Title: The impact of BDNF on the cognitive functions of Ultra-High Risk patients: an exploratory study

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Ultra-high risk (UHR) patients refer to one of the first stages of schizophrenia and consist of individuals with subclinical psychotic symptoms (Fusar-Poli et al., 2013). Cognitive deficits are central to the symptomatology of schizophrenia and are already present in UHR who show global cognitive deficits compared to healthy subjects (Catalan et al., 2021). One of the hypotheses to explain the pathophysiological processes related to the cognitive deficits in patients at early stages of psychosis involves the Brain-Derived Neurotrophic Factor (BDNF) (He et al., 2019). BDNF is a peptide of the neurotrophin family. It has a central role in neuroplasticity, synaptic function, neuronal development and survival, and the formation of dendritic and axonal branches. It also has a neuroprotective function (Miranda et al., 2019). Lowered BDNF levels have been repeatedly found in research in schizophrenia and first episode of psychosis (FEP) (Bora, 2019; Qu et al., 2020). In a recent meta-analysis (Bora, 2019), lower plasma BDNF levels correlated positively with cognitive impairment. The period of brain maturation is particularly sensitive to the environment, and the same biological abnormalities will not necessarily have the same effects once brain maturation is complete. Thus, it is important to uncover the dynamic changes in BDNF protein and messenger RNA (mRNA) during this specific period of psychosis before cognitive dysfunctions crystallize.

We performed an exploratory study on a longitudinal cohort of young UHR patients who converted or not to full-blown psychosis. We hypothesize that (1) before the psychotic conversion, there are differences in the concentration of BDNF mRNA and protein between future converters and non-converters and that (2) these concentrations have an impact on cognitive functions with a different effect depending on the future conversion status.

Patients were part of the prospective longitudinal ICAAR cohort previously described. The study was approved by an ethics committee and all participants signed an informed consent (Chaumette et al., 2016). At-risk patients were followed for one year and classified as converters (C) when the CAARMS threshold for psychosis was reached and as non-converters (NC) when symptoms remained below this symptomatic threshold for full-blown psychosis. Among these patients, BDNF protein levels was assessed for 67 patients (26C; 41 NC) and BDNF mRNA levels for 120 patients (39 C; 81 NC). All clinical and biological measurements were performed at baseline. Methods for cognitive assessment were previously described(Magaud et al., 2014) (Suplementary Figure 1). Analysis of BDNF protein was performed on serum using the ELISA technique. Total mRNA was extracted from whole blood samples. The mRNA expression level of BDNF in each sample was obtained after normalization as previously reported (Chaumette et al., 2019). Statistical analyses were performed on RStudio. A T-test was used if the data followed a normal distribution, and a

Wilcoxon test otherwise. For multiple linear regression models on the total IQ, we controlled for the effect of age, sex, Body Mass Index (BMI), antipsychotic treatments (as chlorpromazine equivalent), and cannabis use in the last 30 days, positive and negative symptoms. The tests were two-sided, and the significance level was $p<0.05$. Characteristics of the population are described in table 1.

There was no significant differences in BDNF protein levels between converters and non-converters. We found a significant difference in BDNF mRNA levels between the two groups ($p=0.0008$), with higher levels in converters. Cohen's effect size (d) for the mRNA difference between groups was $d = 0.32$. BDNF mRNA and protein levels were not significantly correlated. Among converters, there was a significant positive correlation between total IQ scores and BDNF protein levels ($r=0.47$; $p=0.018$). In non-converters, there was no significant correlation between total IQ and BDNF protein levels. However, there was a significant negative correlation between total IQ and BDNF mRNA levels ($r=-0.23$; $p=0.039$) (Supplementary figure 2). In the linear regression, there was a significant interaction between the BDNF protein level and the conversion status on the total IQ ($p=0.020$) with an effect size of $f^2=0.15$ ($R2=0.131$). Similarly, a significant interaction was also found between BDNF mRNA level and conversion status on total IQ ($p=0.013$) with an effect size of $f^2=0.10$ ($R2=0.091$).

Our results show differences in the BDNF mRNA expression between converters and non-converters, but not for protein levels. To the best of our knowledge, no previous study assessed the BDNF mRNA levels in UHR patients. The lack of difference in the BDNF protein levels between converters and non-converters in our study, while this has been reported in FEP(Yee et al., 2018), could be related to the fact that the changes may occur later in the course of the disease. Among converters, higher levels of BDNF protein seem to be beneficial for IQ, whereas a significant negative effect of the BDNF mRNA levels on the IQ was detected among non-converters. Interestingly, the relationship between cognition and BDNF protein levels or cognition and BDNF mRNA levels were similar in each group. This could indicate that the cognitive functions in non-converters are independent of the neuroprotective effect of BDNF and may be more related to other determinants. In converters, a compensatory mechanism for cognitive impairment may involve the BDNF. The interaction between BDNF mRNA and protein levels and conversion status on IQ suggests that the effect of BDNF depends on the later clinical outcome.

This study has some limitations: the sample size is small, and we analyzed the peripheral BDNF expression, which may only partially reveal the pathophysiological mechanisms occurring during conversion to psychosis. This exploratory study on the impact of biological factors on

cognition suggests that BDNF may play an important role in cognition in UHR patients, with a differential effect on IQ depending on the conversion status. Further studies on a larger number of subjects are needed to confirm these preliminary results, to define the role of BDNF in the pathophysiology of cognitive impairment, and to test its importance as a biomarker. A better understanding of these mechanisms could pave the way for personalized therapies.

REFERENCES

Bora, E., 2019. Peripheral inflammatory and neurotrophic biomarkers of cognitive impairment in schizophrenia: a meta-analysis. Psychol Med 49, 1971–1979. https://doi.org/10.1017/S0033291719001685

Catalan, A., Salazar de Pablo, G., Aymerich, C., Damiani, S., Sordi, V., Radua, J., Oliver, D., McGuire, P., Giuliano, A.J., Stone, W.S., Fusar-Poli, P., 2021. Neurocognitive Functioning in Individuals at Clinical High Risk for Psychosis: A Systematic Review and Meta-analysis. JAMA Psychiatry 78, 859–867. https://doi.org/10.1001/jamapsychiatry.2021.1290

Chaumette, B., Kebir, O., Mam-Lam-Fook, C., Morvan, Y., Bourgin, J., Godsil, B.P., Plaze, M., Gaillard, R., Jay, T.M., Krebs, M.-O., 2016. Salivary cortisol in early psychosis: New findings and meta-analysis. Psychoneuroendocrinology 63, 262–270. https://doi.org/10.1016/j.psyneuen.2015.10.007

Chaumette, B., Kebir, O., Pouch, J., Ducos, B., Selimi, F., ICAAR study group, Gaillard, R., Krebs, M.-O., 2019. Longitudinal Analyses of Blood Transcriptome During Conversion to Psychosis. Schizophr Bull 45, 247–255. https://doi.org/10.1093/schbul/sby009

Fusar-Poli, P., Borgwardt, S., Bechdolf, A., Addington, J., Riecher-Rössler, A., Schultze-Lutter, F., Keshavan, M., Wood, S., Ruhrmann, S., Seidman, L.J., Valmaggia, L., Cannon, T., Velthorst, E., De Haan, L., Cornblatt, B., Bonoldi, I., Birchwood, M., McGlashan, T., Carpenter, W., McGorry, P., Klosterkötter, J., McGuire, P., Yung, A., 2013. The psychosis high-risk state: a comprehensive state-of-the-art review. JAMA psychiatry 70, 107–120. https://doi.org/10.1001/jamapsychiatry.2013.269

He, Y., Yuan, L., Li, Z., Zhou, Y., Ma, X., Ouyang, L., Chen, X., 2019. Plasma protein levels of brain-derived neurotrophic factor pathways and their association with cognitive performance in patients with clinical high risk for psychosis and first episode psychosis. Schizophr Res 206, 460–461. https://doi.org/10.1016/j.schres.2018.11.016

Magaud, E., Morvan, Y., Rampazzo, A., Alexandre, C., Willard, D., Gaillard, R., Kazes, M., Krebs, M.-O., 2014. Subjects at Ultra High Risk for psychosis have “heterogeneous” intellectual functioning profile: a multiple-case study. Schizophr Res 152, 415–420. https://doi.org/10.1016/j.schres.2013.11.002

Miranda, M., Morici, J.F., Zanoni, M.B., Bekinschtein, P., 2019. Brain-Derived Neurotrophic Factor: A Key Molecule for Memory in the Healthy and the Pathological Brain. Front Cell Neurosci 13, 363. https://doi.org/10.3389/fncel.2019.00363

Qu, M., Wang, J., Chen, D.C., Chen, S., Xiu, M.H., Zhang, X.Y., 2020. Sex-specific association between peripheral superoxide dismutase, BDNF and cognitive impairment in drug-naive first episode patients with schizophrenia. Free Radic Biol Med 160, 887–893. https://doi.org/10.1016/j.freeradbiomed.2020.09.014

Yee, J.Y., Lee, T.-S., Lee, J., 2018. Levels of Serum Brain-Derived Neurotropic Factor in Individuals at Ultra-High Risk for Psychosis-Findings from the Longitudinal Youth at Risk Study (LYRIKS). Int J Neuropsychopharmacol 21, 734–739. https://doi.org/10.1093/ijnp/pyy036

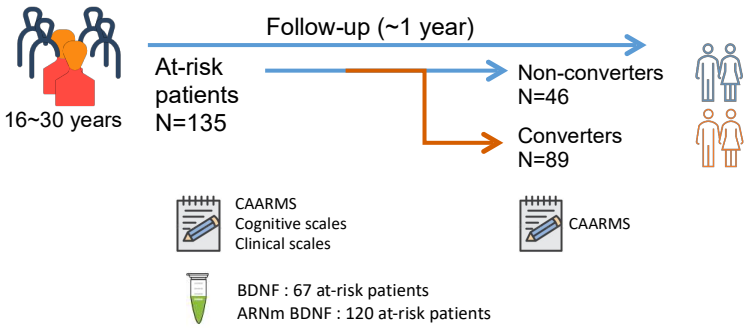
Table 1 : Characteristics of the study population

Characteristics	Converters N = 46[1]	Non-converters N = 89[1]	p-value[2]	Overall, N = 135[1]
Sex			0.3	
F	17 (37%)	41 (46%)		58 (43%)
M	29 (63%)	48 (54%)		77 (57%)
Age	20.0 (19.0, 22.0)	20.0 (18.0, 23.0)	0.6	20.0 (18.5, 23.0)
BMI	20.9 (19.5, 23.8)	21.4 (19.9, 23.2)	0.7	21.4 (19.7, 23.3)
Total QI	98 (90, 107)	103 (94, 108)	0.2	101 (92, 108)
Antipsychotic treatment			0.4	
No	30 (73%)	71 (80%)		101 (78%)
Yes	11 (27%)	18 (20%)		29 (22%)
Antidepressant treatment			>0.9	
No	29 (63%)	56 (63%)		85 (63%)
Yes	17 (37%)	33 (37%)		50 (37%)
Chlorpromazine equivalent (mg)	75 (50, 98)	84 (71, 156)	0.4	77 (50, 156)
Cannabis use within 30 days			**0.011***	
1 : None	21 (58%)	57 (77%)		78 (71%)
2 : Once or twice	3 (8.3%)	2 (2.7%)		5 (4.5%)
3 : Three to nine times	8 (22%)	3 (4.1%)		11 (10%)
4 : More than ten times	4 (11%)	12 (16%)		16 (15%)
Clinical scales				
SOFAS score	45 (40, 50)	48 (41, 55)	0.2	48 (40, 55)
SAPS score	18 (11, 30)	8 (2, 18)	**<0.001***	12 (3, 23)
SANS score	31 (17, 48)	21 (8, 40)	**0.022***	25 (10, 41)
PANSS score	70 (60, 84)	62 (53, 76)	0.055	65 (55, 79)

[1] n (%); Median (Interquartile range)

[2] [2] Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test

Supplementary Figure 1 : Study design



Supplementary Figure 2 : Correlation of total IQ and BDNF (Protein and mRNA) with clinical outcome