Can the Pattern Changes in Brain Perfusion Following an Acute Dose of Oxytocin distinguish between Clinical High Risk for Psychosis and Bulimia Nervosa/Binge Eating Disorder?

Darania Muralitharan

Oxytocin in Neuropsychiatric Disorders

Oxytocin the Neuropeptide

Oxytocin plays a major role in the development and regulation of socio-emotional behaviors centrally as a neuropeptide, relating to a wide range of mental health disorders, such as eating behaviors, metabolism and social cognition (Giel et al., 2018).

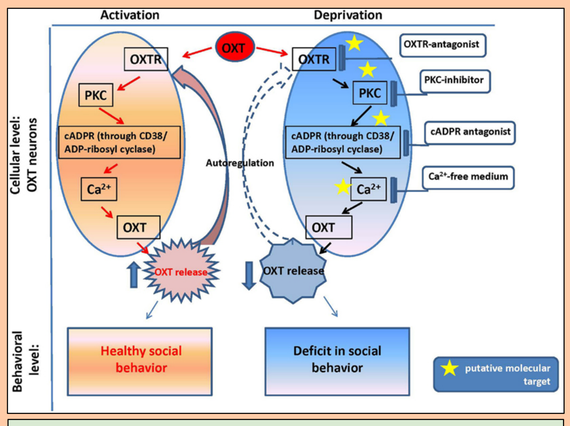


Fig.1. *Diagram to show the three main OT signaling genes (OXT, OXTR and CD38) and how they function to cause biochemical & transcriptional changes leading to immediate/long-term neuromodulatory effects (Lopatina et al., 2013).*

Clinical High Risk for Psychosis (CHR-P)

Patients diagnosed with CHR-P are impaired socially, emotionally and cognitively, and are at a 20% risk of developing psychosis within a two year period (Davies et al., 2018). Epigenetic alterations in the OXTR gene which is responsible for receptor expression in the brain may be a fundamental cause of psychosis onset via disturbances (Bang et al., 2019). Polymorphisms in the OXYR gene contribute to psychosocial stress leading to excessive dopamine release and alterations within the limbic system (Love et al., 2012).

Bulimia Nervosa/Binge Eating Disorder (BN/BED)

BN/BED are characterized by many episodes of uncontrollable binge eating episodes. In BN this leads to compensatory behaviors such as purging/vomiting to avoid weight gain, whereas for BED there is sensation of losing control over eating (Donnelly et al., 2018). Abnormal functioning of the oxytocin system due to polymorphisms with the OXTR gene is associated with greater binge-eating/purging.

Intranasal Oxytocin Administration

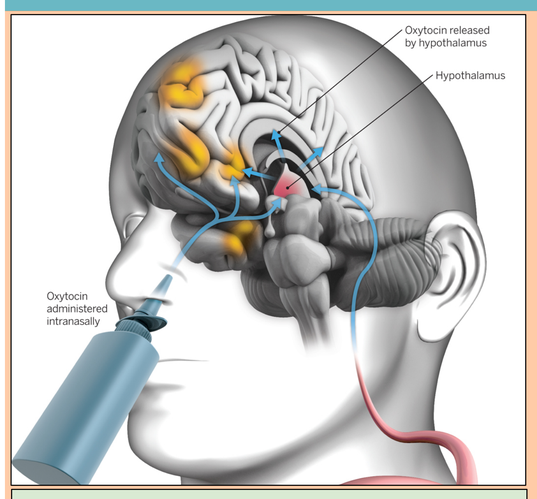


Fig.2. *Administration of IN-OT and the possible ways OT may cross the BBB: directly via extraneuronal/perineuronal routes along trigeminal/olfactory nerve pathways, bulk flow, lymphatic channels, intraneuronal transport or active/passive transport via vasculature. Figure adapted from Young & Barret., 2015.*

Oxytocin is hydrophilic and is unable to cross the blood brain barrier (BBB) in huge amounts (Martins, et al., 2019). It is uncertain exactly how OT crosses the BBB.

IN-OT as a Therapeutic Approach

Intranasal administration of oxytocin for those with BN/BED and CHR-P, have shown that oxytocin has a high therapeutic potential for treating symptoms (Feifel et al., 2016). Most studies have used intranasal oxytocin (IN-OT) as a therapeutic approach without fully understanding its pharmacodynamic effects within the brain (Martins et al., 2019).

Regional Cerebral Blood Flow

Regional cerebral blood flow (rCBF) can be used as a measure of neuronal activity in this response to IN-OT administration (Paulson et al., 2010). This change in rCBF is measured using arterial spin labelling (ASL) whilst the participant is at rest. Before developing future novel therapeutic approaches targeting the OT system for BN/BED and CHR-P patients, it is important to know the exact mechanism of IN-OT's actions within the brain and whether the way OT acts differs for both the disorders. This study aims to use a decoding approach by employing a pattern recognition algorithm to establish whether the direct central effect of IN-OT alone, represented by rCBF data, is different enough to distinguish between BN/BED and CHR-P patients.

Neuroimaging

Arterial Spin Labelling

Task-based blood oxygen level-dependent (BOLD) functional MRI (fMRI) is not ideal whilst focusing on a single physiological factor. ASL is a non-invasive biomarker that can be used to directly measure rCBF changes in response to IN-OT. It is very advantageous compared to other fMRI techniques due to its high reproducibility and its ability to obtain absolute quantifications.

Procedure

Participants self-administered 40IU OT or placebo for a period of 5-10mins in a randomized, placebo-controlled, double blind study. Only the data acquired from the first time point for each dataset (15-23 mins, 20-26 mins and 18-26 mins) and from the first run was used for the statistical analysis. This was to ensure the temporal time window was similar for all the rCBF data for all male, female, healthy and non-healthy participants.

Participants

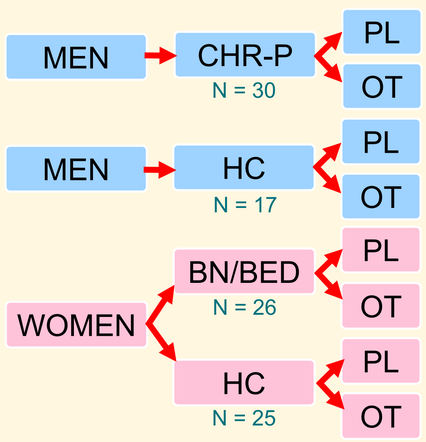


Fig.3. *Three different datasets used in this study. Double blind crossover administration of IN-OT. HC – Healthy Controls. PL - Placebo. OT – Oxytocin.*

Difference Images

To control for the placebo effect of oxytocin and to acquire the true effect of oxytocin, the difference images (Oxytocin minus Placebo) were obtained for all studies. This should remove any individual differences a participant may have as well as sex differences, since this study involved both male and female participants.

Global CBF Measures

The global CBF (gCBF) has to be linearly regressed out as it is considered a confounding nuisance covariate, which adds up with the regional CBF (effect of interest), to give variance to the values measured (Ramsay et al., 1993). It would be impossible to look at the effects of rCBF alone with wide gCBF changes all over the brain.

Multi-Voxel Pattern Analysis (MVPA)

How MVPA can be employed

Oxytocin's time course spreads over a variety of regions within the brain which makes it difficult to employ the standard traditional mass univariate analysis approach. Traditional fMRI analyses tends to spatially average significantly active voxels to reduce noise (Norman et al., 2006). This is flawed as it ignores correlations between voxels that are non-significant but may still have an effect or have information about the activation pathways. Multi-voxel pattern analysis (MVPA) is more promising for statistical analysis as it reduces this complexity by processing all the voxels at the same time. Using a classifier, MVPA can look at the pattern of neuronal activation and predict the value of a regressor to identify how strong a certain cognitive state is. This method can be applied to distinguish variations between the two different disease states, BN/BED and CHR-P category.

Pattern Recognition Classifier

A pattern recognition algorithm or classifier is a tool used to predict labels of unknown samples, which in this case is rCBF difference images. This mechanism is learned from a number of training sets of data with various labels and examples before it is run on some test data where the labels of the datasets aren't visible to the classifier to avoid bias.

K Fold Cross Validation

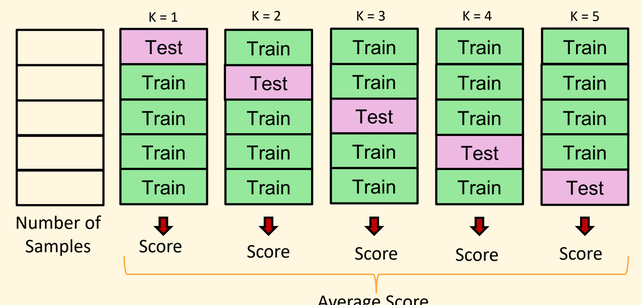


Fig.4. *This analysis employed 5-Fold Cross Validation. This ensured the data placed within the classifier were split into five groups, with 4/5 being the training set and 1/5 being the testing set. This 5-fold cross validation ensured this unbiased form of training and testing were repeated five times with a different unlabeled testing dataset each time*

Statistical Testing of Accuracy

Permutation Tests

Permutation testing is a non-parametric method that was used in this study for hypothesis testing, which is used to estimate what the chances are of gaining a classifier's observed performance (Golland & Fischl, 2003). Statistical significance was established by figuring out how true the classification accuracy score was compared to chance (Pereira & Botvinick, 2011). The **null hypothesis** assumes that a classifier is unable to reliably establish the relationship between the data and label it. The null hypothesis is accepted if the classifier score is statistically insignificant as this means there is no information found about the data variable we are interested in. If null hypothesis is rejected, then it can be declared that both the data are different with a statistically significant classifier accuracy (Nichols & Holmes, 2002).

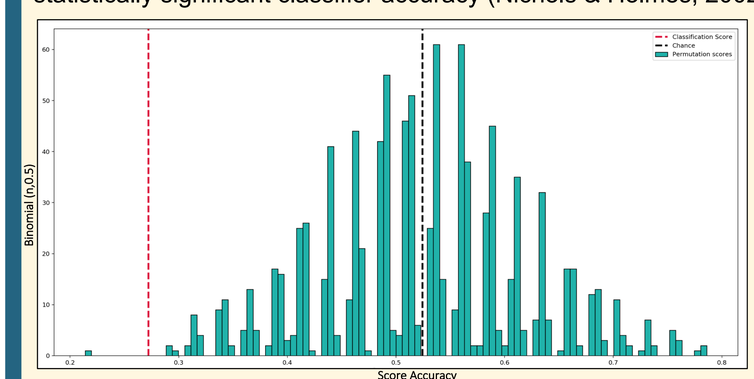


Fig.5. *Histogram to show permutation test between HC Men and HC Women.*

Testing Accuracy Of Classifier

To test that the classifier worked accordingly, the healthy women and men control groups were compared first as it is hypothesised that the classifier will be unable to tell apart the two datasets. As shown on fig.5. and as expected the classifier was only able to distinguish the data with a 27.2% accuracy with a 99.9 % (p=0.999) risk of the predictions being wrong. Hence, null hypothesis is accepted.

Results

CHR-P vs BN/BED

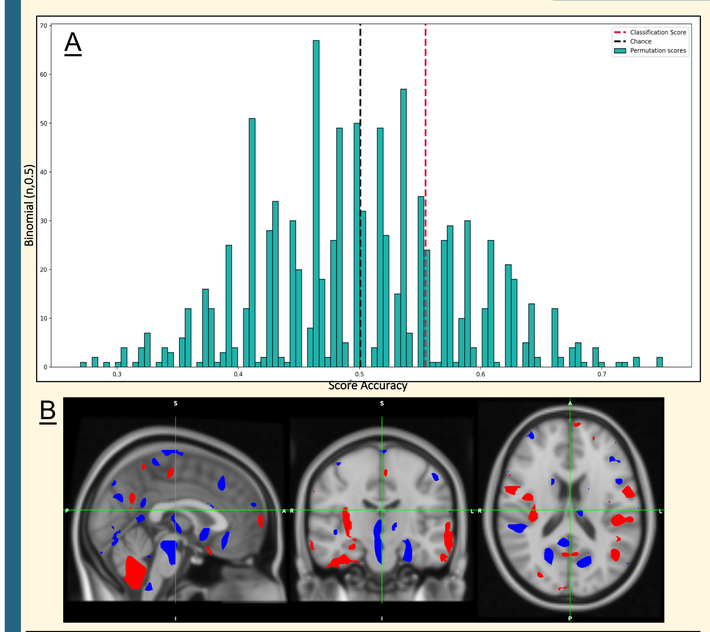


Fig.6. *A) Histogram to show permutation test between CHR-P Men and BN/BED Women. B)* This whole-brain SVM weights brain map obtained from coefficients with a classification accuracy of 55.5% using FSLeyes. Red – CHR-P. Blue – BN/BED.

Whole Brain Analysis

Comparison	Classification Accuracy	Permutation Accuracy	P-value 1000 Permutations
BN/BED vs CHR-P	0. 554545	0.500802	0.251748
BN/BED vs HC	0.234545	0.496487	1
CHR-P vs HC	0.564444	0.561967	0.509491
HC vs HC	0.272222	0.524381	0.999001

Fig.7. *Results obtained from classifier after each dataset were trained and tested in classifier.*

Exploratory Analysis

Comparison	Classification Accuracy	Permutation Accuracy	P-value 1000 Permutations
BN/BED vs CHR-P	0. 572727	0.498682	0.177822

Fig.8. *Results from classifier after classification of CHR-P and BN/BED rCBF difference images using the linear SVM classifier, with 30% feature selection at optimal accuracy.*

As the classifier accuracy was very low for CHR-P and BN/BED (55.5%), a feature selection strategy was used. The classifier now performed feature selection using analysis of variance (ANOVA), where the top features were selected using F-values to plot an error bar showing the percentile of features that provided optimal accuracy.

Discussion

Insignificant Classifier Accuracy

Using the pattern changes in brain perfusion, following IN-OT administration, the classifier is only 55.5% accurate (fig.6) when distinguishing between CHR-P and BN/BED, with only a 25.2% risk of its labels being incorrect.

Although the risk is very low, due to the differences in both disorders the classifier's accuracy was expected to be higher. Even with the exploratory analysis, where feature selection was used to pinpoint a selective 30% of optimal voxels where most of the differences were observed, the classifier again only had 57.3% accuracy (fig.8) in differentiating between CHR-P and BN/BED patients.

This low accuracy score can be explained by looking into the ability of the classifier to label each neuropsychiatric disorder against their respective healthy controls.

CHR-P vs HC — Classifier Accuracy 56.4%

BN/BED vs HC — Classifier Accuracy 23.5%

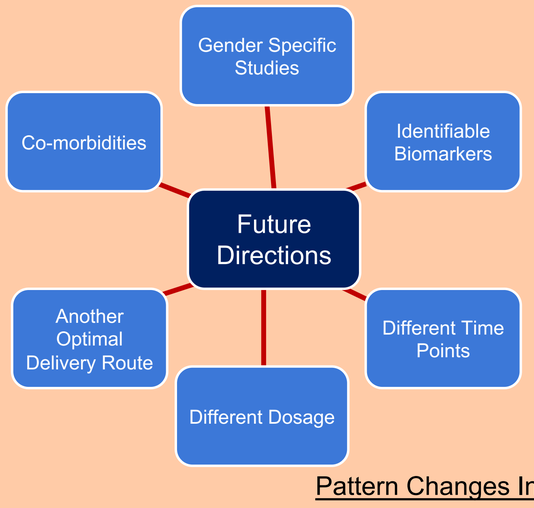
Gender Differences in rCBF Changes at Rest

Looking at the classifier's accuracy score for distinguishing between healthy controls and BN/BED patients, it is a very low 23.5% with a 100% risk of the classifier's labelling ability being wrong. This indicates that the classifier is unable to tell apart from healthy and BN/BED patients and assumes both data are almost the same. From this, it is possible that oxytocin does not cause any rCBF changes for BN/BED women.

MVPA classifier relies on CHR-P Data

The classifier's attempts at distinguishing between CHR-P and healthy control, was slightly better than for BN/BED and healthy control, with an accuracy score of 56.2% with a 50.9% risk of being wrong. Although the accuracy score is higher than for BN/BED, the classifier's ability to separate the CHR-P perfusion data from healthy control is still almost by chance. The pattern recognition algorithm is completely relying on the CHR-P data's labels to distinguish between the two disorders.

Conclusions



Limitations

All of the studies had slightly varying scanning times after IN-OT administration showing that the rCBF changes within those separate times may vary. Previous studies have also pointed out IN-OT's sustained effects over a 15-104 min observation interval (Paloyelis et al., 2016), showing that more studies need to be done following all the time-points for oxytocin. Finally, another limitation is the issue with circular analysis whilst employing feature selection during the exploratory analysis. This selective analysis is acceptable if the results are independent statistically from the data being selected. Although this distortion did not affect the results by a lot in this study, it is still significant.

Pattern Changes In Brain Perfusion

To conclude, it has been established that pattern changes in perfusion within the brain in response to IN-OT cannot be used to tell apart both BN/BED and CHR-P patients using the pattern recognition classifier. It also cannot be used to tell apart BN/BED and healthy control women leading to conclusion that perfusion changes may not occur in women. The results from this study have given further information on differentiating between both the disorders showing IN-OT acts very differently for both CHR-P and BN/BED patients.

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