PROGETTO 2 (facoltativo)/ PROJECT 2 (optional)

Supervisore/*Supervisor*:	FRANCESCO BENEDETTI
Titolo/*Title:*	Biological signature of cognitive impairment in eating disorders.
Corso */PhD Course*	Scienze Cognitive e Comportamentali/*Cognitive and Behavioral Sciences*
Curriculum:	
Link alla pagina personale OSR/UNISR/ *Link to OSR/UniSR personal page:*	https://www.unisr.it/docenti/b/benedetti-francesco https://research.hsr.it/en/divisions/neuroscience/psychiatry-and-clinical-psychobiology/index.html

Descrizione del progetto/Project description (Tra i 2.000 e 3.000 caratteri spazi inclusi/ *Number of characters*, *including spaces*: 2.000 - 3.000):

Several studies have reported an association between metabolic parameters, BMI and white matter structure. Alterations in the microstructure of WM were observed in relation to body weight, increased levels of triglycerides, cholesterol, glucose, insulin, and the highly intercorrelated levels of adipokines and inflammatory cytokines/chemokines. Myelin, of which the white matter is composed, is produced by oligodendrocytes and is composed of 70% lipids (cholesterol and phospholipids) and 30% proteins.

Due to extreme weight loss, patients with anorexia nervosa (AN) suffer reductions in white matter volume, with a reduction in fractional anisotropy (FA) in several white matter bundles, including the superior longitudinal fasciculus, fornix, posterior thalamic radiation and dorsal thalamus, corpus callosum, fronto-occipital association bundles. A recent longitudinal study identified how dynamic, bidirectional changes in white matter microstructure in young patients with AN can be reversed with brief weight-regaining therapy. These abnormalities parallel disrupted functional and effective brain connectivity: higher connectivity from the medial orbitofrontal cortex (OFC) and insula to the inferior frontal gyrus, lower connectivity from the frontal gyrus to the inferior frontal gyrus and cingulate cortex. A study before/after weight restoration showed a persistent positive correlation between structural and functional connectivity and symptom severity in circuits connecting nucleus accumbens and OFC. Multimodal meta-analysis identified reductions of gray matter and functional activity in the anterior and median cingulate in patients with AN.

Abnormal brain functional and structural connectivity could underpin a series of neuropsychological deficits: patients with AN show difficulties related to set-shifting, decision-making, attentional biases towards fearful and negative stimuli, and core coherence, leading to an adherence to detail on the one hand, and an inability to see the bigger picture on the other. Patients with AN may also show reduced responsiveness to rewarding

stimuli, a high ability to delay reward, and a high sensitivity to punishment. These factors and their link to adipokines and cytokines could play a major role in the development and maintenance of the disorder.

In a sample of 60 ptients with AN, this study aims to investigate whether patients show alterations in the structure of the white matter and whether these alterations are associated with metabolic parameters, BMI and cognitive functioning, with an observational design, before/after a course of treatment of the disorder.

Competenze che deve acquisire lo studente/Skills to be acquired by the student (Max 600 caratteri spazi inclusi/ *Number of characters, including spaces*: max 600):

• MRI analyses to explore functional & structural networks: BOLD fMRI (SPM12), VBM, subcortical volumes (Freesurfer) and cortical thickness (CAT12), Tract-Based Spatial Statistics (TBSS; FSL) and tractography analysis of WM tracts, Dynamic Causal Modelling (DCM; SPM12), new fMRI tools for the analysis of seed-to-voxel connectivity maps, ROI-to-ROI connectivity and graph metrics, Independent Components (ICA networks), local homogeneity, intrinsic connectivity, centrality, etc.; resting state fMRI (RestPlus, CONN)

Bibliografia/References (max. 15)

1. Frank GKW. Neuroimaging and eating disorders. Curr Opin Psychiatry. 2019;32(6):478-483.
2. Kaye W. Neurobiology of anorexia and bulimia nervosa. Physiol Behav. 2008 Apr 22;94(1):121-35.
3. Mazza E, Poletti S, Bollettini I, Locatelli C, Falini A, Colombo C, Benedetti F. Body mass index associates with white matter microstructure in bipolar depression. Bipolar Disord. 2017 Mar;19(2):116-127.
4. Mazza E, Calesella F, Paolini M, di Pasquasio C, Poletti S, Lorenzi C, Falini A, Zanardi R, Colombo C, Benedetti F. Insulin resistance disrupts white matter microstructure and amplitude of functional spontaneous activity in bipolar disorder. Bipolar Disord. 2023 Feb;25(1):32-42.
5. McWhinney SR, Abé C, Alda M, **Benedetti F**, Bøen E, Del Mar Bonnin C, Borgers T, Brosch K, Canales-Rodríguez EJ, Cannon DM, Dannlowski U, Diaz-Zuluaga AM, Dietze L, Elvsåshagen T, Eyler LT, Fullerton JM, Goikolea JM, Goltermann J, Grotegerd D, Haarman BCM, Hahn T, Howells FM, Ingvar M, Kircher TTJ, Krug A, Kuplicki RT, Landén M, Lemke H, Liberg B, Lopez-Jaramillo C, Malt UF, Martyn FM, **Mazza E**, McDonald C, McPhilemy G, Meier S, Meinert S, Meller T, Melloni EMT, Mitchell PB, Nabulsi L, Nenadic I, Opel N, Ophoff RA, Overs BJ, Pfarr JK, Pineda-Zapata JA, Pomarol-Clotet E, Raduà J, Repple J, Richter M, Ringwald KG, Roberts G, Ross A, Salvador R, Savitz J, Schmitt S, Schofield PR, Sim K, Stein DJ, Stein F, Temmingh HS, Thiel K, Thomopoulos SI, van Haren NEM, Van Gestel H, Vargas C, Vieta E, Vreeker A, Waltemate L, Yatham LN, Ching CRK, Andreassen OA, Thompson PM, Hajek T; ENIGMA Bipolar Disorders Working Group. Diagnosis of bipolar disorders and body mass index predict clustering based on similarities in cortical thickness-ENIGMA study in 2436 individuals. Bipolar Disord. 2022 Aug;24(5):509-520.
6. McWhinney SR, Abé C, Alda M, **Benedetti F**, Bøen E, Del Mar Bonnin C, Borgers T, Brosch K, Canales-Rodríguez EJ, Cannon DM, Dannlowski U, Díaz-Zuluaga AM, Elvsåshagen T, Eyler LT, Fullerton JM, Goikolea JM, Goltermann J, Grotegerd D, Haarman BCM, Hahn T, Howells FM, Ingvar M, Kircher TTJ, Krug A, Kuplicki RT, Landén M, Lemke H, Liberg B, Lopez-Jaramillo C, Malt UF, Martyn FM, **Mazza E**, McDonald C, McPhilemy G,

Meier S, Meinert S, Meller T, Melloni EMT, Mitchell PB, Nabulsi L, Nenadic I, Opel N, Ophoff RA, Overs BJ, Pfarr JK, Pineda-Zapata JA, Pomarol-Clotet E, Raduà J, Repple J, Richter M, Ringwald KG, Roberts G, Salvador R, Savitz J, Schmitt S, Schofield PR, Sim K, Stein DJ, Stein F, Temmingh HS, Thiel K, van Haren NEM, Gestel HV, Vargas C, Vieta E, Vreeker A, Waltemate L, Yatham LN, Ching CRK, Andreassen O, Thompson PM, Hajek T; ENIGMA Bipolar Disorders Working Group. Association between body mass index and subcortical brain volumes in bipolar disorders-ENIGMA study in 2735 individuals. Mol Psychiatry. 2021 Nov;26(11):6806-6819.

7. McWhinney SR, Abé C, Alda M, **Benedetti F**, Bøen E, Del Mar Bonnin C, Borgers T, Brosch K, Canales-Rodríguez EJ, Cannon DM, Dannlowski U, Diaz-Zuluaga AM, Dietze LMF, Elvsåshagen T, Eyler LT, Fullerton JM, Goikolea JM, Goltermann J, Grotegerd D, Haarman BCM, Hahn T, Howells FM, Ingvar M, Jahanshad N, Kircher TTJ, Krug A, Kuplicki RT, Landén M, Lemke H, Liberg B, Lopez-Jaramillo C, Malt UF, Martyn FM, **Mazza E,** McDonald C, McPhilemy G, Meier S, Meinert S, Meller T, Melloni EMT, Mitchell PB, Nabulsi L, Nenadic I, Opel N, Ophoff RA, Overs BJ, Pfarr JK, Pineda-Zapata JA, Pomarol-Clotet E, Raduà J, Repple J, Richter M, Ringwald KG, Roberts G, Ross A, Salvador R, Savitz J, Schmitt S, Schofield PR, Sim K, Stein DJ, Stein F, Temmingh HS, Thiel K, Thomopoulos SI, van Haren NEM, Vargas C, Vieta E, Vreeker A, Waltemate L, Yatham LN, Ching CRK, Andreassen OA, Thompson PM, Hajek T; ENIGMA Bipolar Disorder Working Group. Mega-analysis of association between obesity and cortical morphology in bipolar disorders: ENIGMA study in 2832 participants. Psychol Med. 2023 Feb 27:1-11.
8. Tural U, Iosifescu DV. Adiponectin in anorexia nervosa and its modifiers: A meta-regression study. Int J Eat Disord. 2022 Oct;55(10):1279-1290.
9. Boghi, A., Sterpone, S., Sales, S., D'Agata, F., Bradac, G. B., Zullo, G., & Munno, D. (2011). In vivo evidence of global and focal brain alterations in anorexia nervosa. Psychiatry Research: Neuroimaging, 192(3), 154-159.
10. Cha, J., Ide, J. S., Bowman, F. D., Simpson, H. B., Posner, J., & Steinglass, J. E. (2016). Abnormal reward circuitry in anorexia nervosa: a longitudinal, multimodal MRI study. Human brain mapping, 37(11), 3835-3846.
11. Foerde, K., Steinglass, J. E., Shohamy, D., & Walsh, B. T. (2015). Neural mechanisms supporting maladaptive food choices in anorexia nervosa. Nature neuroscience, 18(11), 1571.
12. Nagahara, Y., Nakamae, T., Nishizawa, S., Mizuhara, Y., Moritoki, Y., Wada, Y., ... & Yamada, K. (2014). A tract-based spatial statistics study in anorexia nervosa: abnormality in the fornix and the cerebellum. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 51, 72-77.
13. Phillipou, A., Carruthers, S. P., Di Biase, M. A., Zalesky, A., Abel, L. A., Castle, D. J., ... & Rossell, S. L. (2018). White matter microstructure in anorexia nervosa. Human brain mapping, 39(11), 4385-4392.
14. Via, E., Zalesky, A., Sanchez, I., Forcano, L., Harrison, B. J., Pujol, J., … Fornito, A. (2014). Disruption of brain white matter microstructure in women with anorexia nervosa. Journal of Psychiatry & Neuroscience, 39(6), 367–375.
15. von Schwanenflug, N., Müller, D. K., King, J. A., Ritschel, F., Bernardoni, F., Mohammadi, S., ... & Ehrlich, S. (2018). Dynamic changes in white matter microstructure in anorexia nervosa: findings from a longitudinal study. Psychological medicine, 1-10.

UniSR	**Addendum al Progetto proposto nell'ambito dei Corsi di Dottorato in Medicina Molecolare o Scienze Cognitive e Comportamentali - In applicazione del D.M. 118 del 2 marzo 2023**

Periodo di studio e ricerca presso Impresa /Centri di ricerca / Pubblica Amministrazione

Il periodo per un minimo di 6 mesi fino a un massino di 12 mesi è **obbligatorio,** anche non continuativi, per le borse attivate nell'ambito di investimento:

- Transizione digitali e ambientali
- Pubblica amministrazione
- Patrimonio culturale

Sono esclusi quelle di Ricerca PNRR.

Il dottorando svolgerà il periodo **OBBLIGATORIO** presso _____ per n___ mesi

Sede legale:

Paese	
Città	
Indirizzo	

Sede operativa principale, se diversa dalla sede legale, presso cui è svolta l'attività di ricerca del dottorando

Paese	
Città	
Indirizzo	

Periodo di studio e ricerca all'estero

Il periodo per un minimo di 6 mesi fino a un massino di 12 mesi, anche non continuativi, è **obbligatorio** per le borse attivate in tutti e 4 gli ambiti di investimento (Transizione digitali e ambientali, Ricerca PNRR, Pubblica amministrazione e Patrimonio culturale).

Il dottorando svolgerà il periodo **OBBLIGATORIO** presso Technische Universität Dresden - Universitätsklinikum Carl Gustav Carus, Division of Psychological & Social Medicine and Developmental Neurosciences, Fetscherstraße 74, 01307 Dresden per n. 6 mesi

Sede legale:

Paese	GERMANIA
Città	DRESDEN
Indirizzo	Fetscherstraße 74, 01307 Dresden

Sede operativa principale, se diversa dalla sede legale, presso cui è svolta l'attività di ricerca del dottorando

Paese	
Città	
Indirizzo	

I periodi di cui sopra sono distinti e da svolgere presso soggetti distinti.

Entro fine ottobre 2023 sarà necessario fornire una lettera d'impegno degli enti a ospitare il dottorando (il facsimile della lettera sarà fornita dall'Ufficio Dottorati).