Expeditions Fund Report

Expectations of the trip

My primary reason for visiting Newcastle this summer was to gain experience in research. As a future medical professional, I believe it is essential to understand and be involved in research because this is the forefront of medical advances and we have a duty to our patients to improve our knowledge and treatment of conditions. I was expecting to gain an insight into the challenges of research as well as having an opportunity to learn relevant skills so that I could make an informed decision whether to do an intercalated degree and in what subject.
I was also expecting to have a lot of free time at the evenings and weekends to explore the city.

What I did

I participated in the summer school at Newcastle University's Institute of Neuroscience. Working with my supervisor, I learnt how to peer review articles and make recommendations to an editor of a journal. From this activity, I learnt to be critical and recognise the features of a good study as well as consider how it could be improved. My research project entitled 'The effects of antipsychotics on NMDA receptor function' involved both clinical and laboratory work. This allowed me to gain insight into various stages of the research process. On the clinical side of things, I was able to go on home visits with the Early Intervention in Psychosis (EIP) team where I saw how patients are assessed and recruited onto the trial. I also wrote up clinical vignettes to summarise patients' cases. In the laboratory, I did electrophysiology experiments which involved obtaining perfused rat brain slices from PhD students and monitoring their gamma wave activity before adding healthy volunteers' serum and olanzapine to see if this altered the activity in the brain slice. It was satisfying on days when the experiment was successful and slightly frustrating on days when no data could be collected but this is a realistic negative aspect of research which I am willing to accept. A poster summarising my project can be found below.
In addition to the academic side of my trip, there was a personal aspect. Having lived and studied in London all my life, I wanted to explore the culture of a new city. I had the pleasure of meeting many new people, many of whom I am still in contact with and are now good friends of mine. Aside from visiting tourist attractions such as the iconic Angel of the North, in my spare time, I learnt how to knit which was something I had been wanting to learn for many years! Furthermore, these 5 weeks were the first time I was living alone away from home. As you would expect, there were a few teething issues such as the time it took me 40 minutes to realise my food wasn't heating up because I had turned on the grill instead of the oven!

How it contributed to my academic progress

I was fortunate enough to present my poster at the Royal College of Psychiatry's Faculty of General Adult Psychiatry Annual Conference and to my surprise, it was selected as the overall winner of the poster presentation prize. This is beyond what I expected to achieve and has helped me raise my aspirations. The award will be a great contribution to my CV and will contribute to my employability. I have been further enthused about being involved in research and aim to ensure it is a part of my future career.
Having now attained a realistic idea of the demands of research and, from speaking to intercalating students, an insight into what an intercalated degree entails, I am motivated to persue a research-based intercalated degree.

How the award helped

The award subsidised my expenses for the trip, most notably the cost of my accommodation. It contributed to an eye-opening experience which has helped me develop both in a professional, and a personal manner. I am now better equipped to make decisions about intercalation and have acquired research skills on which I hope to build in the future. Living away from home has increased my independence and I would now be more confident in exploring unfamiliar places. This will be helpful in the future, particularly in 5th year when we do an elective.

I would like to take this opportunity to thank Queen Mary for its support in allowing me to partake in this great learning experience.

The effects of antipsychotics on NMDA receptor function

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Introduction

Glutamate receptors are implicated in a number of neurological conditions. One type of ionotropic glutamate receptor, the NMDA receptor (NMDAR) appears particularly relevant for adult psychiatrists; reduced function of the NMDAR has a putative causal role in the development of psychotic disorders[1] and it is now established that an encephalitic disorder caused by autoantibodies against the NMDAR is a differential diagnosis in patients presenting with psychosis, particularly if it is of recent onset or associated with catatonic features[2].

NMDAR activation stimulates production of gamma oscillations therefore, to examine NMDA function, we have developed an electrophysiological technique to measure gamma oscillations produced by a live rat brain slice, which has been perfused with kainate, an NMDA agonist.

Healthy volunteer serum does not impact the gamma oscillations (Fig 1). However, in our preliminary investigation, psychotic patients' serum reduced gamma oscillations in a significant minority of cases showing that an unidentified component of these patients' serum impacted NMDAR function (or its downstream effectors). If this has caused the psychosis (for instance if it is an NMDAR antibody) then further investigation will inform our understanding of the aetiopathophysiology of psychotic disorders. Alternatively, if this component is (directly or indirectly) caused by the psychosis then it will yield different, but nonetheless valid information. The effect of olanzapine, a second generation antipsychotic, on the assay of was therefore examined.

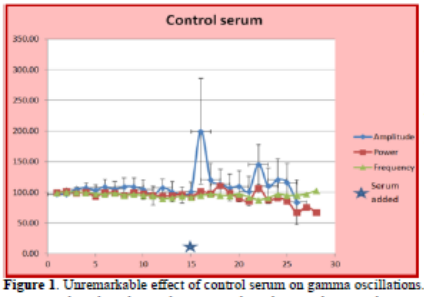

Figure 1. Unremarkable effect of control serum on gamma oscillations. The spike in amplitude is thought to be an aberrant result as the error bars overlap.

Methods

Figure 2. Experiment procedure schematic

- Rat brain slices were perfused with 50 ml of circulating oxygenated aCSF (artificial cerebrospinal fluid). Electrodes were inserted in the mEC (Fig 3) for recording.

Figure 3. Medial entorhinal cortex outlined in rat brain slice

- A concentration of 10μM of olanzapine was used in the experiment and was determined using the knowledge of the molecular weight and also that pathology laboratories use a steady-state reference range of 20 - 40 μg/L.
- Power spectrums were obtained and analysed for power, peak amplitude and peak frequency between 30 & 80 Hz(Fig 4).
- The experiment was repeated 5 times using serum from 3 different healthy controls.

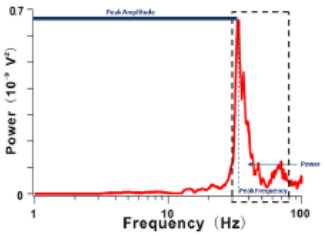

Figure 4. A graph of a single gamma wave. Power is the area under the curve, the maximum y value is the peak amplitude, and the corresponding x value is the peak frequency

Results

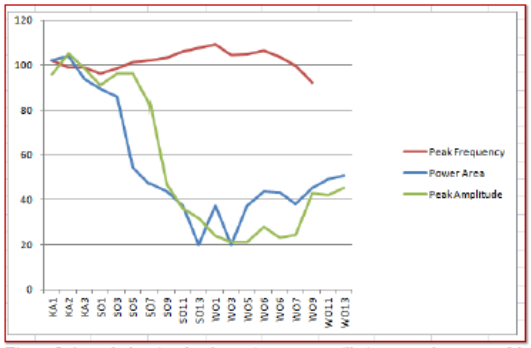

Figure 5. A graph showing the change in gamma oscillations over the course of the experiment using the mean from all 5 samples. The first 3 measures are performed after addition of kainate (KA). Then a series of measures are taken after the addition of healthy serum with added olanzapine (SO) and finally after washout (WO).

All data has been normalized using the 3 concordant readings (within 10% variance) as a stable baseline (KA) of 100% before the addition of healthy patient serum and olanzapine (SO). The x-axis represents time points, recordings taken every 10 minutes.

- **Peak frequency** remained relatively unaffected by the serum and olanzapine ($p=0.265$).
- The **Power (area)** decreases upon addition of the healthy control serum and olanzapine ($p<0.001$). There is some recovery of the oscillations during washout when the serum and olanzapine are removed from the circulating aCSF.
- Similarly, **Peak amplitude** decreased significantly ($p<0.001$), reaching a mean of 37.58% of the baseline at the end of the 1 hour of serum and olanzapine. Again, there appeared to be an increase during the washout period.

Conclusions

Olanzapine decreases the power and peak amplitude (but not peak frequency) of kainate induced gamma oscillations. This suggests an impact on NMDAR function. This finding warrants further investigation and may inform our understanding of the mechanism of action of olanzapine and potentially other antipsychotic drugs.

More patients with known antibodies present in serum need to be evaluated to establish the effect of these on gamma oscillations, and to understand the interactions of the antibody and medication.

By further studying the effect of the antibodies on gamma oscillations, it may be possible to understand the cognitive deficits present in patients, and develop treatment addressing these features.

[1] Pearlman, Daniel M; Najjar Souhel. Schizophrenia Research. 2014
[2] Zandi et al. Journal of Neurology, Neurosurgery & Psychiatry. 2014