RESEARCH PROJECT REPORT

MARCO PAGANI IN THE FRAME OF STM 2010

CREATION OF A NORMATIVE PET/CT DATABASE FOR PSYCHIATRIC STUDIES

During the period financed by CNR's Short Term Mobility 2010 at the Department of Nuclear Medicine, Karolinska Hospital, Stockholm, Sweden we have further developed the pilot study in collaboration with the Department of Psychiatry at S:t Göran's Hospital and with the Department of Clinical Neuroscience, Karolinska Institutet aiming to map the cerebral blood flow (rCBF) of a group of patients with the diagnosis of autism spectrum disorder along with the rCBF of age- and gender-matched control subjects.

Due to a sudden unavailability of [1-^{11}C]Butanol following an unexpected contamination of the hot cells of the Karolinska Hospital Cyclotron, this first phase of the project has been focused on control subjects recruitment and preliminary neuropsychiatric and neuropsychological testing organised by Dr. Susanne Bejerot and Irina Manouilenko, psychiatrists at allowing the preliminary part of this second arm of the study to be initiated. The contacted and recruited subjects have to be matched to the patients in respect of age, gender, handedness, socio-economical status, working capabilities, IQ and verbal skills allowing an interpretation of the results taking in full account all possible variables eliminating the necessity of statistical interpolations and rendering the results more easily readable and reproducible.

During this period a manuscript and a communication at an international scientific conference regarding different aspect of the project were produced and submitted.

Subjects

In this respect the healthy subjects in the recruited control group did not have any physical disorders nor mental disability according to the Structured Clinical Interview for Diagnostic Statistical Manual of Mental Disorders 4th edition (DSM-IV) Axis I Disorders (SCID-I) and Structured Clinical Interview

for DSM-IV-R Personality Disorders (SCID-II). The exclusion criteria for all participants has been alcohol and substance-abuse or dependence, IQ below 70, current epilepsy, psychosis, brain damage or neurological disorders.

Neuropsychiatric assessments

All subjects underwent a full set of 22 neuropsychological and neuropsychiatric tests in order to be properly comparable to patients bearers of various psychiatric disorders. Possible physical or mental disabilities were according to the Structured Clinical Interview for Diagnostic Statistical Manual of Mental Disorders 4th edition (DSM-IV) Axis I Disorders and the Structured Clinical Interview for DSM-IV-R Personality Disorders; the Montgomery-Asberg Depression Rating Scale rated depressive symptoms; Other scales assessed: the NEO Personality Inventory the personality; the Young mania scale the bipolar disorder; the Hamilton Anxiety Scale anxiety; the Liebowitz social anxiety scale social phobia; the Yale-Brown Obsessive Compulsive Scale obsessive compulsive symptoms; the Positive and Negative Syndrome Scale schizophrenia; Alcohol Use Disorders Identification Test alcoholism; the The self-report Drug Use Disorders Identification Test substance abuse; the World Health Organization Adult ADHD Self-Report Scale attention deficit and hyperactivity symptoms; the Ritvo Autism and Asperger Diagnostic Scale Revised autistic spectrum symptoms. The Global Assessment of Functioning the functional level; the Dissociative Experiences Scale post-traumatic stress disorder; the Wechsler Adult Intelligence Scale-Revised the level of intelligence; the Rey complex figure test the executive functions; the Toughness scale the personality profile; the Unraveling the mystery of health the sense of coherence; the Neurological Evaluation Scale the neurological signs; the Modified Waldrop Scale the Minor physical anomalies and hyperactive behavior; the Mini mental test the general cognitive state.

As soon as the hot cells of the Cyclotron will be available for the [1-11C]Butanol production again the second phase of the study will take place, presumably in September – October 2010 and the following methodology will be implemented.

Methods

Radiopharmaceutical

[1-^{11}C]Butanol is to be produced via the reaction (see scheme) of a Grignard reagent, propylmagnesium chloride, with cyclotron-produced carbon-11 labelled carbon dioxide, $^{11}CO_2$, followed by reduction with lithium aluminum hydride.

$$^{11}CO_2 + CH_3CH_2CH_2MgCl \longrightarrow CH_3CH_2CH_2{}^{11}CO_2MgX \longrightarrow CH_3CH_2CH_2{}^{11}CH_2OH$$

After trapping $^{11}CO_2$ in the Grignard the solvent will be evaporated with heating and the radioactive residue hydrolyzed with aqueous hydrochloric acid The [1-^{11}C]butanol will be concentrated on a solid phase extraction column (SepPak C18 Plus) and the column will be subsequently washed with sterile water. The desired [1-^{11}C]butanol will be eluted from the SepPak using aqueous ethanol and will be passed through a sterile 0.22 μm filter into a sterile collecting vial. The radiochemical identity and purity will be analyzed by radio-HPLC before release.

PET/CT

The examinations will be be performed on a Siemens Biograph 64 PET/CT scanner, with a spatial resolution of 6 mm. A periphery catheter will be inserted in the patients' hand. The head will be first scanned by CT, so corrections for attenuation and photon scatter can be made. Thereafter a bolus of [1-^{11}C]butanol (300 MBq) will be injected simultaneously as the PET acquisition will started and data will be acquired in the list mode for 5 minutes. The dynamic data will be reconstructed to transverse images for CBF evaluations.

Preliminary results

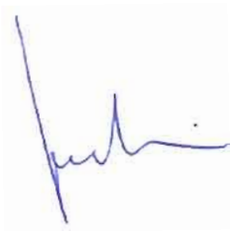
The results from the first study were re-analysed by means of more advanced statistical tools and submitted to the Journal of Autism and Developmental Disorders. Group differences and correlation analyses between CBF and IQ were performed by SPM2. As compared to healthy controls, Autism Spectrum Disorder patients showed significant CBF increases in the right parahippocampal (Brodmann Area, BAs 28, 30), posterior cingulate (BA 30), primary visual (BAs 17) and temporal (BAs 37, 38, 39) cortex, putamen, caudatus, substantia nigra and cerebellum. No statistically significant correlation between CBF and IQ was found. We concluded that using PET/CT [1-11C]butanol reduced considerably the examination time, resulting in less stress to patients. The limbic, posterior associative and cerebellar cortices showed increased blood flow in ASD, underscoring the involvement of these regions in the disease, confirming previous findings about the neuroanatomy of ASD and supporting the use of the implemented methodology.

Furthermore a second aspect of the study has been investigated, the correlations between symptomatic dimensions scores and CBF. This further analysis aimed to investigate the relationship between autistic, attentional, neurological dimensions and regional changes of cerebral blood flow (rCBF) at rest in both subjects with ASD and healthy controls (HC).The scores of the three symptom related scales (The Ritvo Autism and Asperger's Diagnostic Scale (RAADS), the Neurological Evaluation Scale (NES) and the Adult ADHD Self-Report Scale (ASRS) were correlated to rCBF. When RAADS was correlated to CBF, significant regions were found in parahippocampal (Brodmann Areas,

BAs 30, 36), posterior cingulate (BAs 29, 31), inferior and middle temporal temporal (BAs 20, 37) and primary and associative visual (BAs 17, 18, 19) cortices, and cerebellum, bilaterally. NES and CBF correlated significantly in right uncus (BA 28) and associative visual cortex (BAs 18, 19), left posterior cingulate (BA 29) and bilateral parahippocampal cortex and cerebellum. ASRS correlated significantly with CBF in right parahippocampus (BA 27), left globus pallidus and thalamus and bilateral precuneus (BA 31), primary and associative visual (BAs 17, 18, 19) cortex, inferior temporal cortex (BAs 20, 37), We concluded that Significant correlations between CBF and the scores of three symptom related scales were found in posterior cerebral regions largely superimposed in the three analyses. This confirms the appropriateness of using ASRS and NES in the diagnosis and in the symptoms evaluation of ASD.

This latter part of the investigation will be presented in September 2010 at the The Third Autism Neuroscience Conference to be held in Cambridge, UK.

Rome July the 29th 2010



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