Behavioural genetics of Alzheimer's disease: a comprehensive review

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Abstract

Behavioural and psychological symptoms of dementia (BPSD) are present in the course of the illness in up to 90% of patients with Alzheimer's disease (AD). They are the main source of caregiver burden and one of the major factors contributing to early institutionalization. The involvement of a genetic component in BPSD aetiology seems beyond controversy, though the exact significance of particular polymorphisms is uncertain in the majority of cases. Multiple genes have been assessed for their putative influence on BPSD risk. In this paper we review the behavioural genetics of AD, particularly the importance, with respect to BPSD risk, of genes coding for apolipoprotein E and proteins involved in the process of neurotransmission: serotonin receptors, serotonin transporter, COMT, MAO-A, tryptophan hydroxylase and dopamine receptors. A general conclusion is the striking inconsistency of the findings, unsurprising in the field of psychiatric genetics. The potential reasons for such discrepancy are exhaustively discussed.

Key words: Alzheimer's disease, behavioural disturbances, behavioural and psychological symptoms of dementia, genetics, polymorphisms.

Introduction

Dementing disorders can usually be characterized by impairments in cognition and behaviour with resulting subsequent decline in activities of daily living (ADL). In the more advanced stages cognitive function disturbances are usually accompanied by mood disorders, anxiety, apathy, dysphoria, psychotic symptoms (delusions, hallucinations), aggression or agitation. These symptoms, alongside other behavioural disturbances (wandering, inappropriate sexual behaviours), are often clustered together as behavioural and psychological symptoms of dementia (BPSD). In the course of the illness BPSD can be present in as many as 60-98% of demented individuals, with an average of around 80% in subjects with Alzheimer's disease (AD) [1]. The presence of BPSD, as an exponent of the more aggressive disease course, is usually followed by particularly significant prognostic implications: a more rapid decline in both cognitive functions and ADL [2], increased mortality [3] as well as early institutionalization of individuals with AD [4]. The dramatic functional decline of the patients leading to autonomy loss and rapidly progressive caregiver dependence is much more a consequence of peracute psychiatric pathology rather than cognitive impairment *per se*. The presence of BPSD

and consequently the patient's lack of self-containment are also the main sources of caregiver burden and major contributors to the increased prevalence of depression in this population [5]. In the context of the clinical, economical and social significance of BPSD, discovering mechanisms implicated in their pathogenesis is among the top-priority challenges of modern old-age psychiatry. However, our knowledge on the aetiology of these symptoms is still incomplete. Behavioural and psychological symptoms of dementia have been hypothesized to be caused by unmet needs (for example, needs for social contact, activity, relief of pain, or hunger), by the inability of the patient to communicate those needs, and by the inability of the environment to meet those needs [6]. Biological theories have focused on the role of various neurotransmitter systems, including serotonin [5-HT] (aggression, depression, anxiety, psychosis) [7], dopamine [DA] (aggression, psychosis) [8], norepinephrine [NA] (aggression) [9], acetylcholine [ACh] (psychosis, apathy) [10] and γ-aminobutyric acid [GABA] [11]. Neurochemical BPSD theories have led to pharmacological treatments targeting specific neurotransmitters [12]. A wealth of evidence (although conflicting at times) associates behavioural symptoms with the progression of neuropathological changes [13], abnormalities seen in neuroimaging procedures [14], or the results of electrophysiological studies [15]. Furthermore, there are accruing data on the association between genetic factors and behavioural abnormalities in AD. In this paper we review the available evidence on the behavioural genetics of AD.

Behavioural genetics of Alzheimer's disease

One of the most popular hypotheses regarding genetic risk factors states that common complex disorders, besides the small proportion of familial cases with known causative mutations, are governed by DNA variants prevalent in the general population [16]. These variants, such as single nucleotide polymorphisms (SNPs), tend to increase disease risk but are insufficient to actually cause a specific disorder. Unfortunately, a typical feature of gene polymorphisms is their relatively weak effect. It is therefore quite common to be confused by conflicting results of published reports, some of them demonstrating risk-conferring or protective properties of a particular allele, others showing no effect whatsoever. To overcome the potential sources of bias discussed below, a meta-analytic approach has been proposed. Single nucleotide polymorphisms might not only affect the risk of developing the disease, they may also have an impact on particular disease phenotypes or treatment results. The involvement of a genetic component in BPSD aetiology seems beyond controversy, though the exact significance of particular polymorphisms is uncertain in the majority of cases. Multiple genes, coding for proteins involved in various neurotransmitter systems, have been assessed for their putative influence on BPSD risk. Due to significant clinical and aetiological diversity of symptoms typically ascribed to the BPSD construct, in research it is usually broken down into isolated behavioural symptoms or behavioural clusters (e.g. psychosis, apathy, disinhibition, etc.). In the following paragraphs the results of studies assessing the putative contribution of genetic variants to BPSD aetiology in AD will be reviewed.

Search strategy

PubMed and other databases accessible at our University (Blackwell Synergy, EbscoHost, Karger, Ovid, Proquest and Science Direct) were browsed through using multiple queries built from words such as Alzheimer, polymorphism, gene, behaviour/behavioural, BPSD, and specific behavioural symptoms, for example psychosis, delusions, hallucinations, aggression, depression, anxiety, etc., used in various combinations. Query results were examined in the search for relevant papers on BPSD genetic background. The selected papers were then manually reviewed to look for additional references.

Apolipoprotein E

The apolipoprotein E (ApoE) locus is located on the long arm of chromosome 19. The three most common SNPs in the APOE gene lead to changes in the coding sequence and result in three common isoforms of apoE: apoE2 (cys112, cys158), apoE3 (cys112, arg158), and apoE4 (arg112, arg158); although they differ by single amino acids, these differences profoundly alter apoE structure and function. The apolipoprotein E plays a key role in lipoprotein metabolism and cholesterol transport in plasma and the nervous system. To date, it is the only unanimously accepted genetic risk factor for the development of sporadic AD. It has been documented that harbouring the ε4 allele dose-dependently increases the risk of developing AD; it is also associated with an earlier age at onset – subjects homozygous for ApoE ε4 almost always develop AD by the age of 80 [17]. ApoE is a molecule implicated in all the biochemical disturbances characteristic of AD: β-amyloid (Aβ) aggregation, deposition and clearance, neurofibrillary tangle (NFT) formation, neurotoxicity, neuroinflammation, loss of synaptic plasticity, and cholinergic dysfunction [18].

The genetic significance of ApoE inspired research on its potential association with the

psychiatric manifestations of AD – psychosis, depression, aggression, anxiety. We have identified 37 studies evaluating this concept [19-55]. The results of these studies are summarized in Table I. The initial conclusion that could be drawn is the striking inconsistency of the findings; yet this is unsurprising in the field of psychiatric genetics. Regardless of the BPSD symptoms studied, the ε4

Table I. Studies on the association between ApoE genotype and BPSD in AD (positive results in bold)

Reference	No. of participants	Effect of ApoE genotype on BPSD
Lehtovirta *et al.*, 1996 [19]	58	No effect of genotype on psychosis or depression
Ramachandran *et al.*, 1996 [20]	**46**	**ε4 increases risk for psychosis and depression**
Holmes *et al.*, 1996 [21]	**164**	**ε2 increases risk for depression**
Holmes *et al.*, 1997 [22]	**232**	**ε2 increases risk for depression**
Holmes *et al.*, 1998 [23]	**210**	**ε2 increases risk for depression and delusions**
Ballard *et al.*, 1997 [24]	**51**	**ε4 increases risk for psychosis, lowers risk for depression**
Cacabelos *et al.*, 1997 [25]	207	No effect of genotype on behavioural disturbances
Cantillon *et al.*, 1997 [26]	162	No effect of genotype on depression
Forsell *et al.*, 1997 [27]	184 (out of 806 studied)	No effect of genotype on depression
Forsell *et al.*, 1998 [28]	225 (out of 668 studied)	No effect of genotype on psychosis
Lopez *et al.*, 1997 [29]	194	No effect of genotype on psychotic symptoms
Lyketsos *et al.*, 1997 [30]	120	No effect of genotype on psychosis or depression
Murphy *et al.*, 1997 [31]	**77**	**ε4 increases risk for behavioural disturbances**
Hirono *et al.*, 1998 [32]	228	No effect of genotype on psychotic symptoms
Hirono *et al.*, 1999 [33]	175	No effect of genotype on behavioural disturbances
Harwood *et al.*, 1999 [34]	**501**	**ε4 increases risk for psychosis**
Levy *et al.*, 1999 [35]	605	No effect of genotype on behavioural disturbances
Weiner *et al.*, 1999 [36]	**97**	**ε4 marginally associated with delusions and hallucinations**
Gabryelewicz *et al.*, 2002 [37]	139	No effect of genotype on behavioural disturbances
Scarmeas *et al.*, 2002 [38]	**87**	**ε4 increases risk for delusions**
Sweet *et al.*, 2002 [39]	316	Genotype does not predict time to onset of psychosis
Chang *et al.*, 2004 [40]	**135**	**ε4 increases risk for psychosis**
Craig *et al.*, 2004 [41]	**400**	**ε4 increases risk for agitation/aggression**
Craig *et al.*, 2005 [42]	404	No effect of genotype on depression
Robertson *et al.*, 2005 [43]	**125**	**ε4 increases the level of anxiety**
Borroni *et al.*, 2006 [44]	234	No effect of genotype on psychosis
Borroni *et al.*, 2006 [45]	232	No effect of genotype on behavioural disturbances
Craig *et al.*, 2006 [46]	426	No effect of genotype on sleep disruption
Engelborghs *et al.*, 2006 [47]	186	No effect of genotype on behavioural disturbances
Spalletta *et al.*, 2006 [48]	**171**	**ε4 increases risk for delusions**
Pritchard *et al.*, 2007 [49]	388	ε4 increases level of anxiety. No effect of genotype on behavioural disturbances after correction for multiple testing
Sobow *et al.*, 2007 [50]	**44**	**ε4 increases risk for delusions and agitation/aggression**
Zdanys *et al.*, 2007 [51]	**266**	**ε4 increases risk for psychosis**
Borroni *et al.*, 2009 [52]	264	No effect of genotype on depression
Grünblatt *et al.*, 2009 [53]	72	No effect of genotype on depression
Quaranta *et al.*, 2009 [54]	148	No effect of genotype on psychosis
Woods *et al.*, 2009 [55]	36	ε4 increases mean behavioural scores in nursing home patients

allele has been found to increase the risk for a given behavioural pathology by some authors (with an obvious notion that it might somehow be involved in the pathogenesis of the symptoms), while others found the ApoE genotype insignificant in this regard. In a recent study by our group performed in a population of carefully selected AD subjects (very stringent inclusion and exclusion criteria to increase the homogeneity of the participants) ApoE ε4 carriers had a 7-fold increased risk for exhibiting delusions and 4.5-fold increased risk for agitation/aggressive behaviours [50]. The potential explanations of these discrepancies will be discussed in a separate paragraph, as they are largely independent of the particular polymorphism studied.

The mechanism by which ApoE may increase the risk for BPSD is unclear. ApoE has been shown to promote the deposition of neuropathological features of AD – Aβ plaques and NFTs [18]. There are reports associating the degree of AD pathology with behavioural symptoms, e.g. NFT burden, particularly in the anterior cingulate, with agitation [56] or apathy [13]. ApoE4 AD carriers show a more profound loss in cholinergic activity in the hippocampus and the cortex [18]; decreased acetylcholine levels have in turn been implicated in the pathogenesis of BPSD [10]. In neuroimaging studies the presence of the ApoE ε4 allele was associated with a greater rate of hippocampal, cortical and whole-brain atrophy [57], while a link between atrophy, hypoperfusion or hypometabolism of various brain structures and BPSD symptoms has repeatedly been demonstrated [58, 59].

Serotonin receptors

Genes involved in neurotransmitter systems are usually considered one of the primary choices in candidate-gene association studies in psychiatric genetics, as the neurochemicals and their receptors are also targets for treatment of psychiatric disorders (including BPSD). Strong evidence supports the presence of a substantial disruption in global serotonergic neurotransmission in dementia. *In vitro* and *in vivo* studies provide evidence (although inconsistent) to link 5-HT dysfunction with aggressive behaviours, psychotic symptoms, anxiety and depression in AD [7]. The actions of 5-HT are mediated by 14 distinct subtypes of receptors [60]. Polymorphic variations in serotonergic receptors have already been implicated in the pathogenesis of many psychiatric ailments, including schizophrenia, mood disorders, anxiety disorders and eating disorders [61]. Two of these receptors, 5-HT_{2A} and 5-HT_{2C}, have also been examined as possible susceptibility factors for various BPSD symptoms in AD. We have identified 11 studies evaluating the role of 5-HT_{2A} T102C polymorphism [62-72] and 4 studies on cys23ser polymorphism in 5-HT_{2C} [62, 64, 66, 71], as well as one study on 5-HT_6 [73] in the pathogenesis of BPSD. The results of the studies are summarized in Table II.

Carrying the C allele of the 5-HT_{2A} T102C SNP was associated with psychosis [62, 63, 65, 67], agitation [67], apathy [67], aberrant motor behaviour [67] and depression [64], while possession of the T allele was found to be associated with delusions [66], agitation [66], and depression [65]. According to the most recent of papers, T allele carriers could also suffer from diminished antipsychotic efficacy of second generation antipsychotics [72]. However, 4 large recent studies – contrary to all others – found no significant associations of this polymorphism with psychosis, depression, or any behavioural disturbances [68-71] (although in the latest one, distortions in allele frequencies were observed, with a similar, albeit insignificant increase of the C allele in the BPSD group [71]). No biologically plausible explanation of the discordant findings has been proposed as yet. T102C is a synonymous (silent) change with no consequence for the amino acid sequence. The gene, however, is highly polymorphic and this polymorphism may be in linkage disequilibrium (LD) with other SNPs in the gene – potential true susceptibility variants – such as the –1438 G/A promoter polymorphism or the His452Tyr polymorphism. Some conflicting reports could stem from different LD patterns in the evaluated cohorts. Whilst synonymous SNPs have no direct consequences for the protein structure, their importance should not be discounted. The T102C polymorphism might predispose AD patients to various BPSD phenomena via altering gene transcription, RNA stability, editing or splicing, or translational efficiency, or it may influence the post-translational modification of 5-HT_{2A} [61]. The C allele of the T102C variation seems to be associated with reduced 5-HT_{2A} receptor densities in brain tissues (the temporal cortex in particular) [74], a finding typical for AD itself as well. This could lead to worse dopaminergic modulation mediated by the serotonergic system and – taken together with the dopaminergic hypothesis of psychosis – might putatively be responsible for the association of this genetic variant with the psychotic spectrum [75].

The serine allele of the cys23ser polymorphism of the 5-HT_{2C} gene has previously been found to be associated with hallucinations [62], hyperphagia (in females only) [62], and depression [64]. In the most recent study by Pritchard *et al.*, the same C allele was significantly associated with anxiety in females; however, the effects of C allele-containing genotypes (CC and GC) did not reach statistical significance [71]. 5-HT_{2C} is one of the pivotal

Table II. Studies on the association between 5-HT receptor genotype and BPSD in AD (positive results in bold)

Reference	No. of participants	Effect of 5-HT receptor genotype on BPSD
	5-HT$_{2A}$ receptors (T102C polymorphism)	
Holmes *et al.*, 1998 [62]	**211**	**C allele increases risk for hallucinations**
Nacmias *et al.*, 2001 [63]	**275**	**CC genotype and C allele increase risk for psychosis**
Holmes *et al.*, 2003 [64]	**158**	**CC and TT genotypes increase risk for depression**
Rocchi *et al.*, 2003 [65]	**135**	**CC genotype increases risk for psychosis**
Assal *et al.*, 2004 [66]	**96**	**T allele increases risk for delusions and agitation/aggression**
Wa Lam *et al.*, 2004 [67]	**87**	**CC genotype increases risk for delusions, agitation, apathy and aberrant motor behaviour**
Micheli *et al.*, 2006 [68]	208	No effect of genotype on depression
Craig *et al.*, 2007 [69]	406	No effect of genotype on psychosis
Wilkosz *et al.*, 2007 [70]	324	No effect of genotype on time to psychosis onset or depression
Pritchard *et al.*, 2008 [71]	393	No effect of genotype on behavioural disturbances (increase in CC genotype and C allele in psychosis, not significant)
Angelucci *et al.*, 2009 [72]	**80**	**T allele increases risk for delusions and treatment-resistance to second generation antipsychotics**
	5-HT$_{2C}$ receptors (cys23ser polymorphism)	
Holmes *et al.*, 1998 [62]	**211**	**C allele increases risk for hallucinations and hyperphagia (in females)**
Holmes *et al.*, 2003 [64]	**158**	**CC genotype increases risk for depression**
Assal *et al.*, 2004 [66]	96	No effect of genotype on behavioural disturbances
Pritchard *et al.*, 2008 [71]	**394**	**C allele increases risk for anxiety in females**
	5-HT6 receptors	
Liu *et al.*, 2001 [73]	145	No effect of genotype on depression

serotonin receptors highly expressed in multiple brain areas. On a general level it is one of the key elements of the serotonergic inhibitory modulation of the dopaminergic tone, playing a crucial role in a wide range of psychiatric disorders, as diverse as eating disorders, anxiety and mood disorders (which could provide a rationale for the aforementioned results of AD-BPSD studies), and addiction, as well as influencing antipsychotic efficacy and side effects [76]. Unfortunately, the biological relevance of 5-HT$_{2C}$ for psychiatric phenotypes is contradictory to the poor, inconsistent results obtained by genetic investigations. Apart from the incomplete coverage of the gene, with the above described possibility of an LD with yet undiscovered pathogenetically influential SNPs, and some universal pitfalls described in detail in a later paragraph, there are other intriguing confounding factors unique to the 5-HT$_{2C}$ gene and receptor protein, often called "the fine-tuning machinery". These include the modulatory influences of 5-HT$_{2C}$-expressing glutamatergic and GABAergic interneurons exerting regionally specific, frequently different actions, as well as complicated 5-HT$_{2C}$ receptor mRNA editing patterns that can modify its affinity for the binding of serotonin and its efficiency to activate the second messenger cascade [77]. Via a specific editing profile the machinery will probably counteract the effects of genetic variations – more efficiently in some subjects, completely blunting the genetic background, reducing the penetrance of mutations, and making most investigations underpowered, but less efficiently in other subjects, to the point that the variation in the HTR2C turns out to be sufficiently relevant to be associated with a psychiatric disorder [76].

Serotonin transporter

The 5-HT transporter (5-HTT) is central to the control of brain 5-HT neurotransmission by regulating the magnitude and duration of the serotonergic response through the reuptake of 5-HT at the synapse. Furthermore, 5-HTT is a target for several types of pharmacological interventions in psychiatric disorders (e.g. SSRIs). Investigations of possible associations between 5-HTT and BPSD have produced inconsistent findings. Two different variable number tandem repeats (VNTR) polymorphisms in the *SERT* gene (located on chromosome 17q) have been examined in this context; the results are summarized in Table III.

Table III. Studies on the association between 5-HT transporter genotype and BPSD in AD (positive results in bold)

Reference	No. of participants	Effect of 5-HT transporter genotype on BPSD
LPR (linked polymorphic region)		
Li *et al.*, 1997 [79]	196	No effect of genotype on depression
Sukonick *et al.*, 2001 [80]	**137**	**L allele and LL/LS genotypes increase risk for aggression**
Sweet *et al.*, 2001 [81]	**332**	**L allele and LL/LS genotypes increase risk for psychosis and aggression**
Rocchi *et al.*, 2003 [65]	135	No effect of genotype on psychosis
Assal *et al.*, 2004 [66]	96	No effect of genotype on behavioural disturbances
Ha *et al.*, 2005 [82]	65	No effect of genotype on delusions and aggression
Borroni *et al.*, 2006 [44]	**234**	**SS genotype and S allele increase risk for psychosis**
Borroni *et al.*2006 [45]	**232**	**LL genotype decreases risk for "psychosis" endophenotype**
Micheli *et al.*, 2006 [68]	208	No effect of genotype on depression
Pritchard *et al.*, 2007 [83]	**367**	**L allele increases risk for irritability. No effect of genotype on behavioural disturbances after correction for multiple testing**
Ueki *et al.*, 2007 [84]	200	No effect of genotype on behavioural disturbances
Albani *et al.*, 2009 [85]	235	No effect of genotype on behavioural disturbances
Grünblatt *et al.*, 2009 [53]	72	No effect of genotype on depression
Quaranta *et al.*, 2009 [54]	**148**	**L allele increases risk for psychosis in a dose-dependent fashion**
STin2 VNTR (variable number of tandem repeats)		
Li *et al.*, 1997 [79]	196	12-repeat allele non-significantly ($p = 0.07$) associated with depression
Assal *et al.*, 2004 [66]	96	No effect of genotype on behavioural disturbances
Pritchard *et al.*, 2007 [83]	**367**	**10-repeat allele increases risk for psychosis. No effect of genotype after correction for multiple testing**
Ueki *et al.*, 2007 [84]	**200**	**10-repeat allele increases risk for behavioural disturbances and aggression**

Firstly, there is a functional polymorphism in the 5-HTT gene-linked polymorphic region (5-HTTLPR); the long (L) and short (S) alleles are defined by differing numbers of a 44-base pair repetitive sequence. The homozygous S/S genotype has been associated with an increased risk of unipolar and bipolar depression, anxiety, substance abuse, and a predisposition to suicide or depression following stressful life events [78]. Conversely, the homozygous L/L genotype was associated with a predisposition to obsessive-compulsive disorder (OCD) and increased intensity of hallucinations in individuals with schizophrenia [78]. In AD, 5-HTTLPR polymorphism has been evaluated in 14 studies [44, 45, 53, 54, 65, 66, 68, 79-85]. Eight of them proved negative, finding no association whatsoever. Even in the remaining six, the results are conflicting. Four papers, in accordance with the preclinical BPSD aetiological hypotheses suggesting a lower level of synaptic 5-HT, demonstrated a detrimental effect of the L allele on aggression, psychosis, and irritability in AD patients [54, 80, 81, 83]. In one of the studies, however, the result did not remain significant after correction for multiple testing [83]. The putative association between 5-HT depletion and psychosis could further be strengthened by the demonstrated efficacy of a selectively serotonergic antidepressant – citalopram – in the treatment of psychotic disturbances in demented individuals [86]. In contrast, Borroni *et al.* in 2 other studies observed an association between the S allele and SS genotype with psychotic symptoms in AD, and a protective effect of the LL genotype against "psychotic" endophenotype (described above) [44, 45]. The authors provide no attempt to explain these observations on a biological basis. However, in a recent meta-analysis, the S allele carriers demonstrated significantly greater amygdala activation in response to neutral environmental stimuli when compared to the L allele harbouring subjects, providing an indirect clue for the comprehension of the S allele's involvement in BPSD pathogenesis [87].

The numerous studies aiming to reveal associations between polymorphisms in the 5-HTT gene and various behavioural traits are based on the assumption that these polymorphisms, or polymorphisms linked to them, influence the

binding capacity or function of 5-HTT in the human brain. However, some recent studies exploring a possible association between polymorphisms in *SERT* and the expression of 5-HTT protein or 5-HT binding in the brains of healthy controls or patients did not reveal any genotype-dependent differences, blurring the "classic", coherent picture [78, 88]. Drawing conclusions is further complicated by studies on other SNPs within the gene, verifying the existence of subgroups within the dichotomous S/L paradigm, for example converting the activity associated with the L allele to that expected for the S allele [89]. Considering the 5-HTTLPR polymorphism as tri-allelic possibly alters the interpretations of previous association studies based on a simple "L vs S" dichotomy model. Another confounding factor potentially leading to non-replication of results may be a failure to control for epistatic effects. The *SERT* gene is a classical example of the necessity to control for gene-environment interactions, with numerous studies consistently proving that exposure to adverse life events strengthens the association between 5-HTTLPR and a given behavioural phenotype (particularly depression- and anxiety-related) [90].

Another functional polymorphism studied was the VNTR in intron 2 of the 5-HTT gene comprising 9, 10 or 12 copies of a 16/17-base pair element (frequently termed STin2.9, STin2.10 and STin2.12 VNTR, respectively). Association studies have linked this polymorphism to several behavioural phenotypes (as well as antidepressant efficacy), although without consistency [78]. Only 4 research groups have evaluated the significance of STin2 VNTR polymorphism in BPSD in AD [66, 79, 83, 84]. Two of the studies were negative, while in the other two STin2.10 was associated with aggression, psychosis and the total level of behavioural psychopathology (one of those insignificant after correction for multiple testing). The STin2 VNTR displays functionality both *in vitro* and *in vivo* [78, 88]. In expression studies, the 12-repeat allele was found to be a stronger enhancer of transcriptional activity than the 10-repeat allele. Moreover, apart from the number, the primary structure of the repeats could also affect the transcription of the gene. In transgenic mice, STin2 VNTR genotype was demonstrated to exert an important regulatory role in development of the serotonergic system. Transient alterations in fetal 5-HT homeostasis can modify the wiring of brain connections leading to permanent changes in adult behaviour. It is therefore possible that the effects of both 5-HTT polymorphisms are more pronounced during embryogenesis and development [91].

Catechol-O-methyltransferase

The catechol-O-methyltransferase (COMT) gene is a major enzyme in synaptic DA catabolism with a critical role in the prefrontal cortex because of the relative lack of DA transporters in this region. It contains a functional common polymorphism characterized by G to A transition at codon 108/158 (soluble/membrane-bound COMT) resulting in a valine-to-methionine substitution, giving rise to a significant, three-to-fourfold reduction in its enzymatic activity. The presence of valine (H allele = high activity) in the coding sequence corresponds dose-dependently with reduced prefrontal DA levels, subsequently leading to the upregulation of striatal dopamine activity (via increased tyrosine hydroxylase expression, the rate-limiting enzyme in DA synthesis) [92]. This reciprocal association could therefore explain both poorer cognitive scores (lower prefrontal DA) and an increased risk for schizophrenia (higher midbrain DA) [93] in COMT Val158 carriers [94]. The role of COMT genetic variants as BPSD risk modifiers has been analysed in five published papers [44, 45, 95-97], four of which were conducted by Borroni *et al.* The Met158Val polymorphism was evaluated either separately or as part of a four-loci haplotype. Contrary to other genes evaluated in AD behavioural genetics the results on the role of COMT are convergent in demonstrating the COMT*H genotype as a culprit implicated in the aetiology of psychosis in AD (however, the studies by Borroni *et al.* evaluate – at least in part – the same population, although in various aspects). The

Table IV. Studies on the association between catechol-O-methyltransferase (COMT) genotype and BPSD in AD (positive results in bold)

Reference	No. of participants	Effect of COMT genotype on BPSD
Borroni *et al.*, 2004 [95]	**181**	**HH genotype and H allele increase risk for psychosis**
Sweet *et al.*, 2005 [96]	**373**	**A four-locus haplotype increases the risk for psychosis**
Borroni *et al.*, 2006 [44]	**234**	**HH genotype and H allele increase risk for psychosis**
Borroni *et al.*, 2006 [45]	**232**	**HH genotype and H allele decrease risk for "frontal" endophenotype and increase risk for hallucinations**
Borroni *et al.*, 2007 [97]	**246**	**HH genotype and H allele increase risk for psychosis. Alleles at four loci (haplotype) interact to influence psychosis risk**

relevance of the HH genotype or H allele for AD psychosis has been observed both in isolation [44, 45, 95] and in interaction with three other loci forming a haplotype [96, 97]. Furthermore, in one of the studies COMT*H decreased the risk for disinhibition and euphoria grouped together as a "frontal" endophenotype. The susceptibility to a cognitively impaired/psychotic phenotype in COMT 158Val carriers might be explained by the above described modulating role of COMT in DA metabolism with a genotype-dependent inverse balance in striatal/frontal DA activity regulation. This mechanism is of course not restricted to schizophrenia alone, possibly translating into a universally increased proneness to psychosis and cognitive decline, both crucial aspects of a psychotic AD phenotype. However, one has to bear in mind that the reported associations between COMT Met158Val and cognition or psychosis were relatively weak (or even inconsistent on a meta-analytic level [98]); therefore – despite a uniform correlation pattern in AD-BPSD studies – the aetiological significance of this polymorphism alone should not be overestimated.

Dopamine receptors and transporter

The dopaminergic system plays a role in many aspects of human behaviour, including aggression, psychosis, depression, elation and the control of movement. The action of DA is mediated by five distinct receptor subtypes, DRD1-DRD5, and the dopamine transporter (DAT). Dopamine receptors are major targets for antipsychotic agents, one of the most important classes of medications used in the treatment of BPSD, and for drugs of abuse eliciting behavioural and psychological changes. Polymorphisms in DRD1-DRD4 and DAT have been evaluated in various psychiatric disorders, typically with mixed results [99]. Contrary to primarily psychotic disorders, the development of psychotic symptoms in AD does not appear to be associated with brain or plasma concentrations of dopamine or its metabolites (homovanillic acid). Nevertheless, the effects of dopamine in the synapse are dependent not only on its concentrations, but also on receptor densities (as well as post-receptor signal transduction mechanisms). Accordingly, striatal DRD2 and DRD3 availability has recently been proven to increase in AD patients with delusions [100]. The variants DRD1 (A-48G), DRD2 (ser311cys), DRD3 (ser9gly), DRD4 (VNTR) and DAT (3'-UTR) have been investigated in 7 studies on BPSD [8, 53, 101-105], as usual with contradictory results (summarized in Table V). DRD1 A allele, either in homo- (A/A) [8] or heterozygosity (A/G) [101], was found to be associated with psychosis and aggression [8] or aggression and hallucinations (but not delusions) [101]. However, in the latest and largest study, the DRD1 genotype did not correlate with behavioural disturbances [103]. The inconsistent direction of effect suggests spurious associations or LD of the A-48G variant with a true susceptibility factor. Investigations on DRD2 demonstrated no associations of the ser311cys polymorphism with any behavioural symptom [8, 103]. Results on the hypothetically most relevant DRD3 ser9gly variant are conflicting. All possible variants – Ser/Ser or Gly/Gly homozygosity, Ser/Ser genotype, or possession of Gly allele – have been postulated to play a role in the aetiology of delusions or psychosis [8, 101, 104]. However, in other studies DRD3 showed no association with psychosis risk whatsoever [102, 103]. In another recent study ser9gly homozygosity increased the risk for elation [103], although the result did not remain significant after multiple testing. The discordance of the findings might suggest that the observed associations were accidental. For the same reason, the DRD4 VNTR polymorphism seems to play a minor (if any) role in BPSD pathogenesis [8, 53, 103]. DAT1 3'UTR variants were tested in AD patients in a single study, with the 9-repeat allele increasing risk for irritability, while the 10-repeat allele showed an association with aberrant motor behaviour [105]. However, 9- and 10-repeat alleles made up > 97% of all the observed alleles and significance was lost after Bonferroni correction [105].

Other genes

The significance of several other genes has been assessed in single studies. Their detailed analysis is hardly available due to editorial constraints. Two research groups tested the hypothesis that interleukin-1β (IL-1β) might act as a BPSD modifier gene. Craig *et al.* found an association between the CC genotype or C allele (responsible for the diminished production of IL-1β) with both delusions and hallucinations in AD patients [106], while McCulley *et al.* associated depressive symptoms with the possession of a T allele, thus with raised IL-1β levels [107]. To establish a possible relationship between oxidative stress and the non-cognitive symptoms of AD, polymorphic sites in genes coding for heat-shock proteins (HSP) and glutathione-S-transferases (GST) have been evaluated in AD subjects [108, 109]. Clarimon *et al.* reported an allele dose-dependent increase in NPI-measured level of behavioural pathology in carriers of the A2 allele of the HSPA1B gene (involved in the stress response) [108]. Spalletta *et al.* observed an association between genetic variants in the GST polymorphic sites and AD age of onset or rate of progression; however, no effect of GST polymorphisms on behavioural symptom severity was found [109]. Following the track of neurotransmitter-associated

Table V. Studies on the association between dopamine receptors and dopamine transporter genotypes and BPSD in AD (positive results in bold)

Reference	No. of participants	Studied gene	Effect of genotype on BPSD
Sweet *et al.*, 1998 [8]	**275**	**DRD1, DRD2, DRD3, DRD4**	**DRD1 A/A genotype increases risk for psychosis and aggression in whites. DRD3 homozygosity (Ser/Ser or Gly/Gly) increases risk for psychosis in whites.** No effect of DRD3 genotype on aggression. No effect of DRD2 or DRD4 genotypes on psychosis or aggression
Holmes *et al.*, 2001 [101]	**134**	**DRD1, DRD3**	**DRD1 A/G genotype increases risk for aggression and hallucinations.** No effect of DRD1 on delusions. **DRD3 Ser/Ser genotype increases risk for delusions compared with Gly/Gly.** No effect of DRD3 on aggression or hallucinations
Craig *et al.*, 2004 [102]	416	DRD3	No effect of genotype on psychosis
Grünblatt *et al.*, 2009 [53]	72	DRD4	No effect of genotype on depression
Pritchard *et al.*, 2009 [103]	**395**	**DRD1, DRD2, DRD3, DRD4**	**DRD3 homozygosity (Ser/Ser or Gly/Gly) increases risk for elation. DRD4 7-repeat allele increases risk for agitation/aggression, decreases risk for depression. DRD4 4-repeat allele increases risk for depression, decreases risk for agitation/aggression.** No effect of genotype after correction for multiple testing. No effect of genotype on psychosis. No effect of DRD1 or DRD2 genotypes on behavioural disturbances
Sato *et al.*, 2009 [104]	**210**	**DRD3**	**DRD3 Gly allele increases risk for delusions.** No effect of DRD3 on other behavioural disturbances
Pritchard *et al.*, 2008 [105]	**395**	**DAT**	**9-repeat allele increases risk for irritability. 10-repeat allele increases risk for aberrant motor behaviour.** No effect of genotype after correction for multiple testing. No association observed for psychosis, depression, agitation/aggression

DRD1-4 – dopamine receptors D1-D4, DAT – dopamine transporter

candidate genes Craig *et al.* in two separate studies tested the significance of polymorphisms in tryptophan hydroxylase (TPH) and monoamine oxidase-A genes in relation to AD behavioural pathology [46, 110]. The TPH is the rate-limiting enzyme in the biosynthesis of serotonin catalyzing the conversion of tryptophan to 5-HT. It was observed that male AD participants with a history of agitation/aggression were significantly more likely to possess C allele-containing genotypes [110]. In another paper, the authors hypothesized that the risk of sleep disturbance in AD may, at least in part, be influenced by the availability of serotonin used for melatonin synthesis secondary to MAO-A VNTR polymorphic variation. A quantitative sleep disturbance score was significantly higher in the patients possessing MAO-A 4-repeat allele genotypes [46]. Go *et al.* evaluated the significance of neuregulin-1 (NRG1) SNP in conferring extra risk for psychotic symptoms in AD [111]. There is strong evidence from several studies that genetic variation in NRG1 has a substantial impact on schizophrenia risk. Genetic linkage studies in patients with AD with psychosis revealed multiple suggestive peaks, including 8p, within the chromosomal region of NRG1. Go *et al.* observed an association between NRG1 SNP, both in isolation and as part of a 3-loci haplotype, and a psychotic phenotype in AD [111]. Another effort to dissect the genetic background of BPSD focused on the IDE gene coding for insulin-degrading enzyme protein [112]. The IDE plays a key role in degrading several important peptides, including Aβ. A correlation was observed between carrying the C allele of the IDE gene and the risk for affective disturbances in AD, with no effect on other behavioural symptoms [112].

In the most recent study an association between brain-derived neurotrophic factor (BDNF) genetic variants and depression in AD was evaluated [52]. Brain-derived neurotrophic factor is an important regulator of neuronal plasticity and survival. A functional Val66Met SNP in the coding region of the BDNF gene (located on chromosome 11p14) has previously been associated with major depression, geriatric depression, and the risk of AD itself, although with conflicting results. In their study, Borroni *et al.* observed a dose-dependent correlation between presence of the A allele (coding for methionine) and the risk of depression comorbid with AD [52].

Potential sources of between-study variations

One of the major obstacles in the field of psychiatric genetics concerns problems with the consistency of the results, which obviously hinders their interpretation considerably. Typical association studies test the significance of given polymorphisms as risk-conferring or protective factors for a specific disorder in a case-control manner. An important drawback inherent to this strategy is the recruitment process solely based on clinical diagnoses (phenotypes). As complex (multifactorial) disorders suffer from both genetic and phenotypic heterogeneity, simply relying on the ICD-10- or DSM-IV-based symptomatic, biologically undetermined criteria will frequently obscure the genetic signals. In the field of neurodegenerative disorders even accurate application of the criteria leaves some space for uncertainty. Subjects asymptomatic during the interview might have been developing brain pathology for several years, though the clinical symptoms threshold had not yet been reached; the differential diagnosis of dementia without autopsy confirmation can be a source of substantial difficulties as well. In this regard it is beneficial to remember that the same symptoms can have completely diverse pathogenetic backgrounds in different dementing disorders. This applies to the genetic studies as well, e.g. in a study by Engelborghs *et al.* ApoE genotype had no effect on BPSD in AD subjects, in frontotemporal dementia (FTD) patients, however, a dose-dependent effect of the ε4 allele on aggressiveness and the total level of behavioural pathology was identified [47].

Several means of circumventing the issue are usually considered, one of which is substituting diagnoses with endophenotypes – traits biologically and genetically simpler, mediating between susceptibility genes and full expression of the disorder. The studies on AD behavioural genetics follow this line of thought, narrowing the entire phenotype to patients with comorbid behavioural abnormalities, symptom clusters or finally isolated symptoms. Unfortunately, as can be seen from the aforementioned results, the clarity and consistency of the findings did not improve much, still not allowing for firm conclusions. Several sources of such ongoing disparity can be taken into consideration.

Variability in general study design

The BPSD symptoms are rarely very stable phenomena in AD patients. Notwithstanding the general impression that the overall level of

Table VI. Other studies on behavioural genetics in AD (positive results in bold)

Reference	No. of participants	Studied gene	Effect of genotype on BPSD
Craig *et al.*, 2004 [106]	**406**	**IL-1β promoter (-511)**	**CC genotype and C allele increase risk for psychosis**
McCulley *et al.*, 2005 [107]	**133**		**T allele increases risk for depression**
Clarimon *et al.*, 2003 [108]	**77**	**HSP70-2 (HSPA1B)**	**A2 allele increases risk for behavioural disturbances in a dose-dependent fashion**
Craig *et al.*, 2004 [110]	**396**	**TPH**	**CC genotype and C allele increase aggression**
Go *et al.*, 2005 [111]		**NRG1**	**NRG1 SNP increases the risk for psychosis. A 3-SNP haplotype with NRG1 increases the risk for psychosis**
Craig *et al.*, 2006 [46]	**426**	**MAO-A**	**4-repeat allele increases risk for sleep disruption**
Spalletta *et al.*, 2007 [109]	99	GST	No effect of genotype on behavioural disturbances
Sato *et al.*, 2008 [112]	**207**	**IDE**	**C allele increases risk for "affective disturbances".** No association with other behavioural symptoms
Borroni *et al.*, 2009 [113]	**264**	**BDNF**	**A (Met) allele increases risk for depression in a dose-dependent fashion**

GST – glutathione S-transferase, HSP – heat shock protein, IL-1β – interleukin 1β, MAO-A – monoamine oxidase A, NRG – neuregulin, SNP – single nucleotide polymorphism, TPH – tryptophan hydroxylase

psychopathology increases with dementia severity, they have a tendency to wax and wane, their severity fluctuating with time. Not surprisingly, the results of genetic studies will therefore heavily rely on the average disease stage of the AD participants. In a recent study on ApoE and psychosis in AD, Zdanys *et al.* found that the ε4 detrimental effect was statistically significant only for the severe-stage patients [51], a result already seen in some [34] but not all [37] studies. Consequently, an association can be missed if mild-to-moderate stage patients predominate [33, 35]. A significant choice in this context is that of a cross-sectional versus longitudinal study design. Cross-sectional studies can omit episodes that occur outside the assessment period. If patients are being followed over a period of time, a higher frequency of symptoms can be detected, significantly influencing the attribution of patients to predefined study groups.

Diagnostic criteria employed

A variety of methods have been used by the researchers to identify behavioural abnormalities in AD participants. Some older studies relied only on general clinical examination and descriptive assessments, while others used rating scales, or a combination. However, even with rating scales it is difficult to reconcile contradictory reports due to a wide range of scales having been used for any symptom. Some diagnostic tools assess the symptoms qualitatively (simply defining the presence or absence of a given BPSD symptom), while others provide quantitative measures (e.g. the popular Neuropsychiatric Inventory – NPI), permitting the choice of different thresholds of severity and allowing for the inclusion of patients only with clinically significant psychopathology.

Choice of symptoms

The range of symptoms evaluated has to be precisely defined, e.g. in the papers one can find "psychosis", delusions and hallucinations analysed together or separately, or persecutory delusions on their own. In most cases AD patients exhibit more than one behavioural symptom. The isolated symptoms are frequently interrelated, e.g. the presence of delusions could likely be associated with hallucinations, agitation/aggression or sleep disturbances, while depression could increase the chance of comorbid anxiety, sleep and appetite disturbances. This constitutes one of the major limitations for the correct evaluation of BPSD pathogenesis. Therefore, some of the authors propose using clusters of symptoms – behavioural endophenotypes – supposedly linked to specific neurotransmitter abnormalities or even sharing a common genetic basis [45]. In one of the studies carrying the COMT*H allele was not significantly correlated with a "psychotic" phenotype (defined as NPI items delusions + hallucinations + night-time disturbances), but proved to be significantly associated with hallucinations alone [45]. Two different approaches may thus be considered – relating the polymorphic variations to isolated symptoms or symptom clusters.

Selection bias

Apart from the clinical characteristics of the investigated population, the results of genetic studies can heavily depend on its ethnicity or even its genetic homogeneity within one race. Some populations are considered genetically homogeneous, e.g. Northern Ireland inhabitants or Sephardic Jews. This increases the consistency of the findings. Such populations, however, are prone to the founder effect (loss of genetic variation due to shared ancestry). Selection bias can also manifest itself through the choice of setting for patient recruitment: nursing home dwellers, inpatients or patients treated in an ambulatory setting. The most inclusive population-based studies recruit "real-life" patients, making the results much more practical, although at a price of numerous medical, environmental, and drug-related confounders, particularly troublesome in genetic studies.

Statistical power

Commonly, the problem with divergent findings of genetic studies lies with inadequate statistical power owing to an insufficient number of study participants. More studies on larger cohorts with appropriate assessment tools as well as using a meta-analytic approach are potential solutions to overcome the problem.

Another issue worth mentioning in the context of statistical methods is the correction for multiple testing. Some of the observed associations might be spurious as the majority of studies are subject to considerable multiple testing. Employing proper statistical methods can nullify an initially statistically significant result [49].

Carrier status versus dose

Interpretation of genetic studies requires even more caution as some authors evaluate genetic associations dichotomously (carrier vs non-carrier status of a particular allele) [51], while others examine the effect of allele "dose" in relation to BPSD symptoms [38]. Sometimes only a homozygous genotype for a particular allele increases BPSD risk [67]; in other cases it is only the carrier status that matters [63].

Inherent limitations of genetic studies

Genetic studies on complex traits are prone to several limitations. One has to remember that the aetiology of BPSD is multifactorial, with an interplay of genetic, other biological, environmental and social factors, the individual influence of which is rather difficult to disentangle. Multiple genes are usually involved in the pathogenesis of a complex trait, often with a contradictory effect (susceptibility genes, protective genes, modifying genes); moreover, the effects of individual polymorphisms are usually weak, requiring large cohorts to demonstrate. Some of the SNPs are statistically associated with each other in the form of a haplotype increasing the complexity of epistatic (gene-gene) interactions. The discrepant findings might also relate to the fact that some of the polymorphisms studied are not true risk factors themselves but only represent markers located near some unidentified genes associated with AD or BPSD. Importantly, drawing final conclusions and comparing association results is often hampered as genes usually contain many polymorphic sites, whereas the majority of studies only offer analyses of single polymorphisms, sometimes different ones in successive studies (it should be noted that testing all polymorphisms present in a particular gene of interest is usually unfeasible for practical reasons).

Conclusions

The last couple of years have witnessed an unprecedented struggle in the search for the genetic correlates of behavioural symptoms in AD. The strategy of narrowing the studied phenotype to clinically – and hopefully genetically – distinct and homogeneous populations has been becoming increasingly popular as a way to circumvent typical problems of psychiatric genetics (or genetics of most complex traits, more generally speaking). The results of this tactic have been and still are awaited with ongoing expectations. Unfortunately, as one can see from this review, definite answers are hardly available. The reports still mainly fuel discussions on the potential sources of discrepancies rather than providing a stimulus for finding practical applications of purely scientific observations. Such a gloomy perspective could, however, derive from unrealistic expectations. The influence of genetic polymorphisms on BPSD profile might simply be weak enough to suffer from a particular vulnerability to potential confounders, so difficult to control for in genetic association studies, or simply lack of adequate statistical power. Another explanation, not mutually exclusive with the former, could focus our attention on the still limited technical possibilities and their rapid evolution in recent years. With whole-genome scans, the use of microarrays and chips allowing a simultaneous study of thousands of genes and their interactions, and an increasing awareness of the significance of haplotypes, rather than isolated SNPs, the perspectives of genetics should probably be sketched in brighter colours. Finally, interpreting the outcome of genetic research separately from neurochemical, neuropathological, neuroimaging or electrophysiological studies seems an undesired oversimplification. Fusing the available multidisciplinary data can result in discoveries important also in practical terms. Probably the most important lesson from studies on BPSD is that the pathogenesis of the same symptoms (e.g., psychotic or depressive) can be totally divergent in different psychiatric disorders, e.g. the biological basis for the psychotic symptoms in AD seems to be more closely associated with cholinergic-serotonergic imbalance than with dopamine, traditionally given priority in schizophrenia neurobiology. The same is true even for various types of dementia, albeit more closely related at first glance. It is therefore unwise to mechanically project knowledge on "general" psychiatry to neuropsychiatry, on one type of dementia to another, or to rely solely on atheoretical, strictly symptomatic classifications in neurobiological research. From this point on, only one step separates us from translating those conclusions into highly expected, pharmacological applications. One should bear in mind that this has already happened, as in the previously cited study by Pollock *et al.* on the efficacy of serotonergic citalopram in the treatment of psychosis in AD [86], or in a study of the 5-HT agonist tandospirone effective in reducing agitation/aggression, irritability, anxiety and depression in AD patients [113].

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