

## Article

# Adolescent Psychedelic-Assisted Therapy: Addressing Ethical and Clinical Challenges Through a Systems-Psychological Lens

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As the prevalence of adolescent mental ill-health continues to rise, there is a pressing need to develop effective therapeutic interventions. Despite promising results from adult trials of psychedelic-assisted therapies (P-AT), translating these interventions to adolescents presents challenges. Therapeutic outcomes in paediatric contexts cannot be inferred from adult studies, because psychotropic drugs can have age-dependent somatic and psychological effects. Administering psychedelics during adolescence, a period of significant psychological, social, and biological change, demands careful ethical consideration. Emphasising the pro-plasticity nature of psychedelics, we advocate for a systems-psychological approach to P-AT for adolescent depression. Compared to adults, this population is more dependent on, and less able to modify, the socio-ecological context in which their psychopathology emerges. Combined with the pro-plasticity effects of psychedelics, this dependence creates a distinctive risk-benefit profile. We argue this profile warrants a systems-psychological treatment approach to mitigate risks and enhance benefits. Expanded screening, psychosocial formulation, psychoeducation for family members, and bespoke integration and post-trial support are introduced as accommodations for P-AT in this population. Our interdisciplinary approach, drawing on bioethical and clinical considerations, foregrounds the matrix within which adolescents exist and their psychopathology develops. We aim to ensure that P-AT for adolescents is safe, effective, and ethically sound, laying the foundation for developmentally appropriate and contextually sensitive interventions.

As with the global adult population, mental health challenges represent a leading cause of disability amongst young people (Gore et al., 2011; WHO, 2022). The average onset of clini-

cally significant distress in adolescence is 14.5 years (Solmi et al., 2022), with nearly 15% of 12-17 year olds experiencing at least one episode of depression (Avenevoli et al., 2015).

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This figure may be a significant underestimate, with perhaps up to 40% of depression in adolescents going unrecognised (e.g., Stein & Fazel, 2015). Early mental health struggles are strongly associated with chronic mental health conditions and socio-economic disadvantage in adulthood (Clayborne et al., 2019a, 2019b; Gibb et al., 2010; Naicker et al., 2013). However, intervention in adolescence can manage immediate mental health symptoms and reduce their exacerbation into adulthood (D. Johnson, et al., 2018; McGorry & Mei, 2018).

Against this backdrop, itself exacerbated by the COVID-19 pandemic (Racine et al., 2021; Ravens-Sieberer et al., 2022), there are calls for expanding psychedelic-assisted therapy (P-AT) trials to adolescent populations (Jeffrey et al., 2024; Kangaslampi & Zijlmans, 2023). Therapeutic interventions involving classic psychedelics such as psilocybin and LSD have shown promising results in adult populations, with trials demonstrating substantial effect sizes for treatment-resistant depression (TRD) and other conditions (Andersen et al., 2021; Ko et al., 2023; Marchi et al., 2024; for reviews, see Jacobs et al., 2026; Siegel et al., 2026). These compounds are the focus of the present analysis. While MDMA-assisted therapy represents another promising avenue for adolescent mental health, particularly for PTSD (Kangaslampi & Zijlmans, 2023), its distinct pharmacological profile and mechanism of action warrant separate consideration. To the extent that MDMA shares the characteristics of classic psychedelics outlined below, our systems-psychological argument may have relevance; however, we do not assume this generalisation here, and the question merits independent analysis.

Nonetheless, young people are society's largest vulnerable group. Whether the intervention involves classic psychedelics or MDMA, it is imperative that they are not forgotten as 'therapeutic orphans' (Shirkey, 1968), denied timely access to the fruits of clinical research.

However, a wealth of wider pharmacological research shows that therapeutic safety and efficacy in paediatric contexts cannot be

straightforwardly inferred from adult studies. Psychotropic drugs can have age-dependent somatic and psychological effects (Safer, 2011; Safer & Zito, 2006), sometimes producing muted therapeutic impact and higher rates of adverse events in developmental contexts (Le Noury et al., 2015; Solmi et al., 2020). Clinical research of psychotherapeutic interventions must similarly account for the psychological, social, and biological dimensions of adolescent development (Weisz & Hawley, 2002). As the licensing and rollout of P-AT approach, translation to developmental contexts (in which no clinical trials in psychedelics have been completed since 2000; Rajwani et al., 2025) must be carefully informed both by bioethics and developmental clinical psychology. Rather than comprehensively surveying potential ethical hazards in developing P-AT for adolescent populations (for which see Edelson & Sisti, 2023; Rajwani et al., 2025), here we focus on one central feature of P-AT that takes on heightened significance in developmental contexts: the pro-plasticity nature of classic psychedelics such as psilocybin.

This paper has three aims. First, drawing on the pro-plasticity effects of classic psychedelics (their capacity to create a time-limited window of heightened environmental sensitivity), we argue that P-AT outcomes are shaped not only by individual and pharmacological factors, but by the socio-ecological "matrix" (Eisner, 1997; Jacobs et al., *n.d.*) to which patients return following treatment. Second, we show why this matters distinctively for adolescents: their limited autonomy, ongoing psychosocial development, and dependence on familial environments create a risk-benefit profile in which matrix factors are both more consequential and less modifiable by the patient. Third, we outline specific clinical accommodations, including expanded screening; psychosocial formulation; family psychoeducation; and bespoke integration support; to mitigate risks and enhance therapeutic outcomes. We conclude by considering broader implications for others whose capacity to shape their environmental matrix is similarly constrained.

## Appraising the risk profile of psychedelics Evidence for risk in adolescent and adult populations

As acknowledged in a recent editorial, the introduction of P-AT trials for adolescent populations must proceed with the utmost caution (Jeffrey et al., 2024). Early psychedelic research in young populations, as well as lacking the methodological rigour required in contemporary studies, often failed to meet contemporary bioethical standards (Edelsohn and Sisti, 2023; Sigafos et al., 2007). As such, we begin by reviewing the evidence that provides signals, however imperfect, about the risk profile of using psychedelics clinically in adolescent populations.

Contrary to longstanding public perceptions, classic psychedelics have strikingly low physiological toxicity. They have minimal addiction and dependence potential (Griffiths et al., 1979; M. W. Johnson et al., 2019), while the lethal dose of psilocybin is several orders of magnitude higher than an effective dose (Gable, 2004). Recent systematic reviews have found low levels of physical adverse events in clinical trials of psychedelics (Breeksema et al., 2022; Schlag et al., 2022), and one review characterises classic psychedelics as, physiologically, “one of the safest known classes of CNS drugs” (Nichols, 2016, p. 275). Nonetheless, differences between adult and adolescent responses to classic psychedelics remain largely unexplored.

A prospective study of psychological outcomes of naturalistic psychedelic use that compared adolescents aged 16-24 (n=435) and adults 25+ (n=654) reported comparable improvements in psychological wellbeing and other mental health domains between the groups, with findings for adolescents consistent with those in adult research (Izmi et al., 2024). However, the study identified two key elevated risks in adolescent use. The adolescent group displayed higher rates of symptoms of Hallucinogen Persisting Perceptual Disorder (persistent visual disturbances following psychedelic use, ranging from mild to distress-

ing), though only one participant found these effects significantly troubling. Adolescents also reported significantly higher rates of challenging experiences. While challenging acute psychedelic experiences can contribute to longer-term therapeutic or personal benefit for many (Breeksema et al., 2022; Carbonaro et al., 2016; Gashi et al., 2021), elevated rates of such experiences in adolescents warrant careful attention.

Cross-sectional data from a Swedish national survey found that adolescents reporting lifetime psychedelic use had significantly higher anxiety than non-users; however, this association was largely accounted for by neuroticism, rather than psychedelic use *per se*, which explained 1% of additional variance in anxiety outcomes (Sjöström et al., 2025). While this study cannot speak to treatment response from P-AT, it highlights the heterogeneity of adolescents who use psychedelics naturalistically and reinforces the importance of careful screening in any clinical application.

## Risk and its mitigation in clinical settings

The acceptability of research-related risks depends on the probability, severity, and reversibility of adverse events, and on the adequacy of safeguards. For adolescents, with their heightened vulnerability and still-developing autonomy, the threshold for acceptable risk is lower than for adults, even when average outcomes are positive.

Relative to naturalistic use, clinical trials offer mechanisms to reduce the risk of challenging experiences. In the Izmi et al. study, adolescents were more likely to take higher doses of psychedelics, a known risk factor for challenging experiences (Carbonaro et al., 2016; Studerus et al., 2012). Clinical supervision in P-AT research also provides safeguards beyond dosage control: secure psychological containment during challenging experiences, the ability to medically abort extremely distressing trips, and psychotherapeutic support for integrating such experiences afterwards.

Although clinical studies of psychedelics

involve significant screening, preparation and safety practices that substantially reduce certain risks relative to use in uncontrolled settings (Schlag et al., 2022), it should be noted that trials still report serious adverse events (Hinkle et al., 2024). Trials of ayahuasca (Palhano-Fontes et al., 2019) and psilocybin (Goodwin et al., 2022) for TRD are particularly notable. Four of 29 patients in the ayahuasca study were hospitalised for a week due to their “delicate” condition. Suicidal behaviour was reported in three of 79 participants administered 25 mg of psilocybin, each of whom had a history of suicidality. Suicidal ideation was also recorded in the 10 mg and 1 mg “active placebo” cohorts, reflecting the high base rates of suicidality in this population.<sup>1</sup> Nonetheless, all three behavioural events occurred in the high-dose arm, warranting careful consideration of psychedelic-specific risk factors, including demoralisation following non-response (Gukasyan, 2023).

### **The potential role of the wider social environment**

Among the limited evidence for the impact of psychedelics on adolescents is a series of observational studies in the União do Vegetal (UDV) tradition in Brazil. These found no significant psychiatric or behavioural differences in ritual users of ayahuasca compared to controls, except for reduced alcohol consumption (Da Silveira et al., 2005; de Rios et al., 2005; Doering-Silveira et al., 2005a, 2005b; dos Santos, 2013). The absence of negative psychological sequelae among adolescents in psychedelic-using communities elsewhere in the world should not, however, be uncritically assumed to translate into Western therapeutic contexts. The UDV adolescents, but not necessarily the study’s control group, benefited from a supportive and protective religious community, which we know can have beneficial effects on a

range of psychological outcomes.

Moreover, their ayahuasca use happened in a “socially-sanctioned, elder-facilitated and structured religious context” (de Rios et al., 2005, p.135). Within a community with a long-standing tradition of psychedelic use, there will likewise be a shared understanding that psychedelic use is normal, as well as cultural resources for making sense of the complex and symbolic phenomena that arise during acute drug effects. One study of Westerners who experienced extended difficulties following naturalistic psychedelic use includes descriptions of social, existential, and ontological difficulties that may be attributable to, or exacerbated by, the relative uncommonness of psychedelic use in mainstream culture (Evans et al., 2023). While clinical trials incorporate integration sessions as standard practice, such sessions are time-limited professional encounters that may not substitute for the broader cultural scaffolding available in Indigenous contexts (e.g., shared cosmologies, community rituals, and intergenerational transmission of psychedelic knowledge), which provides ongoing, communally embedded support for meaning-making beyond the clinical encounter. In Western clinical contexts, the resources available for sustained integration depend largely on whatever the patient’s existing matrix provides – a distinction that underscores the importance of attending to this environment.

The importance of contextual factors to psychedelic outcomes, and their particular relevance to clinical trials in adolescents, is underlined in one in-depth interview study of 15 individuals reporting long-term negative psychological effects after naturalistic psychedelic use (Bremner et al., 2023). This study identified salient risk factors for adverse outcomes. As well as identifying “young age” as a vulnerability, others included known risk

<sup>1</sup> Approximately 30% of TRD patients attempt suicide at least once during their lifetime, with an estimated incidence of 4.66 attempted suicides per 100 patient-years (Bergfeld et al., 2018). In nationally representative US data, 9.8% of adolescents reported co-occurring major depressive episode and suicidal thoughts in the past year, and 3.5% reported co-occurring depression and a suicide attempt (Lu & Keyes, 2023). For comparison, an FDA meta-analysis of paediatric antidepressant trials (n=4,582) found SSRIs associated with a modestly increased risk of suicidality in depression trials (RR=1.66; 95% CI, 1.02–2.68) (Hammad et al., 2006).

factors for adolescent psychopathology: family history of diagnosed or suspected mental health problems, a stressful time or major life changes surrounding the drug experience, and a lack of social support system during or afterwards (cf. Elsayed et al., 2019; Rojas et al., 2017; Roth et al., 2023). Bremner and colleagues conceptualise these findings within a “plasticity × context” model: the pro-plasticity effects of psychedelics intersect with contextual vulnerabilities to produce outcomes that range from therapeutic to iatrogenic. This framework provides a useful heuristic for thinking about why adolescents warrant distinctive safeguards in P-AT research.

### **Plasticity x Context: Adolescence, Autonomy and Pro-plasticity Drugs**

Classic psychedelics appear to enhance capacity for psychological and behavioural change. This pro-plasticity effect is increasingly understood to play a role in their transdiagnostic therapeutic efficacy (Calder & Hasler, 2023; Rojas et al., 2017; Nardou et al., 2023). Preclinical research provides robust evidence for neurobiological mechanisms, including enhanced structural and functional neuroplasticity (Agnoletti et al., 2025). While direct evidence for such effects in humans remains limited (Calder et al., 2025), our argument does not depend on any particular neurobiological mechanism.

Neurobiological literature increasingly shapes how P-AT is conceptualised. For present purposes, however, what matters is the convergent clinical and qualitative evidence that psychedelics produce a time-limited window of enhanced openness to change: a functional plasticity of thought, feeling, and behaviour that renders individuals more sensitive to contextual influences. The ethical relevance of this window lies less in its underlying mechanism than what it implies for patients: a period during which the social and relational environment may exert disproportionate influence on whether therapeutic gains are consolidated or lost. Whether this window is best understood in terms of neuroplasticity, enhanced learning

(Caulfield et al., 2025), or sensitive-period re-opening (Lepow et al., 2021), the convergent implication is the same: environmental context during this period may be unusually consequential.

Carhart-Harris and Friston’s (2019) REBUS (RElaxed Beliefs Under pSychedelics) model offers one computational framework for understanding these effects. The model proposes that psychedelic administration relaxes the precision of high-level priors or beliefs—representational structures that shape a person’s experiences of themselves, others, and the world, referred to in relational fields as internal working models (Bowlby, 1979). In psychopathologies, these may take the form of maladaptive beliefs about the self or wider world (Carhart-Harris & Friston, 2019; Hipólito et al., 2023). While such beliefs likely perform (or at some point performed) a protective function, the “flattened landscape” of mind and brain following psychedelic use offers a time-limited “plasticity window” that makes possible the transition to more adaptive states, and ultimately more adaptive patterns of thought and behaviour (Nutt et al., 2023; Zeifman et al., 2025). This model is useful here not as a commitment to a specific mechanism, but because it gives precise language to the functional claim we rely on: that psychedelics temporarily loosen entrenched patterns, creating a window in which new inputs carry disproportionate weight.

Whatever we call this enhanced capacity for change, it is not intrinsically a good thing. The same plasticity that enables therapeutic reorganisation also supports the learning and reinforcement of maladaptive patterns, as in the development of some psychopathologies (Branchi, 2011; Pittenger, 2013). In the context of psychedelics, the ambiguous nature of pro-plasticity effects is best understood by considering the *environmental sensitisation* that follows psychedelic use. Inasmuch as plasticity is the capacity of something to be shaped or moulded, it matters what is doing the shaping or moulding. Its full impact depends on the nature of the environment. For instance,

exposure to psychotherapeutic support versus significant life stressors following a plasticity-enhancing psychedelic experience can lead to markedly different outcomes (Bremner et al., 2023; Castrén, 2005; Majić et al., 2015).

These considerations suggest that environmental factors are highly relevant. Post-psychedelic change is rooted in neurobiology, but an exclusive focus on the brain likely provides an incomplete picture. Psychological transformation unfolds within intra- and interpersonal processes in which meaning emerges dialogically - through sequences of response, “response to response and further response” (Bakhtin, 1981). Change is therefore not simply generated internally, but co-constructed within relational and contextual exchanges that shape how experience is interpreted, integrated, and enacted. Crucially, psychedelic administration appears to create a time-limited window during which environmental and relational factors exert amplified influence on subsequent psychological trajectories.

Childhood itself is a period of enhanced plasticity, during which a child’s individual characteristics are shaped by their social environment (Bronfenbrenner, 1979). Adolescence is a period of particularly dramatic change, second only to infancy, with psychosocial development characterised by shifts in sense of identity, goal-directedness, agency, self-consciousness, and relationships with others (Dumontheil, 2015; Luna et al., 2010). These shifts coincide with heightened neurobiological sensitivity to social stimuli: a developmental feature that, while adaptive in many respects, increases susceptibility to mental health difficulties (Blakemore, 2008; 2012; 2019). As social, cognitive, and emotional development proceeds, the relationship between a child and

their social environment becomes more interactional and dynamic, with adolescents exerting more influence on the social milieu around them as they age. This corresponds to increases in autonomy and agency, closely linked to the concept of *self-governance* (Ryan, 1993).<sup>2</sup> Nonetheless, compared to the typical adult, adolescents have considerably less autonomy and agency to control or influence their daily life and environment, with these largely determined by the prevailing norms of their family home and the routines of their schooling. This limited autonomy affects not only the conditions under which adolescent assent or consent to P-AT can be considered meaningful, but also their trajectory during and after —perhaps long after— the trial.

A substantial bioethical literature has been generated seeking means to respect and advance the limited autonomy of adolescents, including in research settings (Michaud et al., 2015), and the complexities of adolescent autonomy and informed consent challenges in psychedelic contexts have been explored at length elsewhere (Jacobs, 2023; Rajwani, 2022; Smith & Sisti 2021). Our contribution to this conversation is to introduce the clinical implications of limited adolescent autonomy for P-AT, to highlight an additional risk that requires mitigation.

Bandura’s (1986; 2006) social-cognitive model recognises *agency* as the process of exerting influence over one’s psychosocial functioning and circumstances, requiring the interplay of intentionality, motivation, self-regulation, self-reflectiveness and self-efficacy, all of which are shaped and constrained by both personal and sociocultural factors. Findings from research in treatment outcome studies implicate agency as both a predictor of symptom severity

<sup>2</sup> In the context of both bioethics and adolescent development, autonomy and agency are conceptualised distinctly and subject to competing accounts, but are nonetheless acknowledged to be deeply interrelated (Beyers et al., 2003; López Barreda et al., 2016; Zimmer-Gembeck & Collins, 2006). Autonomy typically refers to the broader condition of self-governance and independence from external control; agency emphasises the capacity for intentional action and decision-making. In adolescence, both converge on a central developmental challenge: the progressive acquisition of self-determination within social contexts that remain largely, but not entirely beyond the adolescent’s control. For our purposes, the key point is a practical clinical reality: adolescents have limited capacity to modify the environments in which their symptoms develop and to which they return following treatment.

(Jennissen et al., 2022) as well as a mediator of change within psychotherapy contexts (Huber et al., 2021). These findings derive from conventional psychotherapy contexts rather than P-AT, but they suggest a plausible moderating mechanism: psychedelic treatments may enhance motivation and capacity for change, while the actualisation of change depends on environmental affordances and the availability of sufficiently supportive relational contexts.

Qualitative studies on P-AT report increased motivation and commitment to change, with participants noting improvements in confidence, resilience, and lifestyle (Nielson et al., 2018; Noorani et al., 2018; Watts et al., 2017). One preclinical finding is suggestively consistent: stress-susceptible mice administered the psychedelic (R)-DOI showed enhanced active coping in the face of social aggression, including increased escape behaviour and reduced freezing (Krupp et al., 2024). Yet such gains in motivation and openness do not unfold in a vacuum; their realisation depends on an environment that is receptive to change.

When individuals lack direct autonomous agency, as is often the case in childhood and adolescence, others within their system must step in. This may take the form of *proxy agency*, where others act on the young person's behalf, or *collective agency*, where resources and capacities are pooled. In this way, agency is an inherently interpersonal process, occurring in relationships which themselves comprise or at least contribute to the social environment. At the very least, this environment must be compatible with and receptive to such changes. While the typical adult P-AT patient may have sufficient autonomy to effect salutogenic change following treatment, the adolescent will, to some extent, be restricted by a continued dependence on parental structures.<sup>3</sup> Thus, adolescents undergoing P-AT may experience motivation and commitment gains comparable

to adults. Yet their partial dependence on parental structures means they have less capacity to enact change autonomously. The degree to which therapeutic gains are realised will to some extent depend on the responsiveness of the family system: some environments will support and reinforce change, while others may limit or resist it. This makes it crucial to consider alongside individual prognostic indicators in terms of both participant selection and interventional support.

### **Reducing risk and enhancing outcomes in adolescent P-AT: a systems-psychological approach to psychedelic-enhanced plasticity**

As with P-AT trials in any cohort, the period of acute drug effects is the most conspicuous interval in which patient autonomy is compromised, and for which the highest levels of safeguards are appropriate (Brennan et al., 2021; Villiger and Trachsel, 2023). But as outlined above, the autonomy of adolescents is typically restricted even when sober, due to their increased dependence on the adults around them. Outside of drug sessions, the salient feature of limited adolescent autonomy is a reduced ability to select, avoid or upscale various inputs within the social environment. This might include risk factors within the familial landscape, such as parental attachment insecurity (Delgado et al., 2022), or stressors arising from family circumstance (Cuffe et al., 2005).

In psychedelic medicine, Eisner (1997) introduced the term *matrix* to describe the post-treatment environment to which a person returns, proposing it as a third extrapharmacological determinant of outcomes alongside “set and setting”. Though the concept remains somewhat loosely defined (see Jacobs et al., *n.d.*, for a fuller recovery and operationalisation of the matrix concept), it usefully directs attention to how environmental contexts shape

<sup>3</sup> The successful negotiation and relinquishment of this dependence forms part of a wider developmental task, linked to psychosocial functioning and adjustment, as the young person transitions into adulthood (Soenens & Vansteenkiste, 2010; Steinberg & Silverberg, 1986; Zimmer-Gembeck & Collins, 2006) – another dimension for therapist teams to bear in mind in adolescent P-AT.

the consolidation and durability of treatment effects. Adolescent P-AT occurs during a developmental period characterised by heightened environmental sensitivity. Viewed through a differential susceptibility framework, this suggests that the same intervention may produce markedly different outcomes depending on the post-treatment environment—a consideration that warrants particular caution. Nonetheless, as of yet commentary is only beginning to emerge on the interaction between the risks and possible outcomes of P-AT and developmental considerations of adolescence (Jeffrey et al., 2024; Rajwani et al., 2025; Sutherland et al., 2025).

Despite a shift in emphasis toward peer relationships during adolescence, quality of parental relationships remains important, with responsive, consistent care providing “a secure base” for periods of adversity, uncertainty and transition (e.g., Rosenthal & Kobak, 2010). Research shows that specific caregiver factors can partially explain adjustment and mental health outcomes in adolescent populations. These include parenting style (Yap et al. 2014), attachment quality (Brumariu & Kerns, 2010; Darling Rasmussen et al., 2019; Kerns et al., 2015), parental support (van Harmelen et al., 2016) and predictability of home environment (Gillespie & Rao, 2022). Furthermore, parental responses to children’s mental health difficulties can either facilitate or hinder recovery. Caregiver self-efficacy and emotion-focused involvement predict better adolescent symptom outcomes (Ansar et al., 2024; Lafrance Robinson et al., 2016), while parental emotional dysregulation and maladaptive responses are linked with greater post-traumatic stress and slower adjustment (Valentino et al., 2010; Williamson et al., 2017; Wise & Delahanty, 2017). Family functioning as well as parental resources, burden and skills are amongst the strongest mediators of therapeutic outcomes, followed by the role of peer influence and changes in interpersonal functioning (Taubner et al., 2023).

Psychotherapeutic treatment of depression across the lifespan employs formulation to understand the genesis and maintenance of

psychological distress. Formulation identifies factors that trigger and sustain depressive responses, recognizing them as meaningful, albeit maladaptive, strategies within an individual’s context. It helps pinpoint key factors that, if modified, would facilitate therapeutic change. Individual formulation offers an account of the biopsychosocial factors that predispose, precipitate and perpetuate symptoms of ill mental health. *Systemic* formulation locates psychopathology not within the individual, but rather in the nature of interpersonal interactions between the individual and their social system. It recognises that symptoms may serve relational functions: as means of self-regulation, communication, or maintaining equilibrium within the family system. This does not displace the rationale for pharmacological intervention. Rather, it identifies the relational conditions under which drug treatment is most likely to produce durable benefit, and flags where those conditions may need direct attention.

Without a systemic lens, clinician-researchers may overlook how rigid patterns in the adolescent’s social environment —patterns often beyond the adolescent’s capacity to change—contribute to their presenting difficulties. This oversight risks returning the individual to an environment that hinders the therapeutic effects of P-AT, reinforcing depressive cognitive styles or behaviours in an enhanced plasticity context. Worse, returning to an adverse environment in a state of heightened sensitivity could make the intervention iatrogenic: the enhanced plasticity intended to support therapeutic change may instead amplify susceptibility to contextual adversity. Thus, for the adolescent, whose mind, brain and social identity is under construction and acutely sensitised to the interpersonal environment (Blakemore & Mills, 2014; Schriber & Guyer, 2016), the context of post-acute psychedelic experience should be taken all the more seriously. To this end, clinician-researchers should be especially mindful of the matrix in which depression has emerged and to which the individual will return following treatment, with consideration of systemic factors that may stymie therapeutic

effects.

With the risk profile and its developmental dimensions outlined, we now turn to specific accommodations that follow from a systems-psychological reading of these considerations.

### Clinical considerations

In adolescent P-AT, clinician-researchers must consider the readiness not only of the prospective patient, but also of the familial and ecological matrix. Standard clinical assessment of “readiness for treatment” focuses on the individual; here, it should extend to the environment to which they return. Systemic and relational factors are relevant in all adolescent mental health interventions. In P-AT, however, their clinical and ethical salience is temporarily heightened: post-psychedelic environmental sensitivity amplifies the consequences of contextual exposure during the period in which change consolidates. The clinical accommodations we outline below draw on well-established principles in developmental psychopathology and family systems therapy, though their specific application to adolescent P-AT remains empirically underdetermined. They are offered as a principled starting point for trial design, to be tested and refined as direct evidence becomes available.

### Caregiver factors and the family system

Low caregiver self-efficacy and high stress levels hinder recovery in children (Heath et al., 2015; Kazdin & Whitley, 2003; Mackler et al., 2015). This is partly because parents play a crucial role in supporting their children’s emotion regulation (Hughes & Baylin, 2012; Morris et al., 2017). Accordingly, interventions that address parents’ own emotional responses to caregiver stress can improve treatment outcomes

for the young person (Lafrance Robinson et al., 2016; Hibbs et al., 2015). Attention should be given to risk and protective factors within the parent-child relationship affecting symptom maintenance or resolution. Social systems’ tendency towards “homeostatic balance” (Goldenberg & Goldenberg, 2008) necessitates consideration of regulatory functions that may interfere with treatment effects.

A young person who is low in mood and socially withdrawn may become more emotionally expressive following drug administration. However, whether such changes are reinforced or extinguished, and how long they persist, will depend on their relational environment. For instance, if they are closely connected to a caregiver who harbours their own unresolved childhood issues, the young person may not receive adequate reinforcement of the positive emotional and behavioural changes associated with P-AT. Alternatively, the dynamics of the family matrix may reinforce a retreat into greater social withdrawal, particularly where such responses serve an emotionally protective function within the environment. In this way, the young person’s role as the “identified patient” in the family should evoke curiosity in the system of care about what may need to shift *interpersonally* for sustainable change to take root.<sup>4</sup> We therefore suggest that these considerations inform intake to research trials, and that systemically-directed post-trial support be prospectively available. For this population, such support may need to extend well beyond the limited, protocol-defined numbers of integration sessions seen in extant trials of P-AT (Jacobs et al., 2024).

Taken together, it is likely that young people undergoing P-AT would benefit from a semi-structured package of therapeutic support, incorporating a level of standardised psychoeducation around the effects of P-AT,

<sup>4</sup> The systems-psychological concept of the “identified patient” does not deny that adolescents experience genuine psychiatric symptoms with neurobiological correlates. Rather, it recognises that symptoms often acquire additional functions within family systems and that sustainable recovery may require attention to these systemic dynamics. An adolescent’s depression may be both a neurobiologically-mediated response to stress and a focal point around which family interactions organise. Addressing the former without attending to the latter risks incomplete recovery or relapse as systemic patterns reassert themselves.

alongside provision of individual and systemic intervention where clinically indicated. For the most part, the treatment package may follow a similar design used in adult P-AT. The principal difference is that some direct intervention with the individual's family system may be necessary to ensure the matrix is adequately prepared. As such, good clinical practice would combine standard, individual post-trial integration therapy, with additional support that also assesses and targets features of family functioning likely to affect therapeutic outcomes. Ensuring that an adolescent's matrix is conducive to recovery (or can be supported in becoming so), may increase the likelihood of lasting therapeutic integration and reduce the risk of iatrogenic harm. In Eisner's words, "[w]hen a matrix is working properly, it also becomes a process: the setting is one in which individuals can change and mature, and as they grow, the matrix expands to contain the additional growth" (Eisner, 1997, p.215).

### Assessing and strengthening family functioning

One route into assessing family functioning is through parental mentalization: the capacity to understand one's own and one's child's behaviours in terms of underlying mental states (operationalised as "reflective functioning"; see Asen & Fonagy, 2021, pp. 34-5). Parental mentalization is associated with greater sensitivity in caregiving and more secure attachment outcomes (Camoirano, 2017), as well as lower rates of internalising and externalising symptoms, and improved social-emotional competencies in children (Charpentier Mora et al., 2022; Ensink et al., 2017; Wang, 2022). Conversely, difficulties in parental mentalization are associated with impairments in children's capacities for emotion regulation (Esbjörn et al., 2013; Heron-Delaney et al., 2016). Accordingly, clinician-researchers may use frameworks like the Parental Development Interview (Slade & Sled, 2024) and the Parental Reflective Functioning Scale (Sled et al., 2020) to establish suitability. While lower parental re-

flexive functioning need not act as an exclusion criterion, it may indicate a need for more support in the socioemotional environment (Sled et al., 2024), for example, by addressing communication issues within the family to emphasise and strengthen the adolescent-caregiver relationship.

Models such as Mentalization Based Therapy for Families (MBT-F; see Asen & Fonagy, 2021) and Emotion Focused Family Therapy (EFFT; described in detail in Foroughe et al., 2018 and Lafrance et al., 2020) may be useful as shorter-term therapeutic frameworks. Both focus on addressing difficulties and identifying and enhancing strengths within the social matrix of the young person. Where MBT-F addresses family members' mentalization capacities toward improving caregiver sensitivity and thus strengthening the parent-child bond, EFFT employs a more explicit, skills-based approach to target "blocks" to the emotions or behaviours that inhibit strategy implementation. Initially developed as an adjunctive treatment for adolescents with eating disorders (Robinson et al., 2015), EFFT has been implemented for caregivers with children experiencing a wide range of mental health difficulties to good effect (Foroughe et al., 2019). Currently, the most common empirically evaluated format for EFFT delivery is a manualised 2-day multi-caregiver intensive workshop (Foroughe et al., 2019; Lafrance et al., 2020; Lafrance Robinson et al., 2016). A relatively cost-effective intervention, this can accommodate 15-25 caregivers, requiring administration from two trained facilitators (where one is a registered psychologist/psychotherapist).

Implementation of these systemic approaches would require recruiting therapists with family systems training and extending trial contact to include caregivers—modifications that increase per-participant costs. While our suggestions are based on established interventions with demonstrated effectiveness, it remains an open empirical question whether the proposed additional contact hours and modified delivery formats for adolescent P-AT

are justified by improved outcomes: increased per-participant costs may prove cost-effective if they reduce rates of non-response or relapse. Moreover, given the multi-year timescale of adolescent development, interventions that strengthen family functioning may yield benefits extending well beyond the target symptoms, justifying the additional resource allocation. These considerations underscore the importance of carefully designed economic evaluations alongside efficacy trials.

### Extrafamilial stressors

The young person and their support system should also identify social stressors outside the family (e.g., school or community issues) that may affect therapeutic outcomes. Acknowledging the role of extrafamilial stressors is relevant in any mental healthcare context, but particularly so in adolescent P-AT. Acutely sensitised to their environment following psychedelic administration, the adolescent may be at risk of second-order iatrogenic harm through unregulated exposure to environmental stressors. For most adolescents, school represents the primary extrafamilial environment, and one over which they have limited control. Liaison with schools regarding appropriate accommodations during the post-treatment period, when sensitivity to environmental stressors may be elevated, may be worth considering as part of a broader support plan. More broadly, researchers and support systems should help adolescents develop adaptive responses to these stressors, possibly requiring external support to achieve meaningful change. This may involve supporting the young person to draw upon the increased psychological flexibility following P-AT to effect a change in relationship to stressors via shifts in attention, appraisal and response (Gross, 2008).

### Evaluating a formulation-led approach

The accommodations outlined above introduce a degree of individualisation that sits in tension with the standardisation typically expected in clinical trials. A formulation-led

approach tailors assessment and intervention to the circumstances of each participant and their family system. The contrast raises a legitimate methodological concern about the possibility of rigorously evaluating such an approach. We suggest that it can, drawing on established frameworks for evaluating complex interventions in health research (Craig et al., 2008; Skivington et al., 2021; see also Muthukumaraswamy et al., 2025). These frameworks distinguish between standardising the content of an intervention (requiring uniform delivery to all participants) and standardising the decision rules: which domains to assess, what thresholds trigger additional intervention, and how clinicians should select among available responses on the basis of formulation. Under this model, fidelity means following the decision framework, rather than delivering identical content. This model has precedent in complex mental health interventions with adolescents (e.g., Fonagy et al., 2020) and is well suited to the kind of formulation-led, systemically-informed accommodations we propose. The need to optimise risk-benefit ratios in paediatric research, especially where participants face greater-than-minimal risk (Kipnis, 2003; Shaddy et al., 2010), strengthens the ethical case for accommodations that offer practical protection against avoidable adverse outcomes.

### Conclusion & Future Directions

We have argued that the pro-plasticity effects of psychedelics, combined with adolescents' limited ability to modify their social environment, create a distinctive risk-benefit profile for P-AT in this population. Though developmental psychopathology has long recognised that family and environmental factors critically shape adolescent mental health outcomes (Taubner et al., 2023; van Harmelen et al., 2016), these systemic considerations—what Eisner (1997) termed the *matrix* in psychedelic contexts—remain underemphasised in the emerging P-AT literature. A systems-psychological approach foregrounds the young person's matrix, attending to both the adolescent and the relational

environment to which they return following treatment.

This focus has implications for recruitment. Parents who wish to enrol their children into a trial of an undeniably powerful intervention like P-AT may well be experiencing high levels of distress with regard to their child's mental ill-health and difficulties accessing effective treatment. For parental consent, patient assent, and enrollment in P-AT research to be free from undue inducement, it may be advisable that initial trials focus on adolescents with moderately severe symptoms who have not yet exhausted all lines of standard treatment. This would allow safety and tolerability to be established before extending eligibility to those with more severe depression, for whom the risks of suicidality or demoralisation following non-response may be higher (Gukasyan, 2023).

We do not present these proposals as the last word in the ethical design of adolescent P-AT research. They are offered as a principled starting point, to be refined as direct evidence accumulates. Controlled, careful research with adolescents is needed to determine: (i) the optimum dose for this age group, a question made pertinent not only by biological but principally by psychological differences between adults and adolescents; (ii) the tolerance and acceptability of the drug, and the drug experience, itself; (iii) the longer-term impact on psychological outcomes and processes of meaning-making; (iv) the acceptability and perceived value of psychoeducation among family and other matrix members; and (v) the optimal balance of systemic and individual therapeutic work following drug administration.

The least intrusive P-AT intervention for adolescents, in both physiological and psychological terms, remains unknown. Studies to find the minimum effective dose, or enrichment designs that allocate participants to full-dose psychedelic or lower-dose psycholytic arms based on predicted response, deserve particular consideration (Passie et al., 2022). Computational linguistic analysis of clinical interviews shows some promise for predicting treatment response in adults (Carrillo et al.,

2018). If validated in adolescent samples, such methods could match patients to treatment intensity more precisely.

Trial design should also involve prospective patients and their parents directly (Close et al., 2021; Pavarini et al., 2019). Their perspectives are more likely to identify shortcomings than institutional ethics review alone, and their involvement strengthens the sensitivity and relevance of research that demands substantial forethought.

Expanding P-AT research to adolescents will mark a significant threshold for many researchers and clinicians. The current paper is our contribution to a—hopefully expansive—conversation about the appropriate ethical and clinical guardrails for any such crossing. A systems-psychological approach to P-AT offers a more holistic conception of the role for psychedelics in mental health treatment, and makes better targeted interventions conceivable. Systems-psychological formulation allows the clinician to think about a prospective patient (“the identified patient”) in the context of the wider social or relational system of which they are a part. In some cases, an adolescent's symptoms may be manifest in them while being partially sustained by patterns of family interaction. This is not to assign blame—such patterns typically reflect well-intentioned but inadvertently counterproductive adaptations to stress—but rather to recognise that sustainable change may require work at multiple levels of the system, for example by strengthening the family's communication and attachment resources. Addressing parental mental health needs can improve children's wellbeing (Gunlicks & Weissman, 2008). It is conceivable that, in the future, the best application of P-AT to improve mental health for some adolescents could be its judicious use in one or both parents, with post-psychedelic integration sessions involving a mix of family and individual therapy as clinically indicated. Such an approach does not represent a radical innovation: consider the MAPS trial of MDMA-facilitated cognitive-behavioural conjoint therapy in couples in which one partner had posttraumatic stress disorder

(Monson et al., 2020).

Finally, our discussion would not be complete without briefly acknowledging a broader implication of the framework we have outlined. That is, adolescents are not the only sector of society who have limited ability to modify those elements of their environments that are contributory to poor mental health. If psychedelic-enhanced plasticity amplifies sensitivity to environmental context, then the post-treatment matrix may be consequential for anyone whose environment is both adverse and resistant to individual modification. Suggestive evidence points in this direction.

Following population-level studies vaunting the value of naturalistic psychedelic use for a range of positive outcomes, it is telling that others have shown that salutary effects can be diminished, or indeed abolished, in racial minority groups and among those facing structural inequalities (Jones, 2023; Jones & Nock, 2022; Viña, 2025; Viña & Stephens, 2023). These are cross-sectional findings from naturalistic use, and their relevance to clinical P-AT remains to be established. The significance and meaning of these findings merits further research (cf. Neitzke-Spruill, 2020). Nonetheless, marginalisation in all its forms is associated with chronic stress, isolation, economic disadvantage and discrimination, factors known to negatively impact mental health. The short-term effects of P-AT may transiently alleviate a depression born of these factors. But returning patients to an environment that led to depression, in a state of heightened environmental sensitivity no less, gives no guarantee of enduring therapeutic benefit.

Psychedelics, whatever their prospective benefits, will not alone be sufficient to address deep-rooted issues affecting mental health at the societal level.

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### Ethical considerations

No ethical approval was required for this theoretical paper with no human participants.

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The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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