

# From hallucinations to delusions: A narrative review of psychotic-like experiences and their implications

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D – writing the article; E – critical revision of the article; F – final approval of the article

Advances in Clinical and Experimental Medicine, ISSN 1899–5276 (print), ISSN 2451–2680 (online)

Adv Clin Exp Med. 2025

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## Funding sources

None declared

## Conflict of interest

None declared

Received on September 30, 2023

Reviewed on February 22, 2024

Accepted on April 4, 2024

Published online on April 29, 2024

## Abstract

Psychotic-like experiences (PLEs) refer to sub-threshold hallucinations and delusions observed in both clinical samples and the general population. Psychotic-like experiences have far-reaching implications for an individual's coping strategies and daily functioning. They are associated with both psychotic and non-psychotic disorders. This article presents a comprehensive review of the current literature on PLEs, incorporating a detailed exploration of the definition, prevalence, risk factors, functional impairments, and comorbid psychiatric disorders. Medline/PubMed and Embase were searched to establish and identify the literature. A total of 108 studies met our inclusion criteria. The genetic and biochemical backgrounds of PLEs are discussed, focusing on gene polymorphisms, changes in brain gyrification and hypothalamic-pituitary-adrenal (HPA) axis dysfunction. Psychological factors, such as trauma exposure, emotion regulation difficulties, cognitive biases, and attachment issues, were thoroughly examined, especially in terms of their impact on the emergence of PLEs. Here, we show how important the clinical aspects of developmental PLEs are, underlining the significance of an increased risk of self-harm and suicidal behaviors in those individuals and the comorbidity of psychiatric disorders in enabling clinicians to discern specific areas to observe. Although there is limited evidence on effective protocols for PLE management, various treatment approaches are explained. Despite increased research on PLEs in recent years, further investigation is needed to fully understand the nature of PLEs and to optimize therapeutic strategies. This article consolidates the current knowledge by synthesizing information on PLEs, including risk factors, comorbidities, treatments, and their impact on individual's lives.

**Key words:** psychosis, delusions, hallucinations, FK506 binding protein 5, hypothalamic–pituitary–adrenal axis

## Cite as

Logoń K, Świrkosz GJ, Kowalski K. From hallucinations to delusions: A narrative review of psychotic-like experiences and their implications [published online as ahead of print on April 29, 2024]. *Adv Clin Exp Med*. 2025. doi:10.17219/acem/186815

## DOI

10.17219/acem/186815

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## Introduction

Psychotic-like experiences (PLEs) are sub-threshold hallucinations and delusions that cannot be classified according to international diagnostic systems due to their low severity, limited duration or absence of associated functional impairment.<sup>1,2</sup> Positive PLEs include phenomena such as fleeting visual or auditory hallucinations, while negative PLEs include, e.g., blunted affect and physical and social anhedonia.<sup>3</sup> In the last decades, the view of PLEs changed from being previously dichotomously diagnosed psychotic symptoms in clinical samples to a continuum of psychotic experiences, applying also to non-help-seeking individuals from the general population.<sup>3</sup> The prevalence of PLEs is significantly higher among young people and more frequent among women, and those who are non-married, unemployed, have a high educational level, and low socioeconomic status.<sup>4–7</sup> Indirect effects from traumatic life events (TLEs), i.e., physical, sexual and emotional abuse, as well as neglect experiences and exposure to PLEs through perceived stress, dissociation, external locus of control, negative self-schemas, and negative other-schemas were found. They include phenomena such as bizarre experiences, perceptual abnormalities, persecutory ideas, and magical thinking.<sup>8</sup>

Psychotic-like experiences have wide implications for an individual, including maladaptive coping strategies and reduced functioning. Many studies have shown a significant association with poorer social and global functioning,<sup>9,10</sup> as well as impaired social and role functioning.<sup>11</sup> Individuals with PLEs have a lower health-related quality of life.<sup>12</sup> In a large study, PLEs correlated with both interpersonal violence and violence towards objects.<sup>13,14</sup> Childhood PLEs are linked to lower self-esteem and optimism, avoidant coping and school misconduct. They are also associated with poorer school performance, as well as language and mathematical abilities.<sup>15</sup> The presence of PLEs is strongly connected with poorer treatment outcomes, both with pharmacotherapy<sup>16</sup> and psychotherapy.<sup>17</sup>

Furthermore, PLEs increase the risk of conversion to a psychotic disorder, and this conversion depends on the severity or persistence of PLEs.<sup>18</sup> Psychotic-like experiences are associated not only with psychosis, but also with non-psychotic disorders such as depressive episodes, post-traumatic stress disorders or personality dysfunctions.<sup>19</sup> In a 2019 meta-analysis, childhood and adolescent PLEs were associated with over a 3-fold increased risk of affective and substance use disorders.<sup>20</sup> The presence of PLEs in childhood predicts future mental health service use and psychotropic pharmacological treatment.<sup>21</sup> Children with PLEs had higher average total healthcare costs during adolescence.<sup>12</sup> In a large study, PLEs were associated with an increased risk of mortality, especially due to suicide and neoplasms. For people experiencing PLEs, the predicted median lifespan was over 5 years shorter.<sup>22</sup>

Over the years, various terms have been used when referring to non-clinical psychotic symptoms. Firstly, the term attenuated psychotic symptoms (APS) was introduced as a part of the ultra-high risk (UHR) criteria for developing psychosis in the future.<sup>23</sup> The UHR criteria, including APS and brief, limited intermittent psychotic symptoms (BLIPS), are assessed through clinical interviews. Unfortunately, various modifications of UHR criteria were introduced.<sup>24</sup> The term “psychotic-like experiences” was first used by Strauss,<sup>25</sup> but the concept has changed throughout the years. In general, there is no consensus regarding the definition and conceptualization of PLEs, which may create inconsistencies in comparing and interpreting the results of different studies.<sup>26</sup>

## Objectives

Recently, the number of publications regarding PLEs has significantly increased. This study aimed to undertake a comprehensive review with particular attention to recent advancements, notably in dynamic fields like genetics, imaging and biochemical studies. Psychological and clinical aspects, as well as the efficacy of the possible treatments are also discussed.

## Genetics

There is a growing number of studies showing the association between genetic polymorphisms and prevalence of PLEs. Researchers have examined the effects of possible factors, that may increase the risk of experiencing PLEs, such as: the catechol-O-methyltransferase (COMT) rs4680, the dopamine D2 receptor (DRD2) rs6277 and the dopamine transporter (DAT1) rs28363170 variable number tandem repeat (VNTR) genes.<sup>27</sup> Higher severity of PLEs and a history of TLEs correlated with low levels of ASEs in *DAT1* 10R/10R homozygotes. The study implied a probability of increased PLE severity with a history of TLEs only in 10R/10R homozygotes of the *DAT1* 9R/10R VNTR polymorphism. The correlation between a history of TLEs and greater severity of PLEs was found among the *COMT* rs4680 Met allele carriers with high levels of cognitive biases.<sup>28</sup> In a study concerning the connection between *COMT* gene rs4680 polymorphism, executive dysfunction and PLEs, a recessive genetic model was found to moderate this relationship in both the overall sample and among women, but not in men.<sup>29</sup> The *DRD2* rs6277 C allele was associated with an increased occurrence of PLEs.<sup>28</sup> The relationship between zinc finger protein 804A (*ZNF804A*) polymorphisms (rs1344706 and rs7597593) and the positive dimensions of schizotypy and PLEs was investigated.<sup>30</sup> Results indicated a significant correlation between rs7597593 and both schizotypy and PLEs, specifically in women. Carriers of the C allele exhibited higher scores in the positive dimension of both

variables compared to TT homozygotes. Research also shows an association between the regulator of G protein signaling 4 (*RGS4*) polymorphisms and PLEs. Individuals carrying the T allele of rs951436 and/or the A allele of rs2661319 demonstrated higher scores on positive and negative PLEs.<sup>31</sup>

There have been numerous studies to investigate the influence of FK506 binding protein 5 (*FKBP5*) gene polymorphisms on PLEs. In a recent cross-sectional study,<sup>32</sup> a *FKBP5* gene was found to moderate the correlation between perceived stress and attachment style in those with PLEs. Compared to C allele carriers, there was a higher severity of PLEs in TT homozygotes with the single nucleotide polymorphism rs4713902 and a worse self-efficacy and anxious attachment style. Moreover, rs3800373 GG homozygotes demonstrated a greater incidence of PLEs, compared to T allele carriers, which corresponded with the former findings on the association between an enhanced possibility of developing schizophrenia in G allele carriers.<sup>33</sup> One study<sup>34</sup> found that individuals with the rs737054 T allele who experienced emotional neglect exhibited a more severe level of PLEs. Additionally, the rs1360780 CC (rather than the T allele carriers observed in previous studies)<sup>35,36</sup> and rs9296158 GG homozygotes with a history of physical abuse reported a higher severity of PLEs, which is consistent with prior findings.<sup>37,38</sup> The interaction between the *FKBP5* haplotype and bullying was also examined and found to be associated with positive PLEs.<sup>37</sup>

A mega-genome-wide association study<sup>39</sup> investigated the genetic overlap between PLEs in adolescents and schizophrenia, bipolar disorder and major depression in adulthood. A polygenic risk score (PRS) analysis showed that the schizophrenia PRS predicted all adolescent PLEs trait domains, while the major depression PRS predicted only 2 of them in adolescence – anhedonia and parent-rated negative symptoms.

Numerous studies have linked various genetic polymorphisms, such as those in *COMT*, *DRD2*, *DAT1*, *ZNF804A*, *RGS4*, and *FKBP5* genes, to the severity and occurrence of PLEs. These associations are often moderated by factors like TLEs and ASEs. Specifically, certain genotypes, such as *DAT1* 10R/10R homozygotes, *COMT* rs4680 Met allele carriers and *FKBP5* TT homozygotes, are associated with increased severity of PLEs, especially in the presence of TLEs. Additionally, there is evidence of genetic overlap between PLEs in adolescents and schizophrenia, bipolar disorder and major depression in adulthood, as indicated in PRS analyses.

## Biology/biochemistry

There are only a few studies in the literature regarding the biochemical aspects of PLEs. These studies concentrated mainly on the hypothalamic–pituitary–adrenal (HPA) axis, as its dysregulation is thought to be associated with psychosis.<sup>40</sup>

A study conducted by Collip et al. investigated HPA axis functioning in people at above-average genetic risk for psychotic disorders.<sup>41</sup> Diurnal cortisol profiles and the association between HPA axis activity and subclinical psychotic experiences were examined in the siblings of patients with psychotic disorders and a healthy control group.

The results showed that momentary PLEs were associated with increased cortisol levels, which can be interpreted in 2 directions. One interpretation involves the impact of distress connected with psychotic experiences on increased cortisol secretion. However, after the multi-level analyses, it seemed that subclinical PLEs may have a greater contribution than negative effects on increasing cortisol levels. Another interpretation is that the increased cortisol levels are either involved in the pathogenesis of psychotic experiences or reflect secondary processes. These results could be interpreted as evidence for an association between heightened cortisol secretion, the dopaminergic system and subclinical psychotic experiences, but whether it is causal could not be established in this study.

A study by Thompson et al. examined connections between the experience of stressful events, HPA axis activity, and hippocampal and pituitary volumes in young people who met the UHR criteria of developing a psychotic disorder.<sup>42</sup> The criteria included the following groups: (a) experienced subthreshold positive psychotic symptoms during the past year, (b) experienced episodes of frank psychotic symptoms that have not lasted longer than a week and have been self-remitting, or (c) have a first degree relative with a psychotic disorder or the identified patient has a schizotypal personality disorder and they have experienced a significant decrease in functioning during the previous year.

The UHR participants who eventually developed psychosis had significantly lower cortisol levels at baseline than those who did not develop a psychotic episode. This confirms the fact that HPA axis dysfunction is involved in the development of psychosis. A significant correlation existed between experiencing minor stressful events and raised cortisol levels. Higher plasma cortisol levels were associated with higher levels of depression and anxiety but not with psychopathology, psychotic symptoms or general functioning. Hippocampal and pituitary volumes were not associated with either plasma cortisol levels or the number of glucocorticoid receptors.

In another study, the aspect of cortical gyrification in adolescents was investigated using magnetic resonance imaging (MRI). The results showed static gyrification changes in individuals with PLEs experiencing voice-hearing, unusual experiences of receiving messages, or persecutory ideas. The cortical gyrification was lower in the frontotemporal regions of the left hemisphere. This group also showed dynamic gyrification changes with higher gyrifications in the right parietal cortex during late adolescence.<sup>43</sup> A similar study was carried out by Evermann et al. in an adult sample. Psychotic-like experience distress was associated with lower gyrification of the left

precuneus. The PLE's depression dimension was correlated with lower gyrification in the right supramarginal and temporal region.<sup>44</sup> Another study, using deformation-based morphometry, demonstrated the role of the uncus in PLE pathogenesis. In this study, PLEs were associated with a reduced expansion of the uncus. The analysis revealed a developmental involvement of the right uncus in the cerebral basis of PLEs.<sup>45</sup>

A limited amount of literature exists on the biochemical aspect of PLEs with a primary focus on the HPA axis. Studies suggest associations between heightened cortisol secretion and PLEs, potentially implicating HPA axis dysfunction in the pathogenesis of psychosis. Additionally, neuroimaging studies have found structural alterations in brain regions such as the frontal-temporal cortex, precuneus and uncus among individuals experiencing PLEs, suggesting a potential neurobiological correlate to these experiences.

## Psychological aspects, trauma

There have been numerous studies investigating the association between childhood trauma (CT) and PLEs. Prior research suggests that witnessing violence,<sup>46</sup> suffering from emotional<sup>47,48</sup> or sexual abuse, and having experienced 3 or more types of trauma<sup>49</sup> are predominantly correlated with PLEs. A recent study<sup>50</sup> comparing the prevalence of delusions and hallucinations in 30-year-olds who had experienced childhood maltreatment with those who had not, showed a higher likelihood of PLEs in self-reported abuse survivors.

As has been previously suggested, there is a strong connection between peer bullying and PLEs, both significantly increasing suicidality in adolescents.<sup>51</sup> Furthermore, research on the correlation between implicit emotion regulation, discrimination and psychopathological symptoms in children showed that greater levels of discrimination predicted a higher endorsement of PLEs.<sup>52</sup> The association between CT and PLEs during early adulthood was also investigated in terms of wisdom scores in college students. This study showed lower scores of wisdom in those reporting PLEs, wisdom in general was negatively correlated with CT and PLEs, while a decreased wisdom level mediated the association between CT and the occurrence of PLEs.<sup>53</sup>

A number of authors have recognized the relationship between family functioning (FF) and PLEs. For example, Zhan et al.<sup>54</sup> examined the association between PLEs, emotion-regulation (ER) strategies among adolescents and the possibility of a parental relationship impact. It indicated that lower use of reappraisal, greater use of suppression and parental conflict or divorce correlated with the number of PLEs endorsed. Moreover, these factors notably predicted a higher level of distress from PLEs. This has also been explored in terms of the COVID-19 pandemic and lockdown in a study by Wu et al.<sup>55</sup> that not only determined a positive association between increased stress and PLEs but also

showed that better FF may alleviate the adverse influence of elevated perceived stresses on PLEs. Nevertheless, prior research<sup>56</sup> suggests there might be other aspects that have a mediating effect between FF and PLEs. A significant correlation was found among college students who reported, above all, trouble with sleep quality, interpersonal adaptation and loneliness. Studies concerning the relationship between PLEs and higher levels of loneliness are well documented.<sup>57–59</sup> However, a recent cross-lagged panel analysis indicated that, although greater feelings of loneliness and less social support predicted more PLEs over time, these variables may be implicated at earlier stages of psychosis risk.<sup>60</sup> Those findings are consistent with the social deafferentation hypothesis,<sup>61</sup> which suggests that social isolation can contribute to the development of hallucinations and delusions. Additionally, there has been an independent emotional processing pathway identified,<sup>62</sup> associating higher PLEs and loneliness with lower efficiency of recognizing emotion states, further mediated by higher levels of perceived rejection. On the other hand, despite existing research on the connection between the need for closure (NFC) and the occurrence of delusionality and hallucinations in patients with psychotic disorders, 1 study tested this issue on a larger sample from the general population.<sup>63</sup> Psychotic-like experiences, jumping to conclusions (JTC) task, and a full abridged NFC scale, consisting of “Preference for Predictability”, “Discomfort with Ambiguity” and “Decisiveness”, were used to assess the connection. It identified an insignificant correlation between NFC and PLEs, along with no association with JTC results, as well as a negative relationship between “Decisiveness” scores and the severity of PLEs.

Another study<sup>64</sup> found that experiencing distress from positive PLEs was linked to more pronounced challenges with emotion regulation, lower reappraisal self-efficacy and less habitual acceptance use. Similarly, distress from negative PLEs correlated with greater difficulties in emotion regulation and less habitual acceptance use. In a retrospective study considering affective lability (AL), the prevalence of PLE subtypes and PLE's contribution to the specific use of emotion regulation strategies in adulthood were studied.<sup>65</sup> The study has provided evidence that men with “hearing voices” PLEs and women with “special messages” and “bodily changes” PLEs correlated with higher levels of AL, and the use of cognitive reappraisal mediated the relationship between hearing voices during PLEs and AL. These findings suggested a significant negative correlation between the severity of paranoia symptoms and the possibility of utilizing adaptive emotion regulation strategies in men, as well as a significant positive correlation between the severity of paranoia symptoms and the frequency of using maladaptive emotion regulation strategies in women. Prior studies reported corresponding data,<sup>66–68</sup> indicating AL as a salient clinical characteristic for psychotic disorders. The findings of a prospective study revealed that affective dysregulation (AD) is linked

to an increased probability of developing and maintaining paranoid delusions and auditory hallucinations among adolescents and young adults.<sup>69</sup> Researchers also suggested a significant correlation between positive psychotic symptoms and higher levels of AL in patients diagnosed with schizophrenia.<sup>70</sup> Moreover, individuals with high-level PLEs were associated with greater use of emotion suppression and lesser use of acceptance,<sup>64</sup> which correlates with the former characteristics of psychotic disorders.<sup>67,71</sup> These findings implied that emotion regulation skills play a protective role in reducing the distress associated with PLEs. Furthermore, they underscore the importance of early psychotherapeutic interventions aimed at addressing emotion regulation difficulties in individuals experiencing PLEs. There is the potential efficacy of cognitive reappraisal in alleviating the impact that PLEs have on AL, which signals the necessity of further studies regarding this subject.

Psychotic symptoms and PLEs are strongly influenced by negative emotions and cognitive biases. A study investigated the moderating effects of psychosis-related cognitive biases, negative affective states and PLEs,<sup>72</sup> showing that emotional and cognitive processes promote the development of PLEs but do not have a cumulative effect. The study findings indicated that external attribution biases moderated the association between anxiety and positive PLEs, while attention to threat biases moderated the link between depression and positive PLEs, which is in line with former research.<sup>73–75</sup> Additionally, JTC biases were associated with positive PLEs and served as a moderator for the connection between anxiety and depression, as well as negative PLEs, which corresponds with a previous meta-analysis<sup>76</sup> and earlier findings.<sup>74</sup> In a cross-sectional study regarding metacognition and its role in the occurrence of PLEs,<sup>77</sup> results led to the assertion that metacognitive functioning, as an independent element, negatively predicts PLEs, and therefore may prevent the emergence of PLEs.

Researchers recognized possible prodromal mechanisms that may momentarily precede PLEs, such as aberrant salience (i.e., assigning excessive importance to irrelevant stimuli) and ASEs.<sup>78</sup> Some authors have also examined the presence of AD, including low resiliency, low reactive control and negative emotionality prior to the development of PLEs.<sup>79</sup> Affective dysregulation in adolescence predicted the occurrence of PLEs 3 years later. Additionally, PLEs arising during late adolescence were associated with a subsequent increase in AD in young adults.

A connection between PLEs, co-occurring distress, cognitive functioning, and early developmental delays or difficulties in adolescents reporting distressing PLEs has been investigated.<sup>80</sup> Compared to children without PLEs and those with non-distressing PLEs, children experiencing distressing PLEs had lower receptive language and delayed recall, and were more likely to have speech/motor developmental delays or difficulties. These findings emphasize that integrating cognitive strategies that target mechanisms underlying PLE distress may be beneficial.

In a cross-sectional study investigating the association between the 3-dimensional (cognitive, affective and reflective) wisdom levels and subclinical psychotic symptoms,<sup>81</sup> researchers found that high-level PLEs correlated with a lower wisdom level. Moreover, the occurrence and distress caused by PLEs were found to be negatively correlated with wisdom. Compared to affective and cognitive wisdom, reflective wisdom exhibited a negative correlation with the overall frequency and distress levels of PLEs. The findings to date suggest that individuals with PLEs may have an affective wisdom deficit, while affective wisdom is vital for establishing social connections with others. Therefore, further studies may hold the potential to prevent the progression from a high-risk state to full-blown psychosis. These results are consistent with previous research, showing an association between psychosis-proneness and lack of empathy<sup>82</sup> or considerable dysfunction in emotion recognition and interpersonal skills.<sup>83</sup>

Recently, it was examined whether daily-life executive function and attachment difficulties (avoidance and anxiety) can predict PLEs.<sup>84</sup> Positive PLEs were found to be predicted by greater trouble monitoring behavioral impact, less difficulty completing tasks, greater difficulty regulating emotional reactions, and greater difficulty controlling impulses. Negative PLEs were found to be predicted by greater difficulties in alternating attention, transitioning across situations and regulating emotional reactions. Higher attachment anxiety predicted both positive and negative PLEs, in contrast to individuals with schizophrenia, which was connected with attachment avoidance. This highlights the potential role of the distinction between these attachment difficulties in the maintenance of sub-threshold symptoms and the risk of transitioning to a full-fledged psychotic disorder.

To gain a deeper understanding of risk factors related to suicidal ideations (SIs) and suicidal behaviors (SBs) in youths experiencing PLEs, a study<sup>85</sup> was conducted indicating that the occurrence of SI and SB increased as participants grew older for those with higher PLE distress. Furthermore, there was a significant association between PLEs at baseline and a progressive deterioration of both SIs and SBs, which was observed to entail a transition from SI to SB. Another study assessed the correlation between Prodromal Questionnaire-Brief Child Version (PQ-BC)<sup>86</sup> items and PLE distress regarding the prediction of lifetime SIs and SBs.<sup>87</sup> A significant association was found among items indexing thought control, auditory hallucinations, suspiciousness, and particularly nihilistic thinking/dissociative experiences, which exhibited the most substantial effect. Distress was found to be a partial mediator, as well as a moderator, between overall PLEs and PQ-BC items with SI and SB, underlining the significance of addressing it in suicide prevention endeavors.

Numerous studies have explored the association between childhood traumas, EF, emotion regulation, cognitive biases, and PLEs. Childhood trauma, peer bullying

and discrimination predict a higher endorsement of PLEs, while lower levels of wisdom and emotion regulation difficulties are associated with increased PLE distress. Neurodevelopmental delays and difficulties, as well as attachment anxiety, may contribute to the occurrence and distress of PLEs. Additionally, distress from PLEs is linked to SI and behaviors, with distress acting as both a mediator and moderator in this relationship. These findings underscore the complex interplay of various psychosocial and cognitive factors in the development and maintenance of PLEs, highlighting the importance of early intervention and holistic approaches to address these experiences.

## Clinical aspects

Most people with PLEs never develop a psychotic disorder, and approx. 75–90% of developmental PLEs are transitory and benign, but these experiences may become clinically relevant, depending on the level of environmental risk.<sup>88–90</sup> According to various studies, 1–7% of people with PLEs develop a psychotic disorder.<sup>91–93</sup> The frequency of transitions depends on PLE trajectories – the group characterized by stable low levels of PLEs had lower percentages of transitions compared to the group with progressively increasing PLEs (1.28% compared to 3.39%).<sup>93</sup> Predictors of conversion to psychosis are regular cannabis use in adolescence and a family history of mental illnesses.<sup>94</sup>

What is more, PLEs are associated not only with an increased risk for psychosis but also with other, non-psychotic psychiatric disorders. In a study conducted by Bourgin et al., psychotic-like experiences were significantly correlated with 25 psychiatric disorders, such as mood disorders, anxiety disorders, post-traumatic stress disorder (PTSD), attention deficit hyperactivity disorder (ADHD), personality disorders, as well as substance use disorders and pathological gambling. The prevalence of psychiatric disorders was gradually associated with higher prevalence rates of PLEs.<sup>4</sup> In a study by Knight et al., patients with depression or anxiety in the presence of PLEs had more severe symptoms of these disorders at the outset than patients without PLEs. The group with PLEs had significantly lower recovery rates and required many more sessions to reach the threshold for recovery.<sup>95</sup> Psychotic-like experiences are associated with distress and depression, with a strength of this association depending on PLE manifestation.<sup>96</sup>

The meta-analysis from 2019 confirms that PLEs are correlated with a significantly increased possibility of SI, suicide attempts and suicide death.<sup>97</sup> In another study, the odds of suicide attempts were significantly higher in patients with an anxiety disorder, major depressive disorder or behavioral disorder who were experiencing PLEs compared with patients who did not report PLEs.<sup>98</sup> Systematic reviews and meta-analyses have shown that individuals with PLEs were at a 2–3-fold increased risk of self-harm and SBs.<sup>97,99</sup>

Children experiencing PLEs are more likely to experience mental health problems in young adulthood than children without PLEs. Psychotic-like experiences at age 12 increased the risk of low life satisfaction, loneliness, social isolation, sleep problems, overweight, tobacco dependence, parenthood, and low educational attainment. However, many of the associations between childhood PLEs and poor outcomes were explained by familial risk factors.<sup>100</sup>

For the time being, most studies did not differentiate between subtypes of PLEs, although they vary significantly according to distress, associated psychopathology, help-seeking and implications for mental health. Future research considering the heterogeneous character of different PLEs may help assess which PLEs are clinically relevant, improving risk screening and therapeutic strategies.<sup>101</sup>

Psychotic-like experiences are associated with an increased risk of various psychiatric disorders, including psychosis, mood disorders, anxiety disorders, PTSD, ADHD, and substance use disorders. Psychotic-like experiences also correlate with increased distress, depression and suicidality, with children experiencing PLEs more likely to face mental health challenges in adulthood. Differentiating between the subtypes of PLEs may aid in understanding their clinical relevance and improve risk screening and therapeutic interventions.

## Psychotherapy and pharmacotherapy

High-risk criteria for psychotic disorders are based on the presence of PLEs.<sup>102</sup> Considerable research efforts have been invested in developing methods of delaying or preventing psychotic illness onset. Intervening earlier may offset the accumulation of damaging personal, social and economic effects.<sup>103</sup> Intervention during the prodromal stage and the first 3 years, defined as the critical period of illness, has the potential to reduce the ultimate severity.<sup>104</sup>

In a meta-analysis from 2013, cognitive behavioral therapy (CBT) had a moderate effect on reducing the transition to psychosis at 12 months. Low-quality evidence for complex psychosocial interventions also suggested that these interventions are associated with a reduced transition to psychosis. Very low-quality evidence suggests a beneficial effect of the supplementation of omega-3 fatty acids during long-term follow-up,<sup>105</sup> which was also confirmed in a meta-analysis from 2019.<sup>106</sup> The therapeutic effect of omega-3 intake may result from altered membrane fluidity and receptor responses following their incorporation into cell membranes. Omega-3 may also interact with the dopaminergic and serotonergic systems through the modulation of arachidonic acid release. Furthermore, there may be an increase in glutathione levels in the temporal lobes, which protects neurons from excitotoxicity and oxidative stress.<sup>107</sup> Although no other treatments have shown any clear effects, most of the studies

included in this review had several problems, mainly an unclear risk of selection bias, a high risk of detection bias, and a high risk of analytics bias owing to incomplete outcome data.

Two meta-analyses from 2018 indicate that, to date, there is no evidence that any specific intervention is particularly effective over the others in preventing the transition to psychosis. The treatments tested were needs-based interventions (NBI) and their combination with omega-3, ziprasidone, olanzapine, aripiprazole, family therapy, D-serine, CBT, and the French & Morrison protocol (CBT-F). Studies investigating integrated psychological interventions, CBT-F + risperidone + NBI and CBT-van der Gaag protocol (CBT-V) + CBT-F + NBI were also included.<sup>108,109</sup>

In a meta-analysis from 2019, no clear difference between the groups was found in the comparison of anti-psychotic drugs (amisulpride, risperidone and olanzapine) connected with specific care packages (non-drug interventions like supportive, empathic listening and counseling) and specific care packages alone. Although a lower number of participants in the intervention group treated with olanzapine and supportive interventions transitioned to psychosis during follow-up compared to the control group (~25% compared to ~40%), these results were imprecise and did not meet levels of statistical significance. Data for the amisulpride-NFI comparison were so few and low-quality that no conclusion could be stated. There was no evidence that adding risperidone to CBT makes a difference in any outcome, including transition to psychosis. All of the studies were rated as a very low quality of evidence by the authors of the meta-analysis using the GRADE approach. The risk of bias was rated as very serious (regarding the randomization method not being described, allocation concealment method not described and high attrition rates). Furthermore, the imprecision in studies was reported. No evidence was found to support the effectiveness of NBIs, CBT, integrated psychological interventions, or family-focused therapy (FFT) in comparison with each other.<sup>106</sup>

The most recent meta-analysis from 2020 investigated psychological interventions and analyzed the proportion of remissions from PLEs as a primary outcome and changes in psychotic symptoms, depression, anxiety, functioning, distress, and quality of life as a secondary outcome. The findings were primarily null, except that CBT may reduce the distress associated with PLEs, but it was not effective for any other secondary outcome. The limitations included a lack of studies on this issue, a small number of participants and variable study quality. Only 2 studies provided randomized controlled trial evidence that CBT was effective in remission of PLEs. Generally, no strong evidence was found for the supremacy of any intervention. The authors suggest that, despite its limited effectiveness in preventing transitions to psychosis, CBT may be used to reduce the distress connected with PLEs. The lack of consequential evidence for clinical and functional improvements indicates

a necessity for further research into psychological interventions for PLEs.<sup>102</sup>

Research into delaying or preventing psychotic illness onset emphasizes early intervention during the prodromal stage and the critical period of the first 3 years, potentially reducing ultimate severity. Cognitive behavioral therapy shows promise in reducing the transition to psychosis and alleviating distress associated with PLEs. Omega-3 fatty acid supplementation may have beneficial effects. However, evidence for other interventions is inconclusive, with no clear superiority of any specific treatment. Further research is needed to evaluate the efficacy of interventions for PLEs and their impact on clinical and functional outcomes.

## Discussion

Psychotic-like experiences present a significant challenge for both researchers and clinicians due to their varying severity and duration and the absence of associated functional impairments. Numerous studies have connected genetic variations, such as those in *COMT*, *DRD2*, *DAT1*, *ZNF804A*, *RGS4*, and *FKBP5* genes, to the severity and occurrence of PLEs. Certain genotypes, like *DAT1* 10R/10R homozygotes and *COMT* rs4680 Met allele carriers, are linked to an increased PLE severity. Additionally, there is evidence of genetic overlap between PLEs in adolescence and later psychiatric disorders like schizophrenia and depression, as seen through PRS analyses. Research on the biochemical aspect of PLEs, mainly focusing on the HPA axis, suggests an association between heightened cortisol secretion and PLEs. Neuroimaging studies have identified structural brain alterations in individuals with PLEs, particularly in regions like the frontal-temporal cortex, precuneus and uncus.

The association between childhood trauma, FE, emotion regulation, cognitive biases, and PLEs is well documented. Childhood trauma, peer bullying and discrimination predict higher PLE endorsement, while lower wisdom and emotion regulation difficulties contribute to increased PLE distress. Additionally, PLE distress is linked to SIs and SBs, emphasizing the need for early intervention and holistic approaches. Psychotic-like experiences elevate the risk of various psychiatric disorders, including psychosis, mood disorders, anxiety disorders, PTSD, ADHD, and substance use disorders. Further research is crucial to evaluate the efficacy of psychological interventions for PLEs, although CBT and omega-3 fatty acids have demonstrated some efficacy.

This article builds upon previous research by synthesizing findings on the complex interplay of genetic, neurobiological, psychosocial, and cognitive factors in the development and implications of PLEs. It extends our understanding of how various genetic polymorphisms, trauma, family dynamics, emotion regulation, and

cognitive biases contribute to the severity and occurrence of PLEs. Highlighting the association between PLEs and a range of psychiatric disorders, distress and suicidality, it underscores the importance of early intervention and holistic approaches to address these experiences.

The article holds significant importance for both research and clinical practices. It emphasizes the need for a comprehensive understanding of PLEs. The research presented in this paper offers valuable insights into the nature and impact of PLEs on an individual's life. The findings indicate that PLEs have significant functional and psychological implications, including their association with distress, reduced quality of life, and an increased risk of various psychiatric conditions. To address these limitations and advance our understanding of PLEs, several key actions should be considered. Efforts should be made to establish a consensus on the definition and diagnostic criteria of PLEs. A standardized framework will enhance the comparability of research findings and improve the accuracy of PLE diagnoses in clinical settings. Further research is needed to explore the underlying biological mechanisms of PLEs. This may include in-depth investigations into genetic polymorphisms, biochemical pathways and neural correlates associated with PLEs. Continued interdisciplinary collaboration between geneticists, neuroscientists, psychologists, and clinicians is crucial for improving our understanding of the complex etiology and development of PLEs. Leveraging advancements in neuroimaging techniques, genetic sequencing technologies and biomarker identification tools can facilitate the elucidation of biological correlates and pathways associated with PLEs. High-quality, randomized clinical trials are pivotal in assessing the efficacy of diverse treatment approaches for managing PLEs. The inclusion of diverse populations ensures that findings are broadly applicable. Understanding the trajectory of PLEs and their predictive value in the development of psychiatric conditions is crucial. This knowledge informs early intervention strategies and enhances outcomes for individuals at risk. Implementing early intervention strategies that target individuals at risk for PLEs, such as those with a history of trauma or familial predisposition, can help alleviate the progression of symptoms and reduce the likelihood of developing psychiatric disorders. This article underlines the importance of adopting a holistic approach to intervention and prevention efforts.

Research on PLEs has expanded considerably in recent years, fueled by the growing recognition of their prevalence and clinical significance. Studies have shown various factors contributing to the occurrence and persistence of PLEs. They are relatively common in the general population; therefore, understanding them is crucial for several reasons. While most individuals who experience PLEs do not go on to develop a psychotic disorder, these experiences can still cause significant distress and impairment in daily functioning. Psychotic-like experiences can have

a significant impact on the individual's quality of life, affecting various domains, including social relationships, academic or occupational functioning, and overall well-being. Research aimed at understanding and addressing PLEs can lead to an improved quality of life. Moreover, PLEs are considered to be an important risk factor for the development of psychotic disorders. Research on PLEs can help in the early detection of individuals at risk for developing psychosis. Early intervention strategies, informed by research findings, can potentially prevent or mitigate the progression of symptoms and improve long-term outcomes. Psychotic-like experiences also represent important risk factors for non-psychotic disorders, including a number of conditions such as depressive episodes, PTSDs, personality dysfunctions, and substance use disorders. Research on the co-occurrence of PLEs with non-psychotic disorders can improve the development of comprehensive treatment approaches that address both psychotic and non-psychotic symptoms simultaneously. This holistic approach can improve treatment outcomes and the overall wellbeing of individuals experiencing these comorbidities. Psychotic-like experiences have also been linked to an increased risk of SBs. By investigating the relationship between PLEs and SIs, attempts and completed suicides, researchers can identify factors that contribute to this risk and develop targeted interventions to prevent suicide and promote mental health. Furthermore, understanding the biological, psychological and social factors involved in PLEs can help reduce the stigma surrounding this mental illness. Increased awareness and knowledge can foster empathy, support and acceptance for individuals experiencing PLEs and related conditions.

## Limitations

This review also has several limitations that need to be considered. One of the major limitations in studying PLEs is the heterogeneity of experiences, ranging from mild perceptual abnormalities to more distressing hallucinations and delusions. First, the lack of a consensus regarding the definition and diagnostic criteria for PLEs further complicates matters and hinders the comparability of research findings. Second, many studies in this review focused on specific subpopulations, and while these studies provide valuable insights into potential risk factors, they may not fully represent the diversity of individuals with PLEs in the general population, limiting the generalizability of the findings. Third, although the review highlights some genetic and biochemical factors associated with PLEs, the field is still in the early stages of understanding these mechanisms and further research is needed. Fourth, the paper discusses the potential effectiveness of CBT in alleviating distress related to PLEs but notes the lack of robust evidence for other treatment methods. This limitation underscores the need for further research to identify effective interventions for individuals experiencing PLEs.



## Conclusions

This review highlights the complex nature of PLEs and their significant impact on individuals. Psychotic-like experiences have profound functional implications, leading to maladaptive coping strategies, impaired social and global functioning, lower health-related quality of life, and higher violence risk. They are associated with psychosis and a variety of non-psychotic psychiatric disorders. The genetic and biochemical aspects of PLEs have garnered attention, with studies revealing associations between specific gene polymorphisms and dysregulated HPA axis activities, especially elevated cortisol levels. Imaging studies have shown lower cortical gyration in frontal-temporal regions of the left hemisphere, left precuneus, right supramarginal and temporal regions, as well as the uncus. While CBT has shown promise in managing PLEs, there is a lack of strong evidence supporting the efficacy of other procedures.

Future studies are required to better understand the trajectory of PLEs and their predictive value in developing psychotic disorders and other psychiatric conditions. Efforts should be made to establish a consensus on the definition and diagnostic criteria of PLEs. Furthermore, high-quality, randomized clinical trials are necessary to evaluate the efficacy of different treatment approaches in managing PLEs and improving outcomes. In conclusion, while this study presents several challenges and limitations, it also offers promising avenues for research and clinical practice. The continued exploration of the biological, psychological and clinical aspects of PLEs is essential for providing effective interventions and improving the lives of individuals experiencing these phenomena.

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