Author/s:
Cropley, V;Ganella, E;Wannan, C;Zalesky, A;Van Rheenen, T;Bousman, C;Everall, I;Fornito, A;Pantelis, C

Title:
FRONTOSTRIATAL CONNECTIVITY IN TREATMENT-RESISTANT SCHIZOPHRENIA: RELATIONSHIP TO POSITIVE SYMPTOMS AND COGNITIVE FLEXIBILITY

Date:
2018-04

Citation:
Cropley, V., Ganella, E., Wannan, C., Zalesky, A., Van Rheenen, T., Bousman, C., Everall, I., Fornito, A. & Pantelis, C. (2018). FRONTOSTRIATAL CONNECTIVITY IN TREATMENT-RESISTANT SCHIZOPHRENIA: RELATIONSHIP TO POSITIVE SYMPTOMS AND COGNITIVE FLEXIBILITY. [Abstract]. SCHIZOPHRENIA BULLETIN, 44, pp.S176-S177. https://doi.org/10.1093/schbul/sby016.433.

Persistent Link:
https://hdl.handle.net/11343/290303

Discussion: Dimensions of NS at rest were associated with altered resting state perfusion, in particular in brain areas relevant for reward processing. Distinguishable associations of rCBF with NS dimensions point to distinct underlying pathophysiology.

T155. SEPARABLE AND REPLICABLE NEURAL STRATEGIES DURING SOCIAL BRAIN FUNCTION IN PEOPLE WITH AND WITHOUT SEVERE MENTAL ILLNESS

Colin Hawco*[,1], Robert Buchanan[2], Navona Calrco[1], Benoit Mulsant[1], Joseph Viviano[1], Erin Dickie[1], Miklos Argyelan[3], James Gold[2], Marco Iacoboni[4], Pamela DeRosse[3], George Foussias[1], Anil Malhotra[3], Aristotle Voineskos[1]
[1]University of Toronto; [2]Maryland Psychiatric Research Center; [3]The Zucker Hillside Hospital; [4]David Geffen School of Medicine at UCLA

Background: The case-control design and disease heterogeneity may be major limiting factors impeding biomarker discovery in brain disorders, including serious mental illness such as schizophrenia spectrum disorder (SSD) or bipolar disorder (BPD). We propose that this heterogeneity represents an opportunity for discovery by uncovering relevant biologically driven sub-types within disorders. Individuals with schizophrenia spectrum disorder (SSD) have deficits in social cognition related to poor functional outcome.
Methods: A total of 109 SSD and 70 matched healthy controls (HC) were recruited across three sites. Participants performed an fMRI task in which they observed or imitated emotional faces. For each participant, an individual pattern of activity (Imitate > Observe for emotional faces) was identified. Hierarchical clustering (Ward's method) identified clusters of individuals with similar patterns of activity. We then examined whether new data-driven groups of participants (based on patterns of brain activity) demonstrated performance differences on a batter of social and neuro cognitive tests completed out of the scanner. As a validation of the importance of cluster membership, Euclidean distance was compared between participants to members of their own cluster, diagnosis, or site. The clustering analysis was repeated on a replication sample consisting of 32 SSD, 37 euthymic BPD, and 39 HC.
Results: Three clusters with distinct patterns of neural activity were found. Cluster one (24 HC and 44 SSD) represented 'typical activators' (lateral frontal and parietal activity). Cluster two (21 HC and 31 SSD) were identified as 'hyper-activators', showing more intense and extended activity. This was interpreted as a 'compensatory' response of over-activation related to impaired neural circuits, such as is seen in aging. Interestingly, cluster three (25 Controls and 35 SSD) showed a very atypical pattern, including suppression of activity during imitation in regions involved in the default mode network and/or higher order social cognition (e.g. theory of mind). This group also had improved social cognitive performance relative to the other clusters. Participants were found to have more similar patterns of brain activity to members of their cluster rather than to members of their diagnostic group or scanning site. Importantly, when clustering was applied to the replication sample, the same three patterns (typical activators, hyper activators, and deactivators) were identified.
Discussion: In independently collected samples, our findings demonstrate different patterns of neural activity among individuals during a socio-emotional task that were independent of DSM-diagnosis or scan site. Our findings may provide objective neuroimaging endpoints (or biomarkers) for subgroups of individuals in target engagement research aimed at enhancing cognitive performance independent of diagnostic category.

T156. IN VIVO CHARACTERIZATION OF THE FIRST AGONIST DOPAMINE D1 RECEPTORS PET IMAGING TRACER [18F]MNI-968 IN HUMAN

Gilles Tamagnan*[,1], Olivier Barret[1], David Alagille[1], Vincent Carroll[1], Jennifer Madonia[1], Cristian Constantinescu[2], Christine SanDiego[1], Caroline Papin[1], Thomas Morley[1], David Russell[1], Timothy McCarthy[3], Lei Zhang[3], David Gray[3], Anna Villalobos[3], Chewah Lee[3], Jianqing Chen[3], John Seibyl[1], Kenneth Marek[1]
[1]inviCRO; [2]Constantinescu; [3]Pfizer, Inc.

Background: D1 receptors, which couple to inhibitory G-proteins, have been shown to regulate neuronal growth and development, mediate some behavioral responses. Its function has been shown to be altered in both neurologic and psychiatric disorders. To date, there is a lack of agonist PET tracers for the D1 receptors labeled with 18F with relevance in clinical studies. We report the evaluation in non-human primates of [18F]MNI-968 (PF-06730110), a novel PET radiotracer of the D1 receptors
Methods: Four brain PET studies, 2 baselines and 2 blockade studies using PF-2562, a D1 partial agonist compound, were conducted for 90 min in two rhesus monkeys with [18F]MNI-968 (169 ± 31 MBq). [18F]PF-06730110 was administered at the same dose level for both monkeys as a bolus followed by a 2-hour infusion, with [18F]MNI-968 administered 30 min into the infusion. Additionally, six brain PET studies were conducted over 180 min (317 ± 49 MBq) in 6 healthy human volunteers (3 test/retest and 3 test). PET data were modeled with 2-tissue compartmental model (2T), Logan graphical analysis (LGA), and non-invasive Logan graphical analysis (NI-LGA) with cerebellar cortex as reference region to estimate total distribution volume VT, and binding potential BPND.
For the blockade studies in rhesus monkeys, occupancy was estimated from BPND at baseline and post blockade.
Results: In rhesus monkeys, [18F]MNI-968 (PF-06730110), penetrated the brain with a peak whole-brain uptake up to ~3% of the injected dose at ~ 6 min post injection and showed a fast washout. The highest signal was found in the caudate, putamen, with moderate extrastriatal uptake. The lowest signal was in the cerebellum. BPND values were up to ~1.4 in the putamen. All three quantification methods (2T, LGA and NI-LGA) were in excellent agreement, with a similar estimated D1 receptors occupancy of PF-06730110 of ~40% for both monkeys in the caudate and putamen.
In human, [18F]MNI-968 kinetics appeared to be faster compared to non-human primates, with a BPND in the putamen of ~0.8. Initial measurement of test-retest reproducibility was ≤ 7% for BPND in the striatal regions.
Discussion: Our work showed that [18F]MNI-968 ([18F]PF-06730110), is a promising agonist PET radiotracer for imaging D1agnist receptors that can be quantified non-invasively. Studies are currently ongoing both in non-human and human primates to further characterize the tracer.

T157. FRONTOSTRIATAL CONNECTIVITY IN TREATMENT-RESISTANT SCHIZOPHRENIA: RELATIONSHIP TO POSITIVE SYMPTOMS AND COGNITIVE FLEXIBILITY

Vanessa Cropley*[,1], Eleni Ganella[1], Cassandra Wannan[1], Andrew Zalesky[1], Tamsyn Van Rheenen[1], Chad Bousman[2], Ian Everall[3], Alexander Fornito[4], Christos Pantelis[5]
[1]The University of Melbourne; [2]University of Calgary; [3]Institute of Psychiatry, Psychology & Neuroscience, King's College London; [4]School of Psychology and Psychiatry & Monash Biomedical Imaging, Monash University; [5]Melbourne Neuropsychiatry Centre, University of Melbourne

Background: The frontostriatal circuits linking different parts of the frontal cortex to subregions of the striatum are proposed to regulate different aspects of cognition, executive function, affect and reward processing. Dysregulation of these brain circuits is also known to be important in the etiology of psychotic disorders, with the magnitude of dysfunction correlating with the severity of positive symptoms. These observations suggest that the integrity of brain circuits connected to the striatum is important for antipsychotic treatment response as well as specific cognitive processes. However, not all individuals with schizophrenia benefit from antipsychotic treatment, with up to 20% of individuals considered to be treatment-resistant. These individuals also show pervasive impairments in cognition, including cognitive flexibility. Nevertheless, few studies have examined striatal connectivity in treatment-resistant schizophrenia (TRS), particularly in relation to positive symptomatology and specific cognitive deficits subserved by the striatal circuits. This study therefore aimed to (i) assess for disruptions in frontostriatal connectivity in a sample of TRS and (ii) assess the relationship between the frontostriatal circuits with positive symptoms and attentional set-shifting (cognitive flexibility) given recent associations with the dorsal striatal circuit.
Methods: Resting-state functional magnetic resonance imaging was used to investigate functional connectivity (FC) in 42 TRS participants prescribed clozapine (30 males, mean age=41.3(10)), and 42 healthy controls (24 males, mean age=38.4(10)). The whole striatum (caudate, putamen and nucleus accumbens) and the left and right dorsal striatum were separately seeded as regions of interest, and Pearson's correlations between the seeds and all other voxels comprising cortical and subcortical gray matter were investigated. For brain regions that showed significant group differences in FC with the striatal seeds, Pearson's correlations explored the relationship between the strength of connectivity with positive symptoms and attentional set-shifting (extradimensional shift errors) as measured with the CANTAB intra-/extradimensional set shift task.
Results: In comparison with healthy controls, TRS patients displayed significantly reduced FC between the whole striatum and the bilateral anterior cingulate, cerebellum, precuneus, right and left frontal pole and left insular/temporal pole, and reduced FC of the left and right dorsal striatum with cerebellum, and between the right dorsal striatum and bilateral cingulate and right frontal pole. Reduced FC between the whole striatum and precuneus and insular/temporal pole was associated with greater delusions of jealousy ($p<.002$ uncorrected); no other associations with positive symptoms were detected. In the entire sample, reduced FC from all striatal seeds was associated with greater extradimensional errors, indicating worse cognitive flexibility. These associations were not detected in TRS and controls separately.
Discussion: Our preliminary findings reveal reduced striatal FC in TRS, including hypoconnectivity of the dorsal striatal circuit. In contrast to early psychosis, reduced dorsal striatal connectivity does not appear to mediate positive symptoms. Our finding relating hypoconnectivity of the striatal circuits with impaired cognitive flexibility is partly consistent with recent observations in other psychiatric disorders, although such deficits appear not specific to the dorsal circuit and to TRS. Future work will examine connectivity of the ventral striatum, as well as striatal connectivity in early-onset psychosis and siblings of patients with schizophrenia.

T158. THE VALUE OF ACTIGRAPHY FOR MEASURING APATHY IN PATIENTS WITH SCHIZOPHRENIA: ASSOCIATIONS WITH CLINICAL MEASURES AND NEUROIMAGING OF ACTION INITIATION

Marie-José van Tol*[,1], Claire Kos[1], Michelle Servaas[1], Jan Bernard Marsman[1], Nicky Klaasen[1], Oliver Tucha[1], Henderikus Knegtering[1], André Aleman[1]
[1]*University of Groningen*

Background: Apathy is a highly debilitating and frequently occurring behavioral characteristic, present in approximately half of the patients with schizophrenia. Apathy is considered a core negative symptom that relates strongest to lack of initiative and is the strongest predictor of poor functional outcome, poor medication compliance, and high caregiver burden. Notwithstanding, measuring apathy is still a challenge. Therefore, we aimed to investigate whether actigraphy, an objective and continuous measurement of activity levels, could yield an objective quantitative measure of apathy severity in schizophrenia patients. Moreover, we aimed to investigate whether actigraphy related to relevant functional neuroimaging underpinnings of apathy, i.e. self-initiated goal-directed behavior.
Methods: Quantity, variability, and initiation of motor behavior were studied in relation to apathy severity as measured with clinical measures, and in relation to neural correlates of self-initiated behavior using functional Magnetic Resonance Imaging (fMRI). All patients (N=58) suffered from clinical significant apathy, as measured with the Apathy Evaluation Scale and Scale for the Assessment of Negative Symptoms and wore an actigraph for 48 continuous hours. Physical activity was quantified as the total activity counts over the patients' ten most active hours of each day, summed over two weekend days (Activity-total, i.e. 20 hours in total). Variability of motor behavior (Activity-variability) was calculated by taking the root of the Mean Squared Successive Difference of the activity counts. For 31 of these patients, fMRI data during a task tapping into self-initiative was available.
Results: Results showed that quantity, variability, and initiation of motor behavior were associated with negative symptoms, but not specifically with apathy. Motor behavior parameters were associated with brain activation during the self-initiative task in various brain regions including inferior parietal regions. The results were only observed during the condition wherein participants were asked to promptly reply to specific cues and not during the condition where more freedom in timing and selection of behavior was allowed.
Discussion: Actigraphy can be used to measure quantity as well as variability of motor behavior in patients with schizophrenia and with specific relevance for negative symptoms, and that it correlates with selective neural substrates of action selection and activation of motor programs. However, actigraphy may not capture higher-order motivational processes that contribute to apathy severity.

T159. ASSOCIATION BETWEEN VITAMIN D INSUFFICIENCY AND METABOLIC SYNDROME IN PATIENTS WITH PSYCHOTIC DISORDERS

Sung-Wan Kim*[,1], Taeyoung Yoo[1], Jung Jin Kim[2], Jae-Kyeong Kim[3], Ji-Eun Hong[4], Ju-Yeon Lee[5], Jae-Min Kim[1], G. Paul Amminger[6], Michael Berk[7], Jin-Sang Yoon[2]
[1]*Chonnam National University Medical School;* [2]*The Catholic University of Korea Kangnam, St. Mary's Hospital;* [3]*Mindlink, Gwangju Bukgu Mental Health Center;* [4]*Gwangju Mental Health Commission;* [5]*Chonnam National University Medical School, Gwangju Bukgu Community Mental Health Center;* [6]*Orygen - The National Centre of Excellence in Youth Mental Health;* [7]*Deakin University, School of Medicine*

Background: Vitamin D levels are low in patients with schizophrenia. This study examined the association between vitamin D and metabolic syndrome in patients with psychotic disorders.
Methods: The study enrolled 302 community-dwelling patients with psychotic disorders. Sociodemographic and clinical characteristics, including blood pressure, physical activity, and dietary habit were gathered. Laboratory examinations included vitamin D, lipid profile, fasting plasma glucose, HbA1c, liver function, and renal function. Vitamin D insufficiency was defined as < 20 ng/ml. Clinical characteristics associated with vitamin D insufficiency were identified.
Results: Among the 302 participants, 236 patients (78.1%) had a vitamin D insufficiency and 97 (32.1%) had metabolic syndrome. Vitamin D insufficiency was significantly associated with the presence of metabolic syndrome ($p = 0.006$) and hypertension ($p = 0.017$). Significant increases