

Hypothesis

Transgenerational Interaction of Alzheimer's Disease with Schizophrenia through Amyloid Evolvability

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Abstract. Alzheimer's disease (AD), the most common neurodegenerative dementia, leads to memory dysfunction due to widespread neuronal loss associated with aggregation of amyloidogenic proteins (APs), while schizophrenia (SCZ) represents a major psychiatric disorder characterized by delusions, hallucinations, and other cognitive abnormalities, the underlying mechanisms of which remain obscure. Although AD and SCZ partially overlap in terms of psychiatric symptoms and some aspects of cognitive impairment, the causal relationship between AD and SCZ is unclear. Based on the similarity of APs with yeast prion in terms of stress-induced protein aggregation, we recently proposed that evolvability of APs might be an epigenetic phenomenon to transmit stress information of parental brain to cope with the stressors in offspring. Although amyloid evolvability may be beneficial in evolution, AD might be manifested during parental aging as the mechanism of antagonistic pleiotropy phenomenon. Provided that accumulating evidence implicates stress as an important factor in SCZ, the main objective of this paper is to better understand the possible connection of AD and SCZ through amyloid evolvability. Hypothetically, the delivery of information of stress by APs may be less efficient under the decreased evolvability conditions such as disease-modifying treatment, leading to SCZ in offspring. Conversely, the increased evolvability conditions including gene mutations of APs are supposed to be beneficial for offspring, but might lead to AD in parents. Collectively, AD and SCZ might transgenerationally interfere with each other through amyloid evolvability, and this could explain why both AD and SCZ have not been selected out through evolution.

Keywords: Alzheimer's disease, amyloid- β , antagonistic pleiotropy, disease-modifying therapy, evolvability, natural selection, schizophrenia, transgenerational

INTRODUCTION

At present, Alzheimer's disease (AD) remains the most common form of neurodegenerative dementia,

demonstrating progressive memory loss and cognitive and functional decline [1]. It most often occurs in those over the age of 65 years, although ~5% of all cases are due to early-onset familial mutations [2]. Although an understanding of neurodegenerative disease mechanisms has progressed remarkably, the physiological functions of amyloidogenic proteins (APs), including amyloid- β (A β) and α -synuclein (α S), are still elusive [3]. In this regard, based on

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the structural diversity of AP aggregates, we recently proposed that evolvability of APs could be defined as an epigenetic phenomenon transgenerationally transmitted to offspring to cope with the forthcoming diverse stressors in the offspring's brain (Fig. 1A) [4]. Although evolvability may be beneficial for offspring during reproductive life, it manifests during aging as neurodegeneration, possibly through an antagonistic pleiotropy mechanism (Fig. 1A) [5]. It remains obscure, however, why disorders such as AD have escaped natural selection during post-menopausal aging.

On the other hand, the neuropathological mechanisms underlying schizophrenia (SCZ), a mental disorder characterized by delusions, hallucinations, and other cognitive difficulties, remains obscure [6]. Given that SCZ typically occurs between late adolescence and the early twenties, which overlaps with the period of human reproduction and rearing of children, and because it can often be a lifelong disabling condition, SCZ may be considered evolutionarily disadvantageous [7]. Nonetheless, SCZ has not been selected out by evolution, and moreover, epidemiologically, the global prevalence of SCZ is approximately 0.2~0.5% of the population [8]. Therefore, the biological reasons as to why SCZ has not been selected out by evolution, have, to the best of our knowledge, never been adequately explained.

Since AD and SCZ often overlap in terms of various psychiatric symptoms and, to a lesser extent, in cognitive dysfunction, a similar pathogenic mechanism might be a common basis for these conditions. Given that recent study suggests that stress may play an important role in the pathogenesis of SCZ [9, 10], the main objective of this paper is to discuss the possible link of AD and SCZ through evolvability. Specifically, we hypothesize that the effects of evolvability may be differential between AD and SCZ. According to the prevailing view, A β burden may be not associated with cognitive impairment in SCZ [11, 12]. However, it was indeed shown that mice with a deletion of Disrupted-in-Schizophrenia-1 (DISC1), a familial risk factor of SCZ [13], exhibited decreased expression of A β [14]. Furthermore, we suggest that AD and SCZ may interfere with each other through evolvability during evolution. Finally, we predict that our hypothesis might provide a unique insight into therapeutic strategies for these conditions. Collectively, this framework could explain why both AD and SCZ, over evolutionary time, have persisted despite the pressures of natural selection.

CURRENT VIEW OF THE RELATIONSHIP BETWEEN AD AND SCZ

Although AD and SCZ often overlap in terms of altered behaviors, including psychiatric symptoms and cognitive impairment, the causal relationship between AD and SCZ has been yet to be clarified [15, 16].

Psychiatric symptom

Indeed, the psychiatric symptoms, such as delusions and hallucinations, represent mere symptoms that are not specific to AD and SCZ, but can be found in most neurodegenerative diseases, including Parkinson's and Huntington's diseases [17, 18]. Furthermore, these symptoms are relatively rare in AD, whereas are pathognomotic in SCZ.

Cognitive decline

AD is the main cause of dementia among the elderly, and severe cognitive impairment is also observed in elderly patients with SCZ [19]. Whereas cognitive decline represents the first and the pathognomotic symptomatology required for diagnosis of AD, cognitive decline does not represent the first nor the pathognomotic symptomatology required for diagnosis of SCZ [20]. Thus, it is important to recognize that the pattern of cognitive decline differs significantly.

In this context, aggregation and accumulation of A β are early events that precede the onset of cognitive impairment in AD [21], whereas the prevailing view is that A β burden may be not associated with cognitive impairment in SCZ [11, 12]. In support of the latter view, there was no evidence suggesting that A β levels differ in patients with SCZ from elderly control subjects or patients with other psychiatric illnesses [11], while the levels of cortical A β in patients with SCZ were lower than those in patients with AD (Fig. 2A). Furthermore, it was recently shown that there were no association between A β and cognitive impairment in SCZ [12]. Given that the previous studies were performed using small sample sizes, and A β was assessed in cerebrospinal fluid (CSF) rather than cortical region in brain, additional analyses of different brain regions may be required [12].

Notably, a limited number of studies showed that levels of CSF A β_{1-42} in elderly SCZ patients were significantly lower compared to those in healthy elders but higher than those in AD patients

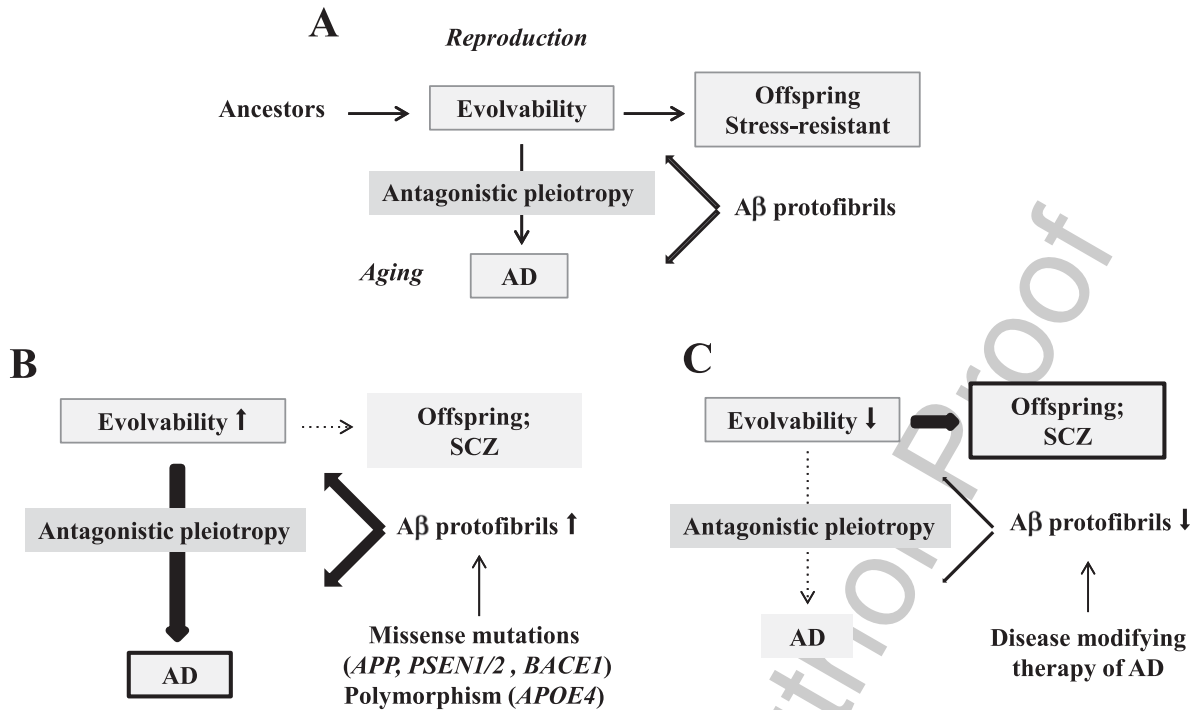


Fig. 1. Schematic of disease manifestation caused by alterations in evolvability. A) Evolvability of APs might be an epigenetic phenomenon transmitted transgenerationally to confer resistance against the stressors such as A β protofibrils in offspring during reproduction, which may be beneficial in evolution. However, evolvability might lead to AD during parental aging through the antagonistic pleiotropy mechanism. B) Increased evolvability of A β caused by missense mutations (*APP, PSEN1/2, BACE1*) and polymorphism (*APOE4*) may result in an efficient delivery of information of stresses for offspring, leading to less frequency of SCZ in offspring (thin dot line) and increased frequency of AD in parents (thick bold line). C) In contrast, inefficient delivery of the information of stresses due to decrease of A β evolvability caused by disease-modifying therapy may result in the increased frequency of SCZ in offspring (thick bold line) and the decreased frequency of AD in parents (thin dot line).

[22, 23]. Consistent with these results, it was shown that A β ₁₋₄₂ and, to a lesser extent, A β ₁₋₄₀, were reduced in the AD model mice deleted with DISC1 (Fig. 2B), suggesting that the processing of the amyloid- β protein precursor might be altered in SCZ [13, 14]. Further investigations are warranted to explore this intriguing possibility.

EMERGENCE OF CLINICAL DISEASE DUE TO ALTERED EVOLVABILITY

Accumulating evidence suggests that APs, such as A β and α S, exhibit a diversity of strains due to structural variation [24–26]. Given that APs are intrinsically disordered protein [27], it is predicted that the structural diversity of APs might correspond to diverse stresses. Furthermore, we speculate that unstable monomer of APs becomes more stable through oligomerization which are feasible for the transgenerational transmission to offspring [4]. Because the evolvability of APs may be attributed

to their protofibrillar forms [4], it is assumed that an increased level of the A β protofibrils may result, during reproduction, in increased transmission of information regarding brain stressors from parent to offspring, and in turn, promote resistance against neuronal stressors and reduce the occurrence of SCZ in offspring (Fig. 1B). However, it is also probable that the accumulation of A β protofibrils in parental brain may also lead to AD and neurodegeneration through the mechanism of antagonistic pleiotropy during aging (Fig. 1B) [5]. This scenario would be predicted based on familial early-onset AD with missense mutations, including amyloid precursor protein (*APP*), presenilin (*PSEN*) 1/2, and β -site APP cleaving enzyme (*BACE*) 1 [28–30], and for polymorphism of *APOE4* [31].

What then might be the consequence of reduced evolvability of A β during reproduction? Because reduced information on forthcoming stressors from parental brain is available to be delivered to offspring, an increased vulnerability to stressors may lead to

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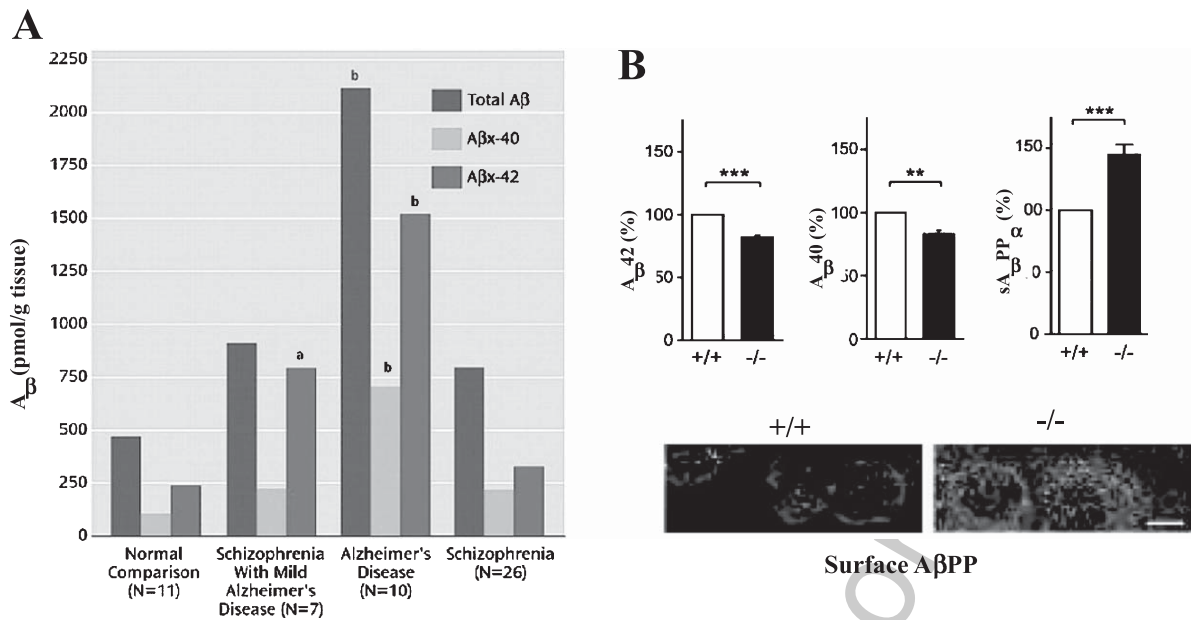


Fig. 2. Alteration of A β expression in SCZ. A) Mean postmortem levels of total A β , A β_{x-40} , and A β_{x-42} in the dorsolateral prefrontal cortex of normal elderly comparison subjects, patients with AD, patients with SCZ only, and patients with SCZ plus mild AD pathology. ^aSignificantly different from all other groups (Newman-Keuls tests, $p < 0.01$). ^bSignificantly different from all other groups (Newman-Keuls tests, $p < 0.001$). Reprinted from Religa et al. [11] with permissions. B) A β PP processing is dysregulated in DISC1 locus mutants of 3XTg mice. Loss of DISC1 in homozygous DISC1 locus impairment (-/-) mice leads to alteration of A β PP processing, compared to wild-type (+/+) controls. a-c) Analysis of cortical lysates by ELISA shows increased sA β PP α and decreased A β_{42} and A β_{40} levels in -/- mice. Bars represent the mean \pm SEM, $n = 5-6$ mice per group. ** $p < 0.01$, *** $p < 0.001$. d) Neurons from -/- mice display higher levels of surface A β PP than those from +/+ mice. Scale bar, 10 μ m. Reprinted from Shahani et al. [14] with permission.

neuronal toxicity, dysfunction and perhaps a pathologic phenotype in offspring. On the other hand, such reduced action of evolvability might inversely reduce the risk of AD and neurodegeneration (Fig. 1C). Such inverse relationships could also apply to a number of developmental brain disorders, including autism spectrum disorder, epilepsy, and psychiatric diseases, such as SCZ, whose precise etiologies are yet to be determined [32]. Notably, it was previously shown that mice with knockdown/deletion of DISC1, a genetic risk factor for a wide range of mental disorders, including SCZ, major depression, and bipolar disorders [13], exhibited altered processing of A β PP and reduced A β production in mouse brain (Fig. 2) [14], consistent with our concept that evolvability through A β protofibrils might be decreased in the setting of SCZ.

Interaction of parental AD and SCZ in offspring through evolvability

Our hypothesis suggests that the presence of AD in aging parents might transgenerationally interact with the occurrence of SCZ in their offspring (Fig. 3).

Given that APs are intrinsically disordered protein [27], it is predicted that the structural diversity of APs might correspond to diverse stresses. Furthermore, it is speculated that unstable monomer of APs becomes more stable through oligomerization which are feasible for the transgenerational transmission to offspring [4].

Because the transmission of APs may confer information regarding stressors from parental brain, evolvability of AP protofibrils should be beneficial for offspring. Therefore, AD should be inevitable at the point at which minimum evolvability is required to reduce the risk of SCZ in offspring (*Emin*). Since evolvability may be beneficial for offspring, it gradually increases until incident AD occurs increasingly early, prior to the postmenopausal period in humans, which then would interfere with reproduction and contravene the law of natural selection. Accordingly, evolvability should also demonstrate a maximal point (*E_{max}*) in which SCZ incidence is markedly reduced to a low level, but does not reach zero. Based on the epidemiological data in which the risk of SCZ currently is estimated to be $\sim 0.5\%$ [33], while that of AD is approximately $\sim 20\%$ [34], the activity of

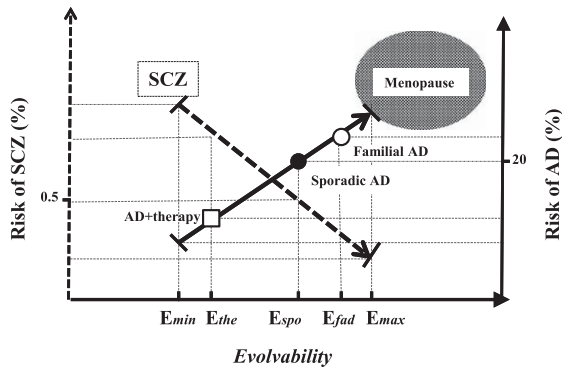


Fig. 3. Schematic representation of the reciprocal transgenerational relationship between AD and SCZ through evolvability. Given that transmission of APs may confer the information on stressors from parental brain, resulting in suppression of SCZ, evolvability of the APs protofibrils would be beneficial for offspring. Therefore, AD would be inevitable in which the minimum of evolvability is required to reduce the risk of SCZ in offspring (*Emin*). The activity of evolvability may gradually increase, but AD is not manifested earlier before the postmenopausal period because of the law of natural selection. Accordingly, it is predicted that evolvability has a maximal point (*Emax*) in which the incidence of SCZ is compromised. Currently, the epidemiological data suggest the risk of SCZ is estimated to be 0.2~0.5% [33], while the risk of AD is approximately ~20% (*Ecurr*) [34]. It is suggested that the activity of the evolvability derived from familial AD should be higher than that derived from sporadic AD, being closer to *Emax* (*Efad*), and foretells that the incidence of SCZ among familial AD should be below the average. In contrast, the activity of evolvability might be decreased in AD patients treated with disease-modifying therapy (*Edmt*), in which the risk of SCZ in offspring might be increased. Thus, it is theoretically predicted that parental AD and SCZ in offspring might exist in a reciprocal relationship through evolvability. ●: Current average of sporadic AD, ○: familial AD, □: AD patients treated with disease-modifying therapy.

evolvability corresponding to sporadic AD may be situated between *Emin* and *Emax* (*Espor*). Extrapolation of this concept would predict that the level of evolvability activity derived from familial AD (*Efad*) due to missense gene mutations such as *APP*, *PSEN1/2*, and *BACE1*, should be higher than *Espor* and closer to *Emax*. At the point of *Efad*, the incidence of SCZ in the familial AD cohort is predicted to be below the observed average. In contrast, as described later, the activity of evolvability might be reduced if AD were treated with an effective disease-modifying therapy at the prodromal stage (*Ethe*), where the risk of SCZ in offspring might be increased. In other words, theoretically, parental AD and SCZ in their offspring might exist in a relative inverse relationship through evolvability. Thus, regulated or constrained activity of evolvability might account for the observed incidences of AD and SCZ, as well as their resistance against the constant pressures of evolution. It follows that factors influencing the

activity of evolvability, which have been discussed previously but remain unclear, may be important in common disease pathogenesis of AD and SCZ [4].

Although SCZ is clinically heterogeneous [35], the precise mechanism remains poorly understood. In this regard, different SCZ subtypes might be in part associated with other APs and their evolvability states. Certainly, it is well known that other forms of aging-associated neurodegenerative diseases, aside from AD, are accompanied by psychiatric behaviors. Naturally, it is predicted that SCZ may be similarly affected by the evolvability of these APs. For instance, α -synucleinopathies, such as Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy, are characterized by motor- and non-motor symptoms which may be derived from evolvability of α S. Because neurodegenerative disorders such as AD and α -synucleinopathies are manifested during postmenopausal senescence, which is a human-specific phenomenon by virtue of the absence of natural predators and abundant nutritional security [5], it is plausible that transgenerational relationships between parental neurodegenerative disease and SCZ in offspring has emerged relatively recently in evolutionary history.

However, a unique situation with regards to AP evolvability may exist for Huntington's disease and other polyglutamine (polyQ) diseases. Since disease onset appears prior to menopause, it is possible that evolvability of polyQ might be less potent than those of other APs, such as A β and α S. Indeed, the psychiatric symptoms associated with polyQ diseases, often paranoia, have less resemblance to SCZ and are perhaps less prominent compared to those in other neurodegenerative conditions, including AD and α -synucleinopathies [36]. Based on the expression of polyQ in microorganisms and plants [37, 38], it is predicted that polyQ may be more primitive relative to other APs across evolution, and might play an important role for the evolution of amyloidgenic evolvability [39]. Thus, it is tempting to speculate that the old prototype of SCZ could be observed in the polyQ evolvability.

Indeed, biological evidence exists which might support this view. For instance, various senescent features are rapidly induced in the spawning salmon, including brain amyloid deposition, which has been known as the "salmon model of AD" [40]. In this situation, the demise of parents due to AD may in turn be beneficial for offspring by ensuring availability of nutrition. Furthermore, in "the grandmother effect," the rearing of grandchildren by a grandmother

300 experiencing post-menopausal aging may benefit
301 their daughter(s) who can birth further children [41],
302 suggesting that aging can evolve as beneficial for off-
303 spring. Although aberrant behaviors in AD are clearly
304 not beneficial for offspring, it is probable that the
305 pathology of AD might be beneficial for offspring
306 indirectly through evolvability. Indeed, such a novel
307 concept may be worthy of further investigation.

308 THERAPEUTIC IMPLICATIONS

309 If this theoretical framework proves correct, then
310 a critical issue will be reduced evolvability of APs
311 connected to the treatment of neurodegenerative
312 disorders with disease-modifying therapies during
313 prodromal disease stages. Regarding the progress
314 of disease-modifying therapies for AD, contrary
315 to the positive preclinical findings, the results of
316 active amyloid immunotherapy for this condition
317 in early-stage clinical trials have been disappoint-
318 ing and accompanied by serious complications, such
319 as meningoencephalitis [42]. Subsequent focus on
320 passive AD immunotherapy using anti-A β mono-
321 clonal antibodies has also not fully demonstrated
322 therapeutic efficacy [3]. The phase III clinical trial
323 (NCT02008357; patients of 55–90 years old), for
324 instance, failed to demonstrate reproducible effi-
325 cacy [43], and, on a cautious note, it was recently
326 reported that an ongoing early phase II trial using the
327 anti-protofibrillar A β antibody, BAN2401 by Eisai,
328 Inc./Biogen, Inc. in mild cognitive impairment and
329 early AD patients, demonstrated non-futility, but lit-
330 tle cognitive improvement at 18 months [44]. Still,
331 the need exists for even earlier intervention in the dis-
332 ease course [3]. As such, secondary prevention trials
333 such as Dominantly inherited Alzheimer Network-
334 Trial Unit (DIAN-TU) (NCT01760005; patients of
335 18 years and older) have already started to assess
336 the potential of new protocols [45, 46] to prevent
337 the disease progression in autosomal-dominant AD
338 individuals without cognitive dysfunction and in
339 cognitively healthy subjects at risk of developing spo-
340 radic AD [45].

341 Again, a key point is that if intervention using
342 disease-modifying therapies during prodromal AD
343 becomes a reality, such treatment may alter the
344 pace of evolvability during the reproductive time of
345 life. It follows that passive immunotherapy using
346 anti-A β monoclonal antibodies could suppress evolva-
347 bility, leading to the compromised resistance against
348 stressors in the brains of offspring. Thus, it is
349 imperative that such potential risks of therapeutic

350 intervention must be considered to establish working
351 disease-modifying therapy in AD.

352 The current hypothesis also provides an impor-
353 tant insight into potential therapeutic strategies for
354 SCZ. Despite significant advances in SCZ pharma-
355 cotherapy [47], treatment remains suboptimal, with
356 many patients having persisting deficits, especially in
357 cognitive and social functioning [48, 49]. Given the
358 differential effects of evolvability on AD and SCZ,
359 one might propose that stimulating the evolvability of
360 relevant APs might significantly reverse such evolva-
361 bility deficits, and improving clinical efficacy for
362 patients. To achieve this, we propose upregulating
363 APs, either directly or indirectly. As for direct upreg-
364 ulation, A β or its derivative could be administered,
365 although side effects such as meningoencephalitis
366 may be a limiting factor based on the previous com-
367 plications of active A β immunotherapy in AD [42].
368 Alternatively, augmenting the synthesis and/or secre-
369 tion of A β might be more effective, where a DISC1
370 knockout mouse model may be an ideal tool to
371 achieve this. A major drawback, however, to using
372 the DISC1 knockout mouse model to demonstrate
373 the above, would be the markedly truncated post-
374 menopausal senescent period in rodents relative to
375 humans [5]. Furthermore, caution must be exercised
376 to the possibility that AD risk might be increased in
377 offspring in the future in either case. Taking consid-
378 eration, however, that protein degradation systems,
379 such as autophagy and ubiquitin proteasome system,
380 are more robust in younger individuals compared to
381 the elderly [50], further exploration of these interest-
382 ing possibilities is warranted.

383 CONCLUSION

384 Currently, no definite conclusions have yet been
385 reached as to the causal relationship between AD
386 and SCZ. As described above, our concept of evolva-
387 bility may provide one plausible explanation for
388 this. To summarize, parental AD and SCZ in off-
389 spring may transgenerationally interact with each
390 other, which may explain why AD and SCZ have
391 not been selected out through evolutionary natural
392 selection. Our current hypothesis, although fascinat-
393 ing, requires a demonstration of the involvement of
394 protofibrils of APs in evolvability.

395 Recently, a number of gene-based studies in
396 SCZ, such as genome-wide association studies, and
397 the mapping of several regions have extensively
398 been performed and have led to the identifica-
399 tion of a number of putative susceptibility genes,

including DISC1, neuregulin-1, dysbindin, and catechol-o-methyltransferase [51–54]. In particular, neuregulin-1 has been identified as a β -secretase substrate, suggesting a link between SCZ and AD [55]. At present, however, no single gene has been demonstrated to be sufficient to result in the SCZ phenotype alone, emphasizing the multifactorial nature of this condition. Although still controversial, the current dominant view of SCZ falls under the ‘common disease-common variant’ hypothesis, suggesting that the genetic component to most common disorders is due to a relatively large number of disease-causing alleles that occur relatively often in the population [56–58]. It is particularly interesting to note that AD with psychosis is associated with polygenic risk for a set of novel loci related to endosomal trafficking, autophagy, and calcium channel signaling, which is inversely associated with polygenic risk for SCZ [59]. Together with the current hypothesis, we suggest that both genetic and epigenetic mechanisms may cooperate in the pathogenesis of SCZ. Thus, a better understanding of the interaction of AD in parents and SCZ in offspring may potentially shed light on novel therapies for both AD and SCZ.

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