with schizophrenia and in the general population.

Visual Working memory (WM) is a cognitive ability that allows to retain and manipulate information for a short period of time. WM is fundamental for mental functions and it supports several everyday activities such as learning, reasoning and language comprehension. In fact, impairments in WM, which are established in clinical conditions such as schizophrenia, have been related to poor quality of life factors, such as work/education status. Despite a large number of studies investigating WM, its underlying

mechanisms are still a matter of debate. A number of landmark studies have shown that early visual areas are active during the maintenance of information in WM, which emphasizes the importance of low-level visual processes in higher-level cognition. However, few studies have examined the basic visual processes underlying encoding into WM.

The current proposal hypothesised that deficits in sensory gain control lead to abnormalities in forming the initial stimulus representation during WM. Sensory gain control is exerted through surround suppression (SS), a well-known phenomenon in which the response to a visual stimulus is diminished by the presence of neighbouring stimuli. In this project, SS has been measured using a visual illusion in which the contrast of a target is perceived as altered depending on the context in which it is embedded. Several studies have demonstrated that, compared to healthy controls, patients with schizophrenia are immune to this illusion as their perception do not appear to be altered by the surrounding context. This effect has been explained as a result of lack of inhibition in schizophrenia.

However, whether SS can impact not only the perception, but also the memory representations of visual stimuli has not been examined.

Therefore, in my PhD, I have investigated over three studies how individual variations in the SS sensitivity affect WM in typical participants (Experiment 1), in patients with schizophrenia (Experiment 2) and in interaction with attention (Experiment 3). Throughout all the experiments, I have used visual stimuli (circular gratings) that were peculiarly designed to trigger a weaker or stronger SS. Specifically, circular gratings were embedded in circular larger surrounds which were either vertically (parallel surround condition) or horizontally (orthogonal surround condition) oriented to the central target (Figure 1). According to previous literature, the parallel surround is meant to induce a stronger SS whereas the orthogonal surround a weaker SS.

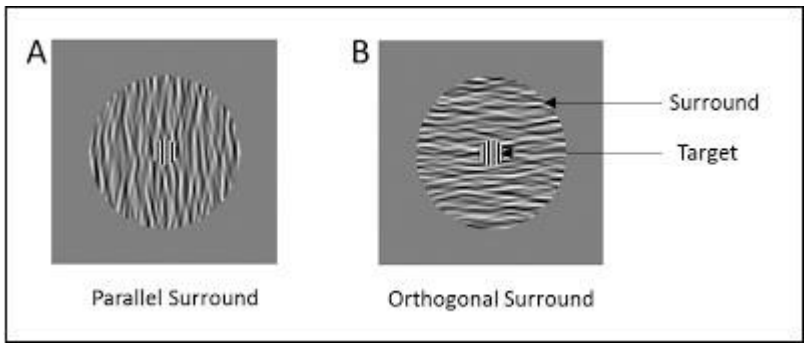

Figure 1. Stimuli used throughout the tasks: small circular gratings (target) embedded in bigger surrounds. In the Parallel Condition (A) the orientation of the surround was equal to the target, in the Orthogonal Condition (B) the orientation of the surround was rotated of 90° compared to the target. Participants were asked to focus on the target. The contrast of the stimuli has been heightened for presentation purposes.

These stimuli were used in a contrast matching (CM) task and in an orientation discrimination (OD) task, in order to test the SS effect on contrast and orientation

perception, respectively. Moreover, the same stimuli were used in a WM task aimed to test SS effects on WM performance. In the WM task, participants viewed one to three sequentially presented circular gratings with different orientations, surrounded by either orthogonal or parallel circular regions. They then judged whether the orientation of a subsequent probe (without a surround) matched any of the targets. In addition, during the WM task, Electroencephalography (EEG) data were recorded and event related potentials (ERPs) were analysed. EEG is a technique that allows to measure brain activity with a high temporal resolution. This allowed us to measure how cognitive and sensory processes evolve in time. ERPs have been used in this project to measure early encoding mechanisms during WM processing.

Experiment 1: In the CM task, 18 healthy participants confirmed that a central target grating appeared to have less contrast in the context of the parallel surround compared to the orthogonal surround condition. WM performance decreased with the increment of load. ERPs results showed that during WM encoding, posterior P2 amplitudes were significantly higher in the orthogonal compared to the parallel surround condition, suggesting that posterior P2 responds to SS mechanisms. With Experiment 1, we have confirmed that SS alters contrast perception and that SS mechanisms can be identified with P2 ERP component.

Experiment 2: We tested 19 patients with schizophrenia and 20 matched controls. At baseline, both populations were tested on two memory tests from the CANTAB battery. Patients performance was reduced compared to controls in both tests. Confirming previous studies, patients contrast perception was not affected by SS. In addition, the OD threshold was significantly higher in patients compared to controls and it negatively correlated with WM performance. This suggests that poor visual skills can be related to lower WM performance. Overall, WM accuracy was lower in patients compared to controls. However, in contrast to controls, WM accuracy was not affected by SS in patients. During encoding, posterior P2 amplitudes were modulated by SS only in controls but not in patients. With Experiment 2 we have confirmed that people with schizophrenia are immune to SS both at a perceptual and at a WM level. Moreover, ERPs results showed that SS processing in the cortex also seems to be altered in schizophrenia.

Experiment 3: here we tested 20 participants on a modified version of the WM task in order to test whether SS interferes with attention. Here, a cue highlighted which item had to be memorised, over a list of three. Only behavioural data were collected. Stimuli cued in the last position were better remembered than the stimuli cued in the other positions but only for the parallel and not for the orthogonal surround. This seems to suggest that the focus of attention might be subjective to perceptual interference triggered by SS.

Overall, this project successfully confirmed SS effects on perceived contrast in typical participants and the lack of SS in patients with schizophrenia. In addition, the difference in surround conditions was reflected in P2 in typical participants (Exp 1) but not in patients (Exp 2), suggesting that encoding processes in schizophrenia might not occur in the same

time window as controls. Moreover, these results showed that lower basic perceptual skills (such as OD) in schizophrenia are associated with decreased WM performance. This suggests that decreased basic perceptual abilities can negatively affect WM performance in SZ.

To conclude, the results of this project seems to highlight that basic sensory deficits in schizophrenia might act as a bottleneck which consequently limits cognitive functioning and, possibly, also response to cognitive behavioural interventions. Future research should investigate the possibility of improving basic visual abilities and if that would ameliorate WM performance in SZ. Ultimately, this might also improve the quality of life of these patients.

I'm currently in the process of writing up the results of this project for a peer-reviewed scientific publication.

2017 Report

Background

Working Memory (WM) deficits are a core feature in Schizophrenia and they are present even when individuals are not experiencing psychiatric symptoms. Impaired WM in Schizophrenia has a negative impact on overall functioning, it seems to be a predictor for poor community functioning, decreased self-care, health maintenance and social functioning (Lawlore-Savage & Goghari, 2014).

However, since WM is a complex neural process, the scientific literature seems to be divided about what the real source of WM impairments in Schizophrenia is. Recent studies have successfully shown that these deficits start at the very beginning, in the encoding phase, when memory items (before being remembered) have to be visually perceived and this seems to have an impact on the overall WM performance (Haenschel et al., 2007; Seymour et al., 2013). Moreover, given that these deficits are not treated by medication, they need to be addressed with alternative approaches (Haenschel & Linden, 2011).

Aims of the project and research questions

This PhD project aims to explore the role of visual perception on working memory in Schizophrenia. Therefore, the project will aim to answer two main questions:

Q1. What is the impact of perceptual deficits on working memory performance in Schizophrenia?

To answer Q1 I have carried out a WM experiment in which participants were asked to

memorise a brief list of items, but the visual characteristics of them were modulated across conditions. The task was performed along with Electroencephalography (EEG) that provides a continuous measure of brain responses to stimuli. Its high temporal resolution allowed to precisely study the different stages of a cognitive process over time. We also asked participants to perform some visual tasks in order to verify their basic visual skills and to test any potential link to WM performance.

I have established this paradigm in a first experiment (Exp.1) on a population of 20 students. The important result from this experiment has been that basic visual abilities influence WM performance and that early visual brain signals (Event Related Potentials – ERPs-) are modulated both by memory load (number of items to remember) and by the visual charatceristics of the items.

These results have already been presented as a poster at the last Cognitive Neuroscience Society meeting in San Francisco. The work has received positive feedbacks from international researchers. Furthermore, the manuscript for this experiment is almost finished.

In experiment 2 (Exp. 2) I'm applying the same paradigm on a population of 20 people with Schizophrenia and 20 healthy matched controls. For this experiment, we have also collected data of general cognitive skills and quality of life for Schizophrenia patients in order to check whether there is a relationship between poor cognition and quality of everyday life. Although the patients sample is now complete there are still a few controls to recruit, therefore analysis for this experiment is still ongoing.

Our preliminary results for Exp.2 show that people with Schizophrenia have general lower accuracy and higher response times compared to control population. Specifically, in both populations memory accuracy is lower when a higher number of items has to be remembered. However, only for people with Schizophrenia specific visual features of the items also affect WM performance.

In addition, the correlation that we found between basic visual skills and WM in control participants, is not present in the patients' cohort. These results suggest that poor perceptual abilities in Schizophrenia might contribute to WM deficits.

At a neural level memory load and visual features of the stimuli seem to modulate early visual Event Related Potentials (ERPs) in visual cortex in control participants, but not in the patients' population.

Q2. Are working memory impairments in Schizophrenia due to purely visual influences or they also depends on high level cognition impairments?

In the first experiment we showed that WM can be influenced by very basic visual abilities. However, this study leaves open whether these effects are purely visual or they can be related to high-level attentional influences controlling visual information. Attention deficits are documented in schizophrenia and several studies have shown impairments in prefrontal cortex activations during WM processing in patients (Heinrichs R.W., Zakzanis K.K., 1998; Goldman-Rakic, 1990). However, it's still not clear what the influence of prefrontal impairments on perceptual processing is during WM.

Therefore, experiment 3 (Exp. 3) is aimed to disentangle the visual and attention contribution to WM. Experiment 3 has a similar design to Exp. 1 and 2 but in the task we will introduce a cue which will indicate exactly which item participants have to pay attention to. This will help to ensure that attention is oriented to a specific item and the perceptual representation of the target item doesn't overlay with the distractors. I am aiming to test 20 control participants by the end of the summer.

Current progress and future plan:

· Exp. 1: writing up of manuscript.

· Exp. 2: finalising data collection and analysis of data.

· Exp. 3: finalising programming and setting up.

· Start of thesis write up in autumn.

Conclusion

The overall challenge of this project is to better understand the underlying causes of WM deficits in Schizophrenia.

So far we have showed that poor visual skills at baseline can play a role in WM impairments in Schizophrenia and also that brain signals coming from the visual cortex during a WM task look different in patients compared to a control population.

The results from this project can lead to implementation of visual trainings aimed to enhance visual perceptual skills and therefore WM performance. The ultimate goal would be to ameliorate quality of life by improving cognition.

2016 Report

Background

Working Memory (WM) deficits are a core feature in Schizophrenia and they are present even when individuals are not experiencing psychiatric symptoms. Impaired WM in Schizophrenia has a negative impact on overall functioning, it seems to be a predictor for poor community functioning, decreased self-care, health maintenance and social functioning (Lawlore-Savage & Goghari, 2014).

However, since WM is a complex neural process, the scientific literature seems to be divided about what the real source of WM impairments in Schizophrenia is. Recent studies have successfully shown that these deficits start at the very beginning, in the encoding phase, when memory items (before being remembered) have to be visually perceived and this seems to have an impact on the overall WM performance (Haenschel et al., 2007; Seymour et al., 2013).

Moreover, given that these deficits are not treated by medication, they need to be addressed with alternative approaches (Haenschel & Linden, 2011).

Aims of the project and research questions

This PhD project aims to explore the role of visual perception on working memory in Schizophrenia and it also intends to improve working memory by training visual perception. Therefore, the project will aim to answer two main questions:

Q1. What is the impact of perceptual deficits on working memory performance in Schizophrenia?

To answer Q1 I'm carrying out WM experiments in which participants are asked to memorise a brief list of items, but the visual characteristics of them are modulated across conditions. The task is performed along with Electroencephalography (EEG) that provides a continuous measure of brain responses to stimuli. Its high temporal resolution allows to precisely study the different stages of a cognitive process over time.
This is an established paradigm that I have already tested in a first experiment (Exp.1) on a population of 20 students. Manuscript of the results for Exp. 1 is in preparation. In experiment 2 (Exp. 2) I'm applying the same paradigm on a population of 20 people with Schizophrenia and 20 healthy matched controls. I have already tested 11 patients and the recruitment of healthy controls has also started.

Our preliminary results for Exp.2 show that people with Schizophrenia have general lower accuracy and higher response times compared to healthy population. Specifically, performance is influenced by the number of items to remember (the more items, the less accuracy) in both population, but for people with Schizophrenia the perceptual characteristics of the items seem to affect memory performance. In patients' cohort, depending on the type of visual item to be remembered, accuracy appears to be better or worse, while healthy participants do not show this trend.
At a brain level very early visual Event Related Potentials (ERPs) in visual cortex seems to be

modulated both by memory load and visual features of the stimuli in healthy participants, but the same signals have lower amplitudes and are delayed in time in people with Schizophrenia.

Q2. Can working memory impairments in Schizophrenia be ameliorated by training perception?

Since experiment 1 seems to show an influence of impaired visual perception on working memory, I am currently preparing a perceptual training. The aim of this training will be to improve perceptual deficits and test whether this can also improve WM performance.

During the training, participants will be asked to exercise everyday over a week on a perceptual task. At the end of the training, the idea is to invite participants to perform again the initial WM task (Exp. 1). We will then verify whether the visual training can account for improvements both in perceptual skills and in WM performance.

Current progress and future plan:

Analysis of data, Perceptual training program and Systematic Review

I am currently writing up the manuscript for Exp.1 which will be submitted for a peer reviewed publication. I am also carrying on with the testing and analysis of data of Exp.2. In the meantime, I am also finalising the design of the perceptual learning which will be piloted shortly on a student population before being applied on people with Schizophrenia.

Finally, I am working on a systematic review of the literature about the effectiveness of perceptual learning in control and clinical populations and its potential impact on cognition.

Conclusion The overall challenge of this project will be to improve the quality of life of patients by ameliorating WM.