Supplemental Table 1: Characteristics, methodology and findings of reviewed studies

Study	Study design	Participants (mean age)	%Female, (ethnicity)	Cognitive level, AD duration if known	Inpatient (1) or outpatient (2) recruitment	Neurotransmitter marker(s) (& brain region if post-mortem)	Method	Measure(s) of agitation	Frequency/timing of agitation measure(s)	Proportion of AD with agitation and severity (score)	Findings
Serotonin system											
Assal 2004	Cross-sectional	96 AD (77)	62 (70% Caucasian)	MMSE 19	2	5-HTTPR, 5-HTTVNTR, and 5-HT2A (102T/C) and 5-HT2C receptor gene polymorphisms	Genetic analysis	NPI (total subscore agitation/aggression)	One assessment to calculate subscore.	41% (mean subscore 1.62)	102T genotype of the 5-HT2A receptor was significantly associated with agitation/aggression. Homozygotes for the 102T genotype had higher agitation/aggression scores than heterozygotes and higher agitation scores than homozygotes for the 102C form. No association between 5-HTTPR or 5-HTTVNTR polymorphism with agitation/aggression.
Ha 2005	Case-control	65 AD (75) 43 HC (73)	73 (100% Korean)	MMSE 15	2	5-HTTLPR polymorphism	Genetic analysis	BEHAVE-AD (aggression subscore) Korean version	One assessment carried out within 2 days of initial assessment	69% (-)	No association between 5-HTTLPR polymorphism and aggressive symptoms of AD.
Holmes 1998	Case-control	211 AD (-) 181 HC (-)	78 (-)	-	2	5-HT2A receptor polymorphism (102T/C) and 5-HT2C receptor polymorphism (Cys23Ser)	Genetic analysis	MOUSEPAD	One assessment to indicate presence or absence of psychopathology.	-	No significant association between either polymorphism and aggression in AD.
Lai 2011	Case-control	24 AD (82), 14 HC (76)	42 (-)	MMSE 6 (AD duration 5	2	5-HT1A receptor, 5-HT2A receptor, and serotonin transporter (5-	Autopsy	PBE (physical aggression score)	Physical aggression considered present if >2 ratings scored >3 (out of 6) or >1 rating scored >3 and 2 ratings	33% (-)	5-HTT sites were preserved or up-regulated in patients with physical aggression.

				yrs)		HTT) binding affinity and density (hippocampus)			of 1-3 at any time during follow up (mean follow up duration 3 yrs, minimum 8 months, frequency every 4 months).		
Lai 2003	Case-control	33 AD (81), 20 HC (77)	47 (-)	-	2	5-HT1A receptor binding affinity and density (orbito-frontal gyrus BA11 and mid temporal gyrus BA21)	Autopsy	PBE (aggressive behavior consisting of verbal and physical aggression and aggressive resistance)	The highest score from each aggressive behaviour component at any time during the course of the study (mean follow up duration 3 yrs, minimum 8 months, frequency every 4 months) were summed to give a 'trait' marker, and the total score from the last interview before death was used as a 'state' marker.	73% moderate/severe aggression (score 3-6)	5-HT1A receptor density in the temporal cortex inversely correlated with 'trait' aggression. No relationship between receptor binding and 'state' aggression.
Lam 2004	Case-control	87 AD (77), 75 HC (74)	(-) (100% Chinese)	-	2	5-HT2A receptor (102 T/C allele) polymorphisms	Genetic analysis	NPI Chinese version	One assessment to calculate a score for each NPI domain (frequency x severity).	26% agitation, 39% aberrant motor behaviour (-)	No significant association between the allele frequencies and neuropsychiatric symptoms. Frequency of agitation and aberrant motor activity appears to be higher in TC than TT/CC.
Lanctot 2002b	Case-control	11 AD (non-aggressive)11 AD (aggressive), mean age 82	83 (-)	MMSE 4 (AD duration 5.5 yrs)	1	Prolactin response to d,l-fenfluramine (60 mg) as an index of central serotonergic function.	Neuroendocrine challenge	NPI (agitation/aggression and irritability subscales); CMAI (verbal and physical aggression subscale); BEHAVE-AD (aggression subscale)	One assessment at baseline to divide AD patients into aggressive and non-aggressive (NPI score aggression/agitation subscale >= 6 "aggressive", =< 4 "non-aggressive".	50% of all AD subjects, (in aggressive patients, mean NPI agitation/aggression subscale 8.7, irritability subscale 6.5, CMAI verbal and physical aggression subscale 11.7, BEHAVE-AD aggression subscale 6.5)	NPI aggression score, NPI irritability score, and Behave-AD aggression score were positively correlated to prolactin concentrations following fenfluramine challenge. Aggressive patients showed greater mean prolactin increase from baseline (= greater 5-HT responsivity) than nonaggressive subjects. The change in PRL concentration depended on level of cognitive impairment and gender: female aggressive subjects with less cognitive impairment had the largest response to fenfluramine challenge.

Lanctot 2002a	RCT (sertraline)	21 AD (82)	91 (-)	MMSE 4 (AD duration 5.5 yrs)	1	Prolactin response to d,l-fenfluramine (60 mg) as an index of central serotonergic function.	Neuroendocrine challenge	NPI (aggression/ agitation subscale); CMAI	Assessments at baseline and before/after treatment with sertraline or placebo.	100% (after initial washout, mean NPI subscale 5.1; mean CMAI 24.9)	38% of participants were sertraline responders and drug responsive behaviors included aggression/agitation,irritability and aberrant motor behavior. Low aggression, female gender and large prolactin increase were associated with a better response.
Mintzer 1998	Case-control	5 AD (+agitation), 5 AD (-agitation), mean age 84	80 (-)	MMSE 4 (agitated), 10 (non-agitated)	1	Prolactin response to d,1-fenfluramine as a probe for 5-HT activity.	Neuroendocrine challenge	CMAI	AD subjects were 'agitated' if they exhibited agitated behaviors for at least 4 weeks prior to inclusion in the study, and in the week before inclusion had "an agitated behavior at severity rating 4 (frequency of several times a week) or 2 behaviors at a severity of 3 (frequency of once or twice a week) in at least one of the following CMAI factors: Factor 1: aggressive behavior, Factor 2: physically nonaggressive behavior, and Factor 3:verbally agitated"	50% of all AD subjects (mean CMAI score 63 in agitated AD, 26 in non agitated AD).	Change in prolactin levels from baseline to 3 hours was significantly larger among the agitated than the non-agitated AD patients. There was a significant positive correlation between change in prolactin levels from baseline and level of agitation.
Peters 2016	RCT (citalopram)	175 AD (80)	46 (72 % White)	MMSE 16 (median duration of AD 4 yrs)	2	Genetic variants for 5-HT2A receptor (102T/C), 5-HT2C receptor (Cys23Ser), 5HTT-LPR, BDNF (Val66-Met), ApoE (E2,E3,E4 variants), and cytP450 (CYP2C19).	Genetic analysis	NPI (agitation domain); CMAI; NBRS (agitation domain); mADCS-CGIC.	Measurements obtained at baseline, weeks 3, 6 and 9.	100% (median baseline scores - NPI agitation subscore 8; CMAI 27; NBRS-Agitation 8).	Significant interactions between 5-HT2A and NPI agitation domain (but not NBRS or CMAI), and the mADCS-CGIC with 5-HTR2C over 9 weeks. Analyses not adjusted for multiple comparisons.
Pritchard	Cohort	367 AD (-)	56 (-)	MMSE 18.6	2	5-HTTPR and 5-HTTVNTR	Genetic analysis	NPI	NPI used to dichotomise patients	-	No association between 5-HTT polymorphism and

2007						polymorphisms			into whether they had ever suffered from a given symptom over the whole study period and give each patient a severity score. Mean frequency of assessments 7.		agitation/aggression.
Pritchard 2008	Cohort	394 AD (74), 15% had additional diagnosis of vascular dementia	56 (97% White)	MMSE 10-25	2	5HT2A receptor (102T/C) and 5HT2C (cys23ser) genotype and allele frequencies	Genetic analysis	NPI	NPI used to dichotomise patients into whether they had ever suffered from a given symptom over the whole study period and give each patient a severity score. Mean frequency of assessments 7.	82% had agitation/aggression, 80% aberrant motor behaviour (-)	No significant associations between 5HT2A 102T/CC or 5HT2C cys23ser polymorphisms and agitation/aggression. Non-significant increased frequency of 5HT2A C allele and CC genotype with aberrant motor behaviour.
Prokselj 2014	Cross-sectional	49 AD (77) divided into 14 aggressive (81), 16 IEED, 19 controls	59 (-)	MMSE 8.6 (aggressive group)	-	Platelet 5-HT concentration	Blood sample/ binding assay	OAS-M	Single assessment to measure severity of aggression.	14 (29%) were aggressive (mean OAS-M score 175, range 12-577)	No association between platelet 5-HT concentrations and aggressive behavior.
Schneider 1988	Case-control	14 agitated AD (76), 15 uncomplicated AD (75), 14 HC (73)	74 (-)	MMSE 13	2	Platelet ^{3}H-imipramine binding density and platelet MAO activity, as indicators of central 5-HT reuptake and turnover/capacity respectively.	Blood sample/ binding assay	One assessment: clinical interviews and history	Agitation = presence of restlessness, pacing, handwringing, pulling of skin or clothing, and behavioral outbursts, and of sufficient magnitude to dominate the clinical presentation, interfere with daily activities, or require clinical intervention or treatment, and had persisted for at least I month. Patients with increased nocturnal	48% (-)	The agitated/delusional AD group showed significantly lower Bmax values than uncomplicated AD or controls. MAO activity was significantly increased among female AD subjects without symptomatic behaviors compared to those who were agitated or to controls.

									activity who were disruptive at night (“sundowners”) were considered to be agitated.		
Sukonick 2001	Case-control	58 AD aggressive (79), 79 AD never aggressive (73)	60 (89 % White)	MMSE 8	-	5-HTTPR genotype and allele frequency (L/L homozygosity for long variant genotype and L allele)	Genetic analysis	Empirical BEHAVE-AD; BRSD	Never aggressive was defined as the absence, on initial and annual follow-up examinations, of verbal and physical aggression as defined by the BRSD. Aggressive was defined by the presence of physical or verbal aggression rated with the Empirical BEHAVE-AD scale.	-	The L/L genotype and L allele frequency were significantly associated with aggression in patients with AD.
Swe et 2001	Cross-sectional	332 AD (75)	64 (91 % White)	MMSE 14	1, 2	5-HTTPR genotype	Genetic analysis	Empirical BEHAVE-AD for inpatients, BRSD for outpatients.	One assessment: aggression was defined by the presence of either verbal or physical aggression occurring at any time during the course of the dementia.	31% ever aggressive, 75% of aggressive subjects had a history of psychosis (-)	Significant association between 5-HTTPR L allele and LL genotype with the combined psychotic and aggressive phenotype. AD subjects with only aggressive behavior demonstrated an intermediate increase in frequencies of the L allele and LL genotype in comparison to uncomplicated AD subjects.
Ueki 2007	Case-control	200 AD (73), 200 HC (73)	67 (-)	Mild AD at recruitment, 140 progressed to moderate AD by the end of the study.	-	5-HTTLPR and 5-HTTVNTR polymorphisms	Genetic analysis	BEHAVE-AD	Assessed at time of AD diagnosis, then checked monthly during mild AD to obtain information about activity disturbance, aggressiveness, diurnal rhythm disturbances. The presence of symptoms was noted, not magnitude of symptoms.	-	Significant associations were observed between presence of 5-HTTVNTR allele 10 and BPSD or aggressiveness.

Dopaminergic system											
Bierer 1993	Cohort	23 AD (70)	21 (-)	Mean ADAS cognitive sub scale score before death = 68	-	Concentrations of DA, HVA and DOPAC (L temporal lobe BA 21 and 22)	Autopsy	ADAS subscale agitation (sum of items “pacing”, “increased activity”, “tremors” and “uncooperative to testing”).	The highest ratings obtained over the period of follow-up for agitation scores were used. The mean interval between the maximum agitation assessment and death was 33.9 months.	100% (mean score 5.65 out of 12)	No relationship between agitation and dopaminergic metabolites in temporal cortex.
Holmes 2001	Cross-sectional	134 AD (84)	77 (100% White)	MMSE 11 (mean duration 5 yrs)	2	DA receptor (DRD1 B1/B2 and DRD3 1/2) gene polymorphisms.	Genetic analysis	MOUSEPAD	One assessment after recruitment.	44% had aggression (-)	DRD1 B1/B2 genotype significantly more likely to show aggressive behaviour than those with B1/B1 genotype. No significant association between DRD3 genotype and aggression.
Pritchard 2009	Cohort	395 AD (-)	56 (96% White)	MMSE 18.6	2	DA receptors DRD1(A-48G),DRD2(ser311cys; C-ins/del), DRD3(ser9gly) and DRD4 (VNTR) genotype and allele frequencies	Genetic analysis	NPI	Assessed for BPSD up to 12 intervals over the study period (166 weeks). Patients were dichotomised into whether they had ever suffered from symptoms or not within the study period and given a severity score.	-	Association between DRD4 and agitation/aggression did not remain significant after correction for multiple testing. No associations between other genetic variants and agitation/aggression or aberrant motor behaviour.
Sato 2009	Case-control	210 AD (74), 224 HC (72)	82 (-)	Mild AD at recruitment, 79% moderate AD by study end	2	DA receptor (DRD3) genotype	Genetic analysis	BEHAVE-AD	Baseline and monthly assessments on presence of BPSD, mean duration of follow up 2.2 years.	70% experienced BPSD of which 35% showed aggressiveness, 22% activity disturbance and 14% diurnal rhythm disturbance.	No significant associations between DRD3 and aggressiveness, activity disturbance, diurnal rhythm disturbance subscales.

Sweet 1998	Cross-sectional	275 AD (73)	66 (94% White)	Initial MDRS score 107	-	DRD1,DRD2,DRD3, and DRD4 gene polymorphisms	Genetic analysis	CBRS	Presence of physical aggression was defined by receiving at any annual CBRS assessment a score indicating a history of any episode of physical aggression during the course of the illness. Absence of aggression was defined as never receiving a score of more than 0 on CBRS item 31.	5.6% (-)	Among white patients, physical aggression (and psychosis) was significantly more frequent in DRD1 B2/B2 homozygotes. No association between DRD2 S311C polymorphism, DRD3 or DRD4 exon III repeat sequence long allele and aggression.
Sweet 1997	Cohort	18 AD out of 21 (2 patients had dementia unspecificed and one organic hallucinosis) (80)	67 (-)	-	-	Plasma HVA as in vivo measure of central DA function	Blood sample	NBRS	Assessment at baseline and after treatment with perphenazine.	Baseline disinhibition/aggression 3.3, agitation 4.4; following treatment, change in score -23.3% and -35.2% respectively.	No correlation between baseline pHVA and improvement in behavioral symptoms at the final assessment. A correlation between baseline pHVA and agitation and hostility was not significant. Mean pHVA did not change during perphenazine treatment but intraindividual pHVA change at day 15 was correlated with improvement in hostility.
Noradrenergic system											
Herrmann 2004a	Cross-sectional	15 AD (82)	27 (-)	MMSE 3.3	1	GH response to clonidine challenge as an index of central a2-adrenergic function	Neuroendocrine challenge	CMAI, NPI, r-OAS	One assessment at baseline	100% (mean NPI score 30.6, CMAI aggression subscale 15)	When patients were divided into those with preserved or blunted GH response to clonidine there were significant differences in CMAI physical aggression subscores. Patients with blunted GH response also had significantly higher levels of aggression against others on r-OAS.
Herrmann 2004	RCT (crossover)	15 AD (82)	27 (-)	MMSE 3.3	1	GH response to clonidine challenge as a measure of	Neuroendocrine challen	NPI, r-OAS	Five assessments: baseline, before and after treatment at each crossover phase.	100% (baseline NPI aggression score 8.6,	Subjects with more aggression (higher baseline r-OAS scores), less cognitive impairment (higher MMSE scores) and a blunted GH

b						central NA responsivity, followed by 7 weeks treatment with pindolol or placebo.	ge			baseline r-OAS score 28.4)	response to clonidine challenge demonstrated greater reductions in aggression following pindolol compared to placebo.
Matthews 2002	Case-control	36 AD (81), 33 HC (74)	48 (-)	MMSE 4.3	1, 2	a2-adrenoceptor density, cortical NA concentration and locus coeruleus cell counts (mid-temporal BA21, superior frontal BA9, mid-frontal BA46, and orbitofrontal BA11 regions).	Autopsy	PBE.	Before death assessments occurred every 4 months. Scores for the behavioral syndromes aggressive behaviour (physical aggression, aggressive resistance, and verbal aggression) and overactivity were achieved by selecting the most severe rating recorded during the course of the study.	Aggressive behaviour factor score 4.3, overactivity factor score 2.7	There was a greater loss of cells from the rostral LC in dementia patients (and AD alone) with aggressive behavior than in those without aggressive behaviour. The a2-adrenergic receptor density was unaltered in AD compared with controls and unrelated to any behavioral syndrome.
Peskind 1998	Case-control	Study 2: 10 AD (70), 10 older HC (71), 11 younger HC (27)	23 (-)	MMSE 14 (study 2)	-	CSF NA concentration	CSF analysis	BPRS	In study 2, assessments after medication administration in each treatment group (yohimbine, clonidine and placebo). Agitation was quantified by summing scores on the Tension, Excitement, and Anxiety items.	Mean agitation score 6	CSF NA increased following yohimbine in AD and older subjects but not in young subjects.The agitation increase following yohimbine was substantially greater in AD subjects than in older or young subjects.
Russo-Neustadt 1997	Case-control	16 AD (80), 7 HC (77)	48 (-)	MMSE 14.4	1, 2	Concentration of b1,b2, and a2-adrenergic receptors (frontal cortex, hypothalamus, cerebellum)	Autopsy	Not reported	Assessed for the presence or absence of aggression, agitation, and disruptive behavior. Method not reported.	50% of AD group (-)	Aggressive AD patients had significantly higher concentrations of a2-receptors in the cerebellar cortex vs nonaggressive patients, and slightly higher concentrations vs HC, suggesting that these receptors are preserved and perhaps increased in this subgroup of AD. The b1 and b2-adrenergic receptors in the cerebellar cortex showed smaller but significant

											increases in concentration in aggressive AD subjects vs both nonaggressive AD and controls. No significant differences in adrenergic receptor concentrations within the frontal cortex or hypothalamus.
Sharp 2007	Case-control	24 AD (82) 25 HC (74)	35 (-)	MMSE 3	-	a1-adrenoceptor (frontal cortex)	Autopsy	PBE	Assessment at 4 monthly intervals. Clinically significant aggression was defined as mean score>3 and a score of 6 on at least two assessment points.	75% (-)	Aggressive behavior significantly correlated with a1-adrenoceptor density and affinity in AD patients. Patients receiving neuroleptics had significantly higher a1-adrenoceptor density than those not receiving neuroleptics.
Other neurotransmitter systems											
Lanctot 2007	Cross-sectional	14 AD (86)	75 (-)	MMSE 4.5	1	GABA levels in plasma	Blood sample	NPI	Single assessment.	Scored >0 on NPI subscales: agitation 93%, irritability 86%, aberrant motor behavior 64%, sleep 36%. (Mean NPI aggression score 6.4)	No relationship between aggression and pGABA concentrations, although a trend was observed.
Minthon 1996	Case-control	34 AD (64), 24 FTD, 11 younger HC (40), 40 older HC (79)	50 (-)	(Mean duration illness 4.7 yrs)	2	Neuropeptide Y	CSF analysis	Organic Brain syndrome confusion subscale	Single assessment.	-	Significant, negative correlation between CSF NPY and anxiety, restlessness and agitation in FTD and AD.
Sultzer 2017	Case-control	24 AD (80), 22 HC (72)	4 (71 % White)	MMSE 19.6 (mean duration illness 4 yrs)	2	α4β2* nicotinic cholinergic receptor	PET (2FA radiotracer)	NBRS	Single assessment.	(Mean agitation/disinhibition factor score 4.38)	Significant inverse correlation between 2FA binding in bilateral anterior cingulate and NBRS agitation/disinhibition factor score in AD.

Multiple neurotransmitter systems											
Brane 1989	Case-control	41 (13 onset <65 [AD] and 28 onset>= 65 [SDAT]) (74), 26 HC (64)	-	GBS mean intellectual impairment subscale 3	1	HVA, 5-HIAA, MHPG concentration	CSF analysis	GBS	Single assessment.	Mean scores for fear-panic (AD 0.33 SDAT 0.74), restlessness (1.25, 2.37), irritability (1.0, 2.26). 0-1 normal, 1-6 abnormal	5-HIAA correlated positively with fear-panic and restlessness, and MHPG correlated positively with restlessness in AD. No relationship with HVA. Ratings of irritability, anxiety and restlessness were significantly higher in SDAT than AD.
Engelboroughs 2008	Cross-sectional	181 AD (79), 28 mixed dementia, 25 FTD, 24 DLB	67 (-)	MMSE 12.9	1, 2	Concentrations of NA, MHPG, 5-HIAA, DOPAC, HVA	CSF analysis	CMAI, Behave-AD	Single assessment at baseline.	Behave-AD total score 10.4, CMAI total 47.3.	No significant correlations between behaviour and CSF metabolite concentration found in AD group.
Garcia-Alloza 2004	Case-control	21 AD (81), 20 HC (75)	54 (-)	MMSE 5	1, 2	5-HT1B/1D and 5-HT6 receptors, ChAT activity (frontal BA10 and temporal BA20 cortex)	Autopsy	PBE	Overactivity and aggressive factors calculated in last interview before death.	Overactivity 3; aggressive behavior 5 (range 0-6)	The best predictor for lowered 5-HT6 receptor density in the temporal cortex was the PBE measure of overactivity. The 5-HT6/ChAT ratio was related to aggression both in the frontal and temporal cortex. ChAT activity both in the frontal and temporal cortex from AD patients was significantly lower than control patients.
Garcia-Alloza 2005	Case-control	22 AD (81), 20 HC (75)	50 (-)	MMSE 5	1, 2	ACh and choline concentrations, AChE and ChAT activity, 5-HT and 5-HIAA concentrations (frontal BA10 and temporal BA20 cortex)	Autopsy	PBE	Overactivity and aggressive factors calculated in last interview before death.	PBE scores : overactivity 3; aggressive behavior 5	The best predictor of lowered ChAT and AChE levels in BA10 and BA20 was aggressive behavior scores. The best predictor for 5-HT reductions in BA10 was overactivity factor score.
Leake 1993	Case-control	32 AD (81), 12 HC (83)	82 (-)	-	-	5-HT and 5-HIAA concentrations,	Autopsy	Clinical records	Patients regarded as suffering from agitation if records showed 'a	38%	In agitated patients the density of brain 5-HT1A receptors was significantly higher than in those

						5-HT1A and 5-HT2 receptor densities and 5-HT reuptake sites, ChAT activity, MHPG and HVA concentrations (frontal cortex BA9)			persistent pattern of agitation or externally directed aggression present for long periods during the illness and of sufficient severity to warrant medication or special nursing'		with no agitation. No significant association between densities of 5-HT2 binding or 5-HT reuptake side, monoamine concentrations, ChAT activity and agitation.
Lopez 1996	Case-control	11 AD (72), 12 HC (68)	61 (-)	Mattis dementia rating scale 87.5	2	Concentrations of HVA and 5-HIAA	CSF analysis	Clinical records	Aggression considered to be present 'when there were ideas and/ or behavior which were angry, hateful or destructive, and were manifested as intention to harm another physically or verbally'.	45% verbal/physical aggression	Patients without aggressive behavior had significantly lower concentrations of HVA and 5-HIAA than those with aggression, in whom concentrations were preserved compared to non-demented controls.
Minger 2000	Case-control	36 AD (81), 32 HC (74)	50 (-)	MMSE 4.3 (mean duration 8.8 yrs)	1, 2	Concentrations of DA, HVA and DOPAC, ChAT activity and DA D1 receptor density (frontal BA9, BA11 BA46 and temporal cortex BA21)	Autopsy	PBE	Assessed 4 monthly until death. The highest values for each behavioural component at any time during the course of dementia were summed to give a factor score ('trait' marker) and factors were calculated from the last interview before death ('state' marker).	-	ChAT:DA and ChAT:D1 ratios in frontal and temporal cortex correlated negatively with overactivity and aggressive behavior respectively. No evidence for disturbance of the presynaptic dopaminergic system, DA, DOPAC or HVA in AD patients.
Minthon 1997	Case-control	34 AD (64), 22 FTD, 10 younger HC (37), 40 older HC (79)	50 (-)	14 mild, 29 moderate, 13 severe (duration illness 4.7 yrs)	2	Neuropeptide Y and somatostatin	CSF analysis	Organic Brain syndrome confusion subscale	Single assessment covering the past 7 days.	-	Reduced somatostatin significantly negatively correlated with agitation, restlessness and irritability in FTD but not AD

Procter 1992	Case-control	17 AD (80), 18 HC (78)	-	-	1	5-HT2 receptor binding, concentrations of 5-HT, GABA, SLIR and ChAT activity (13 areas of cortex)	Autopsy	Clinical notes referring to the entire period from presentation with cognitive impairment to death.	Aggressive behavior present if there were >2 recorded incidents of physical aggression (behavior likely to have caused actual physical harm). Wandering was defined as motor overactivity, either generalised or definite attempts to leave the house or hospital.	24% had aggression, 29% had wandering	In all areas of cerebral cortex, except superior parietal lobe, the 5-HT2 receptor binding is lower in aggressive patients vs non-aggressive. ChAT activity is similar in both groups.
Proitsi 2012	Cross-sectional	1008 AD (82)	82 (100% White)	MMSE 12.8	-	11 polymorphisms: 5HT2A (C102T), 5HT2C (Cys23Ser), DRD148 A/G, DRD2 A1 allele, DRD3 Gly9Ser and COMT Val158Met SNPs, 5HTTLPR and STin2 VNTRs, MAO-A and DAT 3'UTR promoter VNTRs and DRD4 exon 348bp VNTR	Genetic analysis	NPI used to create behavioural subphenotypes ('agitation' composed of irritability, disinhibition and aggression).	Baseline assessment.	-	Significant associations were observed between DAT 3' VNTR and "agitation". Direct associations were identified between the DRD1 and DAT 3' VNTR polymorphisms and aberrant motor behavior; DRD4 VNTR and sleep disturbances.
Vermeiren 2014a	Cross-sectional	40 AD (80)	38 (-)	MMSE 11	2	DA, 5-HT, NA, DOPAC, HVA, 5-HIAA, and MHPG concentrations (frontal BA9, BA10, BA11, temporal BA22, anterior cingulate gyrus BA24, amygdala,hippocampus,	Autopsy	CMAI, Behave-AD	Final behavioural scores before death used ('state' marker)	(Behave-AD total score 9.2, CMAI total 50)	Hippocampal 5-HIAA levels inversely correlated with agitation scores. Cerebellar DOPAC/DA ratios, indicative of DA turnover, correlated with physically agitated behavior.

						thalamus, and cerebellar cortex).					
Vermeiren 2014b	Case-control	17 AD +aggression (78), 23 AD - aggression (82)	38 (-)	MMSE 11	2	Concentrations of DA, 5-HT, NA, and respective metabolites (frontal BA9, BA10, BA11, temporal BA22, anterior cingulate gyrus BA24, amygdala,hippocampus, thalamus, and cerebellar cortex)	Autopsy	CMAI	Final CMAI cluster 1 aggressive behaviour scores before death used ('state' marker) to dichotomise patients into aggressive or nonaggressive.	CMAI cluster 1 scores: AD+agr 20.6, AD-agr 10.0	In AD+aggression, 5-HIAA levels in BA9, 5-HIAA:5-HT ratios in BA11,and MHPG, NA, and 5-HIAA levels in the hippocampus were significantly decreased compared with AD-aggression.
Vermeiren 2016	Case-control	10 AD (60), 10 HC, 10 FTD	55 (-)	GDS 6.6	2	Concentrations of 5-HT, NA, DA, 5-HIAA, MHPG, and DOPAC/HVA (medial and prefrontal cortex BA6, 8, 9, and 10, orbitofrontal cortex BA11, 12, temporal cortex BA22, cingulate gyrus BA24, dorsolateral prefrontal cortex BA46, amygdala, hippocampus.	Autopsy	CMAI, Behave-AD	Final behavioural scores before death used.	Behave AD total 14.3, CMAI total 59	NA levels of the prefrontal cortex (BA12 and BA9) correlated with aggressive behavior in AD, however did not remain statistically significant after correction for multiple comparisons.

Abbreviations: AD = Alzheimer's disease, SDAT = senile dementia of the Alzheimer type, HC = healthy controls, FTD = frontotemporal dementia, DLB = Dementia with Lewy Bodies, IEED= involuntary emotional expression disorder, RCT = randomized controlled trial, 5-HT = serotonin, 5-HTT = serotonin transporter, 5-HTTLPR = 5-HTT-linked polymorphic region, VNTR = variable number of tandem repeats, 5-HIAA = 5-Hydroxyindoleacetic acid, BDNF= brain derived neurotrophic factor, ApoE = Apolipoprotein E, cytP450 = cytochrome P450, MAO = monoamine oxidase, DA = dopamine, DR = dopamine receptor, DAT = dopamine transporter, HVA = homovanillic acid, DOPAC = dihydroxyphenylacetic acid, NA = noradrenaline, MHPG = 3-Methoxy-4-hydroxyphenylglycol, ChAT = cholinacetyltransferase, 2-FA=2-[18F]fluoro-3-(2(S)azetidinylmethoxy)pyridine, GH = growth hormone, SLIR =

somatostatin like immunoreactivity, BA = Brodmann area, CSF = cerebrospinal fluid, MMSE = Mini-mental state examination, MDRS = Mattis Dementia Rating Scale, GDS = global deterioration scale, NPI = Neuropsychiatric Inventory, CMAI = Cohen-Mansfield Inventory, BEHAVE-AD = Behavioural Pathology in Alzheimer's Disease Rating Scale, CBRS = Consortium to Establish a Registry for Alzheimer Disease Behavioral Rating Scale for Dementia, GBS = Gottfries-Brane-Steen scale, NBRS = NeuroBehavioral Rating Scale, MOUSEPAD = Manchester and Oxford Universities Scale for the Psychological Assessment of Dementia, PBE= Present Behavioural Examination, domain), BPRS = Brief Psychiatric Rating Scale, mADCS-CGIC = modified Alzheimer Disease Cooperative Study—Clinical Global Impression of Change scale, BRSD = Behaviour Rating scale for Dementia, r-OAS = retrospective Overt Aggression Scale, OAS-M= Overt Aggression Scale-Modified