

Autonomic responses of autistic children to people and objects

William Hirstein^{1,2*}, Portia Iversen² and V. S. Ramachandran¹

¹Center for Brain and Cognition, University of California, San Diego, La Jolla, CA 92093, USA

²The Cure Autism Now Foundation, 5455 Wilshire Boulevard #715, Los Angeles, CA 90036, USA

Several recent lines of inquiry have pointed to the amygdala as a potential lesion site in autism. Because one function of the amygdala may be to produce autonomic arousal at the sight of a significant face, we compared the responses of autistic children to their mothers' face and to a plain paper cup. Unlike normals, the autistic children as a whole did not show a larger response to the person than to the cup. We also monitored sympathetic activity in autistic children as they engaged in a wide range of everyday behaviours. The children tended to use self-stimulation activities in order to calm hyper-responsive activity of the sympathetic ('fight or flight') branch of the autonomic nervous system. A small percentage of our autistic subjects had hypo-responsive sympathetic activity, with essentially no electrodermal responses except to self-injurious behaviour. We sketch a hypothesis about autism according to which autistic children use overt behaviour in order to control a malfunctioning autonomic nervous system and suggest that they have learned to avoid using certain processing areas in the temporal lobes.

Keywords: autism; electrodermal; autonomic; face recognition; amygdala

1. INTRODUCTION

Childhood autism, which was first described by Kanner (1943), is a breakdown in the normal development process so that the child fails to learn language at the normal rate and fails to develop a normal interest in other people. Autistic children often develop 'self-stimulatory' behaviour, such as rocking, wiggling their fingers in front of their eyes, or obsessively lining up objects such as books or small toys, which they engage in for hours if uninterrupted. Studies have revealed differences between the brains of autistic and normal people in the cerebellum (Courchesne 1997) and the brainstem (Rodier *et al.* 1996), but lately attention has focused on the amygdala. In a recent article, Baron-Cohen *et al.* (2000) proposed what they call the amygdala theory of autism, continuing a line of inquiry initiated by Brothers (1989) and Brothers & Ring (1992). Several pieces of evidence indicate a role for the amygdala in autism. The only current candidate for an animal model of autism derives from Bachevalier's (1994, 1996) important discovery. She ablated the amygdalae and nearby temporal cortices of newborn rhesus monkeys and found that they later exhibited several of the characteristic features of autism, including active withdrawal from other monkeys and motor stereotypies, such as spinning or somersaulting, and had blank, expressionless faces (Bachevalier 1994, 1996). In addition, histopathological examination of autistic brains reveals abnormalities in the amygdala, as well as other parts of the limbic system (Bauman & Kemper 1994). Further, the amygdala has neurons that are sensitive to gaze direction and autistic children have difficulty interpreting gaze information (Baron-Cohen 1995; Baron-Cohen *et al.* 1997).

Two other factors that are not sufficiently emphasized may also indicate a role for amygdala pathology in

autism. First, epilepsy: 35–45% of autistic children have suffered epileptic seizures (Olsson *et al.* 1988; Volkmar & Nelson 1990), a figure that would no doubt be higher if every autistic child was monitored adequately (for at least 24 h) for seizure activity with EEGs. Of the autistic children known to have had seizures 70% have a seizure focus in their temporal lobes. Seizures in the temporal lobes are likely to involve the amygdala—it is one of the most kindling-prone organs in the brain (Goddard *et al.* 1969). Second, autism can also be caused by a bornavirus that is known to have a predilection for limbic structures, including the amygdala (Ludwig & Bode 1997; Pletnikov *et al.* 1999).

There is reason to think that, if the amygdala is damaged in autism, this may produce autonomic disturbances. The amygdala has what is thought to be an excitatory role in producing autonomic responses, such as pupil dilation, sweating of the palms and decreased gastric motility, via its connections with the lateral hypothalamus (Lang *et al.* 1964). Direct electrical stimulation of the amygdala produces strong skin conductance responses (SCRs) in humans (Mangina & Beuzeron-Mangina 1996) and ablation of the amygdala in rhesus monkeys decreases the size of SCRs to tones (Bagshaw *et al.* 1965). SCRs are easy to measure, yet allow a high-resolution measure of activity of the autonomic nervous system. They are produced by activity of the eccrine sweat glands, which are located on the palms and soles of the feet (as opposed to the body-wide apocrine sweat gland system, which functions primarily to regulate body temperature). Because of their connections to high-level brain systems, the eccrine sweat glands provide a window onto certain types of psychological activity. Along with dilation of the pupils and decreased motility of the gastrointestinal tract, sweating of the palms produced by the eccrine system is part of the sympathetic ('fight or flight') branch of the autonomic nervous system. The primary neurotransmitter of the eccrine system is norepinephrine and its main

*Author for correspondence (williamh@elmhurst.edu).

receptor type is an α_1 -adrenergic receptor (Venables 1991; Shields 1993).

Several different cortical areas have been shown to be involved in the production of SCRs or at least to possess the requisite neuroanatomical connections with which to do so. These may be subdivided into two types: those which produce SCRs related to bodily activity, such as hand clenching or deep breathing, and those which produce SCRs related to cognitive activity, such as the sight of a significant person or the sight of a gruesome murder. One route by which a psychological SCR may be produced by visual perception begins in the areas of the temporal lobes responsible for object analysis. It then progresses to the lateral nucleus of the amygdala, from where it travels to the basal nucleus (Amaral *et al.* 1992; Halgren 1992). A circuit is completed when the amygdaloid basal nucleus returns projections to the same areas of the temporal lobes. In addition though, the basal nucleus projects to the central nucleus, which is considered to be the output centre of the amygdala. The central nucleus can initiate sympathetic activity via its connections to the hypothalamus and the nucleus of the solitary tract (Amaral *et al.* 1992). The orbitofrontal cortex also sends projections to the lateral hypothalamic nucleus, both via the amygdala and directly.

Previous SCR studies of autistic children have shown that they do not show the normal rate of habituation in the magnitude of their SCRs to the same stimulus over time (Van Engeland 1984; Barry & James 1988). Palkovitz & Wiesenfeld (1980) failed to find differences in electrodermal responses to auditory stimuli, although they noted that the autistic group had a higher baseline (see below) electrodermal level. However, electrodermal responses to eyes and faces have not been compared with responses to less salient objects. Hutt & Hutt (1965) speculated that autism involves chronically high arousal levels and Barry & James (1988) observed larger tonic electrodermal activity as well as larger responses to sounds in autistic children, but attempts to verify this by measuring blood levels of norepinephrine have been inconsistent: Lake *et al.* (1977) found elevated levels, whereas Young *et al.* (1981) and Gilberg *et al.* (1983) failed to find elevated levels of an epinephrine metabolite.

2. METHODS

(a) *Subjects*

The primary subjects for the two experiments that were performed were a group of 37 autistic children (31 males and six females) aged 3–13 years (mean age 7.7 years) who were recruited through the autism research funding foundation Cure Autism Now. The first experiment had stringent requirements and we were only able to gather sufficient data from 25 of the 37 participants, whereas all 37 subjects took part in the second experiment. All of the autistic subjects met the criteria described in the fourth edition of the *Diagnostic and statistical manual of mental disorders* (American Psychiatric Association 1994). These criteria are (i) impaired reciprocal social interaction, (ii) absent, odd or severely delayed language skill, and (iii) a restricted repertoire of interests and activities. The autistic subjects spanned a wide range of functional levels, as evidenced by differences in their basic verbal abilities: 27% were unable to speak at all, 49% had some ability to communicate verbally (but typically had to be urged to speak and tended not to use

complete sentences), and 24% had normal linguistic ability (while occasionally producing utterances that were pragmatically odd or inappropriate). The control group consisted of children, college undergraduates and adults. When no significant differences were found between the children on the one hand and the adults and college students on the other, all the normals were combined into a single control group for the first experiment, totalling 25 participants.

(b) *Experiment 1: 'look at me'*

(i) *Rationale*

The most salient parts of the human face for normal humans are the eyes. It has been shown that normal people register a larger SCR when a person they are looking at reciprocates their gaze as compared with when the person looks away (Nichols & Champness 1971). We wondered what sort of response autistic children would have to locking gaze with someone as compared with simply looking at an object.

(ii) *Procedure*

Electrodermal activity was measured as skin conductance changes between the volar surfaces of the distal phalanges of the index and middle fingers of the subject's hand (Venables & Christie 1980). Silver/silver chloride electrodes were attached with hook-and-loop fastener straps. SCR signals travelled first to a Biopac GSR100 amplifier module (Biopac Systems Inc., Santa Barbara, CA, USA) and then to an analog-to-digital converter and, finally, to a computer which recorded and displayed the data. The child would be directed to look at either his or her mother's eyes or at a plain paper cup in alternate trials. Responses occurring within 1–3 s after gaze fixation were counted as being caused by the stimulus (Levinson & Edelberg 1985). A total of four trials looking at the cup and four trials looking at their mother were completed for each subject.

Autistic children tend not to hold eye contact for very long (Hutt & Ounsted 1966), so the normal controls were instructed to lock gaze quickly and then look away. In the trials in which the child looked at his or her mother's eyes, the mother verified whether or not eye contact was actually made. Use of an eye-tracking device in order to assure that the child is locking gaze with his or her mother is not practical here because many of our children would have refused to wear the eye-tracking goggles. The use of such goggles also requires a calibration procedure, which is subject to the same doubts about whether the child is actually focusing on the stimulus. Two factors indicate that enough precision can be achieved by having the mother monitor gaze direction. First, the human ability to perceive whether or not someone is looking at us is extremely accurate (see, for example, Anstis *et al.* 1969). In addition, in cases in which children did appear to be looking slightly away from the mother's eyes, the mothers unavoidably worked actively to put their eyes in a position where gaze locking took place.

(c) *Experiment 2: electrodermal activity during self-stimulation behaviours*

(i) *Rationale*

We had informally observed both that some autistic children had extremely high sympathetic activity and that immersion of their hands in a large bowl of dry beans caused steep reductions in electrodermal activity. We hypothesized that it is precisely the calming nature of this and other similar 'mindless' activities that causes autistic children to engage in them for hours: they are

trying to regulate an autonomic system that is not self-regulating by engaging in whatever activities bring their sympathetic tone down to a bearable level. Sometimes the sympathetic activity is so strong the only actions open to the child are simple, repetitive ones that reduce it. 'We have never seen him walk away from the beans', one mother said of her autistic son. We were also curious about whether all 'self-stimulatory activities', including watching segments of video over and over, lining up books or toys in a row, etc., had this calming effect.

(ii) Procedure

The child and his or her parent(s) were seated in the testing room, which was designed to be non-threatening, e.g. it contained toys of all types and resembled a day care centre rather than a laboratory. Electrodermal activity was then monitored for 35 min as the child engaged in (i) sitting quietly, (ii) interaction with parents, (iii) immersion of the hands in dry beans, and (iv) favourite self-stimulation activities, such as watching a favourite video, arranging books or toys, flipping through the pages of a book and so on. Skin conductance testing with autistic children presents several possible problems (see, for example, Edelson *et al.* 1999). Several steps were taken in order to increase our chances of obtaining valid data. Parents were informed prior to testing that the monitoring would involve the use of finger electrodes so that they could tell the child what to expect. Hook-and-loop fastener straps without electrodes were sometimes put on first in order to allow the child to become accustomed to the feel and look of them, or the parent would sometimes put the electrodes on his or her own fingers in order to show the child that they were harmless. The electrodes were then placed on the child's fingers of the non-dominant hand in order to leave the dominant hand free for activity. When a child had trouble understanding or obeying the instruction to keep the electrode hand still, a parent would gently hold the child's open hand by the wrist, keeping it in his or her lap. Movement artefacts can be easily distinguished from data by their jagged appearance on the output trace, as SCR level always changes in a smoothly continuous manner. All such artefacts were excluded from the analysis. In addition, in order to verify that the large SCR changes that we observed in several of the children were not caused by movements, we simultaneously recorded the electromyographic activity in their hands and forearms.

3. RESULTS

(a) *Experiment 1: 'look at me'*

Although the normal subjects produced larger SCRs (mean \pm s.d.) to the person than to the cup (response to person: $0.164 \pm 0.239 \mu\text{S}$, and response to cup: $0.093 \pm 0.116 \mu\text{S}$) ($t = 2.45$, $p < 0.02$ and $n = 25$), the autistic children as a whole showed no difference (response to person: $0.118 \pm 0.105 \mu\text{S}$; and response to cup: $0.099 \pm 0.187 \mu\text{S}$) ($t = 0.535$ and $n = 25$). We also tested identical twins. One of these twins had improved to normal levels of function after being diagnosed as autistic, whereas the second twin had remained autistic. The autistic twin's average SCRs were a response to person of $0.017 \mu\text{S}$ and a response to cup of $0.018 \mu\text{S}$, and the non-autistic twin's average SCRs were a response to person of $0.128 \mu\text{S}$ and a response to cup of $0.04 \mu\text{S}$. Interestingly, we also noticed a trend towards above-normal SCRs to locking eye gaze in our higher functioning subjects, which we are currently testing experimentally.

(b) *Experiment 2: electrodermal activity during self-stimulation behaviours*

A normal skin conductance testing session begins with the establishment of a baseline, i.e. the skin conductance impedance normally present in a person's hand and sweat system of the palms. SCRs are then measured as deviations from this baseline. It became apparent at the start that many of the autistic children did not have normal baseline activity. Their skin conductance levels typically rose steadily after the beginning of testing to above-normal levels. The SCRs seemed to initiate this rise in level by failing to decay, i.e. by failing to return to a baseline, which produced a step effect in the output trace. Once the level was high, short-duration (3 s), large-amplitude (3–5 μS) SCRs were observed in several of the children. However, immersion of the hand in dry beans brought about huge drops in skin conductance levels many times those seen in normal adults or children.

We observed two clearly distinguishable types of autonomic responder in our sample. Most of the autistic children (26 out of 37) had abnormally high electrodermal activity, which could be shut off by immersion of the hands in dry beans; we call these children type A responders. However, there was also a second type of child, who had a very flat response with either no individual SCRs or SCRs produced only by extreme activities, such as self-injurious behaviour; we call these children type B responders. The type A child's response was characterized by a widely varying electrodermal baseline with large SCRs, which stopped completely after immersion of the hands in dry beans. Other activities that were capable of completely shutting down the eccrine system were eating, sucking on sweets, being wrapped in a heavy blanket and deep pressure massage. Attempts at interaction with other people seemed to exacerbate the hyperactivity most strongly. Interruption of their activities by other people, such as turning the television set off during a favourite video, often produced extremely large responses with agitated behaviour following immediately, indicating that the resistance to change one sees in autistic children may be caused or exacerbated by such bursts of sympathetic activity, which the child actively attempts to avoid or tries to damp down.

Because of the way their autonomic activity alternates between hyperarousal and hypoarousal, the type A child exhibits a much larger range of electrodermal levels than normal children. The average difference between the highest and lowest recorded levels of our autistic children was $18.4 \mu\text{S}$ as compared to only $4.7 \mu\text{S}$ for the normal children ($p < 0.001$). Because the difference between the highest and lowest skin conductance levels is most probably relative to the absolute level value (i.e. a high–low range of $5.0 \mu\text{S}$ is more significant in a subject who varied from 3.0 to $8.0 \mu\text{S}$ than in a subject who varied from 16.0 to $21.0 \mu\text{S}$), we recorded range values as a percentage of the highest value. A child who varied from 5.0 to $10.0 \mu\text{S}$ would then have a range score of 50%. This statistic distinguishes autistic children, whose percentages tend to be above 60%, from normal subjects, whose percentages tend to fall below 60%.

Contrary to the widely varying baseline of the type A child, we observed a largely flat baseline in 4 of the 37 children, with either a complete absence of SCRs or

SCRs produced only by extreme, e.g. self-injurious, behaviour. The baseline remained flat even when these children were upset and crying. Self-injurious behaviour was present in two of these four. This sort of lack of response is to be distinguished from hyporesponsive normal subjects, who fail to register SCRs to psychological stimuli, as the autistic children had a much more profound lack of response to many of the normal physical stimuli, such as deep breathing or clenching a fist. One type B child (H.T.) engaged in high-risk behaviour, such as climbing high up in a tree while carrying his skateboard. It is tempting to speculate that the type B child is engaging in self-injurious behaviour or occasionally taking risks in order to produce more autonomic activity. Two of the four may have been hyporesponsive due to the anti-epileptic medications tegretol and topamax. However, the other two appear to be 'natural' type B children. Along these same lines, non-autistic hyperactive children often have low sympathetic activity, which is why ritalin—a stimulant—works to reduce their hyperactivity.

These results might also help explain some of the inconsistencies among earlier studies (e.g. the failure of Palkovitz & Wiesenfeld (1980) to find differences in the SCRs to sounds of autistic and normal children). Because of the fact that hyporesponsive type B children tend to balance out hyper-responsive type A children, depending on the ratios of the two in their experimental group, a study will either find hyper-responsiveness, hyporesponsiveness or, more probably, neither. Even if a study is restricted to type A children they may not show chronically hyperactive sympathetic activity (see, for example, Hutt & Hutt 1965; Barry & James 1988) because of the tremendous capacity the children have for reducing autonomic activity via repetitive and/or somesthetic activity. Instead, it may be truer to say that the type A child has either hyperactive or hypoactive sympathetic activity, depending on what the child is doing. Similar remarks apply to the inconsistent findings about the levels of norepinephrine or its metabolites among autistic children. If the child does not engage in this calming behaviour, either because his or her parents restrict their self-stimulation activity, or he or she is simply unable to find a calming activity, we would expect to see signs of chronically high sympathetic activity.

4. DISCUSSION

The large reductions in sympathetic activity that we observed could explain why autistic children so relentlessly seek out self-stimulatory actions. They are seeking to control an autonomic system that, in spite of its name ('autonomic' means 'self-governing') fails to govern itself and seems to require certain behaviours on their part for its regulation. Hence, the advice often given to parents, namely to prevent their children from self-stimulating, may be unwise. At the very least, children may need to engage briefly in relaxing activities when their arousal levels become too high.

One conception of the amygdala's contribution to higher level cognition is that it ensures that the higher cortical centres engage in cognition that furthers the survival and goals of the organism. The limbic-autonomic

network, far from being merely a primitive producer of emotions, has a vital role in higher level cognition, primarily by attaching a sense of value to different percepts, concepts or thoughts; one might say that it determines what the cognitive system thinks *about*. This sense of value may be particularly vital in tuning the immature cognitive system of the infant. For example, normal children learn that other people are interesting and valuable, and we suggest that autistic children do not. If the autonomic system is either constantly on maximum alert, so that almost everything is tagged as significant, or chaotic, so that the alerts have nothing to do with the normal alerting stimuli (type A), the child simply acts to shut the system off. If, conversely, the system reports that nothing is significant, the child may engage in extreme behaviours in order to produce that sense of significance (type B). One might hypothesize that the cortico-limbic system is responsible for maintaining a kind of *cognitive homeostasis*: significance detection needs to be tuned in order to label events as significant at just the right frequency. This frequency is determined partly by the organism's response time, but also by what its cognitive system is capable of processing.

Two routes of visual processing leave the early cortical visual areas (Ungerleider & Mishkin 1982). A dorsal route that involves mainly peripheral vision moves towards the parietal cortex in order to participate in the computations necessary for navigating our body through space, reaching for things and so on. A ventral route runs forward along the temporal lobes and involves mainly focal vision. Its specialty is the identification of objects, including people; one finds cells along this processing stream that respond most strongly to the sight of faces. Visual processing in the temporal lobe progresses towards the amygdala, which is involved in producing emotional reactions to stimuli (LeDoux 1992). When the amygdala identifies a stimulus as important, it can produce autonomic responses via the connections that the amygdaloid central nucleus has to the hypothalamus as well as to the solitary tract.

The parts of the amygdala connected to the cortex are also the parts damaged by epileptic seizures, i.e. the basal and lateral nuclei (Pitkanen *et al.* 1998). Conversely, the central nucleus is largely undamaged by seizures and, hence, is still able to produce autonomic reactions via its hypothalamic connections. Assuming that this malfunction is at its worst during seizures, we suggest that autistic children with epilepsy simply learn to avoid using those parts of the brain in which a seizure is likely to begin, i.e. the ventral stream. This learned avoidance happens through a very basic conditioning process: engaging in a certain activity causes unpleasant autonomic sensations; therefore, do not engage in that activity. The central nucleus has been strongly implicated in the acquisition of conditioned responses to perceptual objects (Bechara *et al.* 1995; LaBar *et al.* 1995). Interestingly, in 1997, hundreds of Japanese children watching a cartoon had seizures, apparently caused by the flashing eyes of one of the cartoon characters, a phenomenon which highlights the connection between sensitivity to gaze and seizures.

Unfortunately, the activities that a child learns to avoid are those that it is vital that the child learn at that age, such as the activities normally ascribed to the ventral

visual stream, e.g. the visual identification of objects, words and people. One advantage of our hypothesis is that it explains the well-known tendency of autistic children to use their peripheral vision for activities for which we would normally use focal vision: in our hypothesis the use of focal vision activates the ventral stream, which produces unpleasant autonomic sensations via the amygdala–hypothalamus route. This also suggests why flapping of the hands is such a frequently seen behaviour in autistic children: it combines calming repetitive physical activity with maximal stimulation of the peripheral visual centres in the dorsal stream responsive to motion (such as MT) by the quickly moving hands.

We have assembled data from several sources, including our own experiments, in order to form a more detailed hypothesis about the nature of temporal lobe dysfunction in autism. This is a broader conception of the nature of the problem in the temporal lobes of autistic individuals than those which focus on the amygdala. The problems at the tip of the temporal lobe involving the amygdala cause processing not to flow normally through the temporal lobes from the occipital lobes. The bulk of processing resources are instead directed dorsally, toward the relatively intact parietal lobes. The amygdala sits at several pivotal junctions of the systems involved in perception, emotion and thought. Damage there, although local to the amygdala and temporal lobes, might cause the amygdala's output to either vastly exceed its normal bounds (type A) or to simply shut off (type B), resulting in two rather different but equally disastrous brain malfunctions. The children respond by attempting to correct this problem by engaging in certain activities or, in the case of type A children, by doing nothing.

The authors wish to thank the Cure Autism Now Foundation, Brian Keeley, Daniel Kolak, Sandy Bluhm and Austin Burka for help in conceiving and executing these experiments. We also wish to thank M. Goodale, F. H. C. Crick and an anonymous referee for valuable comments.

REFERENCES

- Amaral, D. G., Price, J. L., Pitkanen, A. & Carmichael, S. T. 1992 Anatomical organization of the primate amygdaloid complex. In *The amygdala: neurobiological aspects of emotion, memory, and mental dysfunction* (ed. J. P. Aggleton). New York: Wiley-Liss.
- American Psychiatric Association 1994 *Diagnostic and statistical manual of mental disorders*, 4th edn. Washington, DC: American Psychiatric Press.
- Anstis, S. M., Mayhew, J. E. W. & Morley, T. 1969 The perception of where a face or TV 'portrait' is looking. *Am. J. Psychol.* **82**, 474–489.
- Bachevalier, J. 1994 Medial temporal lobe structures: a review of clinical and experimental findings. *Neuropsychologia* **32**, 627–648.
- Bachevalier, J. 1996 Brief report: medial temporal lobe and autism: a putative animal model in primates. *J. Autism Dev. Disord.* **26**, 217–220.
- Bagshaw, M. H., Kimble, D. P. & Pribram, K. H. 1965 The GSR of monkeys during orientation and habituation and after ablation of the amygdala, hippocampus, and inferotemporal cortex. *Neuropsychologia* **3**, 111–119.
- Baron-Cohen, S. 1995 *Mindblindness*. Cambridge, MA: MIT Press.
- Baron-Cohen, S., Baldwin, D. A. & Crowson, M. 1997 Do children with autism use the speaker's direction of gaze strategy to crack the code of language? *Child Dev.* **68**, 48–57.
- Baron-Cohen, S., Ring, H. A., Bullmore, E. T., Wheelwright, S., Ashwin, C. & Williams, S. C. 2000 The amygdala theory of autism. *Neurosci. Behav. Rev.* **24**, 355–364.
- Barry, R. J. & James, A. L. 1988 Coding of stimulus parameters in autistic, retarded, and normal children: evidence for a two-factor theory of autism. *Int. J. Psychophysiol.* **6**, 139–149.
- Bauman, M. L. & Kemper, T. L. 1994 Neuroanatomic observations of the brain in autism. In *The neurobiology of autism* (ed. M. L. Bauman & T. L. Kemper). Baltimore, MD: Johns Hopkins University Press.
- Bechara, A., Tranel, D., Damasio, H., Adolphs, R., Rockland, C. & Damasio, A. R. 1995 Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. *Science* **269**, 111–115.
- Brothers, L. 1989 A biological perspective on empathy. *Am. J. Psychiat.* **146**, 10–19.
- Brothers, L. & Ring, B. 1992 A neuroethological framework for the representation of minds. *J. Cogn. Neurosci.* **4**, 107–118.
- Courchesne, E. 1997 Brainstem, cerebellar, and limbic neuroanatomical abnormalities in autism. *Curr. Opin. Neurobiol.* **7**, 269–278.
- Edelson, S. M., Edelson, M. G., Kerr, D. C. R. & Grandin, T. 1999 Behavioral and physiological effects of deep pressure on children with autism: a pilot study evaluating the efficacy of Grandin's hug machine. *Am. J. Occupat. Ther.* **53**, 145–152.
- Gilberg, C., Svennerholm, L. & Hamilton-Hellberg, C. 1983 Childhood psychosis and monoamine metabolites in spinal fluid. *J. Autism Dev. Disord.* **13**, 383–396.
- Goddard, G. V., McIntyre, D. C. & Leech, C. K. 1969 A permanent change in brain function resulting from daily electrical stimulation. *Exp. Neurol.* **25**, 295–330.
- Halgren, E. 1992 Emotional neurophysiology of the amygdala within the context of human cognition. In *The amygdala: neurobiological aspects of emotion, memory, and mental dysfunction* (ed. J. P. Aggleton). New York: Wiley-Liss.
- Hutt, C. & Hutt, J. 1965 Effects of environmental complexity on stereotyped behaviors of children. *Anim. Behav.* **13**, 1–14.
- Hutt, C. & Ounsted, C. 1966 The biological significance of gaze aversion with particular reference to the syndrome of infantile autism. *Behav. Sci.* **11**, 346–356.
- Kanner, L. 1943 Autistic disturbances of affective contact. *Nerv. Child.* **2**, 217–250.
- LaBar, K. S., LeDoux, J. E., Spencer, D. D. & Phelps, E. 1995 Impaired fear conditioning following unilateral temporal lobectomy in humans. *J. Neurosci.* **15**, 6846–6855.
- Lake, C. R., Ziegler, M. G. & Murphy, D. L. 1977 Increased norepinephrine levels and decreased dopamine- β -hydroxylase activity in primary autism. *Arch. Gen. Psychiat.* **34**, 553–556.
- Lang, A. H., Tuovinen, T. & Valleala, P. 1964 Amygdaloid after-discharge and galvanic skin response. *Electroencephalogr. Clin. Neurophysiol.* **16**, 366–374.
- LeDoux, J. E. 1992 Brain mechanisms of emotion and emotional learning. *Curr. Opin. Neurobiol.* **2**, 191–197.
- Levinson, D. F. & Edelberg, R. 1985 Scoring criteria for response latency and habituation in electrodermal research: a critique. *Psychophysiology* **22**, 417–426.
- Ludwig, H. & Bode, L. 1997 The neuropathogenesis of Borna disease infections. *Intervirology* **40**, 185–197.
- Mangina, C. A. & Beuzeron-Mangina, J. H. 1996 Direct electrical stimulation of specific human brain structures and bilateral electrodermal activity. *Int. J. Psychophysiol.* **22**, 1–8.
- Nichols, K. A. & Champness, B. G. 1971 Eye gaze and the GSR. *J. Exp. Soc. Psychol.* **7**, 623–626.
- Olsson, L., Steffenberg, S. & Gillberg, C. 1988 Epilepsy in autism and autistic-like conditions: a population-based study. *Arch. Neurol.* **45**, 666–668.

- Palkovitz, R. J. & Wiesenfeld, A. R. 1980 Differential autonomic responses of autistic and normal children. *J. Autism Dev. Disord.* **10**, 347–360.
- Pitkanen, A., Tuunanen, J., Kalviainen, R., Partanen, K. & Salmenpera, T. 1998 Amygdala damage in experimental and human temporal lobe epilepsy. *Epilepsy Res.* **32**, 233–253.
- Pletnikov, M. V., Rubin, S. A., Vasudevan, K., Moran, T. H. & Carbone, K. M. 1999 Developmental brain injury associated with abnormal play behavior in neonatally Borna disease virus-infected Lewis rats: a model of autism. *Behav. Brain Res.* **100**, 43–50.
- Rodier, P. M., Ingram, J. L., Tisdale, B., Nelson, S. & Romano, J. 1996 Embryological origin for autism: developmental anomalies of the cranial nerve motor nuclei. *J. Comp. Neurol.* **370**, 247–261.
- Shields, R. W. 1993 Functional anatomy of the autonomic nervous system. *J. Clin. Neurophysiol.* **10**, 2–13.
- Ungerleider, L. G. & Mishkin, M. 1982 Two cortical visual systems. In *Analysis of visual behavior* (ed. D. J. Ungerleider, M. A. Goodale & R. J. W. Mansfield). Cambridge, MA: MIT Press.
- Van Engeland, H. 1984 The electrodermal orienting response to auditory stimuli in autistic children, normal children, mentally retarded children, and child psychiatric patients. *J. Autism Dev. Disord.* **14**, 261–279.
- Venables, P. H. 1991 Autonomic activity. *Ann. NY Acad. Sci.* **620**, 191–207.
- Venables, P. H. & Christie, M. J. 1980 Electrodermal activity. In *Techniques in psychophysiology* (ed. I. Martin & B. Kruppa). New York: Wiley.
- Volkmar, F. R. & Nelson, I. 1990 Seizure disorders in autism. *J. Am. Acad. Child Adolesc. Psychiat.* **29**, 127–129.
- Young, J. G., Cohen, D. J., Kavanagh, M. E., Landis, H. D., Shaywitz, B. A. & Maas, J. W. 1981 Cerebrospinal fluid, plasma, and urinary MHPG in children. *Life Sci.* **28**, 2837–2845.