Plasma fatty acid-binding protein 7 concentration correlates with depression/anxiety, cognition, and positive symptom in patients with schizophrenia

Minori Koga[a,b,*], Shin Nakagawa[a,c], Asumi Sato[a], Matsuhiko Oka[a], Keisuke Makikhara[a], Yuri Sakai[a], Atsuhito Toyomaki[a], Mayumi Sato[b†], Marie Matsui[b†], Hiroyuki Toda[b], and Ichiro Kusumi[a]

[a]Department of Psychiatry, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan

[b]Department of Psychiatry, National Defense Medical College, Tokorozawa, Saitama, Japan

[c]Yamaguchi University Graduate School of Medicine Division of Neuropsychiatry, Department of Neuroscience

[†]These authors contributed equally.

***Corresponding author:** Minori Koga, PhD
National Defense Medical College
Department of Psychiatry
3-2 Namiki, Tokorozawa, Saitama 359-8513, Japan
Email: mkoga3@ndmc.ac.jp
Tel: +81-4-2995-1619
Fax: +81-4-2996-5203

Abstract

Because of the involvement of the brain in the pathophysiology of psychiatric disorders, obtaining information on the biochemical features that directly contribute to symptoms is challenging. The present study aimed to assess fatty acid-binding protein 7 (FABP7) expressed specifically in the brain and detectable in the peripheral blood and to investigate the correlation between blood FABP7 concentration and symptoms. We recruited 30, 29, and 35 patients with schizophrenia, bipolar disorder, and depression and evaluated using the Positive and Negative Syndrome Scale (PANSS), Young Mania Rating Scale (YMRS), and Hamilton Depression Rating Scale (HAMD-21), respectively. Plasma FABP7 concentrations correlated with PANSS scores ($R^2 = 0.3305$, $p < 0.001$) but not with other scales. In the analysis of the relationship between five dimensions of schizophrenia symptoms derived from the PANSS 5-factor model and measured plasma FABP7 concentrations, severities of depression/anxiety, cognition, and positive symptom were significantly correlated with plasma FABP7 concentrations. Further molecular investigation of the functional and kinetic analyses of FABP7 is necessary to understand the relationship of this protein with schizophrenia pathology. Nevertheless, the present study suggests that FABP7 can be a biological indicator reflecting the pathogenesis of schizophrenia and has potential applications as a biomarker for diagnosis and symptom assessment.

Keywords: Biomarkers, Bipolar Disorder, Depression, Fatty Acid-Binding Protein 7, Schizophrenia

1. Introduction

Because the brain is involved in the pathophysiology of psychiatric disorders, performing biopsy to elucidate the disease pathophysiology is challenging. Thus, identifying molecules expressed in the periphery of the brain that are associated with pathological conditions is essential. These molecules are called "surrogate indicators" or "surrogate markers." However, molecules that function in the periphery have their own dynamics in peripheral tissues, thus making it difficult to assess their association with brain abnormalities. This problem could be resolved by identifying molecules detectable in the periphery that indicate any damage to the disease-affected organ, such as γ-glutamyl transpeptidase (γ-GTP), which is detected in blood and indicate liver diseases. Unfortunately, no such molecules have been associated with psychiatric disorders. Fatty acid-binding proteins (FABPs), which have a high affinity for unsaturated fatty acids and are involved in fatty acid transport, form a family of molecules and are expressed with specificity to organs and cell types (Furuhashi and Hotamisligil, 2008; Storch and Corsico, 2008). Previous studies have reported an association between extracellular leakage and tissue damage for some FABPs. For instance, elevated serum concentrations of FABP3 expressed in the myocardium and elevated urinary concentrations of FABP1 expressed in the upper urinary tract reflect damages caused by inflammation and oxidative stress in the myocardium and kidneys, respectively (Kamijo et al., 2004; Kleine et al., 1992); thus, they are clinically used as diagnostic aid markers for acute myocardial infarctions and renal disorders. Although the molecular function of FABPs remains unclear, FABP1 binds to lipid peroxide and deviates from the cell. This action may contribute to reduced oxidative stress in the tissue, which is involved in the pathophysiology of renal damage. This phenomenon may explain the increase in extracellular FABP1 concentrations in patients with renal function (Yamamoto et al., 2007 3). Although FABP3, FABP5, and FABP 7 are all expressed in the brain, FABP3 and FABP5 are mainly expressed in the myocardium and epidermal cells, respectively, but are also expressed in various other tissues such as the lung, stomach, and kidney. In contrast to FABP3 and FABP5, FABP7 is called brain-type FABP. Although its expression has also been confirmed in the retina and mammary gland, it is expressed mostly in the brain, particularly in the glia. FABP7 is thus more specific the brain than FABP3 and FABP5. In genetic studies, FABP7 had an SNP (rs2279381) that correlates with schizophrenia (Watanabe et al., 2007), and gene expression was higher in the postmortem brain than in controls, suggesting that FABP7 is associated with schizophrenia. Subsequent molecular biological studies showed that FABP7 participates in lipid signaling involved in the regulation of neurogenesis, which is essential for brain development. Studies examining aspects of FABP7 that differ from these findings on its molecular function were

also conducted. Serum concentrations of FABP7 are elevated in patients with neurodegenerative diseases, such as acute stroke, Alzheimer's disease, and Parkinson's disease, suggesting that FABP7 leakage may result from host cell damage. The disruption of the blood–brain barrier caused by cell wounding or cell death is suggested to be the mechanism of release of FABP into the serum (Halford et al., 2017). Although psychiatric disorders are not considered neurodegenerative diseases, previous studies have suggested various common pathophysiological pathways between psychiatric disorders and neurodegenerative diseases. For instance, a number of previous studies have demonstrated abnormal oxidative stress and inflammation-induced neuronal cell death (Andreazza et al., 2008; Black et al., 2015; Koga et al., 2016), abnormal brain volume (de Zwarte et al., 2019; Opel et al., 2020; Steen et al., 2006; Tham et al., 2011), and disruption of the blood–brain barrier (Greene et al., 2020). These findings suggest that a leakage of FABP7 into the blood may occur in psychiatric disorders, similar to that in neurodegenerative diseases. However, plasma FABP7 concentrations in patients with psychiatric disorders have remained uninvestigated so far. In the present study, we aimed to determine whether plasma FABP7 concentrations correlate with clinical scales in schizophrenia, bipolar disorder, and depression, considering FABP7 as a potential objective indicator of symptoms in psychiatric disorders.

2. Methods

2.1. Study participants

We recruited 30 patients with schizophrenia (including 1 with schizoaffective disorder), 30 patients with bipolar disorder, and 34 patients with depression from outpatient and inpatient wards at Hokkaido University Hospital. All were diagnosed using the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV). We also recruited 41 healthy controls that had never been diagnosed with any psychiatric disorders. Table 1 shows the patients' demographic data.

2.2. Preparation of plasma samples

After obtaining informed consent from the participants, we collected whole-blood specimens into EDTA-2K tubes, followed by centrifugation at 1000 *g* to obtain the plasma. The plasma samples were then frozen in 500 μL of aliquots at −80 °C until FABP7 concentration measurement.

2.3. Clinical scales

For patients with schizophrenia and schizoaffective disorder, the symptom severity was measured using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), which comprises 3 subscales, namely, the 7-item positive factor subscale, 7-item negative factor subscale, and 16-item subscale for general psychopathology. Given that some of the items assigned to one subscale are better conceptualized as part of another symptom construct such as "mood" or "cognition," a five-factor model of PANSS was developed through factor analysis based on the original PANSS subscales to assess the core symptoms or five dimensions of schizophrenia, including excitement/hostility, depression/anxiety, cognition, and positive and negative factors (Citrome et al., 2011). For patients with depression and bipolar disorder, depressive and manic symptoms were assessed using the 21-item Hamilton Depression Rating Scale (HAMD-21) (Hamilton, 1960) and the 11-item Young Mania Rating Scale (YMRS) (Young et al., 1978), respectively; both were in Japanese version and rated by an interviewer. Subsequently, we analyzed the correlation between plasma FABP7 concentration and the total scores of HAMD-21 and YMRS in patients with depression and bipolar disorder and PANSS in patients with schizophrenia. In patients with schizophrenia, we also examined the correlation of plasma FABP7 concentration with the five dimensions of schizophrenia.

2.4. Enzyme-linked immunosorbent assay

Human or mouse plasma FABP7 concentrations were determined using a commercially

available enzyme-linked immunosorbent assay (ELISA) kit (Human FABP7 ELISA Kit, SEB277Hu; Cloud-Clone Corp., TX, USA). Then, the plasma was diluted into phosphate-buffered saline at a ratio of 1:5. Subsequently, we dispensed 100 μL of the diluted plasma onto coated ELISA plates and examined FABP7 in the samples according to the manufacturer's instruction. Each sample was assayed in duplicate.

2.5. Ethical statement

All patients provided written informed consent, and the institutional review board at Hokkaido University Graduate School of Medicine approved the study protocol (Approval Number: 014-0190).

2.6. Statistical analysis

According to sex, groups were compared using chi-square test. Differences in the means of age and duration of illness among the groups were analyzed by one-way analysis of variance (ANOVA), followed by Bonferroni *post-hoc* test. The total scores of HAMD-21 and YMRS between the bipolar disorder and depression groups were compared using *t*-test. The plasma FABP7 concentrations determined by ELISA are expressed as mean ± SEM. The association between plasma FABP7 concentration and the scores of clinical scales were investigated by linear regression analysis. These statistical data were analyzed using GraphPad Prism 7 (GraphPad Software, La Jolla, CA, USA). The significance level was set at 0.05. The residual values were obtained from linear regression analysis by regressing plasma FABP7 concentration onto age using SPSS Statistics 26 (IBM Corp., NY, USA).

3. Results

3.1. Demographic data of the participants

Table 1 lists the participants' demographic data, and Supplemental Table 1 summarizes the medication information of each patient group. The male-to-female ratio and the mean illness duration were not significantly different between the three groups (chi-square analysis, $p > 0.05$; Tukey-HSD post-hoc test with one-way ANOVA, $p < 0.05$). The mean age was higher in the bipolar disorder group than in the schizophrenia group (Tukey-HSD post-hoc test with one-way ANOVA, $p < 0.05$). The total scores of HAMD-21 were not significantly different between the bipolar disorder and depression groups (*t*-test, $p > 0.05$), but those of YMRS were higher in the former than in the latter (*t*-test, $p < 0.05$). Chlorpromazine equivalent in the patients with schizophrenia was 797.55 ± 527.64 (average ± standard deviation).

Table 1 Demographic data of the participants in the present study.

176

	Schizophrenia	Bipolar disorder	Depression
Participants (male: female)	17:13	13:17	15:19
Mean age (year)	43.8 ± 8.8 **a**	52.8 ± 9.5 **b**	48.9 ± 12.9 **a b**
Mean duration of illness (year)	21.5 ± 11.3 **a**	20.0 ± 8.4 **a**	16.4 ± 6.9 **a**
Mean PANSS total score	68.8 ± 11.6		
Mean HAMD-21 total score		10.2 ± 7.3 **a**	11.8 ± 7.9 **a**
Mean YMRS total score		3.8 ± 4.2 **a**	1.7 ± 1.8 **b**

177

Population of each group and the means ± standard deviation values of age, duration of illness, PANSS total score, HAMD-21 total score, and YMRS total score. Statistical difference in sex between the groups was determined by chi-square analysis, while the mean values of age and illness duration were determined by one-way ANOVAs with Tukey-HSD *post-hoc* tests. The total scores of HAMD-21 and YMRS were compared using *t*-tests. Factors not associated with the same letters (a, b) were found to be statistically different.

3.2. Association of plasma FABP7 concentrations with sex, age, and disease duration

Plasma FABP7 concentrations in patients with schizophrenia, bipolar disorder, and depression were not significantly different between males and females (Supplemental Fig. 1A–C). In entire participants, patients' age significantly correlated with plasma FABP7 concentrations ($R^2 = 0.03159$, $p < 0.05$, Fig. 1). Furthermore, disease duration had no significant correlation with plasma FABP7 concentrations (Supplemental Fig. 2A–C).

3.3. Correlation of plasma FABP7 concentrations with clinical rating scales

The total score of PANSS positively correlated with plasma FABP7 concentrations in the schizophrenia group ($R^2 = 0.3332$, $p < 0.001$, Fig. 2A). Considering that age significantly correlated with plasma FABP7 concentration, we conducted a correlation analysis adjusted for age. When the plasma FABP7 concentration–age residuals were employed, the correlation remained significant ($R^2 = 0.3387$, $p < 0.001$, Fig. 2B). Conversely, the total scores of HAMD-21 and YMRS in the bipolar disorder and depression groups did not correlate with plasma FABP7 concentration (Fig 2C, E, G, and I), as well as plasma FABP7 concentration–age residuals (Fig. 2D, F, H, and J).

3.4. Five-factor model in PANSS and plasma FABP7 and residual values of FABP7–age

PANSS is a rating scale consisting of 7 items on a positive scale, 7 items on a negative scale, and 16 items on a comprehensive psychopathology scale. Further factor analysis of these subscales demonstrated that the five dimensions of schizophrenia can be assessed (Van den Oord et al., 2006). Considering that PANSS total score significantly correlated with plasma FABP7 concentration, we next assessed its correlation with the five dimensions of schizophrenia. Plasma FABP7 concentration correlated with depression/anxiety ($R^2 = 0.2304$, $p < 0.01$, Fig. 3C), cognition ($R^2 = 0.2852$, $p < 0.01$, Fig. 3E), and positive factor ($R^2 = 0.1843$, $p < 0.01$, Fig. 3G). When plasma FABP7 concentration–age residuals were used, the correlations with depression/anxiety ($R^2 = 0.1953$, $p < 0.01$), cognition ($R^2 = 0.3147$, $p < 0.01$), and positive factor ($R^2 = 0.1937$, $p < 0.01$) remained significant (Fig. 3D, F, and H).

3.5. Effect of drugs on plasma FABP7 concentration

To assess the effect of antipsychotics and antidepressant on plasma FABP7 concentration, we analyzed the correlation of chlorpromazine equivalents and imipramine equivalents with the plasma FABP7 concentration in all participants using linear regression analysis. No significant correlation was found between plasma FABP7 concentrations and chlorpromazine equivalents (Fig. 4A), imipramine equivalents (Fig. 4C), and diazepam

equivalents (Fig. 4E). These correlations did not change with plasma FABP7 concentration–age residuals (Fig. 4B, D, and F)

4. Discussion

FABP7 is specifically expressed in the central nervous system. In this study, by examining the FABP7 concentrations detected in the periphery, we found that plasma FABP7 had a correlation with schizophrenia severity. Particularly, the severity of depression/anxiety, cognitive decline, and positive factor, which are part of the major symptoms of schizophrenia, were positively associated with plasma FABP7 concentration. Plasma FABP7 concentration was found to be positively correlated with age. Abnormal acceleration of aging has been reported in the pathophysiology of psychiatric disorders (Fries et al., 2020; Kirkpatrick and Kennedy, 2018; Luca et al., 2013). However, considering that the correlation between the severity of schizophrenia and plasma FABP7 concentration remained significant despite the adjusted value of plasma FABP7 concentration with age, there may be other underlying pathological pathways apart from those involved in aging.

In postmortem brain studies and proton magnetic resonance spectroscopy (^{1}H-MRS) studies, oxidative stress accumulated excessively in the brain tissue of patients with schizophrenia compared with that of the controls (Koga et al., 2016). The accumulation of excessive oxidative stress may cause neuronal cell death and pathogenesis through the neurodegenerative pathways (Benes, 2004). Prefrontal cortex hypomyelination caused by oxidative stress-induced oligodendrocyte apoptosis is associated with cognitive decline in schizophrenia (Maas et al., 2017). The FABP family has antioxidant properties (Bennaars-Eiden et al., 2002; Kajimoto et al., 2014; Wang et al., 2005). For instance, FABP1 expression is upregulated upon stress to the kidney tissue (Sato et al., 2017), and this protein can capture oxidized lipids generated by kidney damage and remove them from the cells ((Sato et al., 2017; Yamamoto et al., 2007)). In a previous study, the expression of *FABP7* gene was upregulated in the postmortem brains of patients with schizophrenia (Watanabe et al., 2007). If FABP7 has the same effect as FABP1, the increase in FABP7 concentrations in the peripheral blood could be the result of the elimination of excessive oxidative stress in the brain in schizophrenia pathology. Although FABP7 has the same lipid-binding ability as FABP1 (Xu et al., 1996 29), its function of excreting selectively oxidized lipids out of cells has remained unreported. Hence, the molecular role of FABP7 needs further analysis.

Schizophrenia is a neurodevelopmental disorder; however, evidence of progressive worsening of clinical symptoms and changes in neural structure after the onset of psychosis has led to the hypothesis that neurodegenerative aspects may contribute to schizophrenia pathophysiology (Jarskog et al., 2005). In cognitive disorders such as

Alzheimer's disease, the occurrence of large-scale apoptotic neuronal cell death has direct clinical significance (Mattson et al., 2001). Meanwhile, synaptic apoptosis plays a role in synapse remodeling and removal, both physiologically and pathologically, and may also contribute to neuronal plasticity (Garden et al., 2002; Gilman and Mattson, 2002). Cognitive decline is one of the core symptoms of schizophrenia, which is difficult to treat and is associated with functional outcomes (O'Carroll, 2000; Sinkeviciute et al., 2018). Historically, schizophrenia was named dementia praecox by Kraepelin (Lyketsos and Peters, 2015), highlighting the idea that the pathophysiology of cognitive decline in both schizophrenia and dementia might be partially shared. Teunissen et al. reported elevated serum FABP7 concentrations in patients with dementia-related diseases (Teunissen et al., 2011), suggesting common pathophysiological mechanisms.

Although depression/anxiety in the PANSS 5-factor model was found to be significantly correlated with plasma FABP7 concentration, it was not found to be significantly correlated with disease severity in patients with bipolar disorder or depression by HAMD-21. Moreover, positive factor in the PANSS 5-factor model was also found to be correlated with plasma FABP7 concentration. These findings suggest that elevated plasma FABP7 concentrations may be a schizophrenia-specific marker.

This study has some limitations. First, the human samples were only obtained at a single institution. Replication should be verified using samples from other institutions and/or other ethnic groups. Second, the correlation between drug dose and plasma FABP7 concentration was shown to be non-significant. However, it would still be useful to investigate plasma FABP7 concentrations in drug-naïve patients. Third, although our study has investigated only patients with psychiatric disorders, a comparison should be made between the control and disease groups to identify biological markers for clinical application. According to previous studies, the variance of blood FABP7 concentrations of healthy subjects seems to be large. Karvellas et al. have determined serum concentration of FABP7 in healthy controls and found a median serum concentration of 13.5 ng/mL (8.7–20.2, 95% confidence interval) (Karvellas et al., 2017). By contrast, Rogatzki et al. reported mean ± standard deviation serum BLBP (alternative name for FABP7) concentration of 0.96 ± 0.37 ng/mL (0.71–1.21, 95% confidence interval) (Rogatzki et al., 2021) in their control group. Based on these findings, it remains unclear whether there is a difference between healthy controls and patients. All comparison groups should be investigated together with a same method in future studies. Fourth, in the present study, we focused on FABP7, which could be able to specifically reflect abnormalities related to the brain. However, it would be beneficial to investigate the relationship between psychiatric symptoms and FABP3 and FABP5 which though mainly expressed in the periphery are also reflected in the brain.

Nevertheless, our study findings suggest that FABP7 can be an indicator of severity that can separate subsets from the heterogeneous population of schizophrenia with diverse pathologies, with depression/anxiety, cognitive decline, and positive factor. Plasma FABP7 also appears to be unresponsive to drugs, indicating to be a good candidate for symptom assessment. FABP7 is suggested to be potentially useful for elucidating the pathogenesis, diagnosis, and selection of appropriate drug therapies for schizophrenia.

References

Andreazza, A.C., Kauer-Sant'anna, M., Frey, B.N., Bond, D.J., Kapczinski, F., Young, L.T., Yatham, L.N., 2008. Oxidative stress markers in bipolar disorder: a meta-analysis. J. Affect. Disord. 111, 135–144. https://doi.org/10.1016/j.jad.2008.04.013.

Benes, F.M., 2004. The role of apoptosis in neuronal pathology in schizophrenia and bipolar disorder. Curr. Opin. Psychiatry 17. https://doi.org/10.1097/00001504-200405000-00006.

Bennaars-Eiden, A., Higgins, L., Hertzel, A.V., Kapphahn, R.J., Ferrington, D.A., Bernlohr, D.A., 2002. Covalent modification of epithelial fatty acid-binding protein by 4-hydroxynonenal in vitro and in vivo. Evidence for a role in antioxidant biology. J. Biol. Chem. 277, 50693–50702. https://doi.org/10.1074/jbc.M209493200.

Black, C.N., Bot, M., Scheffer, P.G., Cuijpers, P., Penninx, B.W., 2015. Is depression associated with increased oxidative stress? A systematic review and meta-analysis. Psychoneuroendocrinology 51, 164–175. https://doi.org/10.1016/j.psyneuen.2014.09.025.

Citrome, L., Meng, X., Hochfeld, M., 2011. Efficacy of iloperidone in schizophrenia: a PANSS five-factor analysis. Schizophr. Res. 131, 75–81. https://doi.org/10.1016/j.schres.2011.05.018.

de Zwarte, S.M.C., Brouwer, R.M., Agartz, I., Alda, M., Aleman, A., Alpert, K.I., Bearden, C.E., Bertolino, A., Bois, C., Bonvino, A., Bramon, E., Buimer, E.E.L., Cahn, W., Cannon, D.M., Cannon, T.D., Caseras, X., Castro-Fornieles, J., Chen, Q., Chung, Y., De la Serna, E., Di Giorgio, A., Doucet, G.E., Eker, M.C., Erk, S., Fears, S.C., Foley, S.F., Frangou, S., Frankland, A., Fullerton, J.M., Glahn, D.C., Goghari, V.M., Goldman, A.L., Gonul, A.S., Gruber, O., de Haan, L., Hajek, T., Hawkins, E.L., Heinz, A., Hillegers, M.H.J., Hulshoff Pol, H.E., Hultman, C.M., Ingvar, M., Johansson, V., Jonsson, E.G., Kane, F., Kempton, M.J., Koenis, M.M.G., Kopecek, M., Krabbendam, L., Kramer, B., Lawrie, S.M., Lenroot, R.K., Marcelis, M., Marsman, J.C., Mattay, V.S., McDonald, C., Meyer-Lindenberg, A., Michielse, S., Mitchell, P.B., Moreno, D., Murray, R.M., Mwangi, B., Najt, P., Neilson, E., Newport, J., van Os, J., Overs, B., Ozerdem, A., Picchioni, M.M., Richter, A., Roberts, G., Aydogan, A.S., Schofield, P.R., Simsek, F., Soares, J.C., Sugranyes, G., Toulopoulou, T., Tronchin, G., Walter, H., Wang, L., Weinberger, D.R., Whalley, H.C., Yalin, N., Andreassen, O.A., Ching, C.R.K., van Erp, T.G.M., Turner, J.A., Jahanshad, N., Thompson, P.M., Kahn, R.S., van

Haren, N.E.M., 2019. The association between familial risk and brain abnormalities is disease specific: An ENIGMA-relatives study of schizophrenia and bipolar disorder. Biol. Psychiatry 86, 545–556. https://doi.org/10.1016/j.biopsych.2019.03.985.

Fries, G.R., Zamzow, M.J., Andrews, T., Pink, O., Scaini, G., Quevedo, J., 2020. Accelerated aging in bipolar disorder: A comprehensive review of molecular findings and their clinical implications. Neurosci. Biobehav. Rev. 112, 107–116. https://doi.org/10.1016/j.neubiorev.2020.01.035.

Furuhashi, M., Hotamisligil, G.S., 2008. Fatty acid-binding proteins: role in metabolic diseases and potential as drug targets. Nat. Rev. Drug. Discov. 7, 489–503. https://doi.org/10.1038/nrd2589.

Garden, G.A., Budd, S.L., Tsai, E., Hanson, L., Kaul, M., D'Emilia, D.M., Friedlander, R.M., Yuan, J., Masliah, E., Lipton, S.A., 2002. Caspase cascades in human immunodeficiency virus-associated neurodegeneration. J. Neurosci. 22, 4015–4024. https://doi.org/10.1523/JNEUROSCI.22-10-04015.2002.

Gilman, C.P., Mattson, M.P., 2002. Do apoptotic mechanisms regulate synaptic plasticity and growth-cone motility? Neuromolecular. Med. 2, 197–214. https://doi.org/10.1385/NMM:2:2:197.

Greene, C., Hanley, N., Campbell, M., 2020. Blood-brain barrier associated tight junction disruption is a hallmark feature of major psychiatric disorders. Transl. Psychiatry 10, 373. https://doi.org/10.1038/s41398-020-01054-3.

Halford, J., Shen, S., Itamura, K., Levine, J., Chong, A.C., Czerwieniec, G., Glenn, T.C., Hovda, D.A., Vespa, P., Bullock, R., Dietrich, W.D., Mondello, S., Loo, J.A., Wanner, I.B., 2017. New astroglial injury-defined biomarkers for neurotrauma assessment. J Cereb Blood Flow Metab 37, 3278–3299. https://doi.org/10.1177/0271678X17724681.

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry. 23, 56–62. https://doi.org/10.1136/jnnp.23.1.56.

Jarskog, L.F., Glantz, L.A., Gilmore, J.H., Lieberman, J.A., 2005. Apoptotic mechanisms in the pathophysiology of schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 29, 846–858. https://doi.org/10.1016/j.pnpbp.2005.03.010.

Kajimoto, K., Minami, Y., Harashima, H., 2014. Cytoprotective role of the fatty acid binding protein 4 against oxidative and endoplasmic reticulum stress in 3T3-L1 adipocytes. FEBS Open Bio. 4, 602–610. https://doi.org/10.1016/j.fob.2014.06.008.

Kamijo, A., Kimura, K., Sugaya, T., Yamanouchi, M., Hikawa, A., Hirano, N., Hirata, Y., Goto, A., Omata, M., 2004. Urinary fatty acid-binding protein as a new clinical marker of the progression of chronic renal disease. J. Lab. Clin. Med. 143, 23–30. https://doi.org/10.1016/j.lab.2003.08.001.

Karvellas, C.J., Speiser, J.L., Tremblay, M., Lee, W.M., Rose, C.F., Group, U.S.A.L.F.S., 2017. The association between FABP7 serum levels with survival and neurological complications in acetaminophen-induced acute liver failure: a nested case-control study. Ann. Intensive Care 7, 99. https://doi.org/10.1186/s13613-017-0323-0.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276. https://doi.org/10.1093/schbul/13.2.261.

Kirkpatrick, B., Kennedy, B.K., 2018. Accelerated aging in schizophrenia and related disorders: Future research. Schizophr. Res. 196, 4–8. https://doi.org/10.1016/j.schres.2017.06.034.

Kleine, A.H., Glatz, J.F., Van Nieuwenhoven, F.A., Van der Vusse, G.J., 1992. Release of heart fatty acid-binding protein into plasma after acute myocardial infarction in man. Mol. Cell. Biochem. 116, 155–162. https://doi.org/10.1007/BF01270583.

Koga, M., Serritella, A.V., Sawa, A., Sedlak, T.W., 2016. Implications for reactive oxygen species in schizophrenia pathogenesis. Schizophr. Res. 176, 52–71. https://doi.org/10.1016/j.schres.2015.06.022.

Luca, M., Luca, A., Calandra, C., 2013. Accelerated aging in major depression: the role of nitro-oxidative stress. Oxid. Med. Cell Longev. 2013, 230797. https://doi.org/10.1155/2013/230797.

Lyketsos, C.G., Peters, M.E., 2015. Dementia in Patients With Schizophrenia: Evidence for Heterogeneity. JAMA Psychiatry 72, 1075–1076. https://doi.org/10.1001/jamapsychiatry.2015.1745.

Maas, D.A., Vallès, A., Martens, G.J.M., 2017. Oxidative stress, prefrontal cortex hypomyelination and cognitive symptoms in schizophrenia. Transl. Psychiatry 7, e1171–e1171. https://doi.org/10.1038/tp.2017.138.

Mattson, M.P., Duan, W., Pedersen, W.A., Culmsee, C., 2001. Neurodegenerative disorders and ischemic brain diseases. Apoptosis 6, 69–81. https://doi.org/10.1023/A:1009676112184.

O'Carroll, R., 2000. Cognitive impairment in schizophrenia. Adv. Psychiatr. Treat. 6, 161–168. https://doi.org/10.1192/apt.6.3.161.

Opel, N., Goltermann, J., Hermesdorf, M., Berger, K., Baune, B.T., Dannlowski, U., 2020. Cross-disorder analysis of brain structural abnormalities in six major psychiatric disorders: A secondary analysis of mega- and meta-analytical findings from the ENIGMA Consortium. Biol. Psychiatry 88, 678–686. https://doi.org/10.1016/j.biopsych.2020.04.027.

Rogatzki, M.J., Morgan, J.E., Baker, J.S., Knox, A., Serrador, J.M., 2021. Protein S100B and Brain Lipid-Binding Protein Concentrations in the Serum of Recently Concussed Rugby Players. J. Neurotrauma 38, 2247–2254. https://doi.org/10.1089/neu.2021.0004.

Sato, E., Kamijo-Ikemori, A., Oikawa, T., Okuda, A., Sugaya, T., Kimura, K., Nakamura, T., Shibagaki, Y., 2017. Urinary excretion of liver-type fatty acid-binding protein reflects the severity of sepsis. Ren. Replace. Ther. 3, 26. https://doi.org/10.1186/s41100-017-0107-x.

394 Sinkeviciute, I., Begemann, M., Prikken, M., Oranje, B., Johnsen, E., Lei, W.U., Hugdahl, K.,
395 Kroken, R.A., Rau, C., Jacobs, J.D., Mattaroccia, S., Sommer, I.E., 2018. Efficacy of different
396 types of cognitive enhancers for patients with schizophrenia: a meta-analysis. NPJ
397 Schizophr. 4, 22. https://doi.org/10.1038/s41537-018-0064-6.
398 Steen, R.G., Mull, C., McClure, R., Hamer, R.M., Lieberman, J.A., 2006. Brain volume in first-
399 episode schizophrenia: systematic review and meta-analysis of magnetic resonance
400 imaging studies. Br. J. Psychiatry 188, 510–518. https://doi.org/10.1192/bjp.188.6.510.
401 Storch, J., Corsico, B., 2008. The emerging functions and mechanisms of mammalian fatty acid-
402 binding proteins. Annu. Rev. Nutr. 28, 73–95.
403 https://doi.org/10.1146/annurev.nutr.27.061406.093710.
404 Teunissen, C.E., Veerhuis, R., De Vente, J., Verhey, F.R., Vreeling, F., van Boxtel, M.P., Glatz, J.F.,
405 Pelsers, M.A., 2011. Brain-specific fatty acid-binding protein is elevated in serum of
406 patients with dementia-related diseases. Eur. J. Neurol. 18, 865–871.
407 https://doi.org/10.1111/j.1468-1331.2010.03273.x.
408 Tham, M.W., Woon, P.S., Sum, M.Y., Lee, T.S., Sim, K., 2011. White matter abnormalities in
409 major depression: evidence from post-mortem, neuroimaging and genetic studies. J. Affect.
410 Disord. 132, 26–36. https://doi.org/10.1016/j.jad.2010.09.013.
411 Van den Oord, E.J., Rujescu, D., Robles, J.R., Giegling, I., Birrell, C., Bukszar, J., Murrelle, L.,
412 Moller, H.J., Middleton, L., Muglia, P., 2006. Factor structure and external validity of the
413 PANSS revisited. Schizophr. Res. 82, 213–223. https://doi.org/10.1016/j.schres.2005.09.002.
414 Wang, G., Gong, Y., Anderson, J., Sun, D., Minuk, G., Roberts, M.S., Burczynski, F.J., 2005.
415 Antioxidative function of L-FABP in L-FABP stably transfected Chang liver cells.
416 Hepatology 42, 871–879. https://doi.org/10.1002/hep.20857.
417 Watanabe, A., Toyota, T., Owada, Y., Hayashi, T., Iwayama, Y., Matsumata, M., Ishitsuka, Y.,
418 Nakaya, A., Maekawa, M., Ohnishi, T., Arai, R., Sakurai, K., Yamada, K., Kondo, H.,
419 Hashimoto, K., Osumi, N., Yoshikawa, T., 2007. Fabp7 maps to a quantitative trait locus for
420 a schizophrenia endophenotype. PLoS biology 5, e297.
421 https://doi.org/10.1371/journal.pbio.0050297.
422 Xu, L.Z., Sanchez, R., Sali, A., Heintz, N., 1996. Ligand specificity of brain lipid-binding protein.
423 J. Biol. Chem. 271, 24711–24719. https://doi.org/10.1074/jbc.271.40.24711.
424 Yamamoto, T., Noiri, E., Ono, Y., Doi, K., Negishi, K., Kamijo, A., Kimura, K., Fujita, T.,
425 Kinukawa, T., Taniguchi, H., Nakamura, K., Goto, M., Shinozaki, N., Ohshima, S., Sugaya,
426 T., 2007. Renal L-type fatty acid--binding protein in acute ischemic injury. J. Am. Soc.
427 Nephrol. 18, 2894–2902. https://doi.org/10.1681/ASN.2007010097.
428 Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability,
429 validity and sensitivity. Br. J. Psychiatry 133, 429–435. https://doi.org/10.1192/bjp.133.5.429.

Figure Legends

Fig. 1. Correlation between plasma fatty acid-binding protein 7 (FABP7) concentration and age.

Linear regression analysis revealed a significant correlation between age and plasma FABP7 in all participants ($R^2 = 0.03159$, $p < 0.05$).

Fig. 2. Clinical rating scales correlated with plasma fatty acid-binding protein 7 (FABP7) concentrations.

The relationship between plasma FABP7 concentration and clinical rating scales was evaluated by simple regression analysis. The Positive and Negative Syndrome Scale (PANSS) total score significantly correlated with plasma FABP7 concentration in the schizophrenia group (A, $R^2 = 0.3332$, $p < 0.001$). Even the plasma FABP7–age residuals did not affect the correlation (B, $R^2 = 0.3387$, $p < 0.001$). The total scores of Young Mania Rating Scale (YMRS) and 21-item Hamilton Depression Rating Scale (HAMD-21) total score in the bipolar disorder and depression groups (C, E, G, I), and the plasma FABP7–age residuals did not change the correlation (D, F, H, J).

Fig. 3. Correlation between plasma fatty acid-binding protein 7 (FABP7) concentration and five dimensions of schizophrenia symptoms derived from Positive and Negative Syndrome Scale (PANSS) clinical rating scale.

The relationship between plasma FABP7 concentration and the five dimensions of schizophrenia symptoms derived from the factor analysis of the 30 items in PANSS clinical rating scales was analyzed by simple regression analysis. Excitement/hostility had no significant correlation with plasma FABP7 concentration (A) and plasma FABP7–age residuals (B). Depression/anxiety significantly correlated with plasma FABP7 concentration (C, $R^2 = 0.2255$, $p < 0.01$) and plasma FABP7–age residuals (D, $R^2 = 0.1953$, $p < 0.05$). Cognition significantly correlated with plasma FABP7 concentration (E, $R^2 = 0.2909$, $p < 0.01$) and plasma FABP7–age residuals (F, $R^2 = 0.3147$, $p < 0.01$). Positive factor also significantly correlated with plasma FABP7 concentration (G, $R^2 = 0.1876$, $p < 0.05$) and plasma FABP7–age residuals (F, $R^2 = 0.0.1937$, $p < 0.05$). Conversely, negative factor showed no significant correlation with plasma FABP7 concentration (A) and plasma FABP7–age residuals (B).

Fig. 4. Correlation between plasma fatty acid-binding protein 7 (FABP7) concentration and drug.

Simple linear regression analysis indicated no significant correlation between

chlorpromazine equivalents (A), imipramine equivalents (C), or diazepam equivalents (E) and the plasma FABP7 concentration in all participants. These correlations remained with plasma FABP7–age residuals (B, D, F).

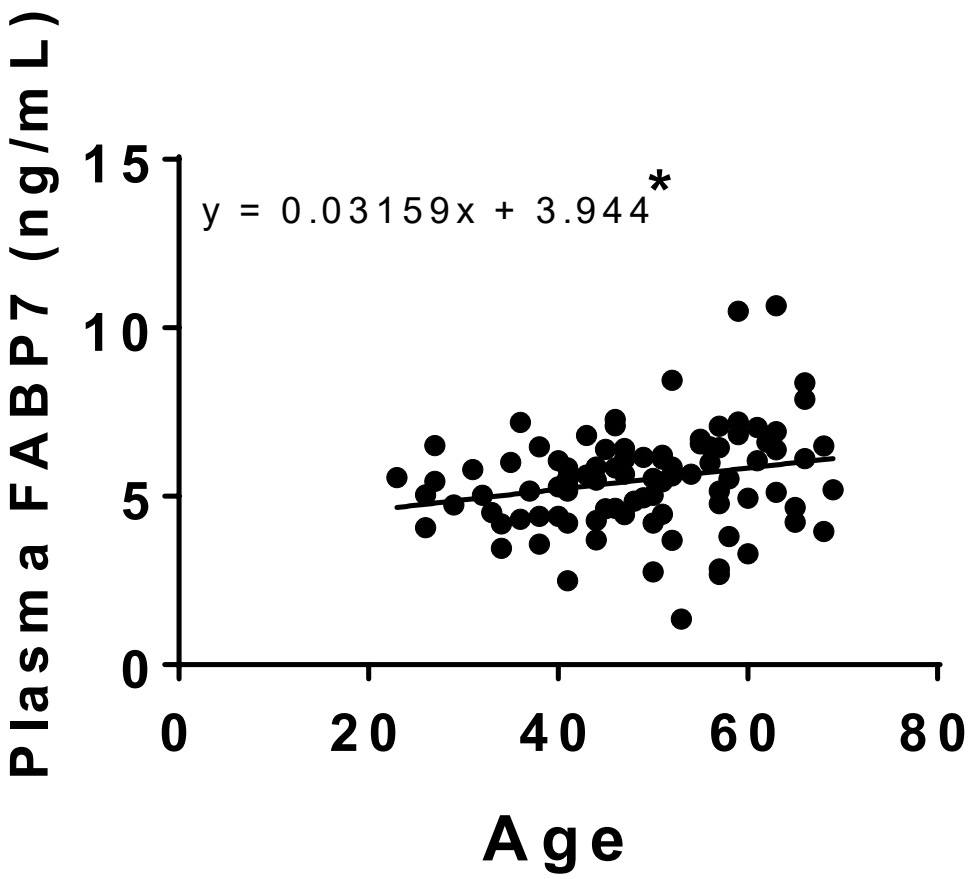

Fig. 1

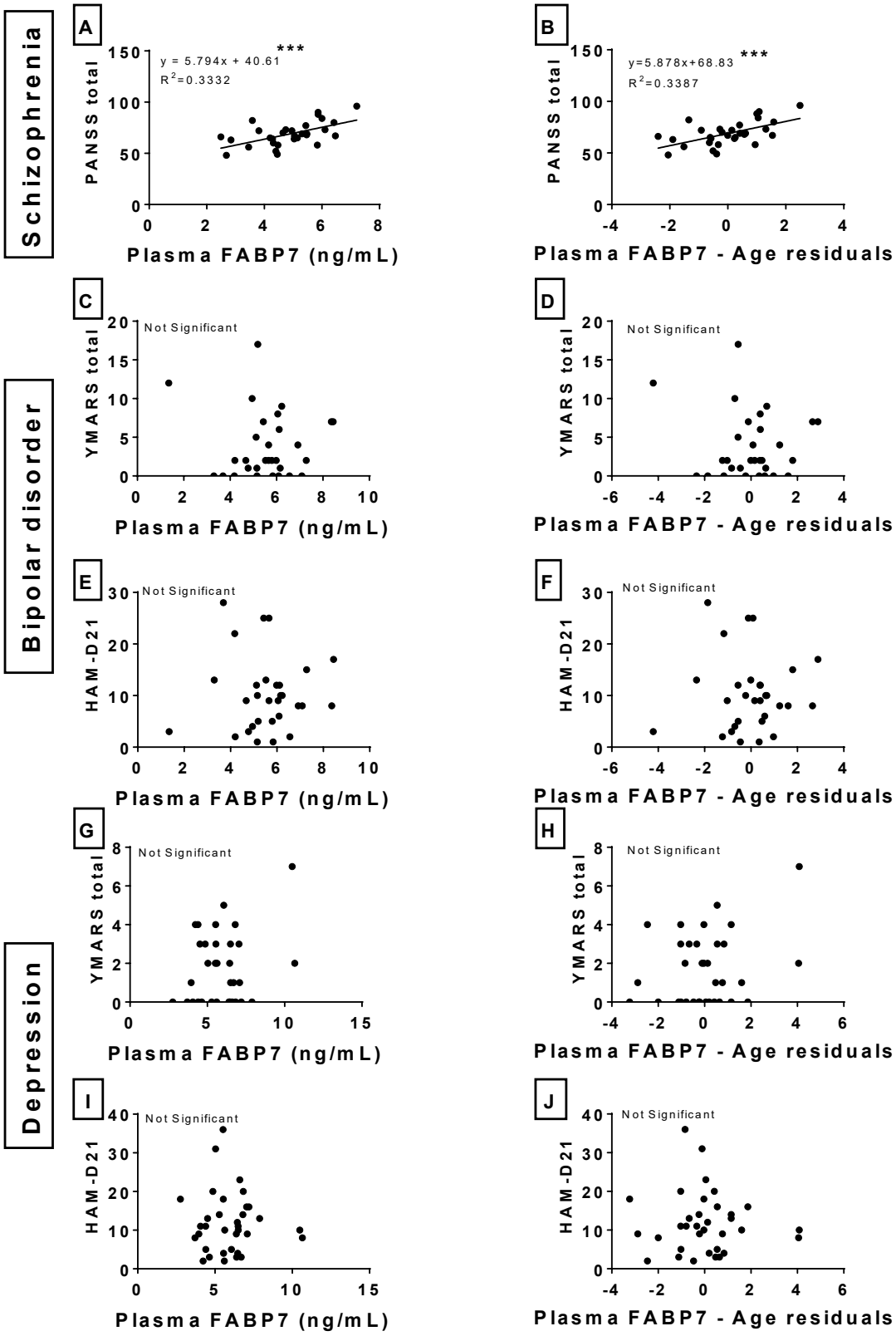
Schizophrenia
Bipolar disorder
Depression
A
y = 5.794x + 40.61
R2=0.3332
***
PANSS total
Plasma FABP7 (ng/mL)
B
y=5.878x+68.83
R2=0.3387
***
PANSS total
Plasma FABP7 - Age residuals
C
Not Significant
YMARS total
Plasma FABP7 (ng/mL)
D
Not Significant
YMARS total
Plasma FABP7 - Age residuals
E
Not Significant
HAM-D21
Plasma FABP7 (ng/mL)
F
Not Significant
HAM-D21
Plasma FABP7 - Age residuals
G
Not Significant
YMARS total
Plasma FABP7 (ng/mL)
H
Not Significant
YMARS total
Plasma FABP7 - Age residuals
I
Not Significant
HAM-D21
Plasma FABP7 (ng/mL)
J
Not Significant
HAM-D21
Plasma FABP7 - Age residuals

Fig. 2

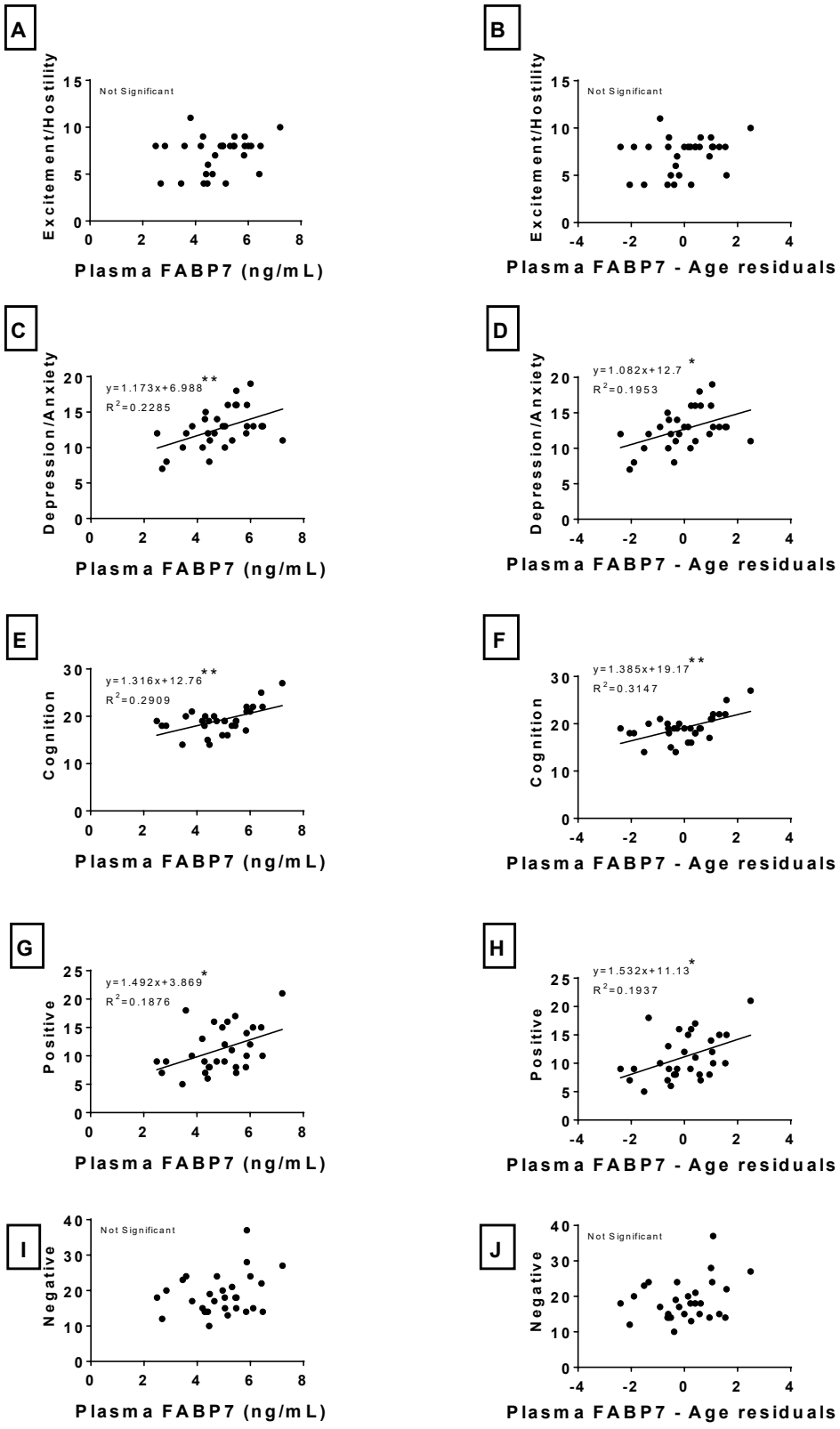
A
Excitement/Hostility
Not Significant
Plasma FABP7 (ng/mL)
B
Excitement/Hostility
Not Significant
Plasma FABP7 - Age residuals
C
Depression/Anxiety
y=1.173x+6.988**
R2=0.2285
Plasma FABP7 (ng/mL)
D
Depression/Anxiety
y=1.082x+12.7*
R2=0.1953
Plasma FABP7 - Age residuals
E
Cognition
y=1.316x+12.76**
R2=0.2909
Plasma FABP7 (ng/mL)
F
Cognition
y=1.385x+19.17**
R2=0.3147
Plasma FABP7 - Age residuals
G
Positive
y=1.492x+3.869*
R2=0.1876
Plasma FABP7 (ng/mL)
H
Positive
y=1.532x+11.13*
R2=0.1937
Plasma FABP7 - Age residuals
I
Negative
Not Significant
Plasma FABP7 (ng/mL)
J
Negative
Not Significant
Plasma FABP7 - Age residuals

Fig. 3

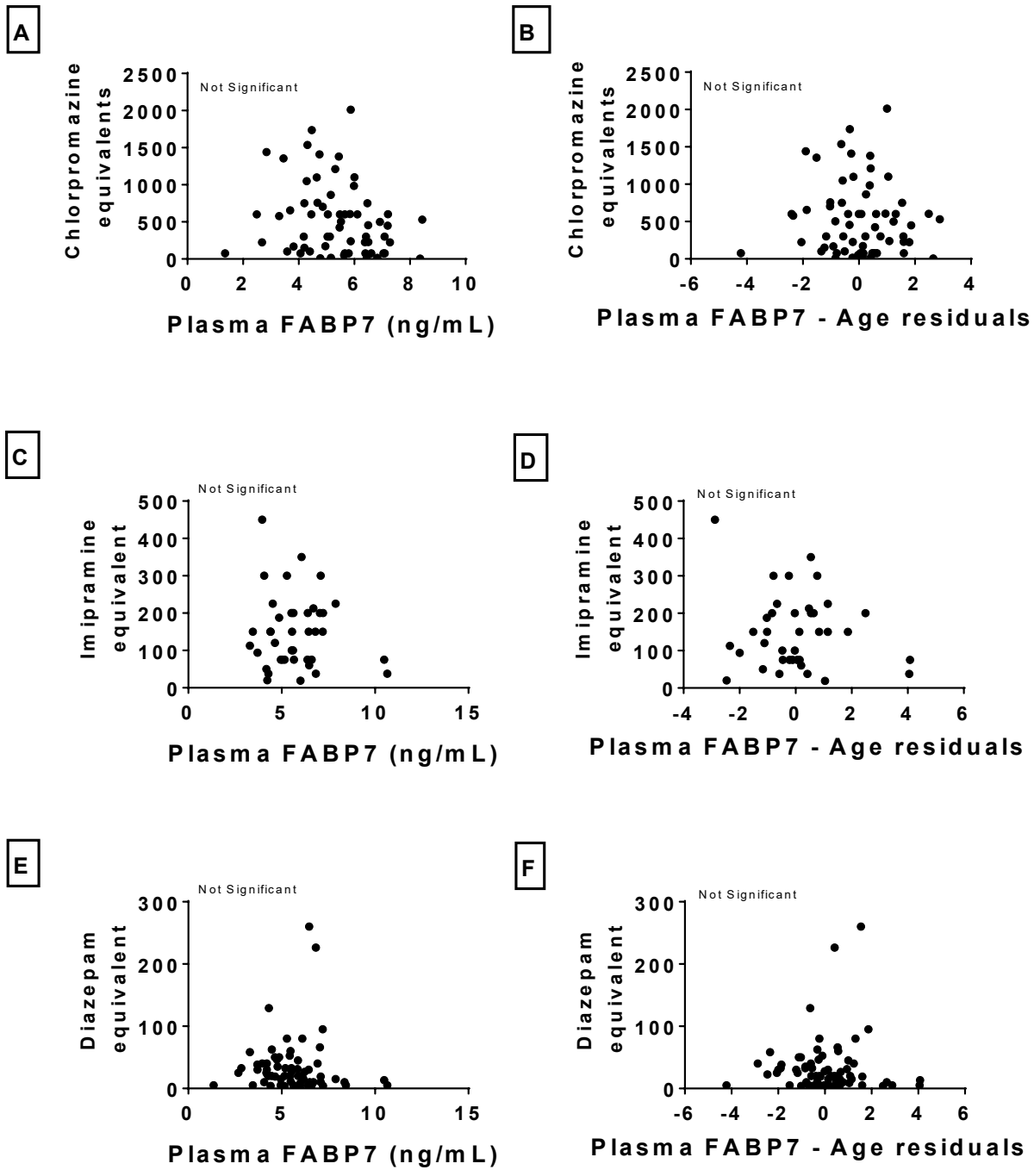
A
Chlorpromazine equivalents
Not Significant
Plasma FABP7 (ng/mL)
B
Chlorpromazine equivalents
Not Significant
Plasma FABP7 - Age residuals
C
Imipramine equivalent
Not Significant
Plasma FABP7 (ng/mL)
D
Imipramine equivalent
Not Significant
Plasma FABP7 - Age residuals
E
Diazepam equivalent
Not Significant
Plasma FABP7 (ng/mL)
F
Diazepam equivalent
Not Significant
Plasma FABP7 - Age residuals

Fig. 4