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From co-morbidity to transdiagnostic potential and novel immunotherapies for psychosis

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A B S T R A C T

One of my first placements in psychiatry training was with the early intervention in psychosis services in Birmingham, in the late 1990′s. It was in this context that I became aware of the frequency and importance of affective co- modbidity and lack of diagnostic certianty in early stages of develping severe mental illness. This challenged the established dichotomy between affective and non-affective severe mental illnesses, and has driven my work and thinking ever since- including that embracing the presence of affective symptoms in schizophrenia may open the door for new treatments. Understanding affective dysfunction as a potential intrisic component of developing psychotic disorders has also shown the potential for transdiagnostic symptoms with shared underlying biological processess, including immune dysfunction, related to remission and functional outcomes. Currently my work focuses on targeting the immune system to improve recovery in clinical trials, and further mechanistic studies that reach beyond traditional diagnostic catagories.

1. Early psychosis and co-morbidity

Early intervention services for first episode psychosis (FEP) were established in the UK in the mid-late 1990′s, led by pioneers such as Max Birchwood who proposed the ‘critical period hypothesis’- intervening with robust biopsychosocial treatment early during schizophrenia could have longer term impact on the trajectory for recovery. I began working in this service as a Specialist Registrar in 2002 and became immediately aware of the significant levels of co-morbidity, particularly of anxiety and affective dysfunction in and after FEP. I completed my PhD supervised by early intervention pioneer Max Birchwood and the expert phenomenologist Professor Femi Oyebode, in work that brought together the development of psychopathology and co-morbidity in a longitudinal early psychosis cohort (eg, Birchwood et al., 2005; Upthegrove et al., 2017). My work has subsequently demonstrated that depression in FEP is related to suicidal behaviour- with risk extending many years after FEP and is also a strong predictor of poor functional outcome(McGinty et al., 2017; McGinty and Upthegrove, 2020; Upthegrove et al., 2010).

Depression in FEP could be thought of as a co-morbidity, as is often the case with other physical or mental health conditions, having a severe chronic illness concurring risk for depression. It may be that risk factors for psychosis, such as childhood adversity, also lead to risk of depression. Childhood adverse events including abuse, neglect, bullying, deprivation, and racism are all now well recognised risk factors for psychosis. However, they also are significant risk factors for other disorders, including anxiety and depression.

My early work also showed that depression could also be seen because of the psychotic experience itself; threat by persecutors, malevolent voices or the powerless position of patient-hood. This framework of appraisal is not unrelated to the experience of childhood adversity; perceiving threat to self from neutral stimuli; powerlessness in relation to persecutory delusions following childhood abuse or bullying. This can lead to a position of subordination, and in social psychiatry terms depression may be viewed as a warning signal of weakened status (Sandhu et al., 2013; Upthegrove et al., 2017).

However, it may also be that depression, or more widely affective dysfunction, is part of the biological process of developing psychosis and that this is particularly identifiable in FEP. It is this latter model of depression as biologically intrinsic to psychotic disorders traditionally perceived ‘non-affective’ psychoses such as schizophrenia that may open transdiagnostic avenues to new treatments. Current pharmacological treatment for psychotic disorders is extremely limited, all focus on dopaminergic blockade and come with considerable side effects. After FEP only 30% of people who reach diagnostic criteria for schizophrenia fully recover- and EIP services have not impacted this figure.

2. Transdiagnostic clusters: data driven approach

One avenue to improve outcomes may be to identify the potential

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subgroup of patients with affective dysfunction in FEP cohorts- and thus target new or repurposed treatments (such as antidepressant medication or therapy). Advanced data science and machine learning may help, where samples of sufficient size and replication data are available. I was fortunate to be able to collaborate with experts such as Nikos Koutsouleris in our EUFP7 funded Personalised Prognostic Tools for Early Psychosis Management (PRONIA); and within this cohort was able to study to identify whether it was possible to distinguish patients with recent onset psychosis (ROP) with depression from those without depression, and patients with recent onset depression (ROD) at the symptom and neuroanatomical level. Using a supervised machine learning classification (SVM) and principal components analysis, it was not possible to identify an affective subgroup of ROP, suggesting that affective dysfunction is intrinsic to the majority of patients (Upthegrove et al., 2020). In a separate analysis combining all ROP and ROD patients from PRONIA, we aimed to identify neurobiologically based transdiagnostic categories with a data driven, brain first approach. A semi-supervised clustering analysis was trained on whole brain volumetric measures from 577 participants and then applied in 404 participants in external validation. Two distinct transdiagnostic clusters were identified of mixed ROP and ROD patients, with an impaired cluster showing more grey matter volume loss, poorer cognition, and psychosocial functioning. In additional analysis there was the suggestion that circulating parkers of inflammation, particularly C- reactive protein (CRP) and TNFα (Lalousis et al., 2022).

3. Immune dysfunction: a common pathway?

Immune dysfunction, and particularly low grade non-resolving inflammation, has been investigated in the aetiology of psychosis for some time, with evidence suggesting potential for causality. Pro-inflammatory cytokines including CRP and Interleukin 6 and its receptor complex (IL6/IL6r) are elevated before the onset of psychosis, and particularly in medication naive samples (Upthegrove et al., 2014). Driven by the understanding of transdiagnostic affective dysfunction in early stages of illness, it was intriguing that these cytokines are also present in those at risk for depression, and more so in treatment resistant and non-responsive cases (Kappelmann et al., 2020). Affective dysfunction precedes the onset of psychosis, and immune dysfunction may be an active driver of chronicity or poor outcome by affecting brain structure and function. Childhood adverse events including abuse, neglect, bullying, deprivation and racism are all environmental exposures that can lead to activation, or re-activation of stress hormones and pro-inflammatory innate defences, with subsequent impact on brain and mental health (Nikkheslat et al., 2020).

Low grade non-resolving inflammation may impact brain structure and function in a variety of ways: IL-6 is a key mediator in the innate immune pathway relevant to brain function, with ability to cross the blood-brain barrier (BBB) and increase its permeability. IL-6 is released from monocytes and T lymphocytes and increase nitric oxide, chemokines and oxidative stress and/or potentially activate brain microglia (Upthegrove and Khandaker, 2020). There is evidence of reduced defence against oxidative stress and antioxidant imbalance in psychosis. Meta-analysis of human neuroimaging (PET) studies shows mixed evidence for microglia activation in schizophrenia, however it could also be that aberrant astrocytic control of microglia is driven by dysfunctional t cell progenitors including T regs (Corsi-Zuelli et al., 2021).

Many theories exist as to the mechanism for inflammatory mediated brain changes in psychosis however a current challenge is the absence of direct measurement of inflammation in the brain. The majority of studies currently assess peripheral measures of inflammation and their association to symptoms without direct examination of brain structure or function. My recent work is now focused on increasing the evidence of direct impact of inflammation on brain structure and function in a transdiagnostic approach in early stages of disorders (Krynicki et al., 2021; Williams et al., 2022).

4. Novel non-dopaminergic treatments

The goal is for new and better treatments for psychosis. Many studies have focused on anti-inflammatory and neuroprotective agents as non-dopaminergic treatments. The larger, more robust and higher quality trials show less effect size with the gold standard BeneMin study being wholly negative (Deakin et al., 2018; Jeppesen et al., 2020). One current challenge is understanding who would benefit from anti-inflammatory a treatment; ie the phenotype of immune active psychosis. Further to this, I am leading work that aims to understand how best to stratify psychosis patients into immunotherapy trials, by symptoms or biomarkers, and what the primary outcome should be: eg negative symptoms, anhedonia or functioning? These questions are being addressed in the ongoing Psychosis Immune Mechanism Stratified Medicine Study (PIMS) programme led by myself and colleague Golam Khandaker; bringing together our epidemiology, genomics, and psychosis and trial expertise. Initial outputs from a data science driven approach will inform an experimental medicine study, with stratification of immune active participants and anhedonia as the primary outcome (Griffiths et al., 2022).

5. Future challenges

Recently, my hypothesis has been that affective dysfunction in early psychosis could be a signal of ongoing non-resolving inflammation and this may be related to the early phase structural and functional brain changes seen in FEP. However, our recent mendelian randomisation study demonstrated a specific relationship between genetically determined IL6/IL6r and brain structure in areas particularly relevant for psychiatric disorders of chronic and potentially neurodevelopmental course (Williams et al., 2022) and this suggests very early exposure to inflammation may be key. Affective symptoms seen within psychosis could indicate pre-existing or ongoing low level inflammatory damage in mental health disorders with poorer outcome.

Psychotic disorders undoubtedly involve dopaminergic dysfunction. However, continued focus only on this mechanism is not likely to aid further advance or better recovery. I believe that embracing the co-morbidity and heterogeneity in developing mental health disorders, from a transdiagnostic perspective and employing the most advanced novel statistical approaches may uncover common and unique phenomenology and neuropathology. Living tissue, cell cultures, microglial models and induced stem cells and further experimental medicine studies within this context are now needed to fully interrogating causality. This approach is essential and now possible with increasing data, analytical techniques, and samples available. Better treatment options for patients will continue to be the ultimate goal.

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References

Birchwood, M., Iqbal, Z., Upthegrove, R., 2005. Psychological pathways to depression in schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci. 255 (3), 202–212. https://doi.org/10.1007/s00406-005-0588-4.

Corsi-Zuelli, F., Deakin, B., de Lima, M.H.F., Qureshi, O., Barnes, N.M., Upthegrove, R., Louzada-Junior, P., Del-Ben, C.M., 2021. T regulatory cells as a potential therapeutic target in psychosis? Current challenges and future perspectives. Brain Behav. Immun. Health 17. https://doi.org/10.1016/j.bbih.2021.100330.

Deakin, B., Suckling, J., Barnes, T.R.E., Byrne, K., Chaudhry, I.B., Dazzan, P., Drake, R.J., Giordano, A., Husain, N., Jones, P.B., Joyce, E., Knox, E., Krynicki, C., Lawrie, S.M.,

Lewis, S., Lisiecka-Ford, D.M., Nikkheslat, N., Pariante, C.M., Smallman, R., Watson, A., Williams, S.C.R., Upthegrove, R., Dunn, G., 2018. The benefit of minocycline on negative symptoms of schizophrenia in patients with recent-onset psychosis (BeneMin): a randomised, double-blind, placebo-controlled trial. Lancet Psychiatry 5, 885–894. https://doi.org/10.1016/S2215-0366(18)30345-6.

Griffiths, S.L., Khandaker, G., Upthegrove, R., 2022. A trial to understand how immune function affects symptoms of psychosis. doi:10.1186/ISRCTN23256704.

Jeppesen, R., Christensen, R.H.B., Pedersen, E.M.J., Nordentoft, M., Hjorthøj, C., Köhler-Forsberg, O., Benros, M.E., 2020. Efficacy and safety of anti-inflammatory agents in treatment of psychotic disorders - a comprehensive systematic review and meta-analysis. Brain Behav. Immun. 90, 364–380. https://doi.org/10.1016/j.bbi.2020.08.028.

Kappelmann, N., Arloth, J., Georgakis, M.K., Czamara, D., Rost, N., Ligthart, S., Khandaker, G.M., Binder, E.B., 2020. Dissecting the association between inflammation, metabolic dysregulation, and specific depressive symptoms: a genetic correlation and 2-sample mendelian randomization study. JAMA Psychiatry. https://doi.org/10.1001/jamapsychiatry.2020.3436.

Krynicki, C.R., Dazzan, P., Pariante, C.M., Barnes, N.M., Vincent, R.C., Roberts, A., BeneMin Study team, 2021. Deconstructing depression and negative symptoms of schizophrenia; differential and longitudinal immune correlates, and response to minocycline treatment. Brain Behav. Immun. 91, 498–504.

Lalousis, P.A., Schmaal, L., Wood, S.J., Reniers, R.L.E.P., Barnes, N.M., Chisholm, K., Griffiths, S.L., Stainton, A., Wen, J., Hwang, G., Davatzikos, C., Wenzel, J., Kambeitz-Ilankovic, L., Andreou, C., Bonivento, C., Dannlowski, U., Ferro, A., Lichtenstein, T., Riecher-Rössler, A., Romer, G., Rosen, M., Bertolino, A., Borgwardt, S., Brambilla, P., Kambeitz, J., Lencer, R., Pantelis, C., Ruhrmann, S., Salokangas, R.K.R., Schultze-Lutter, F., Schmidt, A., Meisenzahl, E., Koutsouleris, N., Dwyer, D., Upthegrove, R., 2022. Neurobiologically based stratification of recent-onset depression and psychosis: identification of two distinct transdiagnostic phenotypes. Biol. Psychiatry. https://doi.org/10.1016/j.biopsych.2022.03.021.

McGinty, J., Sayeed Haque, M., Upthegrove, R., 2017. Depression during first episode psychosis and subsequent suicide risk: a systematic review and meta-analysis of longitudinal studies. Schizophr. Res. 195, 58–66. https://doi.org/10.1016/j.schres.2017.09.040.

McGinty, J., Upthegrove, R., 2020. Depressive symptoms during first episode psychosis and functional outcome: a systematic review and meta-analysis. Schizophr. Res. 218, 14–27. https://doi.org/10.1016/j.schres.2019.12.011.

Nikkheslat, N., McLaughlin, A.P., Hastings, C., Zajkowska, Z., Nettis, M.A., Mariani, N., Enache, D., Lombardo, G., Pointon, L., Cowen, P.J., Cavanagh, J., Harrison, N.A., Bullmore, E.T., Pariante, C.M., Mondelli, V., 2020. Childhood trauma, HPA axis activity and antidepressant response in patients with depression. Brain Behav. Immun. 87, 229–237. https://doi.org/10.1016/j.bbi.2019.11.024.

Upthegrove, R., et al., 2010. The evolution of depression and suicidality in first episode psychosis. Acta Psychiatr. Scand. 122 (3), 211–218.

Sandhu, A., Ives, J., Birchwood, M., Upthegrove, R., 2013. The subjective experience and phenomenology of depression following first episode psychosis: a qualitative study using photo-elicitation. J. Affect. Disord. 149, 166–174. https://doi.org/10.1016/j.jad.2013.01.018.

Upthegrove, R., Khandaker, G.M., 2020. Cytokines, oxidative stress and cellular markers of inflammation in schizophrenia. Neuroinflamm. Schizophr. 49–66. https://doi.org/10.1007/7854_2018_88.

Upthegrove, R., Lalousis, P., Mallikarjun, P., Chisholm, K., Griffiths, S.L., Iqbal, M., Pelton, M., Reniers, R., Stainton, A., Rosen, M., Ruef, A., Dwyer, D.B., Surman, M., Haidl, T., Penzel, N., Kambeitz-llankovic, L., Bertolino, A., 2020. The psychopathology and neuroanatomical markers of depression in early psychosis. Schizophr. Bull. 47 (1), 249–258.

Upthegrove, R., Manzanares-Teson, N., Barnes, N.M., 2014. Cytokine function in medication-naive first episode psychosis: a systematic review and meta-analysis. Schizophr. Res. 155, 101–108. https://doi.org/10.1016/j.schres.2014.03.005.

Upthegrove, R., Marwaha, S., Birchwood, M., 2017. Depression and schizophrenia: cause, consequence, or trans-diagnostic Issue? Schizophr. Bull. 43 (2), 240–244. https://doi.org/10.1093/schbul/sbw097.

Williams, J.A., Burgess, S., Suckling, J., Lalousis, P.A., Batool, F., Griffiths, S.L., Palmer, E., Karwath, A., Barsky, A., Gkoutos, G.v., Wood, S., Barnes, N.M., David, A. S., Donohoe, G., Neill, J.C., Deakin, B., Khandaker, G.M., Upthegrove, R., 2022. Inflammation and brain structure in schizophrenia and other neuropsychiatric disorders: a mendelian randomization study. JAMA Psychiatry 79, 498–507. https://doi.org/10.1001/jamapsychiatry.2022.0407.