

commentary**Social timing, clock genes and autism: a new hypothesis****Abstract**

Background Timing and social timing deficits are fundamental in autism and may play a developmental role in its manifestation. Sleep problems are associated with this disorder, as is a reduction or loss of Purkinje cells associated with regions of the brain which co-ordinate fine motor movements. Genetic studies suggest that a number of genes of limited effect lead to autism and that the genes are epistatic.

Conclusions We suggest that anomalies in clock genes operating as timing genes in high frequency oscillator systems may underlie the timing deficits of autism. We outline how anomalies in methylation-related genes may also be implicated.

Introduction

This paper introduces our theory that timing deficits in autism are fundamental to this developmental disorder and that these deficits result from genetic anomalies associated with clock/timing genes together with methylation-related genes. The evidence we present integrates findings from developmental psychology, cognitive and neuropsychology and molecular genetics.

Background**Autism**

Autism is a developmental disorder characterized by impairments in reciprocal social interaction and communication, restricted and stereotyped patterns of interests and behaviours and the presence of developmental abnormalities by 3 years of age (Bailey *et al.* 1996).

Social timing in autism: preverbal interaction and deficits

Kanner (1943) originally defined autism as 'an innate inability to form the usual, biologically provided affective contact with people'. The primacy of social dysfunction is widely recognized (Fein *et al.* 1986; Hobson 1993) and social reciprocity is pivotal to diagnosis. This paper initially considers how a timing-dependent model of normal social and symbolic development (Newson & Newson 1975; Trevarthen & Aitken 2001) may explain the deficits of autism (Newson 1984; Wimpory 1995; Wimpory & Nash 1999).

There is ample evidence from normal infants that interactive timing is a crucial aspect of preverbal interactions (Trevarthen & Aitken 2001). Such interactions involve flexible cross-modal monitoring of actively generated impulses in infant and adult (Trevarthen 1986; Trevarthen *et al.* 1999). Even new-born infants, through movement or vocalization, can exactly synchronize with certain salient moments in the adult's communication (Malloch

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1999). In protoconversations, turn-taking between the young infant and the adult is based on very sensitive timing (Trevvarthen & Aitken 2001). At 6 weeks old a slow turn-taking rhythm is set up (at 1 in 900 ms). Within 1 month or 2, the beat of shared vocal play in animated games with an infant accelerates (to 1/700 or 1/500 ms). Desynchronization of maternal contributions during interaction with normal infants, via interactive video links, results in the infants showing distress and avoidance such as looking away (Murray & Trevvarthen 1985; Nadel *et al.* 1999).

In autism, the inability to engage in a flow of interaction, at a preverbal and later verbal and non-verbal level, has been clinically described as social timing difficulties (Newson 1984). Both a prospective video and a retrospective parental interview study have shown that interactive turn-taking distinguishes infants with autism from control infants (Kubicek 1980; Wimpory *et al.* 2000). Individuals with autism have difficulties with rapidly shifting attention from one mode to another. They show slowed covert orienting of visuospatial attention independent of motor response and, unlike normal controls, show little evidence of having oriented attention within 100 ms of an attention-directing cue. They orient after 800–1200 ms (Townsend *et al.* 1999). This would sabotage the time-sensitive preverbal mutual co-ordination described above.

There are developmental consequences of preverbal interaction for normal infants. For example, they acquire social use of language through protoconversations (Bates *et al.* 1975; Ninio & Snow 1988, 1996). Furthermore, analysis of gaze-switching during infant–adult interactions has been found to predict the theory of mind abilities at nearly 4 years (Charman *et al.* 2000). Wimpory (1995; Wimpory *et al.* 2000) has previously suggested that the experience of disparate attitudes through teasing within preverbal interaction may enable appreciation of the ‘double meanings’ required for symbolic play (Trevvarthen & Logotheti 1987; Reddy 1991; Hobson 1993). In the light of the above, we recognize both a concurrent and a developmental role for social timing in the social, communicative and symbolic deficits of autism (Newson 1984; Courchesne *et al.* 1994; Wimpory 1995; Wimpory & Nash 1999).

Biophysiological timing

Even able people with autism have a very poor intuitive sense of time (Boucher 2001). They also appear to experience difficulties in the temporal binding of complex perceptual stimuli (Brock *et al.*, 2002). Biophysiological time forms the basis of Boucher’s model of autism which highlights abnormalities in relation to the circadian cycle’s physiological measures (Takahagi *et al.* 1986; Ritvo *et al.* 1993; Nir 1995), as well as abnormal sleep–wake cycles (Richdale & Prior 1995). Central to Boucher’s (2001) theory is that different effects will result from timing problems in ‘biological clocks’ operating at milliseconds, seconds, tens of seconds or minutes. Whilst inter-related biological oscillators (or temporal processors) are essential for information processing, faster oscillators are employed for communication than for movement. Impairment in any of these oscillators would have physiological and psychological consequences, and Boucher suggests that the severity of the impairment would depend on both the sites and the extent of the deficit in an integrated system (Boucher 2001).

Evidence from neurobiology and neuropsychology

The neurobiological basis of autism is not well established. The most consistent microscopic observations, based on postmortem neuropathological research and MRI studies, are the absence or paucity of Purkinje cells in the cerebellar hemispheres (Courchesne 1997). The cerebellum is associated with control of fine motor movements. Purkinje cells form part of the cerebellum and project deep into the motor nuclei of the brain. They integrate complex inputs in the cerebellum and operate as output neurones. The rapid attention shifting difficulties in autism are attributed to this reduction in Purkinje cells. Initial results of Purkinje cell loss in mice do not result in a gross motor dysfunction, but these mice display features which are associated with autism and are timing-related: subtle motor deficits, hyperactivity and enhanced repetitive behaviour (Martin *et al.* 2000). Teitelbaum *et al.* (1998) claim that their analysis of movement and muscle patterns clearly discriminate video recordings of 4–6-month-old infants subsequently diagnosed with autism.

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Evidence from molecular genetics

Evidence for a genetic basis for timing in communication is provided by the fruit fly (*Drosophila*). The fly gene *per* was first identified by the induction of three *per* mutations that shorten, lengthen or obliterate the fly's circadian rhythms (Konopka & Benzer 1971). Additionally, these *per* mutations affect the duration of the interpulse interval of the male fly's love song, a primitive communication leading to mating. The change in the interpulse interval (longer, shorter or nulled) mirrors the mutant's circadian defects. Konopka, Kyriacou & Hall (1996; p. 136) point toward *per* functioning in different roles (circadian or high frequency) in different parts of the CNS of the fly and further entertain the notion that *per* 'influences song rhythmicity by a developmental effect'.

There are striking similarities between the clock genes of flies and mammals. The human gene (*hPer1*) is 44% homologous with *Drosophila per* (Sun *et al.* 1997). The mouse homologue, *mPer1*, is expressed in central nervous system structures related to timing, e.g. the suprachiasmatic nucleus (SCN), retina, pars tuberalis of the pituitary, and, Purkinje cells of the cerebellum (Sun *et al.* 1997; cf. neuroanatomy of autism above). We suggest it is possible that the human genes *hPer1*, *hPer2* and *hPer3* also have a dual function with respect to the timing and (together with the other associated clock genes) may control high frequency oscillators associated with human preverbal communication and concomitant development. If *per* is committed to either circadian function or high frequency oscillatory function concomitantly with its specific tissue location in the CNS, we note that methylation may determine which role the *per* plays, because the methylation status of genes can control whether or not a given gene is expressed in a given tissue location (Cedar 1988).

There are recent unpublished findings of mutations in *mecp2* (a methylation-related gene) in two girls with autism showing none of the classic signs of Rett Syndrome (R. Carney, cited in Foldstein & Rosen-Sheidley, 2001) and base changes have been found for autistic subjects in other methylation-related genes: *mbd1*, *mbd2* and *mbd3* (Yamagata *et al.* 2001). The implication of methylation may

also help to account for the sex ratio in autism (three males to every female).

A precedent of clock genes playing a causative role in a psychiatric disorder that was previously only behaviourally identifiable is provided by *hPer2* (Toh *et al.* 2001). A single point mutation in *hPer2* has been found to be responsible for Familial Advanced Sleep Phase Syndrome. There is also some intriguing evidence that tentatively points towards an association between *hPer2* and autism. A case of autism was recently reported to have a deletion on chromosome 2q37.3 (Smith *et al.* 2001). *HPer2* is one of 15 genes affected by this deletion on the paternally derived chromosome. Smith *et al.* (2001) cite nine additional cases of patients with autism or autistic type behaviour showing cytogenetic abnormalities involving chromosome 2q37 including a study of 10 autistic patients who appeared normal on standard cytogenetic analysis which revealed one with a deletion at *hPer2*'s location (2q37.3; Wolff *et al.* 2000).

Evidence from genome scans

In genome-wide scans for autism using the strictest diagnostic criteria for the disorder, 2q is the only locus identified as above the level recognized as statistically significant (Lander & Kruglyak 1995) in linkage study (Buxbaum *et al.* 2001; IMGSAC 2001). The International Molecular Genetic Study of Autism Consortium's (IMGSAC 2001) multipoint maximum LOD score of 4.8 for a marker mapping on 2q31.1 decreased to 3.74 when additional subjects were included who failed to reach the full diagnostic criteria for autism. Buxbaum and colleagues achieved a similar directional effect for strictly, as opposed to broadly, defined cases of autism on markers mapping 2q31.1 and 2q32.1. Their maximal multipoint nonparametric linkage scores were 3.32 and 2.39 for strictly and broadly defined cases, respectively. This indicates that 2q may hold a susceptibility locus for autism specifically, as opposed to the overlapping/associated disorders that may comprise Pervasive Developmental Disorders. In addition to two clock genes on 2q, *hper2* and *npas2*, there is also a putative methylation-related gene at the region identified with significant linkage (*kiaa1461* at 2q31.1, see Table 1).

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Table 1 Human clock genes and two methylation-related genes

Gene	Location	Supporting evidence from autism studies
hPER3	1p36.23	
NPAS2/MOP4	2q12.1	Two case studies of patients with autism and fra(2)(q13) (Jayakar <i>et al.</i> 1986; Saliba & Griffiths 1990) (NPAS2 is a specific brain homologue of CLOCK 4q12)
KIAA1461 (a putative methylation-related gene)	2q31.1	Genome screen data: i) Buxbaum <i>et al.</i> (2001) gave highest nonparametric linkage scores of 3.32 and 2.39 for markers mapping on 2q31.1 and 2q32.1, respectively. ii) IMGSAC 2001's most significant MLS (4.8 for strictest diagnosed cases) was at a marker mapping 2q31.1
hPER2	2q37.3	Ten case studies of patients with autism or autistic type behaviour showing cytogenetic abnormalities involving chromosome 2q37 (all cited by Smith <i>et al.</i> 2001) including: A study of 10 autistic patients appearing normal on standard cytogenetic analysis which found one with a telomeric deletion (2q37.3) Wolff <i>et al.</i> (2000), and molecular delineation of 2q37.3 in an autism case identifying hPER2 as 1 of 15 genes (Smith <i>et al.</i> 2001)
CRY2	11p11.2	
NPAS3/MOP3/BMAL1	11p15.2	RFLP analysis highlights HRAS region (11p15.3) showing increased heterozygosity and decreased homozygosity in autistic subjects vs. controls ($P < 0.01$; Herault <i>et al.</i> 1994).
TIMELESS	12q13.3	Genome screen data: (i) Barrett <i>et al.</i> (1999) gave highest 2-point lod (1.3) at a marker mapping on 11p15.3 ii) Risch <i>et al.</i> (1999) gave MLS (> 1) at a marker mapping on 11p13
CRY1	12q23.3	Single case re: fra(12)q13; Autism & SMR (Wassink <i>et al.</i> 2001) Case study re 12q23.3 Autistic behaviour and TS with SMR (Fahsold <i>et al.</i> 1991) IMGSAC's (1998) genome screen gave MLS (.86) at a marker mapping on 12q23.3
hPER1/RIGUI	17p12	Four case studies re: deletion on 17p11.2 with autism or some autistic behaviour (Mariner <i>et al.</i> 1986; Lockwood <i>et al.</i> 1988; Cabral <i>et al.</i> 1989; Vostanis <i>et al.</i> 1994) Asperger's Syndrome case study re: balanced <i>de novo</i> translocation involving 17p13.3 (Anneren <i>et al.</i> 1995) Risch <i>et al.</i> 's (1999) genome screen gave MLS (1.21) at a marker mapping on 17p13.2 (this marker was their second most significant MLS for FSZ).
NPAS1/MOP5	19q13.33	Genome screen data: IMGSAC (1998) gave MLS (1.16) for an unmapped marker; the nearest marker maps on 19q13.11 Liu <i>et al.</i> (2001) gave MLS (1.7) for a marker mapping to 19q13.41 (re: strictly diagnosed autism)
MBD3 (a methylation-related gene)	19p13.3	Case study re: fra(19)(p13) with autistic behaviour (Chodirker <i>et al.</i> 1987) Genome screen data: Philippe <i>et al.</i> (1999) gave MLS (1.17) at a marker mapping on 19p13.12 (i.e. second highest MLS in the whole study) Liu <i>et al.</i> (2001) gave MLS (2.53) at a marker mapping to 19p13.11 (i.e. region of greatest significance for strictly diagnosed autism)

(MLS = Maximum LOD Score; MMR = Moderate Mental Retardation; SMR = Severe Mental Retardation; TS = Tuberculous Sclerosis).

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The general lack of statistical significance from linkage studies supports the hypothesis that a number of genes of limited effect are operating in autism (Risch *et al.* 1999). 'In an analysis of family history data, Andrew Pickles and colleagues rejected single-locus and heterogeneity models in favour of anything from two to 10 loci, with three epistatic (interacting) loci being most plausible. Using a different approach, Paul Van Eerdewegh, obtained similar results.' (Foldstein & Rosen-Sheidley 2001; p.946; Pickles *et al.* 1995; P. Van Eerdewegh, unpublished observations). The core element of the mammalian clock involves seven genes that are epistatic: *per1*, *per2*, *per3*, *npas3*, *clock*, *cry1* and *cry2* (Shearman *et al.* 2000). In addition to this core clock mechanism are the genes: *npas2* (a brain specific homologue of clock), *npas1*, and *Drosophila* timeless homologues awaiting further description. Table 1 shows clock genes in relation to data from autism studies together with the two methylation-related genes with loci highlighted by genome scans for autism.

Conclusion

We conclude that the mutation in an epistatic clock (methylation-related) gene mechanism of concerted output effect (timing) could; firstly fulfil Risch, Pickles and Van Eerdewegh's requirements for epistasis and a number of genes of small effect; secondly, explain the cases of hPer2 and methylation-related genes linked to the disorder, and thirdly, also explain the timing deficits that accompany, and we propose are causal in, autism.

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D. Wimpory,¹ B. Nicholas² & S. Nash¹

¹School of Psychology, University of Wales, Bangor LL57 2AS, UK.

²Cefn yr Ynys, Mynydd Llandegai LL57 4BZ, UK.

E-mail: d.wimpory@bangor.ac.uk