UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

*Praca doktorska*

# ROLA POLIMORFIZMU GENU *FKBP5* W ROZWOJU DOŚWIADCZEŃ PODOBNYCH DO OBJAWÓW PSYCHOTYCZNYCH W WYNIKU TRAUMATYCZNYCH WYDARZEŃ ŻYCIOWYCH

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## I. Nota informacyjna

Niniejsza rozprawa doktorska autorstwa lekarza Filipa Strameckiego zatytułowana „Rola polimorfizmu genu *FKBP5* w rozwoju doświadczeń podobnych do objawów psychotycznych w wyniku traumatycznych wydarzeń życiowych" oparta jest o cykl trzech powiązanych tematycznie artykułów. Składa się z dwóch badań oryginalnych oraz jednej pracy przeglądowej. Badania oryginalne powstały w oparciu o projekt dla Młodych Naukowców UMW pt. „Rola interakcji między polimorfizmem genu *FKBP5* a traumatycznymi wydarzeniami życiowymi w rozwoju zniekształceń poznawczych" (nr projektu: STM.C230.10.034, termin realizacji od 01.01.2018 r. do 31.12.2021 r.), który otrzymał zgodę Komisji Bioetycznej UMW (nr protokołu: 254/2018; decyzja z dnia 19.07.2018 r.). Każda z prac opublikowana została w anglojęzycznych czasopismach naukowych o zasięgu międzynarodowym o łącznej wartości współczynnika wpływu (ang. *Impact Factor, IF*) 7,636. Lekarz Filip Stramecki jest pierwszym autorem wszystkich trzech artykułów.

Publikacje wchodzące w skład rozprawy doktorskiej:

1. Stramecki F., Frydecka D., Misiak B. (2020). The role of the interaction between the FKBP5 gene and stressful life events in the pathophysiology of schizophrenia: A narrative review. *Archives of Psychiatry and Psychotherapy* 2020, 22(3):7-16. pkt. MNiSW/KBN: 70

2. Stramecki F., Frydecka D., Gawęda Ł., Prochwicz K., Kłosowska J., Samochowiec J., Szczygieł K., Pawlak E., Szmida E., Skiba P., Cechnicki A., Misiak B. (2021). The Impact of the FKBP5 Gene Polymorphisms on the Relationship between Traumatic Life Events and Psychotic-Like Experiences in Non-Clinical Adults, *Brain Sci.* 2021, Apr 28;11(5):561. IF: 3,394, pkt. MNiSW/KBN: 100

3. Stramecki F., Misiak, B., Gawęda Ł., Prochwicz K., Kłosowska J., Samochowiec J., Samochowiec A., Pawlak E., Szmida E., Skiba P., Cechnicki A., Frydecka D. (2022). The Moderating Role of the FKBP5 Gene Polymorphisms in the Relationship between Attachment Style, Perceived Stress and Psychotic-like Experiences in Non-Clinical Young Adults, *J. Clin. Med*. 2022, 11(6), 1614. IF: 4,242, pkt. MNiSW/KBN: 140

Oświadczenia współautorów prac określające indywidualny wkład każdego z nich zawiera załącznik nr 2.

## II. Streszczenie

**Wstęp:** Wiele dotychczasowych badań wskazuje na istotny wpływ czynników genetycznych i środowiskowych na rozwój zaburzeń ze spectrum schizofrenii. W ostatnich latach coraz więcej badań podkreśla znaczącą rolę interakcji pomiędzy zmiennością genetyczną a doświadczeniem traumatycznych wydarzeń życiowych na rozwój nie tylko schizofrenii, a także na rozwój objawów prodromalnych, takich jak doświadczenia podobne do objawów psychotycznych (ang. *psychotic-like experiences,* PLEs), które mogą występować u osób w stanie ryzyka rozwoju psychozy (ang. *at-risk mental state,* ARMS). Wykazywano wcześniej, że indywidualna podatność na rozwój psychozy i PLEs jest związana z polimorfizmem genu *FKBP5*, kodującego białko wiążące FK-506 (ang. *FK-605 binding protein 5*, *FKBP5*), który jest odpowiedzialny za regulację odpowiedzi na stres związaną z regulacją działania osi podwzgórze-przysadka-nadnercza. Stwierdzono również związek pomiędzy poziomem postrzeganego stresu a nasileniem objawów psychotycznych zarówno w schizofrenii, jak i PLEs. Podobnie, stwierdzono związek pomiędzy stylem przywiązania a nasileniem PLEs oraz objawów psychotycznych w schizofrenii.

**Cel badania:** Celem niniejszej pracy było zbadanie wpływu polimorfizmów genu *FKBP5* na ryzyko rozwoju PLEs w związku z wydarzeniami traumatycznymi doświadczonymi w przeciągu całego życia, a także ocena zależności pomiędzy wybranymi polimorfizmami genu *FKBP5* a stylami przywiązania i poziomem postrzeganego stresu w kontekście rozwoju PLEs.

**Materiał i metody:** Uczestnikami badania było 535 młodych osób z populacji nieklinicznej. Wykorzystano Kwestionariusz Wydarzeń Traumatycznych (ang. *Traumatic Events Checklist,* TEC), Kwestionariusz Oceny Doświadczeń Psychotycznych (ang. *Prodromal Questionaire,* PQ16), Kwestionariusz PAM (ang. *Psychosis Attachment Measure* (PAM) oraz Skalę Odczuwanego Stresu (ang. *Perceived Stress Scale-10* (PSS-10). Do badania materiału genetycznego wykorzystano komórki nabłonka jamy ustnej. Zbadano sześć polimorfizmów pojedynczego nukleotydu (ang. *single nucleotide polymorphism*, SNP) genu *FKBP5* (rs3800373, rs9470080, rs4713902, rs737054, rs1360780 i rs9296158).

**Wyniki:** Wykazano wpływ polimorfizmów rs1360780, rs9296158 rs737054 na nasilenie PLEs u osób, które doświadczyły traumatycznych wydarzeń w okresie całego życia. Stwierdzono, że zarówno lękowy styl przywiązania jak i wyższy poziom postrzeganego stresu wiążą się z większym nasileniem PLEs. Zaobserwowano zależność pomiędzy SNP rs3800373 a nasileniem PLEs. Ponadto, u osób z dominującym lękowym stylem przywiązania, zaobserwowano istotny wpływ interakcji między SNP rs4713902 a poziomem postrzeganego stresu, dokładniej poziomem poczucia własnej skuteczności, na nasilenie PLEs. U osób, u których nie dominował lękowy styl przywiązania, niski poziom poczucia własnej

skuteczności wiązał się z większą liczbą zgłaszanych PLEs, niezależnie od posiadanego genotypu.

**Wnioski:** Polimorfizmy genu *FKBP5* wpływają na rozwój PLEs w odpowiedzi na traumatyczne wydarzenia życiowe u młodych osób w populacji nieklinicznej. Lękowy styl przywiązania, jak i wysoki poziom postrzeganego stresu, związane są z większym ryzykiem rozwoju PLEs u osób młodych w populacji nieklinicznej. Gen *FKBP5* moderuje wpływ interakcji pomiędzy stylem przywiązania a poziomem postrzeganego stresu na rozwój PLEs u młodych osób w populacji nieklinicznej. Wyniki te sugerują, że istnieje wiele złożonych interakcji pomiędzy czynnikami genetycznymi i środowiskowymi wyjaśniających odmienne mechanizmy podatności na rozwój psychozy.

## III. Abstract

**Introduction**: To date, multiple studies have focused on the impact of genetic and environmental factors on the development of schizophrenia spectrum disorders. In recent years, numerous reports highlight an important role of the interactions between genetic variability and traumatic experiences in the development of schizophrenia but also development of psychotic-like experiences (PLEs), which may occur in people at risk of developing psychosis (at-risk mental state, ARMS). It has been previously reported that individual susceptibility to the development of psychosis and PLEs is associated with polymorphism of the gene encoding the FK-506 binding protein 5 (*FKBP5* gene), responsible for the regulation of the hypothalamic-pituitary-adrenal axis stress response. Moreover, the relationship between the level of perceived stress and the severity of both psychosis and PLEs has been demonstrated in non-clinical populations. Similarly, it has been found that there is an association of attachment style with the severity of PLEs and psychotic symptoms in schizophrenia.

**Aim**: The aim of this study was to investigate the impact of the *FKBP5* gene polymorphism on the development of PLEs in response to traumatic life experiences. Moreover, we aimed to examine the role of the *FKBP5* gene polymorphism in the relationship between attachment styles and the level of perceived stress in the context of PLEs development.

**Material and methods:** We recruited 535 young adults from a non-clinical population. Respondents completed the following self-report questionnaires: the Traumatic Events Checklist (TEC), the Prodromal Questionnaire (PQ16), the Psychosis Attachment Measure (PAM) and the Perceived Stress Scale (PSS-10). DNA was collected with the use of buccal swabs. We examined six *FKBP5* single nucleotide gene polymorphisms (SNP) (rs3800373, rs9470080, rs4713902, rs737054, rs1360780 and rs9296158).

**Results:** The rs1360780, rs9296158 and rs737054 polymorphisms have been shown to influence the severity of PLEs in individuals with traumatic life experiences. The anxious attachment style and high level of perceived stress have been found to be associated with greater number of PLEs. We observed a relationship between the SNP rs3800373 and the number of PLEs reported. In individuals with dominant anxious attachment style, a significant influence of the interaction between the SNP rs4713902 polymorphism and the level of perceived stress, more specifically the level of perceived self-efficacy on the severity of PLEs has been observed. Among participants with non-dominant anxious attachment style, low level of perceived self-efficacy was associated with a greater number of reported PLEs, regardless of genotype.

**Conclusions**: The polymorphism of the *FKBP5* gene has an impact on the development of PLEs in response to traumatic life events in young adults from non-clinical population. Anxious attachment style and higher level of perceived stress are associated with a greater risk

for PLEs development in non-clinical population. The *FKBP5* gene plays moderating role in the relationship between attachment style, level of perceived stress and the development of PLEs in young adults in non-clinical population. These results suggest that there are many levels of interactions between genetic and environmental factors explaining the different mechanisms of susceptibility to the development of psychosis.

## IV. Wstęp

### 1. Doświadczenia podobne do objawów psychotycznych

Zaburzenia psychotyczne należą go grupy zaburzeń psychicznych o rozpowszechnieniu sięgającym ok. 3% populacji ogólnej (Pearla i wsp., 2007). Objawy psychotyczne mogą występować w psychozach ze spektrum schizofrenii, zaburzeniach schizoafektywnych oraz w chorobach afektywnych, takich jak zaburzenie afektywne dwubiegunowe lub depresja z objawami psychotycznymi i obejmują takie objawy jak urojenia i halucynacje. Rozwój zaburzeń psychotycznych najczęściej poprzedzony jest okresem stopniowego pogorszenia funkcjonowania, w którym pojawiają się objawy prodromalne, niespełniające kryteriów objawów psychotycznych pozwalających na rozpoznanie zaburzeń psychicznych zgodnie z powszechnie przyjętymi kryteriami diagnostycznymi. Stan ten określany jest w literaturze jako stan ryzyka rozwoju psychozy (ang. *at-risk mental state, ARMS)*. Obejmuje on osoby z genetycznie podwyższonym ryzykiem wystąpienia psychozy i obniżonym poziomem ogólnego funkcjonowania lub doświadczające podprogowych lub samoistnie przemijających objawów psychozy (Fusar-Poli i wsp., 2013). Doświadczenia podobne do objawów psychotycznych (ang. *psychotic-like experiences*, PLEs) są uważane za nie w pełni rozwinięte objawy psychotyczne, których rozpowszechnienie w populacji ogólnej wynosi ok. 7.2 % (Linscott i Van Os, 2013). Obejmują one nietypowe, powodujące dyskomfort doświadczenia, takie jak słyszenie nieprawdziwych dźwięków, iluzje wzrokowe, zaburzenia treści myślenia o charakterze m.in. nastawienia prześladowczego czy wzmożonej ksobności, w których często obecne są też zniekształcenia poznawcze. Wielokrotnie wykazywano, że mogą występować w populacji nieklinicznej (Haely i wsp., 2020; Kelleher i wsp., 2011; Yung i wsp., 2009; Van Os i Reininghaus,2016), często nie wiążąc się ze znacznym dystresem czy brakiem wglądu (Kelleher i wsp., 2011)

### 2. Wpływ traumatycznych wydarzeń życiowych na rozwój objawów psychotycznych

Wykazano, że wiele czynników środowiskowych może mieć udział w rozwoju zaburzeń psychotycznych, w tym m.in.: infekcje prenatalne, nadużywanie lub uzależnienie od substancji psychoaktywnych a także stresujące wydarzenia życiowe i doświadczenie traumy wczesnodziecięcej (Misiak i wsp., 2017). Doświadczenie traumy we wczesnym okresie życia jest jednym najlepiej zbadanych czynników ryzyka związanych z rozwojem psychozy, co potwierdzają liczne meta-analizy (Kraan i wsp., 2015; Varese i wsp., 2012; Matheson i wsp., 2013). Traumatyczne wydarzenia życiowe zwiększają ryzyko rozwoju psychozy zarówno w populacji ogólnej (Baudini i wsp., 2017; Misiak i wsp., 2017), jak i u osób ze zwiększoną

predyspozycją związaną z występowaniem zaburzeń psychotycznych w rodzinie (Tomassi i wsp., 2017). Doświadczenie traumy wczesnodziecięcej predysponuje też do konwersji ze stanu podprogowych objawów psychotycznych do pełnoobjawowej psychozy (Misiak i wsp., 2016). Dotychczasowe badania wykazały, że osoby narażone na traumę w okresie dzieciństwa, zwłaszcza emocjonalne i seksualne nadużycie, są bardziej narażone na rozwój PLEs (Lu i wsp., 2020; Sun i wsp., 2017a). Traumatyczne wydarzenia we wczesnym okresie życia u młodych dorosłych mogą prowadzić również do rozwoju zaburzeń spostrzegania i doświadczeń o charakterze urojeniowym (Sun i wsp., 2017b). Ponadto, stwierdzono istotny wpływ traumatycznych wydarzeń z całego życia na rozwój PLEs w populacji nieklinicznej (Gawęda i wsp., 2019; Turley i wsp., 2019), jak też i na nasilenie objawów psychotycznych u osób dorosłych chorujących na schizofrenię (Liu i wsp., 2020). Badania meta-analityczne wskazują, że narażenie na traumatyczne zdarzenia życiowe w wywiadzie jest prawie trzykrotnie częściej obserwowane w populacji pacjentów z psychozą (Varese i wsp., 2012). Stwierdzono, że doświadczenie traumy może wiązać się z większym nasileniem objawów psychotycznych, gorszym funkcjonowaniem poznawczym, a nawet gorszą odpowiedzią na leczenie przeciwpsychotyczne (Duhig i wsp., 2015; Ruby i wsp., 2017; Misiak i Frydecka, 2016; Misiak i wsp., 2017). Większość dotychczasowych badań skupiała się na wpływie traumy z okresu dziecięcego na rozwój PLEs. Istnieją jednak doniesienia, że również doświadczenie traumy w dorosłości może wiązać się nasileniem objawów pozytywnych w schizofrenii (Liu i wsp., 2020)

3. Wpływ deregulacji działania osi podwzgórze-przysadka-nadnercza na rozwój objawów psychotycznych

Oś podwzgórze-przysadka-nadnercza (PPN) pełni istotną rolę w regulowaniu somatycznej i mózgowej odpowiedzi na stres (Borges i wsp., 2013). Głównym hormonem odpowiedzialnym za prawidłowe działanie osi PPN jest kortyzol, wydzielany przez nadnercza podczas narażenia na stres. Po połączeniu z cytoplazmatycznym receptorem glikokortykosteroidowym, powstały kompleks ulega on translokacji do jądra komórkowego, regulując tym samym odpowiedź na stres (De Kloet i wsp., 2005). Zaobserwowano szereg odmienności w funkcjonowaniu osi PPN u pacjentów chorujących na schizofrenię w porównaniu do osób zdrowych (Bradley i wsp., 2010). Badania meta-analityczne wykazały podwyższone stężenie kortyzolu u pacjentów z pierwszym epizodem psychotycznym (Hubbard i wsp., 2019). Zarówno u pacjentów chorujących na schizofrenię (Berger i wsp., 2016), jak i osób z ryzykownym stanem psychicznym (Day i wsp., 2017) stwierdzono podwyższone stężenie porannego kortyzolu. Wykazano pozytywną korelację z podwyższonym stężeniem kortyzolu w ciągu dnia

a zaburzeniami funkcji poznawczych i nasileniem objawów pozytywnych u pacjentów z pierwszym epizodem schizofrenii (Havelka i wsp., 2016), a także u pacjentów chorujących przewlekle na schizofrenię (Walder i wsp., 2020). Podwyższone stężenie kortyzolu obserwowano zarówno u pacjentów z pierwszym epizodem psychozy (Ryan i wsp., 2004; Braehler i wsp., 2005), jak i w nieklinicznych populacjach osób z grupy zwiększonego ryzyka rozwoju psychozy w porównaniu do grup kontrolnych (Walker i wsp., 2010).

4. Funkcja genu *FKBP5* w rozwoju objawów psychotycznych i PLEs

Gen *FKBP5*, zlokalizowany na chromosomie 6p21, koduje białko wiążące FK506 (ang. *FK506 binding protein*) które pełni funkcję białka opiekuńczego dla białka szoku cieplnego hsp90 (ang. *90 kDa heat shock protein*) i reguluje wrażliwość receptora glikokortykosteroidowego na kortyzol (Binder i wsp., 2009). Kompleks powstały w momencie połączenia białka FKBP5 z receptorem glikokortykosteroidowym wykazuje mniejsze powinowactwo do kortyzolu, co niesie za sobą osłabioną translokację jądrową (Wochnik i wsp., 2005; Schammel i wsp., 2001). Większe stężenia białka FKBP5 prowadzą do obniżenia wrażliwości receptora glikokortykosteroidowego na kortyzol, co wiąże się z zahamowaniem negatywnego sprzężenia zwrotnego osi PPN. W rezultacie potrzeba więcej czasu, żeby ograniczyć wydzielanie kortyzolu przez nadnercza, co powoduje przedłużoną odpowiedź organizmu na stres (Binder i wsp., 2009). Wykazano, że polimorfizm pojedynczego genu (ang. *single nucleotide polymorphism*, SNP) rs1360870 genu *FKBP5* związany jest z funkcjonowaniem hipokampa i odmiennym postrzeganiem zagrożenia (Fani i wsp., 2013), jak też z odpowiedzią osi PPN na stres u osób, które doświadczyły traumy w dzieciństwie (Buchmann i wsp., 2014). W przeprowadzonych do tej pory badaniach nad genem *FKBP5* wykazano, że polimorfizmy rs1360780, rs3800373, rs9296158 i rs9470080 są związane ze zmniejszaną wrażliwością receptora glikokortykosteroidowego na kortyzol, powodując osłabienie negatywnego sprzężenia zwrotnego osi PPN, tym samym zaburzając odpowiedź organizmu na stres i zwiększając ryzyko wystąpienia psychozy (Cristóbal-Narváez i wsp, 2020; Mihaljevic i wsp., 2017). Zaobserwowano również, że SNP rs9470080 i SNP rs9394309 wpływają na reaktywność ciał migdałowatych u osób narażonych na traumę w okresie dziecięcym (White i wsp., 2012). Ponadto wykazano, że SNP rs9296158 i SNP rs4713016 mają związek ze stężeniem kortyzolu u osób narażonych na traumatyczne wydarzenia w dzieciństwie (Collip i wsp., 2013). U nosicieli allelu C w SNP rs4713903 genu *FKBP5* obserwowano wyższe dobowe stężenia kortyzolu w porównaniu z homozygotami TT (Mahon i wsp., 2013). Na uwagę zasługuje też fakt, iż SNP rs737054 genu *FKBP5* jest zlokalizowany w intronie 5, który pełni ważną funkcję regulatorową genu (Siepel i wsp., 2005; King i wsp., 2005).

5. Wpyw interakcji pomiędzy zmiennością genetyczną a traumatycznymi wydarzeniami na rozwój objawów psychotycznych

Dotychczas udokumentowano wpływ wielu czynników środowiskowych i genetycznych na rozwój i nasilenie objawów psychotycznych (Misiak i wsp., 2018) oraz PLEs (Alemany i wsp., 2011; Cristóbal-Narváez i wsp., 2016a). Wykazano, że poszczególne polimorfizmy genu FKBP5 związane są z nasileniem objawów psychotycznych u pacjentów, którzy doświadczyli traumatycznych wydarzeń życiowych w przeszłości (Cristóbal-Narváez i wsp, 2020; Mihaljevic i wsp., 2017). Zaobserwowano również, że obecność allelu G w SNP rs38003737 zwiększa ryzyko rozwoju psychozy w porównaniu z homozygotami TT (Mihajlievic i wsp., 2017). Wykazano, że polimorfizmy genu FKBP5 pełnią istotną rolę w rozwoju PLEs w populacjach nieklinicznych (Ajnakina i wsp., 2014; Cristóbal-Narváez i wsp., 2016a). Stwierdzono związek pomiędzy SNP rs1360870 genu FKBP5 a odpowiedzią osi PPN na stres u osób, które doświadczyły traumy w dzieciństwie (Buchmann i wsp., 2014). Potwierdzono również, że SNP rs1360780 może wpływać na kliniczną odpowiedź na leczenie przeciwpsychotyczne u pacjentów ze schizofrenią (Mitjans i wsp., 2015). Dowiedziono, że nosicielstwo allelu T w SNP rs1386070 wpływa na zwiększenie nasilenia pozytywnych i negatywnych PLEs u osób, które doświadczyły znęcania w dzieciństwie (Cristóbal-Narváez i wsp., 2017; Alemany i wsp., 2016). Podobną zależność potwierdzono dla SNP rs9296158, gdzie obecność allelu A była pozytywnie skorelowana z nasileniem PLEs w odpowiedzi na traumę w dzieciństwie (Cristóbal-Narváez i wsp., 2016b). Kolejne badanie nad SNP rs9296158 stwierdziło związek między obecnością traumatycznych wydarzeń życiowych a nasileniem objawów psychotycznych oraz zaburzeń funkcji poznawczych u pacjentów chorujących na schizofrenię (Mihaljevic i wsp., 2017). Dotychczasowe doniesienia naukowe potwierdzają związek polimorfizmów genu FKBP5 z nasileniem obrazu klinicznego schizofrenii u pacjentów, którzy doświadczyli traumy w okresie dzieciństwa (Green i wsp. 2015). Wykazano również, że polimorfizmy genu FKBP5 pełnią istotną rolę w rozwoju PLEs w populacji nieklinicznej (Alemany i wsp., 2016; Cristóbal-Narváez i wsp., 2016a). Powyższe badania pokazują, że polimorfizmy genu FKBP5 mają istotny wpływ zarówno na przebieg i objawy schizofrenii, a także na nasilenie PLEs w populacjach nieklinicznych w odpowiedzi na doświadczenie traumy.

## 6. Style przywiązania i poziom postrzeganego stresu oraz ich wpływ na objawy psychotyczne

Teoria przywiązania opisuje wpływ wczesnych interakcji pomiędzy noworodkiem i opiekunami na funkcjonowanie w późniejszym życiu i przedstawia styl przywiązania jako mentalną reprezentacje obrazu siebie w relacjach z ważnymi dla jednostki osobami (Bowlby, 1982). Styl przywiązania kształtuje się głównie w pierwszych trzech latach życia i zależy od ilości poświęconej uwagi przez opiekunów oraz ich zachowań zaspokajających potrzebę bliskości i poczucia bezpieczeństwa, które są odpowiedzialne za kształtowanie się wzorców więzi emocjonalnych. U osób, które w dzieciństwie otrzymały wystarczającą ilość wsparcia i uwagi, rozwija się styl przywiązania, związany z poczuciem bezpieczeństwa w relacjach interpersonalnych. Z kolei, niezapewnienie odpowiedniej bliskości i dostępności matki, doświadczanie odrzucenia i braku empatii ze strony opiekuna wiąże się z rozwojem nieprawidłowych stylów przywiązania. W literaturze przedmiotu definiuje się między innymi lękowy i unikający styl przywiązania (Bowlby, 1982). Lękowy styl przywiązania charakteryzuje się brakiem poczucia bezpieczeństwa w relacjach interpersonalnych, silną potrzebą bliskości a jednocześnie ciągłą obawą o stabilność relacji i silnym strachem przed odrzuceniem. Rozwijające się reakcje obronne prowadzą do rozwoju dezadaptacyjnych zachowań, których celem jest utrzymywania bliskości, uwagi i wsparcia niezależnie od ponoszonych kosztów (Mikulincer i wsp., 2003; Mikulincer i Shaver, 2007). Unikający styl przywiązania związany jest z trudnościami w budowaniu bliskich relacji i intymności, brakiem zdolności do regulacji napięcia emocjonalnego poprzez szukanie wsparcia. U osób z unikającym stylem przywiązania obserwuje się strategie obronne polegające na wycofywaniu się z relacji, emocjonalnym dystansowaniu się od innych i odczuwaniu silnej potrzeby samodzielności (Mikulincer i wsp., 2003; Mikulincer i Shaver, 2007). Podwyższony poziom stresu i zwiększona wrażliwość na stres uważane są za istotny psychospołeczny czynnik ryzyka rozwoju psychozy. Poziom postrzeganego stresu może odpowiadać poziomowi w jaki dana osoba postrzega swoją skuteczność lub bezradność wobec stresujących sytuacji życiowych (Cohen i wsp., 1983). Dowiedziono, że osoby stosujące nieadaptacyjne strategie radzenia sobie ze stresem mogą odbierać neutralne sytuacje jako stresujące, co zwiększa poziom postrzeganego przez nie stresu (Ered i wsp., 2017). Wykazano również, że wyższy poziom postrzeganego stresu wiąże się z większą częstotliwością występowania PLEs (Ered i wsp., 2017; Prochwicz i wsp., 2020). Wśród psychospołecznych czynników związanych ze zwiększonym ryzykiem rozwoju psychozy uwagę zwracają także lękowy i unikający styl przywiązania. Potwierdzono ich wpływ zarówno na rozwój psychozy (Pilton i wsp., 2016; Sheinbaum i wsp., 2014; Sheinbaum i wsp., 2015; Sitko i wsp., 2014; van Dam i wsp., 2014),

jak i na rozwój PLEs w populacji nieklinicznej (Sheinbaum i wsp., 2014; Scheiinbaum i wsp., 2015; Goodal i wsp., 2015). Z uwagi na fakt, iż oś PPN jest głównym endogennym układem zaangażowanym w reakcję na stres, prawdopodobnie odgrywa też pośredniczącą rolę we wpływie stylu przywiązania na reakcję na stres (Monteleone i wsp., 2008). Istnieją doniesienia potwierdzające, iż osoby z lękowym stylem przywiązania mają tendencję do stosowania bardziej dezadaptacyjnych strategii radzenia sobie ze stresem i są bardziej skłonne do odczuwania wyższego poziomu stresu (Hawkins i wsp., 2007; Li i wsp., 2008; Bayrak i wsp., 2018). Narażenie na stres we wczesnym okresie życia, pociągające za sobą rozregulowanie aktywności osi PPN i podwyższenie dobowego poziomu kortyzolu, ma istotny wpływ na reakcję na stres w późniejszym okresie życia (Heim i wsp., 2008).

Przewlekle podwyższone stężenie kortyzolu wynikające z niekorzystnego wpływu środowiska, jakim może być niezapewniające bliskości i prawidłowej opieki rodzicielstwo, może wpływać na funkcjonowanie osi PPN i wiąże się z rozwojem niepewnego przywiązania (Monteleone i wsp., 2008; Brent i wsp., 2014). Dotychczas wykazano, że lękowy styl przywiązania zwiększa ryzyko wystąpienia PLEs u osób narażonych w dzieciństwie na niezapewniające prawidłowej opieki rodzicielstwo (Scheinbaum i wsp., 2004; Sheinbaum i wsp., 2005). Stwierdzono ponadto, że zarówno lękowy styl przywiązania, jak i wysoki poziom postrzeganego stresu związane są z większym rozwojem PLEs (Debbane i wsp., 2016; Collip i wsp., 2013b). Potwierdzono też wpływ styli przywiązania na nasilenie objawów psychotycznych u pacjentów z zaburzeniami ze spektrum schizofrenii, narażonych na traumatyczne wydarzenia w dzieciństwie (Pilton i wsp., 2016; van Dam i wsp., 2014; Pearce i wsp., 2017).

## V. Założenia i cele

### Część pierwsza

*Stramecki F., Frydecka D., Misiak B. (2020). The role of the interaction between the FKBP5 gene and stressful life events in the pathophysiology of schizophrenia: A narrative review. Archives of Psychiatry and Psychotherapy 2020, 22(3):7-16*

Celem pracy przeglądowej było omówienie funkcjonowania osi PPN w zaburzeniach ze spektrum schizofrenii, przedstawienie roli białka FKBP5 w patofizjologii psychozy oraz przybliżenie mechanizmu wpływu genu *FKBP5* na rozwój zaburzeń ze spektrum schizofrenii w odpowiedzi na czynniki środowiskowe. Cel osiągnięto poprzez podsumowanie wyników aktualnej literatury naukowej dotyczącej związku pomiędzy genem *FKBP5* a doświadczeniem traumy i jego wpływu rozwój i nasilenie prodromalnych objawów psychotycznych w populacjach nieklinicznych oraz rozwój i nasilenie objawów psychotycznych i zaburzeń funkcji poznawczych w populacjach pacjentów ze spektrum psychozy. Zaproponowano również kierunek dalszych badań, który stał się podstawą do przeprowadzenia badań wchodzących w skład rozprawy doktorskiej.

### Część druga

*Stramecki F., Frydecka D., Gawęda Ł., Prochwicz K., Kłosowska J., Samochowiec J., Szczygieł K., Pawlak E., Szmida E., Skiba P., Cechnicki A., Misiak B. (2021). The Impact of the FKBP5 Gene Polymorphisms on the Relationship between Traumatic Life Events and Psychotic-Like Experiences in Non-Clinical Adults, Brain Sci. 2021, Apr 28;11(5):561*

Dostępne źródła wskazują na znaczenie doświadczeń traumatycznych na rozwój PLEs oraz na wpływ poszczególnych polimorfizmów genu *FKBP5* na częstotliwość występowania i nasilenie PLEs w populacji ogólnej, oraz na nasilenie objawów psychotycznych w schizofrenii (Green i wsp., 2015; Alemany i wsp., 2016; Cristóbal-Narváez i wsp., 2017). Na podstawie powyższych założeń celem drugiej pracy była ocena wpływu wybranych polimorfizmów genu *FKBP5* na rozwój PLEs w odpowiedzi na doświadczenie wydarzeń traumatycznych w okresie całego życia.

**Część trzecia**

*Stramecki F., Misiak, B., Gawęda Ł., Prochwicz K., Kłosowska J., Samochowiec J., Samochowiec A., Pawlak E., Szmida E., Skiba P., Cechnicki A., Frydecka D. (2022). The Moderating Role of the FKBP5 Gene Polymorphisms in the Relationship between Attachment Style, Perceived Stress and Psychotic-like Experiences in Non-Clinical Young Adults, J. Clin. Med. 2022, 11(6), 1614*

W dotychczas przeprowadzonych badaniach wykazano wpływ lękowego i unikającego stylu przywiązania na nasilenie objawów psychotycznych i PLEs u osób narażonych na traumatyczne wydarzenia w dzieciństwie (Scheinbaum i wsp., 2004; Sheinbaum i wsp., 2005; Pilton i wsp., 2016; van Dam i wsp., 2014; Pearce i wsp., 2017). Stwierdzono również, że istnieje pozytywna zależność pomiędzy poziomem postrzeganego stresu a rozwojem PLEs (Turley i wsp., 2019; Cristóbal-Narváez i wsp., 2016a; Ered i wsp., 2017). Wcześniejsze doniesienia potwierdzały związek genu *FKBP5* zarówno ze stylami przywiązania (Borelli i wsp., 2017; Luijk i wsp., 2010; Mulder i wsp., 2017), jak i ze zwiększonym ryzykiem rozwoju PLEs (de Castro-Catala i wsp., 2017; Alemany i wsp., 2011; Ajnakina i wsp., 2014; Cristóbal-Narváez i wsp., 2016a) w szczególności u osób z doświadczeniami traumatycznymi w dzieciństwie (Alemany i wsp., 2011; Cristóbal-Narváez i wsp., 2016b; Collip i wsp., 2013).

Celem ostatniej pracy była ocena zależności pomiędzy wybranymi polimorfizmami genu *FKBP5* a stylami przywiązania i poziomem postrzeganego stresu w kontekście rozwoju PLEs u osób z grupy nieklinicznej.

## VI. Materiał i metody pracy

### 1. Materiał do badań

Do projektu zostało zrekrutowanych 535 osób z populacji nieklinicznej w wieku 18-35 lat. Osobami badanymi byli studenci z trzech dużych miast w Polsce (Wrocław, Szczecin i Kraków), studiujący na różnych kierunkach (matematyka, informatyka, pedagogika, medycyna, pielęgniarstwo oraz psychologia). Wszystkie badane osoby były rasy kaukaskiej. Uczestnicy nie byli ze sobą spokrewnieni. Osoby badane wyraziły świadomą zgodę na udział w badaniu.

### 2. Metody badań kwestionariuszami

1. Kwestionariusz Wydarzeń Traumatycznych (ang. *Traumatic Events Checklist, TEC*) (Nijenhuis i wsp., 2002) to samoopisowy kwestionariusz, służący do oceny doświadczenia różnych, potencjalnie traumatycznych wydarzeń życiowych. Zawiera 29 pozycji oceniających doświadczenie emocjonalnego zaniedbania, znęcania emocjonalnego i fizycznego, zagrożenia życia, molestowania lub nadużycia seksualnego. W badaniu wykorzystano polską wersję kwestionariusza, która została przygotowana z użyciem procedury tłumaczenia zwrotnego.

2. Kwestionariusz Oceny Doświadczeń Psychotycznych (ang. *Prodromal Questionaire, PQ-16*) (Ising i wsp., 2012). Kwestionariusz samoopisowy PQ-16 służy do oceny ryzyka wystąpienia psychozy poprzez badanie objawów podobnych do psychotycznych. Składa się z dwóch skal, z których pierwsza ocenia obecność pozytywnych oraz negatywnych objawów podobnych do psychotycznych, a druga mierzy wiążący się z nimi dyskomfort psychiczny. W badaniu wykorzystano polską wersję kwestionariusza, która została przygotowana z użyciem procedury tłumaczenia zwrotnego.

3. Kwestionariusz PAM (ang. *Psychosis Attachment Measure* (PAM) (Berry i wsp., 2008). Samoopisowy kwestionariusz służący do oceny stylu przywiązania. Składa się z 16 pozycji mierzących lękowy i unikający styl przywiązania poprzez ocenę przywiązania do kluczowych osób w życiu respondenta. W badaniu użyto polską wersję

kwestionariusza (Szpak i Białecka, 2008). W oparciu o uzyskane wyniki, uczestnicy zostali podzieleni na tych z dominującym lękowym stylem przywiązania i innych.

4. Skala Odczuwanego Stresu (ang. *Perceived Stress Scale-10* (PSS-10) (Cohen i wsp., 1983). Samoopisowy kwestionariusz służący do mierzenia poziomu postrzeganego stresu poprzez ocenę stopnia, w jakim respondenci uważają swoje życie za nieprzewidywalne, niekontrolowane czy przytłaczające. Składa się z 10 pozycji oceniających częstotliwość z jaką respondent doświadczał różnych stresujących sytuacji w ostatnim miesiącu. Zawiera dwie podskale, z których pierwsza mierzy poziom poczucia własnej skuteczności, a druga poziom poczucia własnej bezradności. W badaniu użyto polską wersję kwestionariusza.

### 3. Metody badań genetycznych

Materiał DNA osób biorących udział w badaniu został pobrany z komórek nabłonka policzka za pomocą zestawu prepIT-L2P (DNA Genotec, Ottawa, Kanada). Polimorfizmy pojedynczego nukleotydu zlokalizowane w genie *FKBP5* (rs3800373, rs9470080, rs4713902, rs737054, rs1360780 i rs9296158) oznaczono techniką dyskryminacji alleli (ang. *allelic discrimination*, AD) z wykorzystaniem firmowych zwalidowanych zestawów TaqMan®SNP Genotyping Assays (kolejno C___27489960_10, C___92160_10, C___30559929_10, C___1256778_10, C___8852038_10, C___1256775_30,) zgodnie z zaleceniami producenta (ThermoFisher Scientific Inc.).

### 4. Metody statystyczne

Do oceny zgodności rozkładu genotypów dla badanych polimorfizmów z prawem Hardy'ego-Weinberga (ang. *Hardy-Weinberg Equillibrium*, HWE) użyto testu $\chi^2$, porównującego otrzymane i oczekiwane rozkłady genotypów. Współczynnik korelacji rang Spearmana został wykorzystany celem testowania zależności między zmiennymi ciągłymi. Do wykonania porównań zmiennych ciągłych użyto testu Manna-Whitneya. Celem wykluczenia wpływu czynników zakłócających na testowane zmienne zależne korzystano z analizy kowariancji (ang. *analysis of covariance*, ANCOVA). Uzyskane wyniki uznawano za istotne statystycznie, jeśli wartość p (ang. *p-value*) była niższa niż 0.05. W przypadku wielokrotnego testowania użyto poprawki Benjamina– Hochberga. Porównania post-hoc przeprowadzono za pomocą testu Gamesa–Howella w przypadku istotnych interakcji. Wszystkie analizy

statystyczne przeprowadzono przy użyciu Pakietu Statystycznego dla Nauk Społecznych (ang. *Statistical Package for Social Sciences*, SPSS), wersja 20 (SPSS Inc., Chicago, IL, USA).

## VII. Podsumowanie wyników i wnioski

### 1. Podsumowanie wyników

**Część pierwsza**

*Stramecki F., Frydecka D., Misiak B. (2020). The role of the interaction between the FKBP5 gene and stressful life events in the pathophysiology of schizophrenia: A narrative review. Archives of Psychiatry and Psychotherapy 2020, 22(3):7-16.* 3

Wiele dotychczasowych badań wykazało, że gen *FKBP5* wpływa na podatność rozwoju oraz na symptomatologię wielu zaburzeń psychicznych u osób narażonych na niekorzystne i stresujące wydarzenia życiowe (Zannas i wsp, 2014; Matosin i wsp., 2018). Z analizy literatury naukowej wynika, iż poszczególne polimorfizmy genu *FKBP5* mają znaczący wpływ zarówno na rozwój psychozy i na nasilenie objawów oraz zaburzeń funkcji poznawczych u pacjentów ze schizofrenią (Collip i wsp., 2013a; Mihaljevic i wsp., 2017; Green i wsp., 2015), a także na rozwój i nasilenie PLEs w odpowiedzi na doświadczenie traumy w okresie dzieciństwa (Cristóbal-Narváez i wsp., 2016a; Cristóbal-Narváez i wsp., 2017). Gen *FKBP5* pełni ważną rolę w rozwoju i przebiegu psychozy w odpowiedzi na przewlekły i ostry stres poprzez wpływanie na strukturę oraz aktywność rejonów w centralnym układzie nerwowym związanych z hormonalną odpowiedzią na stres (Mihaljevic i wsp., 2017; Klengel i wsp., 2013; Tomassi i wsp., 2017). Oznacza to, że niektóre wersje genu *FKBP5* mogą zwiększać, a inne zmniejszać ryzyko rozwoju choroby i być odpowiedzialne za możliwe zaostrzenia psychozy, a nawet odpowiedź na leczenie przeciwpsychotyczne.

Z analizy wyników aktualnej literatury naukowej wynika, że gen *FKBP5* odgrywa istotną rolę zarówno w rozwoju i nasileniu prodromalnych objawów psychotycznych w populacjach nieklinicznych, a także w rozwoju i nasileniu objawów psychotycznych oraz zaburzeń funkcji poznawczych u pacjentów chorujących na zaburzenia ze spektrum schizofrenii w odpowiedzi na doświadczenie traumy.

**Część druga**

*Stramecki F., Frydecka D., Gawęda Ł., Prochwicz K., Kłosowska J., Samochowiec J., Szczygieł K., Pawlak E., Szmida E., Skiba P., Cechnicki A., Misiak B. (2021). The Impact of the FKBP5 Gene Polymorphisms on the Relationship between Traumatic Life Events and Psychotic-Like Experiences in Non-Clinical Adults, Brain Sci. 2021, Apr 28;11(5):561*

Wyniki pierwszej pracy oryginalnej potwierdzają wcześniejsze wnioski z badań nad wpływem polimorfizmów genu *FKBP5* na związek między ekspozycją na traumę a ryzykiem rozwoju psychozy i PLEs. Stwierdzono, że doświadczenie w ciągu życia nadużyć fizycznych przez osoby będące homozygotami rs1360780 CC związane było z większym nasileniem zgłaszanych PLEs. Zależności tej nie zaobserwowano u nosicielu allelu T rs1360780. Podobnie, historia nadużyć fizycznych była powiązana z większym nasileniem PLEs wśród homozygot rs9296158 GG, ale nie u nosicieli allelu rs9296158 A. Ponadto, zaniedbanie emocjonalne było związane ze znacznie wyższymi wynikami PQ-16 u nosicieli allelu T rs737054, w przeciwieństwie do homozygot rs737054 CC.

**Część trzecia**

*Stramecki F., Misiak, B., Gawęda Ł., Prochwicz K., Kłosowska J., Samochowiec J., Samochowiec A., Pawlak E., Szmida E., Skiba P., Cechnicki A., Frydecka D. (2022). The Moderating Role of the FKBP5 Gene Polymorphisms in the Relationship between Attachment Style, Perceived Stress and Psychotic-like Experiences in Non-Clinical Young Adults, J. Clin. Med. 2022, 11(6), 1614*

Wyniki ostatniego badania wykazały, że u osób z dominującym lękowym stylem przywiązania obserwuje się znacznie więcej PLEs. Zaobserwowaliśmy specyficzny wpływ lękowego stylu przywiązania na rozwój PLEs. Może to wyjaśniać fakt, że w unikającym stylu przywiązania dominują strategie oparte na wycofaniu, które prowadzą do narastania dysfunkcji w relacjach społecznych, podczas gdy osoby z lękowym stylem przywiązania częściej pozostają zaangażowane w życie społeczne, co może chronić je przed rozwojem psychozy. Uczestnicy badania z wyższym poziomem postrzeganego stresu, przejawiającym się niższym poziomem postrzegania własnej skuteczności i wyższym poziomem postrzeganej bezradności, zgłaszały większą liczbę PLEs. Homozygoty rs3800373 GG częściej zgłaszają wyższą liczbę PLEs w porównaniu z nosicielami allelu T rs3800373. U osób z dominującym lękowym stylem przywiązania wystąpił istotny wpływ interakcji między SNP rs4713902 a poczuciem własnej

skuteczności na nasilenie PLEs. Wśród homozygot rs4713902 TT niski poziom postrzeganego poczucia własnej skuteczności związany był z wyższym nasileniem PLEs w porównaniu z nosicielami alleli C. W grupie osób z niedominującym przywiązaniem lękowym niski poziom poczucia własnej skuteczności wiązał się z większą liczbą PLEs, niezależnie od posiadanego genotypu.

## 2. Wnioski

Uzyskane wyniki badań pozwalają na wyciągnięcie następujących wniosków:

A: Polimorfizmy genu *FKBP5* wpływają na rozwój PLEs w odpowiedzi na traumatyczne wydarzenia życiowe (nadużycie fizyczne i zaniedbanie emocjonalne) u młodych osób w populacji nieklinicznej.

B: Lękowy styl przywiązania, jak i wysoki poziom postrzeganego stresu, związane są z większym ryzykiem rozwoju PLEs u osób młodych w populacji nieklinicznej.

C: Gen *FKBP5* moderuje wpływ interakcji pomiędzy stylem przywiązania a poziomem postrzeganego stresu na rozwój PLEs u młodych osób w populacji nieklinicznej

## VIII. Piśmiennictwo


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## IX. Cykl publikacji stanowiących podstawę rozprawy doktorskiej

1. The role of the interaction between the FKBP5 gene and stressful life events in the pathophysiology of schizophrenia: A narrative review. [Opublikowano w *Archives of Psychiatry and Psychotherapy* 2020, 22(3):7-16]

2. The Impact of the FKBP5 Gene Polymorphisms on the Relationship between Traumatic Life Events and Psychotic-Like Experiences in Non-Clinical Adults [Opublikowano w *Brain Sciences* 2021, Apr 28;11(5):561]

3. The Moderating Role of the FKBP5 Gene Polymorphisms in the Relationship between Attachment Style, Perceived Stress and Psychotic-like Experiences in Non-Clinical Young Adults [Opublikowano w *Journal of Clinical Medicine*, 2022, 11(6), 1614]

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# The role of the interaction between the FKBP5 gene and stressful life events in the pathophysiology of schizophrenia: A narrative review

Filip Stramecki, Błażej Misiak, Dorota Frydecka

**Summary**

Stressful life events have been associated with increased risk for development of schizophrenia and play a pivotal role in its psychopathology. Genes related to stress response, such as *FKBP5* gene associated with hypothalamic–pituitary–adrenal (HPA) axis, modulate brain response to childhood trauma and determine individual susceptibility for development and course of psychosis. It this review we provide an overview of *FKBP5* gene role in human neurophysiology, its association with HPA axis and its role in stress response system in animals and humans. Moreover, we took a closer look on the studies showing the interaction between *FKBP5* gene and stressful life events in the pathophysiology of schizophrenia. We explain how interactions between trauma and *FKBP5* gene polymorphisms contribute to development of the disease, severity of psychotic symptoms and cognitive disturbances. We also discuss epigenetic modifications that may contribute to altered HPA axis reactivity to stress entailing higher risk for development of psychosis. Considering the pivotal role of *FKBP5* gene in physiopathology of schizophrenia we discuss a possible use of new therapeutic agents that may influence HPA axis activity related to the FKBP5 protein especially in individuals exposed to early trauma.

**FKBP5, gene-environment interaction, schizophrenia, psychosis, childhood trauma**

## INTRODUCTION

Schizophrenia is a complex mental disorder with multiple risk factors determining its onset, course and psychopathology. In the recent years, the growing body of research on schizophrenia focuses on gene – environment interactions. This approach differs from the linear gene-phenotype models by positioning an important causal role that is not limited to genetic variability or the environment as isolated factors, but for their synergistic influence on schizophrenia origin and its course (for the review see [1]). There are numerous environmental factors that have been associated with schizophrenia, such as childhood trauma, cannabis use, prenatal maternal infections and obstetric complications [2-4]. Among these factors, early life adversity is one of the most extensively studied social factor associated with the development of psychosis as shown by several meta-analytic studies [5-7]. Traumatic events have been found to be a risk factor for the development of psychosis either in the general population (8,9) or in subjects at familial high risk (10). Moreover, a great body of evidence shows an influence of traumatic life experiences on the psychopathology of psychotic disorders [9,11-15]. It has been repeatedly demonstrated that a history of childhood trauma results in deterioration of cognitive functioning [16-18] exac-

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erbations of the disease and increased intensity of both positive and negative symptoms [16, 19, 20], as well as higher risk of suicide in patients suffering from schizophrenia [21-23].

Due to numerous studies on the impact of stress and trauma on the development and the course of schizophrenia, the role of the hypothalamic–pituitary–adrenal (HPA) axis, a key system in stress response in humans, has also been investigated [24]. It has been shown that early life traumatic experiences may provoke a cascade of biological effects resulting in dysregulation of the HPA axis [25, 26] and thus increasing the risk of psychosis. In this line of research, stress hormones levels have been investigated as well as their association with schizophrenia symptomatology providing mixed results. In the recent years, more attention has also been given to genetic polymorphisms and epigenetic modifications that may contribute to the variability of HPA axis reactivity to stress in hope to find more consistent results linking childhood trauma with the development of psychosis in later life [27]. In this narrative review, we concentrate on one of the genes related to the response to stress associated with the HPA axis – the *FKBP5* gene. Firstly, we provide an overview of the HPA axis alterations observed in schizophrenia and early psychosis. Next, we present the physiological role of *FKBP5* signaling and its relevance to the pathophysiology of psychosis. Finally, we provide a summary of evidence and directions for future studies.

## 2. CHARACTERISTIC OF FKBP5 GENE ROLE IN HUMAN NEUROPATOPHYSIOLOGY

### 2.1. HPA axis in schizophrenia

The HPA axis plays an important role in regulating somatic and brain response to day life stressors and controlling correct functioning of circadian rhythm [28, 29]. Corticotropin releasing hormone (CRH) secreted by the hypothalamus stimulates the pituitary to release adrenocorticotropin hormone (ACTH) responsible for adrenal stimulation and secretion of the key glucocorticoid hormone – cortisol, which acts by the negative feedback loop inhibiting CRH and ACTH release (30). Cortisol acts through its cytoplasmic glucocorticoid receptor (GR) that is translocated to the nucleus after its activation. The GR is acting as a transcription factor which can bind to specific DNA sequences and thus regulate the transcriptional response to stress [31]. Alterations in the HPA axis activation have repeatedly been observed in schizophrenia [32-34]. One of recent meta-analyses in this field found elevated cortisol levels in individuals with FEP [35].

Abnormalities in cortisol awakening response have been demonstrated in individuals at ultra-high risk of psychosis [36] and schizophrenia patients as summarized by recent review and meta-analysis showing blunted response when compared to healthy controls [37]. One of early HPA axis alterations in psychosis is pituitary enlargement demonstrated in ultra-high risk individuals, especially those who later develop psychosis [38]. Several studies reported the dysregulation in diurnal cortisol levels, showing elevated diurnal and afternoon levels of cortisol in schizophrenia patients [39]. The literature on stress responsivity in schizophrenia is fairly consistent showing a pattern of blunted cortisol levels in response to stressors [40] However, several factors that may account for cortisol alterations in high-risk individuals or those with overt psychosis should be taken into consideration. These include the phase of illness, chronicity, environmental factors, stress vulnerability, medication effects and clinical history (for review see [41]).

Dysregulation of HPA axis plays an important role in the psychopathology of schizophrenia. It has been demonstrated that elevated afternoon cortisol level positively correlates with worse cognitive functioning in patients with FEP, causing an impairment in memory performance across various domains, such as working memory, delayed memory, short-term verbal memory and memory recall [42]. Similar results were obtained in chronic schizophrenia patients, showing a negative correlation between basal cortisol level and cognitive performance [43]. Cortisol level may also impact a symptomatic severity. It has been reported that increased salivary cortisol level positively correlates with negative symptoms severity [44]. Positive and disorganized symptoms have been found to be greater in patients with higher basal cortisol level [43].

### 2.2 The role of *FKBP5* gene in stress response

The *FKBP5* gene, located on the chromosome 6p21, encodes the FK-506 binding protein, which is a co-chaperone of the hsp90 heat shock protein that regulates GR sensitivity to its ligand – cortisol [45]. The complex formed when the FKBP5 protein is combined with the GR has a lower affinity for cortisol entailing repressed nuclear translocation (Figure 1) [46, 47]. Nonetheless, stress and thus cortisol by itself are responsible for strong upregulation of the *FKBP5* gene, diminishing the GR activity by a FKBP5 protein bounded to the GR complex. Higher levels of FKBP5 protein lead eventually to reduced sensitivity of the GR to cortisol, causing diminished negative feedback regulation of the HPA axis. Hence, the stress response is unusually prolonged because it takes longer to reduce cortisol secretion [45].

There is evidence that the *FKBP5* gene single nucleotide polymorphism (SNP) (rs1360870) is associated with hippocampal structure and function, resulting in greater spatial displacement of hippocampus entailing attention bias for perceived threat for TT/TC vs CC genotypes [48]. Moreover, in the study looking into the interaction between childhood maltreatment and several *FKBP5* SNPs it has been shown that two *FKBP5* variants (rs9470080 and rs9394309) affect threat-related amygdala reactivity in the individuals exposed to childhood emotional neglect [49]. There is also a report showing that the interaction between the *FKBP5* gene SNPs (rs9296158, rs4713016) and trauma has influence on cortisol levels in individuals from the general population [50]. Moreover, a significant interaction between *FKBP5* gene SNP (rs1360780) and childhood maltreatment has been reported to influence cortisol response to stress [51]. Thus, the *FKBP5* gene can be considered as a candidate gene for the studies looking into gene-environment interactions, especially in the context of stressful life experiences, as well as a molecular risk and resilience factor of different psychiatric disorders.

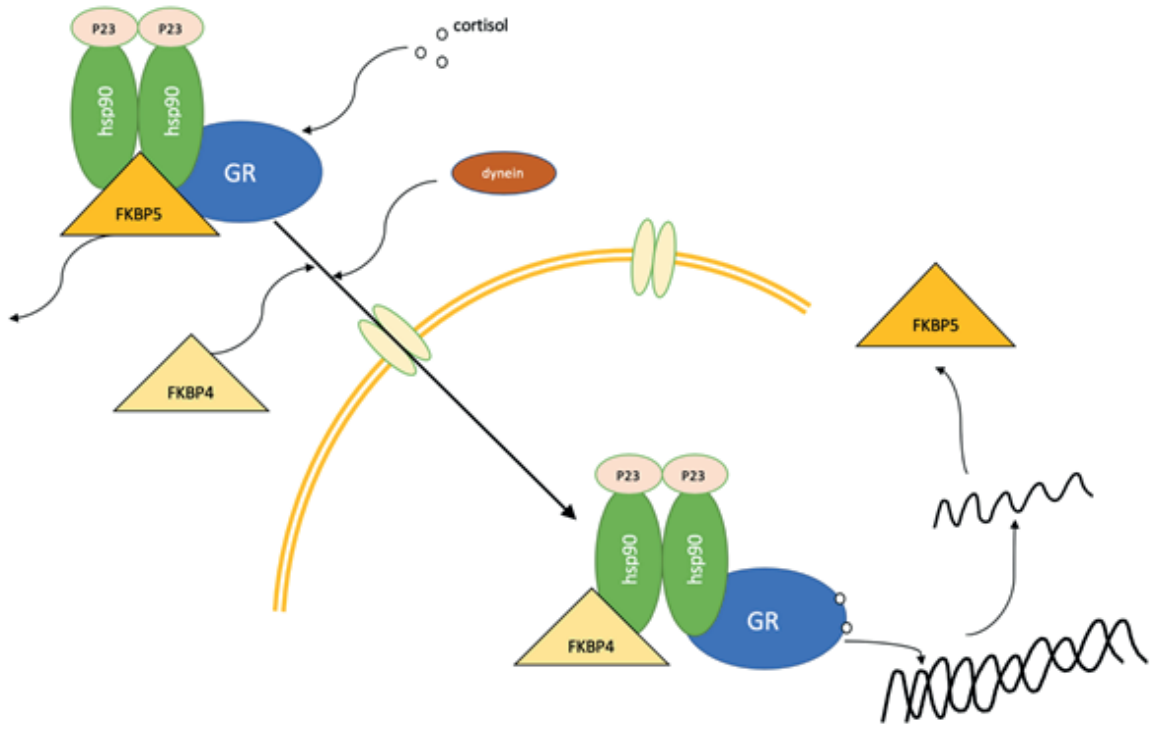


**Figure 1** – Functional diagram of the glucocorticoid receptor complex, based on (45) – GR – glucocorticoid receptor, hsp90 – heat shock protein 90. Complex formed by GR and cortisol enhances expression of FKBP5 protein. When cortisol is bound to GR, FKBP5 is exchanged against FKBP4 which binds dynein, what enables nuclear translocation of GR-complex and binding to DNA contributing to increased FKBP5 transcription.

### 2.3 Animal model studies on *FKBP5* gene and HPA axis

The influence of the *FKBP5* gene on the development of psychiatric symptoms after exposure to trauma has been shown in animal model studies [51]. Corticosterone or dexamethasone supply, restrained stress and food deprivation in mice have been found to result in increased *FKBP5* expression in the hippocampus, paraventricular nucleus and central amygdala [53, 54]. Chronic stress in mice may also result in higher *FKBP5* expression in the dorsal and ventral hippocampus, enhancing dysregulation of the HPA axis activity [55]. This has been further supported by research showing an increase *FKBP5* expression in ventral hippocampus and prefrontal cortex in response to chronic mild stress in rats [56]. Indeed, stress-induced overexpression of the *FKBP5* gene has been associated with a decrease in active stress coping behaviors in mice. Moreover, it has been observed that depletion of the *FKBP5* gene in mice results in reduced HPA axis activity, increase in active coping style strategy and diminished response to acute stress, making *FKBP5*-knockout mice more resilient to acute and chronic stress [57-59]. Repeated unpredictable stress in mice contributes to downregulation of the *FKBP5* in hypothalamus, lower plasma level of ACTH and corticosterone and decreased hippocampal volume [60]. These changes contribute to blunted HPA axis activity and result in increased use of passive coping strategies, anxiety and deficit in weight gain [60]. Stress-induced overexpression of *FKBP5* in the prefrontal cortex, hippocampus and hypothalamus has been demonstrated to result in the development of anxiety-like behaviors in mice exposed to stressful environment in early life [61].

## 3. FKBP5 AND SCHIZOPHRENIA

### 3.1. *FKBP5* gene expression in schizophrenia

The *FKBP5* gene expression differs among patients with schizophrenia and healthy individuals. Higher peripheral *FKBP5* mRNA levels have been observed in people with schizophrenia when compared to healthy controls [62]. Interestingly, the same study did not observe analogous differences between patients with schizoaffective disorder and healthy control subjects. Sinclair et al. [63] analyzed 8 SNPs in patients with schizophrenia and revealed increased expression of *FKBP5* mRNA in dorsolateral prefrontal cortex in the brains of patients with schizophrenia when compared to healthy control subjects. Increased *FKBP5* expression in the hippocampus has been reported in brains of patients with schizophrenia [64]. Thus, altered *FKBP5* expression may be associated with the impairment of the HPA axis regulation. It has also been reported that the lowest gene expression of the *FKBP5* mRNA occurs in school-age individuals and rises after adolescence [65]. In turn, the peak of the GR protein levels and the neuronal GR expression coincides with adolescent period [66]. This discrepancy might account for increased sensitivity to stress and greater vulnerability to develop psychosis in response to trauma in young adults. There is however one study that failed to find altered expression of *FKBP5* gene in the brains of patients with schizophrenia [67]. Increased *FKBP5* mRNA expression has also been reported in individuals with major depressive disorder with coexisting psychosis [68].

### 3.2. Interaction between trauma and *FKBP5* gene polymorphisms with the risk of schizophrenia

Individual gene variations resulting in different GR sensitivity to cortisol cause different body and brain response to stressful situations entailing different susceptibility to development of schizophrenia [69]. Increased risk of schizophrenia development has been observed in carriers of risk G allele in rs3800373 SNP of *FKBP5* gene after accounting for childhood trauma [69]. Similarly, a high genetic influence of risk A allele of rs9296158 on schizophrenia development has been observed after inclusion the childhood adversity as the confounding factor [69].

### 3.3 PSYCHOTIC SYMPTOMS

The influence of different SNPs of the *FKBP5* gene on the course and psychopathology of schizophrenia has been widely studied (2,69–

71). The SNP rs1360780 (risk allele C) has been found to be associated with development of psychosis after adjustment for traumatic environmental factor – parental separation in the childhood [70]. Interestingly, the study obtained the same results for cannabis use showing that this common SNP increases the risk of psychosis development in marijuana users [70]. The *FKBP5* polymorphism can influence the severity of psychotic symptoms in patients with schizophrenia previously exposed to traumatic life events. Collip and coauthors have shown that schizophrenia patients who carry a SNP rs9296158 risk A allele are more likely to develop severe psychotic symptoms [50]. Nevertheless, the influence of *FKBP5* on psychotic experiences can also be observed in the general population and the *FKBP5* gene has been shown to impact an intensity of subclinical psychosis [72]. Two studies have shown that healthy individuals who are TT homozygotes of rs1360780 SNP are more vulnerable to the psychosis-inducing effects of childhood trauma when compared to CC homozygotes [50,73]. The T allele of SNP rs1360780 and A alleles for SNPs rs9296158 and rs1043805 interacting with childhood trauma have been indicated as significant risk factors of subclinical psychosis in general twin population [50]. In the group of unaffected siblings of patients with psychotic disorder the positive correlation between level of positive schizotypy and trauma in carriers of SNPs rs1043805/rs992105 (risk C allele) and SNP rs4713916 (risk A allele) has been observed (50). In turn, risk haplotype CATT of the *FKBP5* gene (SNPs rs3800373, rs9296158, rs1360780 and rs4470080) has been found to be responsible for development and intensity of psychotic experiences in an early psychosis individuals exposed to childhood trauma in the past [72].

### 3.4 Effects of interaction between the *FKB5* gene polymorphisms and trauma on cognitive performance in schizophrenia

It has been demonstrated that a common variation in the *FKBP5* gene (rs1360780) interacts with childhood trauma to negatively affect cognitive performance, especially in the domain of attention in both patients with schizophrenia and healthy controls [74]. This effect was most significant for the CC homozygotes. In turn, the TT homozygotes showed significantly worse general neuropsychological functioning in the group of patients with schizophrenia, independently from previous trauma exposure. This relationship has also been examined for the *FKBP5* rs3800373 SNP; however, the study did not obtain results supporting its influence on cognitive performance neither in schizophrenia patients nor in healthy controls [75]. Nevertheless, the authors did not record a history of childhood trauma, which could have influenced the relationship between *FKBP5* and cognition. The *FKBP5* rs9296158, rs4713916, rs992105 and rs3800373 SNPs have been found to be irrelevant in the association between childhood trauma and cognitive functioning in patients with psychotic disorder [76]. In turn, it has been observed that the *FKBP5* rs4713902 SNP significantly influences IQ levels in healthy controls, but not in patients with schizophrenia [74]. Interestingly, childhood trauma has been reported to enhance this interaction contributing to lower IQ scores in individuals who experienced maltreatment in early life [74].

## 4. *FKBP5* METHYLATION STATUS AND PSYCHOSIS.

Epigenetic mechanisms have been shown to underlie the effects of environmental exposures on DNA expression, being possibly responsible for the relationship between childhood trauma and the development of psychosis [77]. Lower methylation status has been observed in patients with first-episode psychosis reporting traumatic experiences [78]. Considering the relationship between trauma and the *FKBP5* gene, the level of methylation of this gene in the population of patients with childhood trauma experience has also been examined. Is has been observed that the level of physical and emotional abuse is negatively correlated with the methylation level of the *FKBP5* gene [79]. Interestingly, the correlation has been observed in the risk A allele carries of the rs1360780 polymorphism but not in the protective G allele, independently of heterozygosity of the allele [79]. Similar results have been obtained in the animal model study, showing

that increased and chronic corticosterone supply is positively correlated with decreased methylation of the *FKBP5* gene in the hippocampus and the hypothalamus in mice (54). Moreover, it has been demonstrated that childhood trauma-induced hypo-methylation in the promoter region of the *FKBP5* gene results in increased gene transcription entailing down-regulation of the GR complex [79 80]. Decrease in DNA methylation status has been found in children exposed to trauma, especially to physical and or sexual abuse [79, 80]. This epigenetic mechanism may provoke dysregulation of the stress hormone system leading to psychosis development [81].

## 5. CONCLUSIONS

Epidemiological studies show that both genetic and environmental factors, particularly exposure to stressful life events, contribute to the development of psychiatric disorders. Of special interest for future studies are genes that have been shown to modulate stress response through the influence on the HPA axis reactivity. One of such genes is the *FKBP5* gene encoding protein that is stress responsive [82]. Numerous studies have shown that *FKBP5* gene affects the susceptibility and symptomatology of many psychiatric disorders by interacting with life adversities and stressful life events, mainly post-traumatic stress disorder (PTSD), anxiety disorders, substance abuse disorders and depression [83]. There have been 31 independent studies comprising over thirty thousand individuals investigating interaction of *FKBP5* with life adversities with the majority of these studies showing significant interactive effect of early trauma and higher risk of psychopathology (for the review see [84]).

It has been demonstrated that particular *FKBP5* gene polymorphisms have significant influence on the development of psychosis, severity of symptoms and the level of cognitive impairment in patients with schizophrenia [50, 69, 85]. Moreover, genetic polymorphisms of the *FKBP5* have also been reported to affect the level of psychotic-like experiences in non-clinical population [72]. Bullying, neglect and abuse in childhood have been associated with the development of psychotic-like, negative-like and paranoid symptoms in young adults [86], which is in line with still growing body of research examining the impact of early life traumatic experiences on the development of psychosis. The *FKBP5* gene plays an important role in development of psychosis and the course of schizophrenia in response to chronic and acute stress by altering the structure or activity of brain regions related to stress hormone system [10, 69, 79]. Thus, several variants of this gene may both enhance or diminish the risk of illness and be responsible for possible exacerbations of psychosis and response to treatment in schizophrenia. Knowing the level of the risk could provide grounds for personalized care and prevention in subjects at risk of psychosis.

Taking into the consideration the body of studies supporting the pivotal role of the *FKBP5* in the pathophysiology of psychotic disorders, especially in individuals exposed to early trauma, future studies could focus on possible pharmacotherapeutic agents that may influence GR activity related to the FKBP5 protein. Several studies proposed that compounds with the activity of interacting with the FKBP506-binding protein could be helpful in the treatment of stress-related disorders [83, 87, 88]. Animal model studies show that administration of selective inhibitor of the FKBP506-binding protein via microinjections to adrenal gland or intraperitoneal injections results in both reduction of anxiety-related behaviors and increase in active coping behaviors in mice [89, 90]. In turn, intra-amygdala injection of neuropsin, which is a serine protease involved in the regulation of the *FKBP5* gene expression, results in enhanced resilience to stress exposure in mice [91]. To date, no similar research has been performed on humans, and no study has examined the influence of above-mentioned novel agents on the severity of psychotic symptoms. However, considering the strong association of the *FKBP5* gene with stress-related disorders, this field should remain open for future experimental studies. According to relatively low number of studies examining the relationship between the *FKBP5* gene, trauma experience and their influence on the development of preclinical psychotic experiences more studies are needed to verify current findings and empower possible therapeutic strategies. However, several

limitations of previous studies need to be taken into account. These include low sample size and a lack of considering timing of exposure. Indeed, it has been recommended that sample size required to detect interactions should be at least four times higher compared to sample sizes of studies that aim to detect main effects of comparable magnitude [2, 92]. Timing of exposure might be of great importance for a history of childhood trauma, which is recorded under the age of 17-18 years by the majority of self-reports. At least theoretically, this broad definition may create latent confounding related to attribution of silent stressful experiences to psychotic outcomes [93]. Moreover, there is evidence that simple models might be insufficient to address gene x environment interactions in psychosis [94]. Indeed, early-life stress might also be a pre-requisite for various psychological processes, such as ineffective stress coping, cognitive biases and self-disturbances that make individuals more prone to develop psychotic-like experience or overt psychotic symptoms. Finally, longitudinal studies are also required to understand causal associations between the *FKBP5* gene, early-life stress and psychosis.

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# The Impact of the *FKBP5* Gene Polymorphisms on the Relationship between Traumatic Life Events and Psychotic-Like Experiences in Non-Clinical Adults

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**Abstract:** Common variations of the *FKBP5* gene are implicated in psychotic disorders, by modulating the hypothalamic–pituitary–adrenal axis reactivity to stress. It has been demonstrated that some of them might moderate the effects of childhood trauma on psychosis proneness. However, these associations have not been investigated with respect to traumatic life events (TLEs). Therefore, we aimed to explore whether the *FKBP5* polymorphisms moderate the effects of TLEs on the level of psychotic-like experiences (PLEs). A total of 535 non-clinical adults were approached for participation, and genotyping of six *FKBP5* polymorphisms (rs3800373, rs9470080, rs4713902, rs737054, rs1360780 and rs9296158) was performed. The Prodromal Questionnaire-16 (PQ-16) and the Traumatic Events Checklist (TEC) were administered to assess PLEs and TLEs, respectively. Among the rs1360780 CC homozygotes, a history of physical abuse was associated with significantly higher PQ-16 scores. This difference was not significant in the rs1360780 T allele carriers. Similarly, a history of physical abuse was associated with significantly higher PQ-16 scores in the rs9296158 GG homozygotes but not in the rs9296158 A allele carriers. Finally, emotional neglect was related to significantly higher PQ-16 scores in the rs737054 T allele carriers but not in the rs737054 CC homozygotes. The present study indicates that variation in the *FKBP5* gene might moderate the effects of lifetime traumatic events on psychosis proneness.

**Keywords:** schizophrenia; genetics; cortisol; HPA axis



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## 1. Introduction

In recent years, a growing body of studies focus on the role of gene–environment interactions in the development of numerous mental disorders, including schizophrenia [1]. Traumatic life events (TLEs) have been considered a significant risk factor for the development of psychosis [2] and cognitive impairments in patients with schizophrenia [3], as well as cognitive biases [4] and psychotic-like experiences (PLEs) in non-clinical subjects [5,6]. Moreover, TLEs play a pivotal role in the pathophysiology of various mental disorders,

including schizophrenia [2,3,7]. Although it has been reported that childhood traumatic experiences may lead to the development of psychosis [8], it has also been observed that cumulative lifetime trauma exposure has a significant influence on a risk of psychosis [9].

Notably, PLEs are considered one of the phenomena that lie on the continuum of psychosis, where non-clinical psychotic symptoms precede the onset of overt psychosis [10]. These experiences include bizarre experiences, perceptual abnormalities (e.g., hearing unusual sounds such as clicking, humming or ringing) and delusional-like ideas (e.g., persecutory ideations or magical thinking) that range from perceptual illusions to subclinical attenuated positive symptoms [5]. During the past two decades, the body of research on PLEs has systematically grown [11–14]. It was repeatedly reported that PLEs are common in the general population [15–18] and are often not associated with severe distress or a lack of insight [16]. The recent cross-national analysis based on more than 31,000 respondents in 18 counties estimated the prevalence rate of PLEs at 7.2% [19]. Moreover, it has been reported that individuals exposed to childhood trauma (especially emotional or sexual abuse) are more likely to experience PLEs [20]. Moreover, early life traumatic experiences increase the prevalence of PLEs in young adults [21], some of whom may even experience frequent hallucinatory and delusional experiences [22].

Exposure to acute and/or chronic stress alters proper functioning of the main stress hormone system—the hypothalamic–pituitary–adrenal (HPA) axis [23,24], and activates a cascade of biological interactions that increase a risk of psychosis [25,26]. The HPA axis response can be modulated by the FK-506 binding protein 5, encoded by the *FKBP5* gene located on the chromosome 6p21 [27]. The FKBP5 is a co-chaperone of the heat shock protein hsp90, which modulates the glucocorticoid receptor (GR) sensitivity to the main stress hormone—cortisol [27]. The interaction of the FKBP5 protein with the GR leads to decreased receptor affinity and entails suppressed nuclear translocation [28,29]. This interaction indicates that stress exposure, by causing an increase in the cortisol level, leads to up-regulated *FKBP5* expression and reduced GR activity [27]. It has been shown that patients with psychosis present increased expression of *FKBP5* mRNA in the dorsolateral prefrontal cortex [30] and the hippocampus [31] when compared to healthy controls. Hence, altered expression of the *FKBP5* gene may be correlated with the HPA axis dysregulation. It has been shown that patients with schizophrenia [32] and first-episode psychosis [33] present elevated blood levels of circulating cortisol when compared to healthy controls. Moreover, the cortisol awakening response in patients with schizophrenia is significantly flattened when compared to healthy controls [34]. Meta-analysis investigating the HPA axis response to experimental social stress revealed that patients with psychosis have lower cortisol levels both in anticipation and after exposure to social stress [35]. It has also been observed that individuals at ultra-high risk of psychosis present significantly higher salivary cortisol levels than healthy controls [36].

In the past two decades, numerous studies have focused on genetic polymorphisms and epigenetic modifications that may influence the HPA axis reactivity to stress [37]. It has previously been reported that four single nucleotide polymorphisms (SNPs), including rs1360780, rs3800373, rs9296158 and rs9470080, are associated with decreased sensitivity of GR to circulating cortisol, leading to diminished negative feedback of the HPA axis [38,39]. The *FKBP5* gene contains several polymorphic sites that may affect stress response, and thus a risk of psychosis [39]. It has been reported that specific SNPs of the *FKBP5* gene may have an impact on the severity of psychotic symptoms in patients with psychosis after adjustment for exposure to TLEs [38,39]. Indeed, the study by Mihaljevic et al. [39] revealed that the rs3800373 G allele carriers had presented a higher risk of schizophrenia after accounting for childhood trauma exposure than the TT homozygotes. However, individual SNPs of the *FKBP5* gene may also play a role in the development of PLEs in a non-clinical population [40–42]. Accordingly, the rs13860780 T allele carriers have been shown to present higher levels of positive and negative PLEs after exposure to childhood abuse [43,44]. A similar relationship was observed for the rs92961558 polymorphism in non-clinical young adults exposed to bullying in childhood, where the A allele was

positively correlated with the level of PLEs [45]. It has been observed that the rs3800373 C allele carries exposed to trauma present decreased anxiety sensitivity [46]. Moreover, the rs4713902 C allele carries have been found to show higher baseline cortisol level than the rs4713902 TT homozygotes [47]. In turn, the rs737054 polymorphism is located within a highly conserved region of the *FKBP5* intron 5 that has high regulatory potential [48,49].

So far, studies investigating interactions of the *FKBP5* gene with stress exposure in individuals with psychosis and PLEs have mostly focused on childhood trauma experience [41,45,46,50]. Therefore, in this study we aimed to investigate the influence of the *FKBP5* gene polymorphisms on the association between the level of PLEs and lifetime exposure to stress.

## 2. Materials and Methods

### *2.1. Participants*

The sample included 535 individuals aged 18 to 30 (23.4 ± 3.0 years) recruited from university students of various faculties (computer science, mathematics, medicine, nursing, pedagogy and psychology) from three big cities in Poland (Krakow, Wroclaw, and Szczecin). All participants represented Caucasian ethnicity and were non-consanguineous. A history of clinical diagnosis was provided with a self-report questionnaire designed for the study. The Ethics Committee at Wroclaw Medical University (Wroclaw, Poland) approved the study protocol, and all participants gave written informed consent (project number: STM C230.018.34; approval number: 254/2018; issued on 19 July 2018).

### *2.2. Measures*

#### 2.2.1. The Traumatic Events Checklist (TEC)

The TEC was used to assess a history of TLEs [51]. It is a self-report questionnaire that consists of 29 items. To measure emotional neglect (EN) we used the item: "When you were a child or a teenager have you ever felt emotionally neglected (e.g., being left alone, insufficient affection) by your parents, brothers or sisters?". Emotional abuse (EA) was assessed with the use of the item: "When you were a child or a teenager have you ever felt emotionally abused (e.g., being belittled, teased, called names, threatened verbally, or unjustly punished) by your parents, brothers or sisters?". Physical abuse (PA) and bullying was evaluated with the item: "When you were a child or teenager, did you experience physical abuse (e.g., tormenting, beating, psychically hurting) from your parents, brothers or sisters or peers?". Sexual abuse (SA) was measured with the item: "When you were a child or a teenager have you ever been sexually harassed or abused by your parents, brothers or sisters or strangers?".

#### 2.2.2. The Prodromal Questionnaire 16 (PQ-16)

The PQ-16 is a 16-item self-report questionnaire screening for psychosis risk and the presence of PLEs [52]. It consists of items assessing experiences of positive symptoms (nine items investigating perceptual aberrations as well as five items screening for delusional ideation, unusual thought content and paranoia) and two items focusing on negative symptoms. The original questionnaire consists of two scales, where the first investigates PLEs presence by "present" and "non-present"; the second measures associated emotional distress by a four-point Likert scale. We used the Polish version of PQ-16, which was developed with the use of a back-translocation procedure and also was used in our previous studies [53]. In the present study, the level of distress associated with experiencing PLEs, further referred to as the PQ-16 score, was used as the outcome variable. Considering that perceptual abnormalities and delusional ideas are the first anomalies that can lead to psychosis development, we excluded items "1" and "7", which investigate negative symptoms.

### 2.3. Genotyping

In the present study, we selected six SNPs (rs3800373, rs9470080, rs4713902, rs737054, rs1360780 and rs9296158) based on their functional impact on the *FKBP5* gene and the HPA axis activity. DNA samples were obtained using buccal swabs and the prepIT•L2P kit (DNA Genotek, Ottawa, ON, Canada). Although blood is usually collected to obtain DNA (it provides not only nucleated cells containing DNA but also many other physiological factors contained in plasma), the alternative, noninvasive sampling methods based on cheek-cell collection (oral or buccal epithelial cells collected with swabs, brushes or mouthwashes) are recommended in cases of large, population-based and multicentric studies [54]. Preference of buccal cells to obtain DNA is also related to unavailability of medical staff required to collect blood, and provides sufficient DNA quantity and quality. It should also be noted that buccal swabs are less contaminated by proteins compared to other methods of collecting oral biological material, and thus they enable improved quality and quantity of DNA [54,55]. Six common SNPs of the *FKBP5* gene (rs3800373, rs9470080, rs4713902, rs737054, rs1360780 and rs9296158) were genotyped with the allelic discrimination technique using validated and predesigned TaqMan®SNP Genotyping Assays (C__27489960_10, C_____92160_10, C__30559929_10, C___1256778_10, C___8852038_10, and C___1256775_30, respectively) according to the manufacturer's instructions (ThermoFisher Scientific Inc., Waltham, MA, U.S.). In accordance with current recommendations for buccal cell collection, we decided to perform genotyping in duplicates for 25% of randomly selected samples to control for genotyping accuracy [56,57]; we decided to control our results (25% of randomly chosen samples from both groups) to check for genotyping accuracy. The results were controlled (25% of randomly chosen samples from both groups) to check for genotyping accuracy. Identical genotypes were identified in all duplicates. Subjects involved in genotyping were blinded to ID of participants and the data collected by specific questionnaires used in this study.

### 2.4. Statistics

The $\chi^2$ test was used to assess whether the distribution of genotypes followed the Hardy–Weinberg equilibrium (HWE). Bivariate comparisons were performed using the Mann–Whitney U test. The analysis of covariance (ANCOVA) was performed to test the effects of specific TLEs, SNPs and interactions between TLEs and SNPs on the PQ-16 score. Age and gender were added as the covariates. Separate models for specific SNPs and TLEs were tested. Post hoc comparisons were performed using the Games–Howell test in case of significant two-way interactions. Due to multiple testing, the Benjamini–Hochberg correction with the false discovery rate of 25% was applied. After this correction, results of all tests were considered significant if the $p$-value was less $\leq 0.022$.

## 3. Results

Main characteristics of all participants are presented in Table 1. Out of 535 individuals approached for participation, 461 individuals provided data on a history of TLEs and the level of PQ-16 (86.2%). Sufficient quality of DNA was obtained for 441–449 participants (82.4–83.9%). Rates of EN, EA, PA and SA were as follows: 34.1%, 41.4%, 15.4%, and 8.2% participants, respectively. As expected, a history of all categories of TLEs was associated with significantly higher PQ-16 scores (Table 2). Clinical diagnosis (mood and anxiety disorders) was reported by 8.2% of the sample. None of these participants reported being diagnosed with psychotic disorders.

Main and interactive effects of the *FKBP5* SNPs on the PQ-16 score are shown in Table 3. There were significant effects of interactions between PA and two *FKBP5* SNPs (rs1360780 and rs9296158) on the PQ-16 score. Similarly, the interaction between EN and the rs737054 polymorphism was significantly associated with the PQ-16 score. In the majority of models, significant main effects of age and TLEs were found. In two models, main effects of the rs3800373 (the model with EA) and the rs9296158 (the model with PA) were observed.

**Table 1.** General characteristics of the sample.

| | ***n*** | **Mean ± SD or *n* (%)** |
|---|---|---|
| Age, years | 461 | 23.4 ± 3.0 |
| Gender, M/F | 460 | 133/327 (40.7/59.3) |
| Clinical diagnosis | 461 | 38 (8.2) |
| EN | 461 | 157 (34.1) |
| EA | 461 | 191 (41.4) |
| PA | 461 | 71 (15.4) |
| SA | 461 | 38 (8.2) |
| PQ-16 | 461 | 4.1 ± 4.6 |
| rs1360780 | 444 | |
| CC | | 260 (58.56) |
| CT | | 159 (3.46) |
| TT | | 31 (6.98) |
| rs9296158 | 445 | |
| AA | | 26 (5.84) |
| AG | | 159 (35.73) |
| GG | | 260 (58.43) |
| rs3800373 | 443 | |
| GG | | 37 (8.35) |
| TG | | 144 (32.51) |
| TT | | 262 (59.14) |
| rs9470080 | 443 | |
| CC | | 245 (55.30) |
| CT | | 151 (34.09) |
| TT | | 47 (10.61) |
| rs4713902 | 441 | |
| CC | | 50 (11.34) |
| CT | | 154 (34.92) |
| TT | | 237 (53.74) |
| rs737054 | 449 | |
| CC | | 224 (49.89) |
| CT | | 182 (40.53) |
| TT | | 43 (9.58) |

Abbreviations: TEC, Traumatic Events Checklist; EN, emotional neglect; EA, emotional abuse; PA, physical abuse; SA, sexual abuse; PQ-16, the Prodromal Questionnaire 16.

**Table 2.** The PQ-16 score with respect to a history of TLEs.

| | **TLEs (+)** | **TLEs (-)** | ***p*** |
|---|---|---|---|
| EA | 5.10 ± 5.25 | 3.41 ± 3.81 | <0.001 |
| EN | 5.25 ± 5.46 | 3.52 ± 3.91 | <0.001 |
| PA | 5.24 ± 5.69 | 3.90 ± 4.30 | 0.022 |
| SA | 7.10 ± 6.76 | 3.83 ± 4.22 | <0.001 |

Abbreviations: TLEs(+), positive history of traumatic life events; TLEs(-), negative history of traumatic life events; EN, emotional neglect; EA, emotional abuse; PA, physical abuse; SA, sexual abuse.

**Table 3.** Main and interactive effects of the FKBP5 variants on the PQ-16 score.

| TLEs | IV or Covariate | rs1360780 | rs9296158 | rs3800373 | rs9470080 | rs4713902 | rs737054 |
|---|---|---|---|---|---|---|---|
| EN | Age | $F = 48.00$, $p < 0.001$ | $F = 47.28$, $p < 0.001$ | $F = 43.37$, $p < 0.001$ | $F = 42.87$, $p < 0.001$ | $F = 41.92$, $p < 0.001$ | $F = 45.36$, $p < 0.001$ |
| | Gender | $F = 1.62$, $p = 0.204$ | $F = 1.67$, $p = 0.197$ | $F = 1.59$, $p = 0.208$ | $F = 1.76$, $p = 0.186$ | $F = 1.55$, $p = 0.214$ | $F = 2.20$, $p = 0.139$ |
| | TLEs | $F = 15.48$, $p < 0.001$ | $F = 14.54$, $p < 0.001$ | $F = 1.60$, $p = 0.207$ | $F = 0.33$, $p = 0.564$ | $F = 16.48$, $p < 0.001$ | $F = 17.54$, $p < 0.001$ |
| | *FKBP5* | $F = 1.15$, $p = 0.285$ | $F = 1.96$, $p = 0.162$ | $F = 3.24$, $p = 0.073$ | $F = 1.07$, $p = 0.301$ | $F = 0.24$, $p = 0.627$ | $F = 0.19$, $p = 0.660$ |
| | *FKBP5* × TLEs | $F = 1.04$, $p = 0.309$ | $F = 1.21$, $p = 0.273$ | $F = 1.43$, $p = 0.232$ | $F = 5.35$, $p = 0.21$ | $F = 2.45$, $p = 0.118$ | $F = 7.84$, $p = 0.005$ |
| | $R^2$ | 0.142 | 0.141 | 0.150 | 0.144 | 0.134 | 0.141 |
| EA | Age | $F = 48.84$, $p < 0.001$ | $F = 47.94$, $p < 0.001$ | $F = 43.58$, $p < 0.001$ | $F = 42.56$, $p < 0.001$ | $F = 44.25$, $p < 0.001$ | $F = 45.82$, $p < 0.001$ |
| | Gender | $F = 2.48$, $p = 0.116$ | $F = 2.53$, $p = 0.112$ | $F = 2.20$, $p = 0.139$ | $F = 2.14$, $p = 0.145$ | $F = 2.22$, $p = 0.137$ | $F = 2.67$, $p = 0.103$ |
| | TLEs | $F = 20.13$, $p < 0.001$ | $F = 19.35$, $p < 0.001$ | $F = 2.55$, $p = 0.111$ | $F = 2.50$, $p = 0.115$ | $F = 19.79$, $p < 0.001$ | $F = 19.57$, $p < 0.001$ |
| | *FKBP5* | $F = 0.10$, $p = 0.747$ | $F = 0.48$, $p = 0.491$ | $F = 4.64$, $p = 0.032$ | $F = 2.45$, $p = 0.119$ | $F = 1.89$, $p = 0.170$ | $F = 0.67$, $p = 0.414$ |
| | *FKBP5* × TLEs | $F = 0.12$, $p = 0.731$ | $F = 0.06$, $p = 0.815$ | $F = 1.12$, $p = 0.290$ | $F = 2.18$, $p = 0.141$ | $F = 0.11$, $p = 0.739$ | $F = 0.832$, $p = 0.362$ |
| | $R^2$ | 0.147 | 0.145 | 0.155 | 0.147 | 0.138 | 0.143 |
| PA | Age | $F = 49.06$, $p < 0.001$ | $F = 48.56$, $p < 0.001$ | $F = 42.46$, $p < 0.001$ | $F = 41.35$, $p < 0.001$ | $F = 41.52$, $p < 0.001$ | $F = 45.54$, $p < 0.001$ |
| | Gender | $F = 4.43$, $p = 0.038$ | $F = 4.07$, $p = 0.044$ | $F = 3.59$, $p = 0.059$ | $F = 3.33$, $p = 0.069$ | $F = 3.15$, $p = 0.077$ | $F = 3.79$, $p = 0.052$ |
| | TLEs | $F = 8.87$, $p = 0.003$ | $F = 7.44$, $p = 0.007$ | $F = 1.83$, $p = 0.177$ | $F = 2.17$, $p = 0.142$ | $F = 5.78$, $p = 0.017$ | $F = 8.305$, $p = 0.004$ |
| | *FKBP5* | $F = 4.12$, $p = 0.43$ | $F = 5.90$, $p = 0.016$ | $F = 1.95$, $p = 0.164$ | $F = 1.23$, $p = 0.269$ | $F = 0.90$, $p = 0.343$ | $F = 0.12$, $p = 0.729$ |
| | *FKBP5* × TLEs | $F = 5.53$, $p = 0.019$ | $F = 6.80$, $p = 0.009$ | $F = 0.10$, $p = 0.752$ | $F = 0.01$, $p = 0.925$ | $F = 0.00$, $p = 0.927$ | $F = 1.88$, $p = 0.171$ |
| | $R^2$ | 0.141 | 0.141 | 0.131 | 0.121 | 0.111 | 0.125 |
| SA | Age | $F = 45.09$, $p < 0.001$ | $F = 44.19$, $p < 0.001$ | $F = 39.66$, $p < 0.001$ | $F = 39.19$, $p < 0.001$ | $F = 40.52$, $p < 0.001$ | $F = 42.56$, $p < 0.001$ |
| | Gender | $F = 1.33$, $p = 0.250$ | $F = 1.42$, $p = 0.235$ | $F = 1.31$, $p = 0.252$ | $F = 1.35$, $p = 0.245$ | $F = 1.38$, $p = 0.242$ | $F = 1.57$, $p = 0.211$ |
| | TLEs | $F = 16.78$, $p < 0.001$ | $F = 15.05$, $p < 0.001$ | $F = 5.95$, $p = 0.015$ | $F = 6.70$, $p = 0.010$ | $F = 11.50$, $p = 0.001$ | $F = 17.68$, $p < 0.001$ |
| | *FKBP5* | $F = 1.19$, $p = 0.275$ | $F = 0.96$, $p = 0.329$ | $F = 1.05$, $p = 0.305$ | $F = 1,79$, $p = 0.182$ | $F = 1.47$, $p = 0.227$ | $F = 0.18$, $p = 0.671$ |
| | *FKBP5* × TLEs | $F = 0.93$, $p = 0.337$ | $F = 0.37$, $p = 0.543$ | $F = 0.39$, $p = 0.531$ | $F = 0.19$, $p = 0.732$ | $F = 0.38$, $p = 0.538$ | $F = 0.93$, $p = 0.336$ |
| | $R^2$ | 0.146 | 0.141 | 0.145 | 0.129 | 0.125 | 0.139 |

Abbreviations: IV, independent variable; TLEs, traumatic life events; EN—emotional neglect; EA—emotional abuse; PA—physical abuse; SA—sexual abuse, PQ-16—Prodromal Questionnaire 16.

Results of post hoc analyses are presented in Figure 1. Among the rs1360780 CC homozygotes, a history of PA was associated with significantly higher PQ-16 scores. This difference was not significant in the rs1360780 T allele carriers. Similar findings were observed for the rs9296158 polymorphism. Indeed, a history of PA was associated with significantly higher PQ-16 scores in the rs9296158 GG homozygotes. The rs9296158 GG homozygotes reporting a history of PA had also significantly higher PQ-16 scores in comparison with the rs9296158 A allele carriers without a history of PA. Finally, EN was related to significantly higher PQ-16 scores in the rs737054 T allele carriers but not in the rs737054 CC homozygotes. The rs737054 T allele carriers had significantly higher PQ-16 scores with a history of EN in comparison with the rs737054 CC homozygotes who did not report EN.

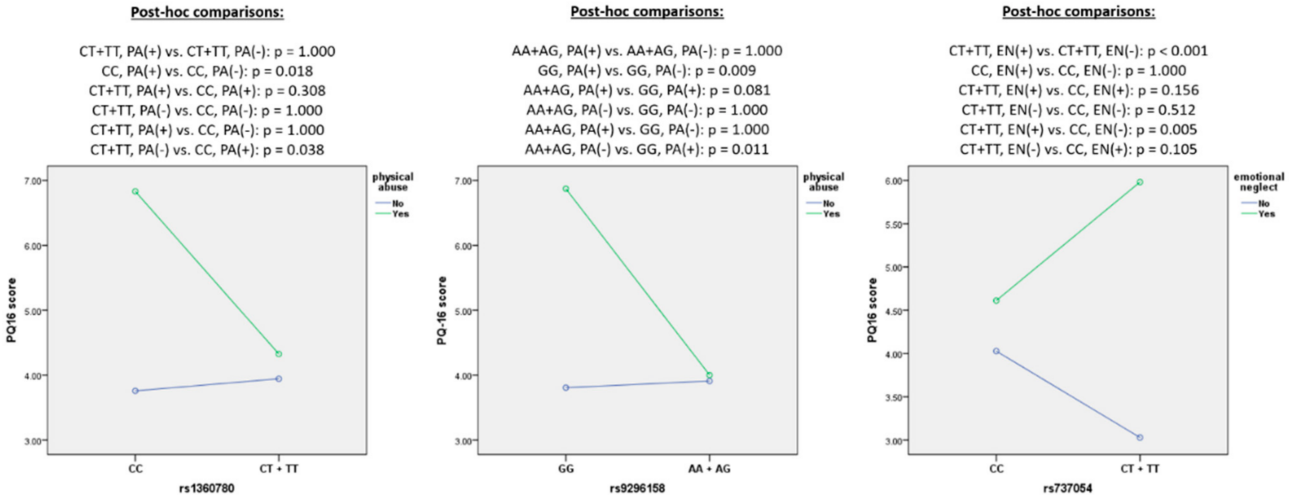


**Figure 1.** Interactive effects of the *FKBP5* genotype and TLEs on the PQ-16 score.

## 4. Discussion

Results of this study support previous findings from studies testing the moderating effects of the *FKBP5* gene polymorphisms on the association between trauma exposure and a risk of psychosis or PLEs. More specifically, we found that a history of PA increases a severity of PLEs in the rs1360780 CC and the rs9296158 GG homozygotes. This may be explained by the role of the rs1380780 polymorphism in inducing the *FKBP5* gene transcription in response to GR activation [58] followed by stronger cortisol reactivity in response to stress [59] in individuals exposed to trauma carrying the "risk" T allele. Disinhibited induction of the *FKBP5* mRNA is responsible for GR resistance and causes diminished negative feedback of the HPA axis, leading to its dysregulation [60]. This stays in line with previous research supporting the role of the rs1360780 and rs9296158 in moderating the effects of childhood trauma on the development of positive PLEs [43–45]. However, these studies have reported that carries of rs1360780 T allele are more prone to develop psychotic symptoms [44] or greater subclinical psychotic symptoms [49] after exposure to childhood trauma, while we observed the opposite association, where the C allele was associated with greater severity of PLEs in response to PA. These mixed findings may be associated the fact that previous studies focused only on childhood trauma, while we assessed lifetime TLEs. Interestingly, Yaylac et al. observed that the rs1380780 C allele carriers and the rs9296158 G allele carriers exposed to childhood maltreatment develop significantly more severe dissociative symptoms when compared to traumatized subjects carrying the rs1380790 T allele and the rs9296158 A allele, respectively [61]. In turn, dissociation has been associated with the development of overt psychosis and PLEs [62,63]. The study by Mitjans et al. investigated the effect of the *FKBP5* gene polymorphisms on treatment outcome in patients with schizophrenia showing that TT homozygotes for the rs13860780 polymorphism have higher risk of non-response to clozapine than the C allele

carries [64]. Previous studies have proposed that compound with the ability to interact with FKBP5 could be beneficial in the treatment of stress-related disorders [57,65,66]. Taking into account the body of studies supporting the role of *FKBP5* in pathophysiology of stress-related disorders, including schizophrenia, future studies could consider the *FKBP5* gene as a potential target for the treatment of psychosis.

The present study also demonstrated that the rs737054 T allele is associated with a higher severity of PLEs in subjects exposed to EN. The effect of the rs737054 polymorphism on the development of PLEs has not been widely addressed. The only study investigating its role in the development of PLEs in response to childhood trauma failed to find significant associations [39]. Moreover, there are only two studies examining this SNP. One study did not confirm that the rs737054 polymorphism affects susceptibility to borderline personality disorder after considering the role of childhood trauma [67]. In turn, it has been shown that male carries of the T allele at this SNP, exposed to childhood trauma, present significantly greater anxiety sensitivity when compared to the CC homozygotes [46], suggesting the role of the rs737054 polymorphism in stress response by modulating the HPA axis reactivity. Our results suggest that there is an association between variants of the *FKBP5*, lifetime traumatic events and risk of psychosis. The mechanism of genetic variability influencing psychosis development in response to stress remains unclear. It has also been shown that neurotrophic factors, including the brain-derived neurotrophic factor (BDNF), responsible for neuroplasticity in the human brain, plays a moderating role in the development of psychosis [1,68] and PLEs [69] in individuals exposed to psychosocial stress. Despite multiple observations suggesting that gene–environment interactions may be responsible for individual differences in response to TLEs, further studies are required to understand the exact mechanisms underlying the effects of interactions between genes regulating response to stress and neuroplasticity on the risk of psychosis.

The present study has several methodological limitations that should be taken into consideration when interpreting our findings. In our study, we determined only six variants that may not cover the whole *FKBP5* gene. It is likely that genome-wide association studies would provide more comprehensive insight into the effects of variation in the *FKBP5* and its interaction with variants in other genes. Some of them did not follow the HWE, suggesting that representativeness of the sample might be limited. Secondly, the proportion of variance in the level of PLEs was also relatively low, suggesting that other factors not recorded by our study might be associated with PLEs. These factors might include familial liability for psychosis, depressive and anxiety symptoms and the level of perceived stress. Third, the data collected from the participants were based on self-reports, which might be characterized by a recall bias. However, reliability of trauma self-reports has been found to be stable over time in patients with psychosis [70]. Another limitation is that our sample had limited size, and independent replication of our findings was not performed. Moreover, this study was based on a non-clinical population, and thus generalization of findings cannot be made. Finally, a cross-sectional design does not allow for making conclusions on causal associations. Nevertheless, it is important to highlight that in contrary to multiple previous studies investigating the role of childhood trauma in the development of psychosis, this study focused also on cumulative lifetime traumatic experiences. To date, the body of studies on adulthood trauma in association with psychosis is very poor. It has previously been reported that TLEs in adulthood may have a different influence on the development of psychosis than childhood trauma. For instance, the study by Liu et al. observed that traumatic events occurring in the adulthood are associated with more severe positive symptoms in patients with schizophrenia, whereas childhood trauma is rather related to more severe depressive symptoms [71].

## 5. Conclusions

The present study indicates that variation in the *FKBP5* gene also moderates the effects of lifetime traumatic events on psychosis proneness. These findings provide grounds for developing more personalized approaches in predicting the outcomes of TLEs and

selecting interventions that aim to restore psychological well-being in this population. However, before their application, larger longitudinal studies that combine results of genetic testing based on high throughput technologies with detailed assessment of complex psychological processes mediating the association between traumatic life events and psychosis are needed.

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**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** The data presented in this study are available on request from the corresponding author.

**Conflicts of Interest:** The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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# The Moderating Role of the *FKBP5* Gene Polymorphisms in the Relationship between Attachment Style, Perceived Stress and Psychotic-like Experiences in Non-Clinical Young Adults

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**Abstract:** Numerous studies have reported that stressful life experiences increase the risk of psychosis and psychotic-like experiences (PLEs). Common variations of the *FKBP5* gene have been reported to impact the risk of psychosis by moderating the effects of environmental exposures. Moreover, anxious and avoidant attachment styles have been shown to increase both the level of perceived stress and the risk for psychosis development. In the present cross-sectional study, we aimed to investigate whether variants of the *FKBP5* gene moderate the effects of attachment styles and the level of perceived stress on the development of PLEs. A total of 535 non-clinical undergraduates were genotyped for six *FKBP5* single nucleotide polymorphisms (SNPs) (rs3800373, rs9470080, rs4713902, rs737054, rs1360780 and rs9296158). The Psychosis Attachment Measure (PAM), the Perceived Stress Scale-10 (PSS-10) and the Prodromal Questionnaire 16 (PQ-16) were administered to assess attachment styles, the level of perceived stress and PLEs, respectively. Anxious attachment style, lower levels of perceived self-efficacy and higher levels of perceived helplessness were associated with a significantly higher number of PLEs. The main effects of attachment style on the severity of PLEs were significant in models testing for the associations with perceived self-efficacy and three FKBP5 SNPs (rs1360780, rs9296158 and rs9470080). The main effect of rs38003733 on the number of PLEs was observed, with GG homozygotes reporting a significantly higher number of PLEs in comparison to T allele carriers. In individuals with dominant anxious attachment style, there was a significant effect of the interaction between the *FKBP5* rs4713902 SNP and self-efficacy on the severity of PLEs. Among rs4713902 TT homozygotes, a low level of perceived self-efficacy was associated with higher severity of PLEs. In subjects with non-dominant anxious attachment, a low level of perceived self-efficacy was associated with a higher number of PLEs, regardless of the genotype. Our results indicate that the *FKBP5* gene might moderate the relationship between attachment, perceived stress and PLEs.



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## 1. Introduction

In past decades, numerous studies have focused on risk factors for the development of psychosis and have demonstrated the importance of genetic and environmental factors [1–3]. According to the continuum model [4], psychotic-like experiences (PLEs) are being described as subclinical psychotic symptoms which can be present in non-clinical populations with the prevalence rate estimated at 7.2% in the general population [5].

Several models have been proposed so far in the development of PLEs, showing the association of genetic background [6,7], cannabis use [8], cognitive biases [9,10], self-disturbances [11], insecure attachment style [12] and early traumatic adversities [13] with the higher risk of PLEs [14]. Moreover, it has been reported that childhood trauma and PLEs are associated with increased suicidal risk in young adults [15].

Elevated levels of stress and increased stress sensitivity have been found to serve as important psychosocial risk factors for psychosis development. Exposure to stressful life experiences in childhood has been reported more frequently in individuals with PLEs than in the general population [16]. A greater level of perceived stress has been correlated with a higher frequency of PLEs, and this relationship has been found to be mediated by maladaptive coping strategies [17]. It has been shown that using maladaptive coping strategies makes individuals more prone to evaluate a neutral situation as stressful and increases the level of perceived stress [17]. On the other hand, the level of perceived stress has been found to be associated with a greater likelihood to report PLEs [18]. Moreover, several studies have shown that individuals with anxious attachment styles tend to use more ineffective coping strategies, and are more likely to perceive higher levels of stress [19–21].

Among psychosocial factors involved in psychosis development, insecure attachment styles have been shown to increase the risk for clinical psychosis [22–26] as well as the risk of PLEs [23,24,27]. Attachment theory proposed by Bowlby describes the impact of early interactions of a newborn with their primary caregivers on an individual's psychological functioning in later life and defines attachment style as a mental representation of the self in relation to others [28]. Insecure attachment—that includes anxious and avoidant attachment style—is characterized by the failure to relieve distress by proximity seeking and triggers the use of secondary attachment strategies [29]. Attachment anxiety involves a strong need for closeness, worries about relationships, and fear of being rejected, leading to the development of hyperactive strategies for regulating distress, such as intense attempts to maintain proximity and support in the relation to others [29,30]. In turn, the avoidant attachment style is associated with compulsive self-reliance, and preference for emotional distance from others, need for being independent as well as difficulties with close relations and intimacy [29,30].

Since the hypothalamic–pituitary–adrenal (HPA) axis is the main endogenous system involved in the stress response, it is likely to play a key role in mediating the effect of attachment style on the human stress response [31]. Stress directly activates the HPA axis activity and triggers several other hormonal responses. Exposure to early-life stress, entailing the dysregulation of HPA axis activity has an important influence on stress response later in life, which corresponds to an increased level of diurnal cortisol [32]. Elevated cortisol levels have been observed both in patients with first-episode psychosis [33,34] and in non-clinical at-risk subjects [35] when compared to heathy controls. Chronically elevated cortisol levels resulting from adverse environments and poor parenting can affect the functioning of the HPA axis and has been associated with insecure attachment development [31,36].

It has been found that the HPA axis activity is modulated by a number of *FKBP5* gene variants. The *FKBP5* gene encodes the FK506 binding protein 51 (FKBP5), which is a co-chaperone of the glucocorticoid receptor (GR) [37]. The FKBP5 binds to GR and diminishes its affinity to cortisol, which modulates individual stress response [38]. Several

single nucleotide polymorphisms (SNPs) in the *FKBP5* gene have been found to affect stress-related psychiatric conditions [39] mostly by moderating the effect of traumatic experiences on the severity of the psychiatric symptomatology [40]. SNPs rs9296158 and rs4713016 were found to increase the risk for psychosis development by affecting cortisol levels in response to trauma and rs9296158 was associated with the development of more severe psychotic symptoms [41]. Our recent study on a non-clinical sample supports the moderating role of SNPs rs9296158, rs1360780 and rs737054 on PLEs severity in response to early life trauma [42].

Although there are reports showing relationships between the *FKBP5* gene polymorphisms, attachment styles, perceived stress, and the severity of PLEs, to our knowledge, there has been no study analyzing all these variables interacting together in one comprehensive model. In accordance with previous studies, we hypothesized that the effect of attachment style and level of perceived stress on PLEs development might be moderated by specific SNPs of the *FKBP5* gene in a non-clinical sample of young adults.

## 2. Materials and Methods

### *2.1. Participants*

A total of 535 participants aged 23.4 ± 3.4 years (range: 18–30 years) were recruited among university students of various faculties from three large Polish cities (Kraków, Wrocław and Szczecin) in the years 2017–2019. All participants represented Caucasian ethnicity and were not related to each other. The history of clinical diagnosis and frequency of substance use were provided with a self-report questionnaire designed for this study. No participant reported a history of psychosis spectrum disorder. Frequent substance use was defined as the use of any psychoactive substance, including alcohol, more than once a week. The study has a cross-sectional design. The Ethics Committee at Wroclaw Medical University in Poland approved the study (approval number: 254/2018; issued on 19th July 2018). All participants gave written informed consent for participation in the study.

### *2.2. Measures*

#### 2.2.1. The Prodromal Questionnaire 16 (PQ-16)

The 16-item PQ-16 is a self-report screening tool for at-risk mental states and the presence of PLEs with sensitivity and specificity estimated at 87% [43]. It consists of nine items assessing perceptual alterations, five items to investigate delusional ideation, paranoia and unusual thought, and two items to screen for attenuated negative symptoms. In our study, we used the Polish version of the questionnaire that was prepared using a back-translation procedure and was used in our several previous studies [6,12,18]. The original PQ-16 consists of two scales, where the first one records whether PLEs are "present" or "non-present", and the second one assesses the level of distress associated with PLEs on a four-point Likert-like scale. In the present study, we focused on the number of PLEs being reported by each participant. Therefore, the total score on the PQ-16 was calculated by adding up the agreed items. The Cronbach's alpha of the PQ-16 was 0.75 in our sample, indicating acceptable internal consistency.

#### 2.2.2. Psychosis Attachment Measure (PAM)

The Psychosis Attachment Measure (PAM) is a 16-item self-report questionnaire [44]. It records two different attachment styles: anxious and avoidant. There are eight items measuring attachment anxiety and eight items recording attachment avoidance. Participants are asked how they relate to the key people from their life on a four-point Likert. Internal consistency was acceptable (Cronbach's alpha = 0.80) for the anxious attachment subscale and good (Cronbach's alpha = 0.82) for the avoidance attachment subscale. In the present study, we used the Polish version of the questionnaire [45]. Based on the PAM scoring, we divided the respondents into those with dominant attachment anxiety and others.

#### 2.2.3. Perceived Stress Scale-10 (PSS-10)

The level of perceived stress was assessed using the Perceived Stress Scale-10 (PSS-10) [46]. The PSS-10 is a 10-item self-report questionnaire designed to measure the degree that respondents find their life unpredictable, uncontrollable, and overwhelming in the preceding month. It consists of 10 items rating the frequency with which participants experience certain situations. The items are scored on a five-point Likert-like scale with responses ranging from "never" to "very often". The PSS-10 consists of two subscales measuring the level of self-efficacy (PSE) and helplessness (PHS). Internal consistency of the PSS-10 in our sample was acceptable (the Cronbach's alpha = 0.74). We used the Polish version of the PSS-10 and measured the intensity of perceived stress related to the current life situation, specifically 30 days prior to the assessment. Participants were divided into those with the PSS-10 score above and below the mean value.

### *2.3. Genotyping*

Based on the functional impact on the *FKBP5* gene and HPA-axis activity, we selected six *SNPs* (rs3800373, rs9470080, rs4713902, rs737054, rs1360780 and rs9296158). DNA samples were collected by swabs from the inner cheeks. We confirmed the accuracy of genotypes by performing duplicate genotyping for 25% of randomly selected samples. Subjects performing the genotyping were blinded to the ID of participants and the data collected using specific questionaries. The details of the genetic analysis were described in our previous study [42].

### *2.4. Statistical Analysis*

The $\chi^2$ test was used to assess the agreement of genotype distribution with the Hardy–Weinberg equilibrium (HWE). Correlations between continuous variables were tested using the Spearman rank correlation coefficients. The Mann–Whitney U test was employed to perform bivariate comparisons. Due to potential effects of age, sex, a history of clinical diagnosis and substance use, the analysis of co-variance (ANCOVA) was performed. Before running the ANCOVA, participants were divided into individuals with predominant anxious attachment (scores of anxious attachment higher than those for avoidant attachment) and those employing other attachment styles (scores of avoidant attachment higher than or equal to those for anxious attachment). Similarly, the PSS scores of both subscales (perceived helplessness and perceived self-efficacy) were dichotomized based on the mean values (i.e., participants were divided into those with the PSS scores above and below the mean value). In the first step, the association between exposure (low vs. high PSS score) and outcome (the PQ-16 score) was tested. Next, covariates (age, gender, a history of clinical diagnosis and frequent substance use) were added to the model. Finally, the following moderators were added: (1) main effects (the *FKBP5* gene polymorphisms and predominant attachment style); (2) two-way interactions (the *FKBP5* polymorphism × the PSS score; the *FKBP5* polymorphism × predominant anxious attachment and the PSS score × predominant anxious attachment) and (3) the three-way interaction (the *FKBP5* polymorphism × the PSS score × predominant anxious attachment). In case of significant interactions, the Games–Howell test was applied to perform post-hoc comparisons. The level of significance was set at $p < 0.05$. All analyses were carried out using the Statistical Package for Social Sciences, version 20 (SPSS Inc., Chicago, IL, USA).

## 3. Results

The general characteristics of all participants are presented in Table 1. Out of 535 participants enrolled in the present study, 460 individuals provided complete data on the occurrence of PLEs, attachment styles and the level of perceived stress (86.2%). Sufficient quality and quantity of DNA was obtained for 441–450 participants (82.4–83.9%) depending on the specific SNPs. Predominant anxious attachment style was reported by 186 individuals (40.4%). The PSS-10 scores of perceived self-efficacy and helplessness were 10 ± 2.90 and 12 ± 5.19, respectively. Clinical diagnosis, including mood or anxiety disorders, was

reported by 8.2% of the participants. None of these respondents reported to be diagnosed with a psychotic spectrum disorder. Frequent use of substances was reported by 21.1% of all participants.

**Table 1.** General characteristics of the sample.

| | **Mean ± SD or n (%)** |
|---|---|
| Age, years | 23.4 ± 3.0 |
| Gender, M/F | 133/327 (40.7/59.3) |
| Clinical diagnosis | 38 (8.2) |
| Anxious attachment | 1.22 ± 0.65 |
| Avoidant attachment | 1.21 ± 0.65 |
| Predominant anxious attachment | 186 (40.4) |
| Perceived helplessness | 12 ± 5.19 |
| Perceived self-efficacy | 10 ± 2.90 |
| Frequent use of substances (>once per week) | 97 (21.1) |
| PQ-16 | 4.1 ± 4.6 |
| rs1360780<br>CC<br>CT<br>TT | 450<br>260 (58.56)<br>159 (34.46)<br>31 (6.98) |
| rs9296158<br>AA<br>AG<br>GG | 444<br>26 (5.84)<br>159 (35.73)<br>260 (58.43) |
| rs3800373<br>GG<br>TG<br>TT | 443<br>37 (8.35)<br>144 (32.51)<br>262 (59.14) |
| rs9470080<br>CC<br>CT<br>TT | 443<br>245 (55.30)<br>151 (34.09)<br>47 (10.61) |
| rs4713902<br>CC<br>CT<br>TT | 441<br>50 (11.34)<br>154 (34.92)<br>237 (53.74) |
| rs737054<br>CC<br>CT<br>TT | 449<br>224 (49.89)<br>182 (40.53)<br>43 (9.58) |

Direct effects of exposure (categories of perceived stress) are shown in Table 2. Participants with lower levels of perceived self-efficacy had a significantly higher number of PLEs (4.1 ± 2.9 vs. 2.9 ± 2.6), even after controlling for age, gender, a history of clinical diagnosis and frequent substance use. Similarly, higher levels of perceived helplessness were associated with a significantly higher number of PLEs (4.3 ± 2.9 vs. 2.8 ± 2.5), even after co-varying for age, gender, a history of clinical diagnosis and frequent substance use. Individuals with a predominant anxious attachment style had a significantly higher number of PLEs (4.0 ± 2.9 vs. 3.2 ± 2.7, $p = 0.001$).

**Table 2.** Effects of perceived stress on the PQ-16 score after adjustment for general characteristics of the sample.

| Model | Effect | Perceived Helplessness | Perceived Self-Efficacy |
|---|---|---|---|
| Model 1 (exposure) | Perceived stress | F = 43.90, ***p* < 0.001** | F = 25.90, ***p* < 0.001** |
| | $R^2$ | 0.088 | 0.054 |
| Model 2 (exposure and covariates) | Perceived stress | F = 24.62, ***p* < 0.001** | F = 12.90, ***p* < 0.001** |
| | Age | F = 39.21, ***p* < 0.001** | F = 42.35, ***p* < 0.001** |
| | Sex | F = 0.68, $p = 0.412$ | F = 0.60, $p = 0.441$ |
| | Clinical diagnosis | F = 4.63, $p = 0.032$ | F = 5.29, $p = 0.022$ |
| | Frequent substance use | F = 2.09, $p = 0.149$ | F = 2.92, $p = 0.09$ |
| | $R^2$ | 0.178 | 0.155 |

Table 3 presents the results from the analysis of the relationships between the SNPs of the *FKBP5* gene, attachment styles and perceived stress. There were significant effects of the two-way interaction (*FKBP5* rs4713902 polymorphism × perceived self-efficacy) and the three-way interaction (*FKBP5* rs4713902 polymorphism × perceived self-efficacy × attachment) on the number of PLEs. The main effects of age, perceived stress and clinical diagnosis were significant in all models. The main effects of predominant attachment were significant only in three models testing for the associations with perceived self-efficacy and three *FKBP5* polymorphisms (rs1360780, rs9296158 and rs9470080). A significant main effect of the rs3800373 polymorphism on the number of PLEs was observed. Specifically, the rs3800373 GG homozygotes reported a significantly higher number of PLEs compared to the rs3800373 T allele carriers (5.1 ± 3.0 vs. 3.4 ± 2.7, $p < 0.001$).

Post-hoc comparisons are reported in Figure 1. Among the rs4713902 TT homozygotes, a low level of perceived self-efficacy was associated with a significantly higher number of PLEs. The rs4713902 TT homozygotes with a low level of perceived self-efficacy had a significantly higher number of PLEs compared to the rs4713902 C allele carriers with high and low levels of perceived self-efficacy. Further stratification of the sample demonstrated that a low level of perceived self-efficacy is associated with a significantly higher number of PLEs only in subjects with the rs4713902 TT genotype and predominant anxious attachment style. Among individuals with non-dominant anxious attachment style, a low level of perceived self-efficacy was associated with a significantly higher number of PLEs, regardless of the rs4713902 genotype.

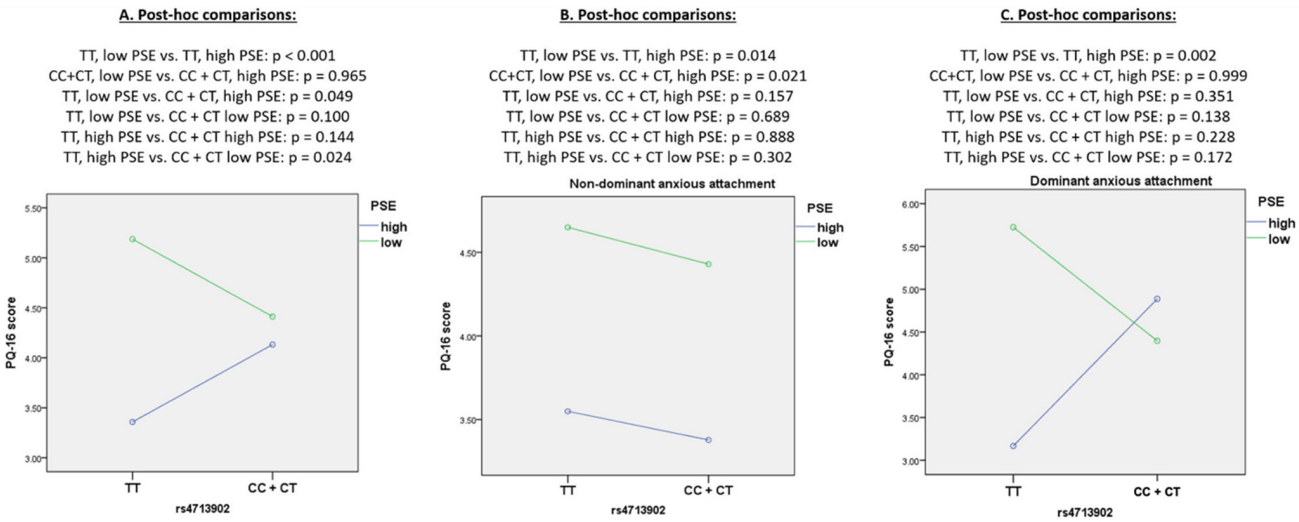


**Figure 1.** Post-hoc comparisons of interactions between *FKBP5* rs4713903 polymorphism total PQ-16 score and attachment style. Abbreviations: PSE—perceived self-efficacy, PQ-16—Prodromal Questionnaire 16.

**Table 3.** Interactions between the *FKBP5* gene polymorphisms, perceived stress and attachment style (effects of exposure, covariates and moderators).

| Stress Category | Effect | rs1360780 | rs9296158 | rs3800373 | rs9470080 | rs4713902 | rs737054 |
|---|---|---|---|---|---|---|---|
| Perceived helplessness | Age | F = 34.11; ***p* < 0.001** | F = 33.28; ***p* < 0.001** | F = 29.09; ***p* < 0.001** | F = 30.96; ***p* < 0.001** | F = 29.61; ***p* < 0.001** | F = 29.83; ***p* < 0.001** |
| | Gender | F < 0.01; $p = 0.940$ | F < 0.01; $p = 0.956$ | F = 0.02; $p = 0.889$ | F = 0.01; $p = 0.922$ | F = 0.01; $p = 0.915$ | F = 0.03; $p = 0.854$ |
| | Clinical diagnosis | F = 4.51; ***p* = 0.034** | F = 4.32; ***p* = 0.038** | F = 5.76; ***p* = 0.017** | F = 4.64; ***p* = 0.032** | F = 4.88; ***p* = 0.028** | F = 4.19; ***p* = 0.041** |
| | Frequent substance use | F = 2.85; $p = 0.092$ | F = 2.90; $p = 0.089$ | F = 2.21; $p = 0.138$ | F = 2.05; $p = 0.153$ | F = 1.28; $p = 0.259$ | F = 1.93; $p = 0.165$ |
| | Perceived helplessness | F = 19.68; ***p* < 0.001** | F = 21.62; ***p* < 0.001** | F = 7.00; ***p* = 0.009** | F = 20.53; ***p* < 0.001** | F = 20.70; ***p* < 0.001** | F = 23.14; ***p* < 0.001** |
| | Attachment | F = 3.23; $p = 0.073$ | F = 3.25; $p = 0.072$ | F = 0.62; $p = 0.433$ | F = 3.62; $p = 0.058$ | F = 2.79; $p = 0.096$ | F = 2.85; $p= 0.092$ |
| | *FKBP5* | F = 1.11; $p = 0.294$ | F = 2.36; $p = 0.126$ | F = 8.82; ***p* = 0.003** | F = 0.81; $p = 0.370$ | F = 0.10; $p = 0.748$ | F = 0.16; $p = 0.687$ |
| | Perceived helplessness × attachment | F = 0.15; $p = 0.696$ | F = 0.06; $p = 0.811$ | F = 0.39; $p = 0.534$ | F = 0.17; $p = 0.684$ | F = 0.80; $p = 0.779$ | F = 0.08; $p = 0.776$ |
| | *FKBP5* × attachment | F = 0.23; $p = 0.629$ | F = 0.06; $p = 0.808$ | F = 0.03; $p = 0.875$ | F = 0.12; $p = 0.732$ | F = 0.25; $p = 0.615$ | F = 0.52; $p = 0.473$ |
| | *FKBP5* × perceived helplessness | F < 0.01; $p = 0.996$ | F = 0.06; $p = 0.813$ | F < 0.01; $p = 0.989$ | F = 0.23; $p = 0.634$ | F = 3.49; $p = 0.062$ | F = 1.66; $p = 0.199$ |
| | *FKBP5* × perceived helplessness × attachment | F = 0.57; $p = 0.452$ | F = 1.02; $p = 0.314$ | F = 1.34; $p = 0.238$ | F = 1.32; $p = 0.251$ | F = 1.64; $p = 0.201$ | F = 1.80; $p = 0.180$ |
| | $R^2$ | 0.189 | 0.192 | 0.207 | 0.182 | 0.184 | 0.192 |
| Perceived self-efficacy | Age | F = 36.37; ***p* < 0.001** | F = 35.61, ***p* < 0.001** | F = 31.18; ***p* < 0.001** | F = 33.53; ***p* < 0.001** | F = 31.60; ***p* < 0.001** | F = 33.00; ***p* < 0.001** |
| | Gender | F < 0.01; $p = 0.991$ | F < 0.01; $p = 0.985$ | F < 0.01; $p =0.990$ | F < 0.01; $p = 0.937$ | F = 0.00; $p = 0.979$ | F = 0.02; $p = 0.901$ |
| | Clinical diagnosis | F = 5.69; ***p* = 0.018** | F = 5.46; ***p* = 0.020** | F = 6.11; ***p* = 0.014** | F = 5.70; ***p* = 0.017** | F = 6.33; ***p* = 0.012** | F = 5.32; ***p* = 0.022** |
| | Frequent substance use | F = 3.71; $p = 0.055$ | F = 3.59; $p = 0.059$ | F = 3.28; $p = 0.071$ | F = 2.75; $p = 0.098$ | F = 1.97; $p = 0.161$ | F = 2.84; $p = 0.093$ |
| | Perceived self-efficacy | F = 10.72; ***p* = 0.001** | F = 11.46; ***p* = 0.001** | F = 4.60; ***p* = 0.033** | F = 11.00; ***p* = 0.001** | F = 12.00; ***p* = 0.001** | F = 11.04; ***p* = 0.001** |
| | Attachment | F = 3.96; ***p* = 0.047** | F = 4.46; ***p* = 0.035** | F = 0.52; $p = 0.474$ | F = 4.39; ***p* = 0.037** | F = 3.02; $p = 0.083$ | F = 3.71; $p = 0.055$ |
| | *FKBP5* | F = 0.73; $p = 0.394$ | F = 1.74; $p = 0.188$ | F = 8.78; ***p* = 0.003** | F = 0.24; $p = 0.626$ | F < 0.01; $p = 1.000$ | F = 0.18; $p = 0.668$ |
| | Perceived self-efficacy × attachment | F = 0.06; $p = 0.803$ | F = 0.01; $p = 0.920$ | F = 0.02; $p = 0.884$ | F = 0,02; $p = 0.882$ | F = 0.01; $p = 0.945$ | F = 0.17; $p = 0.678$ |

**Table 3.** *Cont.*

| Stress Category | Effect | rs1360780 | rs9296158 | rs3800373 | rs9470080 | rs4713902 | rs737054 |
|---|---|---|---|---|---|---|---|
| Perceived self-efficacy | *FKBP5* × attachment | F = 0.01; $p$ = 0.924 | F = 0.19; $p$ = 0.891 | F = 0.14; $p$ = 0.714 | F = 0.01; $p$ = 0.917 | F = 0.42; $p$ = 0.519 | F = 0.40; $p$ = 0.528 |
| | *FKBP5* × perceived self-efficacy | F = 2.53; $p$ = 0.113 | F = 1.93; $p$ = 0.166 | F = 0.09; $p$ = 0.762 | F = 1.14; $p$ = 0.286 | F = 6.64; **$p$ = 0.010** | F = 2.44; $p$ = 0.119 |
| | *FKBP5* × perceived self-efficacy × attachment | F = 2.14; $p$ = 0.144 | F = 3.17; $p$ = 0.076 | F = 0.06; $p$ = 0.805 | F = 1.57; $p$ = 0.211 | F = 6.18; **$p$ = 0.013** | F = 2.18; $p$ = 0.141 |
| | $R^2$ | 0.170 | 0.172 | 0.183 | 0.160 | 0.175 | 0.169 |

## 4. Discussion

We found that the predominant anxious attachment style is associated with a significantly higher number of PLEs. The development of an anxious attachment style is an effect of unprotective parenting corresponding to early life environmental stressors. This may contribute to neurodevelopmental alterations which lead to a higher likelihood of PLEs development [47]. This stays in line with previous studies showing that anxious attachment style increases the risk for PLEs development in individuals exposed to poor parenting [23,24]. Associations between attachment style and PLEs development are supported by studies on patients with schizophrenia-spectrum disorders showing that insecure attachment style mediates the influence of traumatic experiences on the severity of psychotic symptoms in schizophrenia-spectrum disorders [22,26,48].

It is worth noting that we observed a specific influence of attachment anxiety rather than attachment avoidance on PLEs development. This has been previously proposed as an explanation of why symptoms remain subthreshold with individuals with anxious attachment and do not lead to full blown psychosis. Avoidant behaviors observed in negative psychotic symptoms predispose to social withdrawal which leads to growing relational impairments while people with anxious attachment remain involved in social life which may protect them to develop clinical psychosis [49].

Moreover, we observed that participants with lower levels of perceived self-efficacy and higher levels of perceived helplessness reported a higher number of PLEs which supports previous reports on the positive correlation between perceived stress level and PLEs development [17,18,50]. This may indicate that increased stress level makes individuals more vulnerable to developing PLEs. However, it might also signify that PLEs themselves are responsible for elevated levels of perceived stress.

We observed that rs3800373 GG homozygotes are more likely to report a higher number of PLEs in comparison to the rs3800373 T allele carriers. This stays in line with a previous study showing that carrying the rs3800373 G allele of the *FKBP5* gene is associated with a higher risk for schizophrenia development [51]. Moreover, the C allele of rs3800373 has been found to promote higher attachment insecurity in response to parenting insensitivity [52]. These results suggest that *FKBP5* rs3800373 SNP plays an important role in the phenomenon of the psychosis continuum. Considering that the *FKBP5* gene moderates the brain response and HPA-axis reactivity to stress, it seems reasonable that it is also responsible for the variable susceptibility to PLEs development. However, the body of research on *FKBP5* polymorphism is too small to draw conclusions about the exact mechanisms of specific SNPs on PLEs.

We have found that the main effects of attachment style on the severity of PLEs were significant in models testing for the associations with perceived self-efficacy and three *FKBP5* SNPs (rs1360780, rs9296158 and rs9470080). The results of the present study support previous reports showing the relationship between *FKBP5* gene polymorphisms and attachment [52–55]. Only a few studies assessed *FKBP5* gene polymorphism in the context of attachment. It has been demonstrated that insecure attachment is associated with greater cortisol reactivity levels in T allele carriers of rs1360780 *FKBP5* gene polymorphism [53–55]. Accordingly, individuals carrying the T allele of rs1360780 were more likely to develop an insecure attachment style, and thus experience more difficulties in coping when compared to the CC homozygotes [54]. This may suggest that early life adversities like poor parenting and an unprotective environment are responsible for altered neurodevelopment and dysregulation of the stress-response system which results in higher proneness to PLEs and impaired stress perception in adult life.

In individuals with dominant anxious attachment style, there was a significant effect of the interaction between the *FKBP5* rs4713902 SNP and self-efficacy on the severity of PLEs. Among rs4713902 TT homozygotes, a low level of perceived self-efficacy was associated with higher severity of PLEs. In subjects with non-dominant anxious attachment, a low level of perceived self-efficacy was associated with a higher number of PLEs, regardless of the genotype. Both attachment anxiety and a high level of perceived stress have been

found to be associated with greater development of PLEs [56,57]. Therefore, considering that the *FKBP5* gene has been implicated in the development and severity of psychosis and PLEs [41,42], it may suggest that anxious attachment style is associated with different neurobiological mechanisms compared to other insecure attachment styles i.e., avoidant attachment. Although we observed significant relationships between attachment, level of perceived stress and PLEs it is impossible to establish the exact causality of PLEs development. Disturbed attachment results from harmful and non-supportive environment considered as early life adversity and may itself predispose to greater stress perception, maladaptive coping strategies and leads to higher psychosis proneness. Nevertheless, our results indicate that *FKBP5* gene polymorphisms are responsible mostly for different stress responses and HPA-axis reactivity plays a moderating role in these relationships. Therefore, it can be hypothesized that carrying the T allele of SNP rs4713902 of the FKBP5 gene increases the risk for attachment anxiety which may further lead to both increased level of perceived stress and greater risk for PLEs.

However, the findings of the present study should be interpreted in the light of several limitations. First, we assessed only six SNPs. Hence, this may not fully represent the moderating effect of the *FKBP5* gene on assessed variables. Second, our study had a relatively limited sample size. Furthermore, it is important to note that the assessment of the variables was based on self-report questionnaires. This could cause recall bias which might be characterized by overestimation of PLEs reported by respondents [58]. Moreover, we did not exclude participants with a history of clinical diagnosis. Taking into consideration that the proportion of variance in the level of PLEs was relatively low, this may suggest that other factors might be associated with PLEs. However, it is important to highlight that none of the participants reported to be diagnosed with psychosis spectrum disorders. Although the study was based on a non-clinical sample which may increase generalizability to the general population, it might also limit the translation of findings to clinical samples. However, the generalizability of the present results may also be limited by a slightly higher number of female participants. Finally, a cross-sectional study design does not allow to draw conclusions on causal effects. Further research should investigate both non-clinical and clinical samples to identify whether the moderating effect of variants in the *FKBP5* gene on presented associations is relevant for the whole psychosis continuum. Likewise, future studies may assess a higher number of SNPs in larger samples to enable a relevant generalization of findings. Although we did not observe direct relationships between specific insecure attachment styles and negative and positive PLEs it might be worth considering examining these relationships in further research.

## 5. Conclusions

Despite several limitations, our results provide a novel contribution by showing that the *FKBP5* gene plays a moderating role in the relationships between perceived stress and attachment style in the context of PLEs, increasing the risk of their development in TT homozygotes of single nucleotide polymorphism rs4713902 with both low-level self-efficacy and anxious attachment style when compared to C allele carriers. The GG homozygotes of SNP rs3800373 are more likely to report PLEs than T allele carriers. Non-dominant anxious attachment style and a low level of perceived self-efficacy were associated with a higher number of reported PLEs. These results may indicate the importance of exploring the field of the *FKBP5* gene role in the development of PLEs to enable the design of novel therapeutic directions which may focus on psychosis prevention. The present results suggest that simple relations between attachment style and perceived stress level may not be sufficient to comprehend its impact on the development of subthreshold psychotic symptoms. The findings imply that candidate genes involved in stress-response may play a pivotal role in moderating these associations. Future studies on larger samples and based on extensive genetic assessment should consider replication of the findings and include also other domains of the psychosis continuum.

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**Institutional Review Board Statement:** The study was conducted in accordance with the Declaration of Helsinki. The Ethics Committee at Wroclaw Medical University in Poland approved the study (approval number: 254/2018; issued on 19 July 2018).

**Informed Consent Statement:** All participants gave written informed consent for participation in the study.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

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## X. Załączniki

- Załącznik nr 1 – źródło finansowania badań

  Badanie to zostało zrealizowane w ramach Projektu dla Młodych Naukowców finansowanego przez Uniwersytet Medyczny we Wrocławiu (numer projektu: STM.C230.18.034), projektu OPUS „Interakcja pomiędzy traumą, osobowością a funkcjami poznawczymi jako predyktor zwiększonego rozwoju psychozy w populacji osób w wieku 18 – 35 lat. Badanie prospektywne" realizowanego w latach 2017-2021 (nr projektu: 2016/21/B/HS6/03210) oraz programu realizowanego przez Ministerstwo Nauki i Szkolnictwa Wyższego „Regionalna Inicjatywa Doskonałości" na lata 2019-2022.

- Załącznik nr 2 – oświadczenia współautorów

Prof. dr. hab. n. med. Andrzej Cechnicki

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OŚWIADCZENIE

Oświadczam, że w pracy Stramecki F., Frydecka D., Gawęda Ł., Prochwicz K., Kłosowska J., Samochowiec J., Szczygieł K., Pawlak E., Szmida E., Skiba P., Cechnicki A., Misiak B. (2021). The Impact of the FKBP5 Gene Polymorphisms on the Relationship between Traumatic Life Events and Psychotic-Like Experiences in Non-Clinical Adults, *Brain Sci.* 2021, Apr 28;11(5):561 mój udział polegał na przygotowaniu tekstu manuskryptu, a także jego korekcie i ostatecznej akceptacji

Podpis

Ośrodek Psychiatrii Środowiskowej
i Badań nad Psychozami UJ CM
prof. dr hab. Andrzej Cechnicki
p.o kierownik

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Wrocław, 31.03.2022

OŚWIADCZENIE

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Podpis

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Podpis

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OŚWIADCZENIE

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Elżbieta Szmida
Podpis

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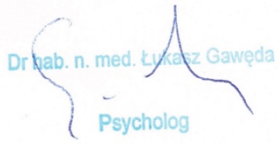
OŚWIADCZENIE

Oświadczam, że w pracy Stramecki F., Frydecka D., Gawęda Ł., Prochwicz K., Kłosowska J., Samochowiec J., Szczygieł K., Pawlak E., Szmida E., Skiba P., Cechnicki A., Misiak B. (2021). The Impact of the FKBP5 Gene Polymorphisms on the Relationship between Traumatic Life Events and Psychotic-Like Experiences in Non-Clinical Adults, *Brain Sci.* 2021, Apr 28;11(5):561 mój udział polegał na analizie oraz krytycznej ocenie projektu, zbieraniu danych oraz ich analizie i interpretacji, przygotowaniu tekstu manuskryptu, a także jego korekcie i ostatecznej akceptacji

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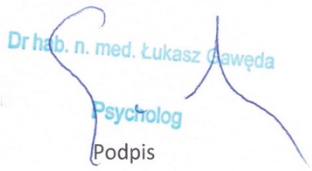


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Szczecin, 31.03.2022

OŚWIADCZENIE

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Podpis

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Szczecin, 31.03.2022

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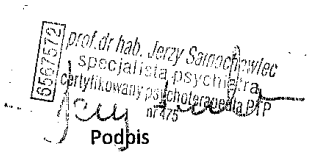


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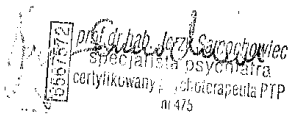

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Wrocław, 31.03.2022

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Podpis

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Kraków, 31.03.2022

OŚWIADCZENIE

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Podpis

INSTYTUT IMMUNOLOGII I TERAPII DOŚWIADCZALNEJ
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Edyta Pawlak
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tel. 71 337-11-72, fax: 71 337-13-82
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Szczecin, 31.03.2022

OŚWIADCZENIE

Oświadczam, że udział lek. Krzysztofa Szczygła w pracy Stramecki F., Frydecka D., Gawęda Ł., Prochwicz K., Kłosowska J., Samochowiec J., Szczygieł K., Pawlak E., Szmida E., Skiba P., Cechnicki A., Misiak B. (2021). The Impact of the FKBP5 Gene Polymorphisms on the Relationship between Traumatic Life Events and Psychotic-Like Experiences in Non-Clinical Adults, *Brain Sci.* 2021, Apr 28;11(5):561 polegał na przygotowaniu tekstu manuskryptu, a także jego korekcie i ostatecznej akceptacji.

Podpis

dr Joanna Kłosowska
Zakład Psychologii Klinicznej
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Kraków, 31.03.2022

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J. Kłosowska
Podpis

Oświadczam, że w pracy Stramecki F., Misiak, B., Gawęda Ł., Prochwicz K., Kłosowska J., Samochowiec J., Samochowiec A., Pawlak E., Szmida E., Skiba P., Cechnicki A., Frydecka D. (2022). The Moderating Role of the FKBP5 Gene Polymorphisms in the Relationship between Attachment Style, Perceived Stress and Psychotic-like Experiences in Non-Clinical Young Adults, *J. Clin. Med*. 2022, 11(6), 1614 mój udział polegał na przeprowadzeniu części badań, edycji tekstu manuskryptu, a także jego korekcie i ostatecznej akceptacji

J. Kłosowska
Podpis

- Załącznik nr 3 - nota biograficzna autora

Filip Stramecki urodził się 6 maja 1991 r. we Wrocławiu. W roku 2016 ukończył studia na Wydziale Lekarskim Uniwersytety Medycznego we Wrocławiu i uzyskał tytuł i prawo wykonywania zawodu lekarza. Od 2017 roku jest doktorantem w Katedrze i Klinice Psychiatrii Uniwersytetu Medycznego we Wrocławiu. W 2018 roku rozpoczął szkolenie specjalizacyjne z psychiatrii w Dolnośląskim Centrum Zdrowia Psychicznego we Wrocławiu. Od 2019 roku pracuje w Oddziale Psychiatrycznym dla Dzieci i Młodzieży Sudeckiego Centrum Zdrowia w Pieszycach, w Centrum Medycznym Ginemedica we Wrocławiu i Centrum Diagnozy i Psychoterapii CEBET w Nysie. Doświadczenie zawodowe i naukowe zdobył uczestnicząc czynnie w projektach Narodowego Centrum Nauki w międzynarodowych konferencjach międzynarodowych naukowych. Filip Stramecki jest autorem 17 publikacji pełnotekstowych o liczbie punktów MNiSW 1268 (IF=56.084).

- Załącznik nr 4 – wykaz publikacji autora

**Wykaz publikacji**

**Filip Stramecki**

***Pełne prace:***

| Lp. | Tytuł, autorzy, źródło | IF | PK |
|---|---|---|---|
| 1. | **Adjuvant anti-inflammatory therapy in schizophrenia - current evidence = Adjuwantowa terapia przeciwzapalna w schizofrenii - aktualny stan wiedzy.** [AUT.] FILIP STRAMECKI, BŁAŻEJ MISIAK, DOROTA FRYDECKA. *Farmakoter.Psychiatr.Neurol.* 2017 Vol.33 nr 3-4 s.225-238, bibliogr. 59 poz., streszcz., summ. DOI: 10.17393/fpn.2017.12.008 | 0,000 | 8,00 |
| 2. | **Obszary stygmatyzacji i dyskryminacji osób chorujących psychicznie wśród respondentów internetowych w Polsce (Areas of stigma and discrimination of mentally ill people among Internet respondents in Poland).** [AUT.] MATEUSZ BABICKI, KAMILA KOTOWICZ, PATRYK PIOTROWSKI, FILIP STRAMECKI, AGNIESZKA KOBYŁKO, JOANNA RYMASZEWSKA. *Psychiatr.Pol.* 2018 T.52 nr 1 s.93-102, ryc., tab., bibliogr. 18 poz., summ. DOI: 10.12740/PP/76861 | 1,311 | 15,00 |
| 3. | **Assessment of the association between cigarette smoking and cognitive performance in patients with schizophrenia-spectrum disorders: a case-control study.** [AUT.] FILIP STRAMECKI, KAMILA D. KOTOWICZ, PATRYK PIOTROWSKI, DOROTA FRYDECKA, JOANNA RYMASZEWSKA, JAN ALEKSANDER BESZŁEJ, JERZY SAMOCHOWIEC, MARCIN JABŁOŃSKI, MICHAŁ WROŃSKI, AHMED A. MOUSTAFA, BŁAŻEJ MISIAK. *Front.Psychiatr.* 2018 Vol.9 art.642 [7 s.], tab., bibliogr. 49 poz., summ. DOI: 10.3389/fpsyt.2018.00642 | 3,161 | 10,00 |
| 4. | **Decreased use of active coping styles contributes to elevated allostatic load index in first-episode psychosis.** [AUT.] BŁAŻEJ MISIAK, KAMILA KOTOWICZ, OLGA LOSKA, FILIP STRAMECKI, JAN ALEKSANDER BESZŁEJ, JERZY SAMOCHOWIEC, MARCIN JABŁOŃSKI, PIOTR PODWALSKI, KATARZYNA WASZCZUK, MICHAŁ WROŃSKI, ANNA MICHALCZYK, LESZEK SAGAN, PATRYK PIOTROWSKI. *Psychoneuroendocrinology* 2018 Vol.96 s.166-172, ryc., tab., bibliogr., summ. DOI: 10.1016/j.psyneuen.2018.06.021 | 4,013 | 40,00 |
| 5. | **Vascular endothelial growth factor in patients with schizophrenia: a systematic review and meta-analysis.** [AUT.] BŁAŻEJ MISIAK, FILIP STRAMECKI, BARTŁOMIEJ STAŃCZYKIEWICZ, DOROTA FRYDECKA, ALBA LUBEIRO. *Prog.Neuro-Psychopharmacol.Biol.Psychiatry* 2018 Vol.86 s.24-29, ryc., tab., bibliogr., summ. DOI: 10.1016/j.pnpbp.2018.05.005 | 4,315 | 35,00 |
| 6. | **Interactions between variation in candidate genes and environmental factors in the etiology of schizophrenia and bipolar disorder: a systematic review.** [AUT.] BŁAŻEJ MISIAK, FILIP STRAMECKI, ŁUKASZ GAWĘDA, KATARZYNA PROCHWICZ, MARIA M. SĄSIADEK, AHMED A. MOUSTAFA, DOROTA FRYDECKA. *Mol.Neurobiol.* 2018 Vol.55 no.6 s.5075–5100, ryc., tab., bibliogr. 174 poz., summ. DOI: 10.1007/s12035-017-0708-y | 4,586 | 40,00 |
| 7. | **Profiling inflammatory signatures of schizophrenia: a cross-sectional and meta-analysis study.** [AUT.] DOROTA FRYDECKA, MAŁGORZATA KRZYSTEK-KORPACKA, ALBA LUBEIRO, FILIP STRAMECKI, BARTŁOMIEJ STAŃCZYKIEWICZ, JAN ALEKSANDER BESZŁEJ, PATRYK PIOTROWSKI, KAMILA KOTOWICZ, MONIKA SZEWCZUK-BOGUSŁAWSKA, EDYTA PAWLAK-ADAMSKA, BŁAŻEJ MISIAK. *Brain Behav.Immun.* 2018 Vol.71 s.28-36, tab., bibliogr. summ. DOI: 10.1016/j.bbi.2018.05.002 | 6,170 | 40,00 |

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| 8. | **Coping styles and symptomatic manifestation of first-episode psychosis: focus on cognitive performance.** [AUT.] FILIP STRAMECKI, KAMILA KOTOWICZ, PATRYK PIOTROWSKI, JAN ALEKSANDER BESZŁEJ, JOANNA RYMASZEWSKA, JERZY SAMOCHOWIEC, AGNIESZKA SAMOCHOWIEC, AHMED A. MOUSTAFA, MARCIN JABŁOŃSKI, PIOTR PODWALSKI, KATARZYNA WASZCZUK, MICHAŁ WROŃSKI, BŁAŻEJ MISIAK. *Psychiatry Res.* 2019 Vol.272 s.246-251, tab., bibliogr., summ. DOI: 10.1016/j.psychres.2018.12.083 | 2,118 | 100,00 |
| 9. | **Elevated allostatic load index is associated with working memory deficits in first-episode psychosis [letter to the editor].** [AUT.] BŁAŻEJ MISIAK, KAMILA KOTOWICZ, OLGA LOSKA, FILIP STRAMECKI, JAN ALEKSANDER BESZŁEJ, JERZY SAMOCHOWIEC, AGNIESZKA SAMOCHOWIEC, MARCIN JABŁOŃSKI, PIOTR PODWALSKI, KATARZYNA WASZCZUK, MICHAŁ WROŃSKI, ANNA MICHALCZYK, LESZEK SAGAN, PATRYK PIOTROWSKI. *Schizophr.Res.* 2019 Vol.204 s.439-441, tab., bibliogr. DOI: 10.1016/j.schres.2018.09.003 | 3,759 | 140,00 |
| 10. | **Adiponectin levels in patients with bipolar disorder: a systematic review and meta-analysis.** [AUT.] BŁAŻEJ MISIAK, FILIP STRAMECKI, JUSTYNA KASZNIA, MICHAŁ LIS, BARTŁOMIEJ STAŃCZYKIEWICZ. *Psychoneuroendocrinology* 2019 Vol.104 s.74-79, ryc., tab., bibliogr., summ. DOI: 10.1016/j.psyneuen.2019.02.019 | 4,732 | 140,00 |
| 11. | **Appetite regulating hormones in first-episode psychosis: a systematic review and meta-analysis.** [AUT.] BŁAŻEJ MISIAK, FRANCESCO BARTOLI, FILIP STRAMECKI, JERZY SAMOCHOWIEC, MICHAŁ LIS, JUSTYNA KASZNIA, KONRAD JAROSZ, BARTŁOMIEJ STAŃCZYKIEWICZ. *Neurosci.Biobehav.Rev.* 2019 Vol.102 s.362-370, ryc., tab., bibliogr., summ. DOI: 10.1016/j.neubiorev.2019.05.018 | 8,329 | 200,00 |
| 12. | **Czynniki ryzyka rozwoju schizofrenii u mężczyzn.** [AUT.] BARTŁOMIEJ STAŃCZYKIEWICZ, FILIP STRAMECKI, BŁAŻEJ MISIAK. W: Schizofrenia u mężczyzn Warszawa 2020, Medical Education, s.39-57, ryc., bibliogr. 140 poz, 978-83-65471-88-8. | 0,000 | 20,00 |
| 13. | **The role of the interaction between the FKBP5 gene and stressful life events in the pathophysiology of schizophrenia: a narrative review.** [AUT. KORESP.] FILIP STRAMECKI, [AUT.] BŁAŻEJ MISIAK, DOROTA FRYDECKA. *Arch.Psychiatr.Psychother.* 2020 Vol.22 no.3 s.7-16, ryc., bibliogr. 94 poz., summ. DOI: 10.12740/APP/124985 | 0,000 | 70,00 |
| 14. | **Przezczaszkowa stymulacja magnetyczna (TMS) w terapii zaburzeń psychicznych - aktualny przegląd badań (Transcranial magnetic stimulation (TMS) in treatment of psychiatric disorders - review of current studies).** [AUT.] TOMASZ WIECZOREK, [AUT. KORESP.] AGNIESZKA KOBYŁKO, [AUT.] FILIP STRAMECKI, KAROLINA FILA-WITECKA, JAN ALEKSANDER BESZŁEJ, MARTA JAKUBCZYK, PATRYK PIOTROWSKI, ADRIANNA SENCZYSZYN, DAMIAN SIWICKI, DOROTA SZCZEŚNIAK, JOANNA RYMASZEWSKA. *Psychiatr.Pol.* 2021 T.55 nr 3 s.565-583, ryc., tab., bibliogr. 51 poz., summ. DOI: 10.12740/PP/OnlineFirst/115556 | 1,657* | 100,00 |
| 15. | **The impact of the FKBP5 gene polymorphisms on the relationship between traumatic life events and psychotic-like experiences in non-clinical adults.** [AUT.] FILIP STRAMECKI, DOROTA FRYDECKA, ŁUKASZ GAWĘDA, KATARZYNA PROCHOWICZ, JOANNA KŁOSOWSKA, JERZY SAMOCHOWIEC, KRZYSZTOF SZCZYGIEŁ, EDYTA PAWLAK, ELŻBIETA SZMIDA, PAWEŁ SKIBA, ANDRZEJ CECHNICKI, [AUT. KORESP.] BŁAŻEJ MISIAK. *Brain Sci.* 2021 Vol.11 no.5 art.561 [13 s.], ryc., tab., bibliogr. 71 poz., summ. DOI: 10.3390/brainsci11050561 | 3,394* | 100,00 |
| 16. | **The relationship between childhood trauma, early-life stress, and alcohol and drug use, abuse, and addiction: an integrative review.** [AUT. KORESP.] AHMED A. MOUSTAFA, [AUT.] DENISE PARKES, LOUISE FITZGERALD, DYLAN UNDERHILL, JULIA GARAMI, EINAT LEVY-GIGI, FILIP STRAMECKI, AHMAD VALIKHANI, DOROTA FRYDECKA, BŁAŻEJ MISIAK. *Curr.Psychol.* 2021 Vol.40 no.2 s.579-584, bibliogr., summ. DOI: 10.1007/s12144-018-9973-9 | 4,297* | 70,00 |

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| 17. | **The moderating role of the FKBP5 gene polymorphisms in the relationship between attachment style, perceived stress and psychotic-like experiences in non-clinical young adults.** [AUT.] FILIP STRAMECKI, BŁAŻEJ MISIAK, ŁUKASZ GAWĘDA, KATARZYNA PROCHWICZ, JOANNA KŁOSOWSKA, JERZY SAMOCHOWIEC, AGNIESZKA SAMOCHOWIEC, EDYTA PAWLAK, ELŻBIETA SZMIDA, PAWEŁ SKIBA, ANDRZEJ CECHNICKI, [AUT. KORESP.] DOROTA FRYDECKA. *J.Clin.Med.* 2022 Vol.11 no.6 art.1614 [13 s.], ryc., tab., bibliogr. 58 poz., summ. DOI: 10.3390/jcm11061614 | 4,242* | 140,00 |
| **Suma:** | | **56,084** | **1268,0** |

***IF za 2020 r.**

***Streszczenia:***

| Lp. | Tytuł, autorzy, źródło |
|---|---|
| 1. | **Assessment of DNA methylation status in HERV-K sequences in patients with first-episode schizophrenia.** [AUT.] B[ŁAŻEJ] MISIAK, F[ILIP] STRAMECKI, E[LŻBIETA] SZMIDA, P[AWEŁ] KARPIŃSKI, P[ATRYK] PIOTROWSKI, J[AN] A[LEKSANDER] BESZŁEJ, D[OROTA] FRYDECKA. *Eur.Neuropsychopharmacol.* 2017 Vol.27 suppl.4 s.S589-S590 poz.P.1.a.022, 30th ECNP Congress. Paris (France), 2-5 September 2017. Abstracts. |
| 2. | **Rzut okiem na immunologiczny aspekt schizofrenii w kontekście nowych metod leczenia.** [AUT.] FILIP STRAMECKI. W: Konferencja "Interdyscyplinarność przyszłością nauki". Zieleniec, 10-12 listopada 2017. Księga abstraktów, s.39. |
| 3. | **Traumatyczne wydarzenia życiowe i ich wpływ na rozwój zaburzeń seksualnych i psychotycznych - opis przypadku.** [AUT.] FILIP STRAMECKI. W: Konferencja "Interdyscyplinarność przyszłością nauki". Zieleniec, 13-15 kwietnia 2018. Księga abstraktów, s.16. |
| 4. | **Endemiczne zaburzenia psychiczne - Japonia.** [AUT.] FILIP STRAMECKI. W: Konferencja "Interdyscyplinarność przyszłością nauki". Zieleniec, 15-17.11.2019. Księga abstraktów, Wrocław 2019, s.38. |
| 5. | **The impact of tobacco smoking on cognitive performance in patients with schizophrenia.** [AUT.] F[ILIP] STRAMECKI, K[AMILA] KOTOWICZ, P[ATRYK] PIOTROWSKI, D[OROTA] FRYDECKA, J[OANNA] RYMASZEWSKA, J[AN] A[LEKSANDER] BESZŁEJ, J. SAMOCHOWIEC, M. JABŁOŃSKI, M. WROŃSKI, A.A. MOUSTAFA, B[ŁAŻEJ] MISIAK. *Eur.Psychiatr.* 2019 Vol.56 suppl.1 s.S392 poz.E-PP1177, 27th European Congress of Psychiatry. Warsaw, Poland, 6-9 April 2019. |
| 6. | **Clinical correlates of allostatic load in first-episode psychosis: focus on cognition.** [AUT.] BŁAŻEJ MISIAK, KAMILA KOTOWICZ, OLGA LOSKA, MARCIN JABŁOŃSKI, PIOTR PODWALSKI, KATARZYNA WASZCZUK, MICHAŁ WROŃSKI, ANNA MICHALCZYK, JERZY SAMOCHOWIEC, JAN BESZŁEJ, FILIP STRAMECKI, PATRYK PIOTROWSKI. *Psychoneuroendocrinology* 2019 Vol.100 suppl. s.S30-S31, 48th ISPNE Annual Conference. Irvine, USA, September 6-8, 2018. DOI: 10.1016/j.psyneuen.2018.12.111 |
| 7. | **Czy to charakter, czy schizofrenia - czyli gdy nie wiadomo o co chodzi, chodzi o zaburzenia osobowości.** [AUT.] FILIP STRAMECKI. W: Interdyscyplinarność przyszłością nauki. Zieleniec, 12-14 kwietnia 2019. Księga abstraktów, s.40, [Dostęp 12.09.2019]. Dostępny w: http://www.doktoranci.umed.wroc.pl/wp-content/uploads/2019/09/Wiosna-2019-Biomed-1.pdf. |

**Sumaryczny impact factor: 56,084 (liczba prac: 14)**

| | **Punktacja MNiSW** |
|---|---|
| do roku 2018 | **188,0** |
| od roku 2019 | **1080,0** |
| **Razem:** | **1268,0** |