

The World Journal of Biological Psychiatry

VOLUME 5

Number 4

October 2004



**The Official Journal of the World Federation
of Societies of Biological Psychiatry**

The World Journal of Biological Psychiatry

ISSN print edition 1562-2975

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Publisher

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Biological Psychiatry
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Printers

Printed in Belgium by the
World Federation of Societies of
Biological Psychiatry.

Subscription Information

- Volume 5 of The World Journal of Biological Psychiatry (ISSN print edition 1562-2975) is printed in 4 issues.
- The subscription price of Volume 5 (which excludes postage) is €200/£140 (USA, Canada and Mexico US\$240) for institutions; €100/£70 (USA, Canada and Mexico US\$120) for individuals. Single parts cost €60/£38 (USA, Canada and Mexico US\$64) plus postage.
- Orders may be sent to the Editorial Assistant at the address given above.
- All subscriptions are entered on a December to December year basis and must be pre-paid. Missing issues must be claimed within three months of non-receipt or upon receipt of the subsequent issues, whichever is longer. No cancellations will be accepted after the first issue has been mailed.

Indexing

The World Journal of Biological Psychiatry is included in the following:
Index Medicus/MEDLINE
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Editorial

SSRIs: Are the Accusations Justified?

A wave of uncertainty is currently rolling through child and adolescent psychiatry. It was triggered by information and warnings from various national licensing and regulatory authorities such as the British Medicines and Healthcare Products Regulatory Agency (MHRA) and the American Food and Drug Administration (FDA). They claim that induction of suicidality should be seen as a serious side effect of SSRIs in children and adolescents, and that extreme care should therefore be taken in considering whether SSRIs or other treatment approaches are indicated in depressive children or in those suffering from compulsive disorders. The licensing authorities mentioned above, whose warnings were followed by other licensing authorities, formulated their statements somewhat differently and also specified somewhat different conditions. However, the principal message remains the same. This information was taken up not only by professional circles but also by the general media, who often presented it in their usual distorted manner. This led to a great deal of concern and uncertainty, particularly by treating physicians and their patients.

These events are an echo of something that occurred over 10 years ago, shortly after the introduction to adult psychiatry of the first widely applied SSRI, fluoxetine. At that time the discussion was initiated in particular by Teicher et al. (1990) whose publication presented the suicide-inducing potential of fluoxetine in a series of case reports. Further case reports followed. The case reports were far from evidentiary and it was questionable how Teicher found out that fluoxetine should be implicated when most of the patients were being treated with several drugs simultaneously. Various pooled analyses of all data from placebo-controlled clinical studies available from pharmaceutical companies, e.g. for fluoxetine and paroxetine, could not confirm the case reports-based hypothesis that SSRIs induce suicidality. Pooled analyses of a large number of licensing studies performed over the past few years and submitted to the FDA or European Medicines Agency (EMA) have also not delivered any statistical confirmation of this hypothesis (Kahn et al. 2000; Storosum et al. 2001).

It is noteworthy that the data which formed the basis for the registration of various SSRIs and which were obtained from controlled studies performed in child and adolescent psychiatry do not allow any significant conclusions to be drawn, either for an individual drug or overall. At the most a numeric difference can be determined, although this is on a very low level (3.7 % in the treated group and 2.5 % in the placebo group). In this context it is also of interest that of the 4100 children and adolescents included in the SSRI studies, not one committed suicide (Vitiello et al. 2004). The statements of the licensing authorities may have been particularly stressed since there is an unfavourable ratio between the allegedly recognised risk and the benefit, i.e. the efficacy. The better part of the SSRI studies in depressive children and adolescents could not show a statistically significant superiority of the medication versus placebo with respect to antidepressive efficacy (Jureidini et al. 2004). The current situation may be explained by the emotional aspect, i.e. that the use of psychopharmacological drugs in children and adolescents is viewed particularly critically by the general population and that certain risks which may be seen as acceptable for adults can on no account be accepted for children and adolescents.

Much ado about nothing? Unfortunately, the current discussion has resulted in a renewed debate, particularly in the wider medical fraternity i.e. not only among specialists, as well as in the general population, about the basic question whether psychopharmaceuticals are indicated at all in the treatment of mental disorders in children and adolescents. Furthermore, the discussion about child and adolescent psychiatry has refuelled the earlier discussion about SSRI-induced suicidality in adults mentioned above.

In this context it is important to summarise briefly a few principal views on the basic evaluation of this question: clinically we basically assume that antidepressants reduce the suicidality associated with depression. In isolated cases an antidepressant, and also other psychopharmaceuticals such as benzodiazepines, can induce or increase suicidality or bring about other paradoxical effects (Möller 1992). It remains unclear whether drive-increasing or non-sedating antidepressants carry greater risks in this respect than non-drive-increasing or sedating antidepressants. In some European countries e.g. Germany there is a long clinical tradition to associate drive-increasing/non-sedating antidepressants with such risks. Based on this tradition, in such countries it is common to give a sedating drug, e.g. a benzodiazepine, when administering a non-sedating antidepressant, at least at the beginning of treatment. It is quite unclear whether certain pharmacological mechanisms of

action, such as serotonin reuptake inhibition, for example, are associated with a particular risk of suicide induction. None of the meta-analytical evaluations mentioned above have produced any clear indications in this direction. Even so, serotonergic over-stimulation, especially during the final dosing phase of an SSRI, and the associated increased drive or even agitation (there have even been some reports about akathisia-like agitation) may explain a possible increase of suicidality in individual cases. However, this is obviously so seldom that it does not become apparent with statistical significance in the large sets of data from placebo-controlled studies.

If one undertakes such explanations or interpretations of single cases, it is imperative to consider the basic risk of drawing wrong conclusions in the face of the complex situation of the clinical single case. Even if there appears to be a temporal association with the introduction of the antidepressant one still has to consider the alternative hypothesis that the antidepressant was introduced at a time when the depressive and perhaps also the suicidal symptoms were increasing in intensity.

Despite all the critical discussions about the risk of old and newer antidepressants and the necessity to investigate consistently any signs of side effects, it should not be forgotten that antidepressants are a central component of an effective depression treatment and that any doubts in this respect, especially by the general public, should be avoided. The discussion should therefore be conducted, alike in professional circles, with the necessary sensibility and not be transferred too quickly to the general media, always on the lookout for scandals as they are.

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The Insular Lobe of Reil—its Anatomico-Functional, Behavioural and Neuropsychiatric Attributes in Humans—A Review

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Summary

There is considerable clinical and experimental research to explore the anatomico-functional correlations of the limbic lobe to establish its relevance in modern neuroscience. The insula being a pivotal structure in the concept of the greater limbic lobe, we have attempted to highlight in this review the topographical anatomy and development, the remarkable heterogeneity of the insular cortical architecture, the widespread multifaceted spectrum of functional connectivity patterns and how this is translated to its behavioural specialisation in humans. The insula serves as an integration cortex for multimodal convergence of distributed neural networks such as the somesthetic-limbic, insulo-limbic, insulo-orbito-temporal and the prefrontal-striato-pallidal-basal forebrain. This provides the conceptual framework to facilitate functional and clinical considerations relevant to the various behavioural and neuropsychiatric disorders outlined in this review. The functional role of the insula in these disorders with particular reference to the current functional neuroimaging data has been also reviewed in this article.

Key words: *insula, insular cortex, insular lobe, behaviour, neuropsychiatry.*

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Acknowledgement

Dr. Shelley is a Research Fellow and is funded by the Raymond Way Research Group, Institute of Neurology, Queen Square, London. There are no conflicts of interest.

Introduction

The Island of Reil, or the insular cortex, is named after the eminent anatomist Dr. Johann Christian Reil, who was responsible for the earliest influential treatise to focus on this 'hidden' portion of the cerebral cortex. It forms the base of the Sylvian fissure, and was named 'die Insel', in 1809 (Reil 1809a, b). Since that time, the Island of Reil has been the accepted nomenclature for this area.

An awareness of the insula has existed at least since 1543, when Vesalius (Saunders and O'Malley 1982) made simplistic sketches of the area, presumably based on his dissections in his 'de Humani Corporis Fabrica Libri Septem'. However, the first unmistakable illustration of the insula was not published until 1641, in the 'Institutiones Anatomicae' of Casper Bartholin (Bartholin 1641). Vicq d'Azyr was the first to declare an interest in this area of the brain and described it as 'the convolutions situated between the Sylvian fissure and the corpus striatum' (Vicq d'Azyr 1786).

Monro depicted the three anterior gyri brevis in a sagittal plane after removing the anterior cerebrum, but had neither named nor described them (Monro 1783). During the next 50 years, the insula attracted little attention. It was in 1860, as a result of studies encompassing the anatomical and topographic attempts at identifying and localising various brain functions, that renewed interest was directed toward the study of the insula.

One of the debates at this time involved determining the connections of the insula to the surrounding neuronal structures. Another related to its role in speech. Broca identified the motor speech centre as the left frontal operculum, and disproved the role of the insula by comparing post-mortem findings in the brains of aphasic patients with normals (Broca 1861a, b).

The earliest, most complete, morphological outline of the insula was by Eberstaller. His contributions and terminology form the basis for most of the subsequent anatomical descriptions (Eberstaller 1887). At the end of the 19th century several landmark articles were

published, in which the anatomy of the insula and surrounding areas were described in detail. Von Economo published his work on the anatomy of the brain, including the insula, with comprehensive illustrations of its intricate gyral and sulcal patterns (von Economo 1929).

The role of the insula in behavioural specialisation stems from the concept that it is an integral component of an 'insulo-orbito-temporopolar complex', forming a multifunctional region of the paralimbic brain where a remarkably wide range of neural processes modulate behaviours which primarily depend on interactions between the extrapersonal world and the 'milieu interieur' of Bernard and Cannon (Mesulam 1985a, b). Thus, the insula has come to be seen as a pivotal structure in the concept of the limbic lobe, which provides bridges to permit the adaptation of the organism to the external environment.

In the early 1900s several fundamental contributions were made with respect to architecture of cortical neurones (cytoarchitectonics) and the arrangement of cortical fibres (myeloarchitectonics) (Clarke and O'Malley 1968). Brodmann, best known today for his classical cortical architectonic maps, actually defined five lobes of the brain, the fifth being the insular lobe (Vogt and Vogt 1903; Brodmann 1909). The human insular lobe includes Brodmann areas 13 to 16. The elegant efforts of many investigators have made it possible to unravel the intricate organisational complexity of the insula, its neuro-anatomical circuitry, and to propose theories regarding its functional role. The electroencephalographic recordings of Penfield and colleagues (Penfield and Jasper 1954; Penfield and Faulk 1955) demonstrated associations between the temporal and insular lobes in temporal lobe seizures, and mapped some of the visceral and somesthetic networks of the insular cortex.

Although the insula is encased within the depths of the Sylvian fissure, erecting an obstacle to experimental explorations, the modern era of neuroimaging has made it possible to explore the morphological, anatomical and functional aspects of the insula.

Topographical anatomy—a review

Much literature on the gross anatomical features of the insular lobe has been derived from experimental comparative animal studies, especially of the cat and of primates. A complete anatomical description of the insula is beyond the scope of this review; the reader is referred to the articles by Ture et al. (1999), Mesulam and Mufson (1985) and Augustine (1985).

In humans, the insula is a highly developed structure, totally encased within the brain at the

depths of the Sylvian fissure, and covered by the fronto-orbital, fronto-parietal, and the temporal opercula. It becomes visible only when the Sylvian fissure is widely opened. In the process of 'telencephalisation', which leads to massive frontal, parietal and temporal opercularisation, the Sylvian fissure is formed, with the result that structures situated on the surface of the cerebrum during fetal stages become buried from the time of birth onwards. While its growth may not keep pace with this telencephalisation process, the insula is by no means a vestigial structure: it has undergone a gradual increase in the complexity of its organisation in the course of primate and hominid evolution. In terms of the sulcation patterns, comparative studies of the insula reveal that the insula of the New World monkey is entirely smooth, with no evidence of sulci/gyri formation. There is a single orbitoinsular groove in Old World monkey brains and the human insula has 5-7 sulci. The insula of cetaceans is the most complex in the entire animal kingdom with up to 20 sulci. The human insula is considerably greater in size when compared to the macaque brain and it has also been observed that the insula is longer in its antero-posterior length in humans, baboons and macaques than in the orang-utan and chimpanzee.

The insula, lying at the base of the Sylvian fissure, covers the claustrum and the basal ganglia. The circular, periinsular sulci (anterior, superior, and inferior) of the fronto-orbital, fronto-parietal, and temporal opercula cover and enclose the insula, and the removal of these opercula reveals the entire insula in the shape of an inverted pyramid (Figure 1). The limen insulae is located in the depths of the Sylvian fissure and constitutes the anterobasal portion of the insula.

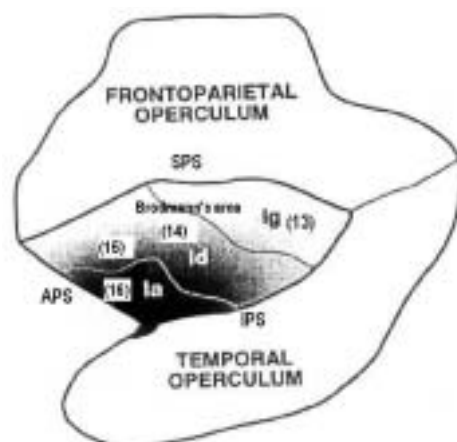


Figure 1 Schematic drawing showing the rostro-caudal architectonic organisation of the human insular lobe with Brodmann representation - areas 13 to 16 (SPS = superior periinsular sulcus; IPS = inferior periinsular sulcus; APS = anterior periinsular sulcus; Ig = granular insula; Id = dysgranular insula; Ia = agranular insula)

A central insular sulcus (*sulcus centralis insulae*) divides the surface of the insula into two portions, the larger anterior insula and the smaller posterior insula. The anterior insula is composed of three principal short insular gyri (anterior, middle and posterior) as well as the accessory and transverse insular gyri. All five gyri converge at the insular apex, which represents the most superficial aspect of the insula. The posterior insula is composed of the anterior and posterior long insular gyri and the postcentral insular sulcus, which separates them (Figure 2). At the smooth, low ridge called the *limen insulae* there is no definite topographic boundary between the anterior insula and the adjacent orbitofrontal cortex. The insular stem is located in the depths of the Sylvian fissure, and constitutes the anterobasal portion of the insula. The *limen insulae* is located in the insular stem and forms the threshold to the insula, a place where the anterior perforated space continues with the anteroventral agranular insular olfactory cortex.

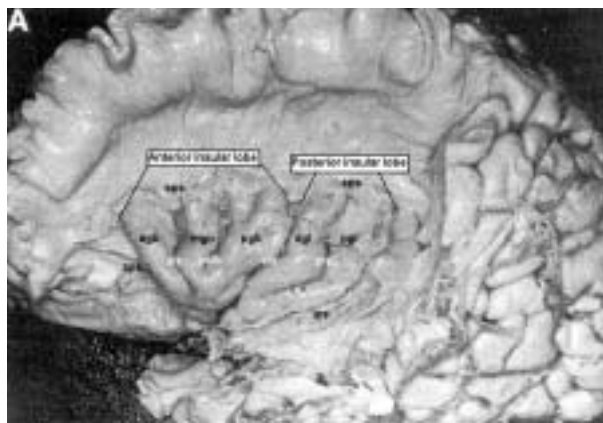


Figure 2

Photograph showing typical five lobed human insular cortex with the overlying frontal, parietal and temporal opercula removed (sps = superior periinsular sulcus; aps = anterior periinsular sulcus; ips = inferior periinsular sulcus; agb = anterior gyrus brevis; mgb = middle gyrus brevis; pgb = posterior gyrus brevis; agl = anterior gyrus longus; pgl = posterior gyrus longus; sis = short insular sulcus; pcis = precentral insular sulcus; cis = central insular sulcus; pis = postcentral insular sulcus)

The anterior insula is connected exclusively to the frontal lobe, whereas the posterior insula is connected to both the parietal and temporal lobes. Gyri and sulci of the opercula interdigitate, and also interdigitate with the gyri and sulci of the insula. The three opercula that cover the insula are separated by the horizontal and posterior rami of the Sylvian fissure. The horizontal ramus interposes the fronto-orbital and frontoparietal opercula, and the posterior ramus interposes the frontoparietal and temporal opercula.

Extensive anatomical studies of the insula have been done from a neurosurgical perspective to delineate its vasculature by adult cadaveric hemispheric dissections (Varnavas and Grand

1999; Ture et al. 2000). They described the arterial and venous anatomy of the insula, and its great variability. The main arterial supply of the insula stems from the middle cerebral artery, with predominance from the M2 segment. The insular arteries principally supply the insular cortex, the capsula extrema and sporadically the claustrum and the capsula externa.

Development of the insular lobe

The human insula displays consistent asymmetries during development. The sulcal markings appear earlier in the right insula, although the left insula in the normal adult is said to reach a larger size. During early development in human fetuses, the temporal lobe shifts downwards and anteriorly forming a depression, the primordium of the insula, on the superolateral surface of the cerebral hemisphere (Lockard 1948). As the insula is firmly attached to underlying structures it retains its position while the temporal lobe pivots around it. Since the insular area develops more slowly, its growth does not keep pace with the massive development of the surrounding neocortex and it thus becomes covered over as these lobes enlarge in an enclosed space, and as the opercula of the lateral sulcus are brought together making the insula the 'hidden fifth lobe' of the brain (Cunningham 1891).

The surface of the insula remains smooth up to the middle of the fifth month of development. At about 15 weeks, the inferior and superior limiting sulci appear, joining to form the circular insular sulcus that outlines the anatomical boundaries of the insula. At about 19 weeks, the insula enlarges, by now with an anterior and a posterior portion visible. By 19-20 weeks the central sulcus becomes evident, in line with the central sulcus on the superolateral surface of the cerebral hemisphere (Cunningham 1891). The precentral insular sulcus appears before the end of the fifth month, whereas the postcentral insular sulcus appears by the middle of the sixth month and all insular sulci are present by 31 weeks of development. Secondary gyri and sulci appear by 40-44 weeks of development and the newborn insula presents an almost adult appearance (Cunningham 1891).

Structure (cyto-, myelo-, and chemoarchitectonics) of the insula

The general architectonic plan of the human insula is very similar to that observed in the macaque brain. The insular lobe has been considered as a limbic cortex for ontogenetic and phylogenetic reasons. The interested reader is referred to the exhaustive descriptions on the cytoarchitectonics of the insular cortex and on the cyto-chemoarchitectonics, connectivity and function of the primate insular cortex (Mesulam

and Mufson 1982a; Mufson et al. 1997).

Most of the human cerebral cortex is phylogenetically recent, and termed the 'neocortex/neopallium', also referred to as 'isocortex' (Vogt and Vogt 1903) and 'homogenetic cortex' (Brodmann 1909). The phylogenetically older cortices, comprising the hippocampus, parts of the amygdala, and the olfactory cortex are referred to as the 'archipallium' or 'allocortex'.

The Brodmann areas 13 to 16 represent the human insular lobe. A dorsocaudal granular field is designated as area 13 while a ventrolateral agranular field is assigned to areas 14 to 16 (Brodmann 1909). The insular cortex shows a gradual transition from agranular and dysgranular cortex in the rostral two-thirds to a fully-fledged granular cortex in its caudal part (Figure 1). The boundary between the agranular and the dysgranular zones of the insula is not sharp.

There is preferential interconnectivity and concordance between the cytoarchitectonics of regions that are connected to the insula and the architecture of the insular cortex (Vogt and Vogt 1903). The agranular part of the orbitofrontal cortex is preferentially linked to the agranular part of the insula and the granular orbitofrontal cortex is preferentially linked to the granular insula. The granular sector is the most heavily myelinated one in the insula.

In terms of architectonics, the anterior parts of the insula receive direct input from the gustatory and olfactory cortex, and the posterior parts receive input from the somatosensory and auditory areas. The insula thus forms a site of multimodal convergence of inputs and plays a pivotal role in limbic interactions, which provides i) a means for interrelating events of the extrapersonal world with relevant motivational states and ii) an affective colouring and hedonic valence to perceptual experience.

Insular circuitry

Much of the progress in understanding the insula and its circuitry is based on animal studies (Chikama et al. 1997). There is a concordance between the architecture of the brain regions connected to the insula and the architecture of the insular sector that acts as a focus for that connection (Vogt and Vogt 1903). With the aid of a variety of methods, numerous investigators since the early 1980s have demonstrated the abundance of the afferent and efferent connections of the insula as well as its local intransular connections. They have been studied in macaque cerebra (Berke 1960; Kreig 1965; Mesulam and Mufson 1982b; Mettler 1945), baboon, mangabey (Mettler 1945), macaca mulatta (Hurst 1959; Showers and Lauer

1961; Turner et al. 1980), macaca iris (Hurst 1959), saimiri sciureus (Forbes and Moskowitz 1974), and humans (Rae 1954). The different methods used by various investigators to reveal the essential outlines of insular connections include injections of titrated amino acids (TAA), horseradish peroxidase (HRP), neuro-histochemistry (anterograde and retrograde axonal methods), strychnine neuronography, the Marchi method (Berke 1960) and Weil-stained (Lockard 1948) preparations. The insular connections with the basal nuclei, the amygdaloid body, other limbic areas and the dorsal thalamus were studied by various silver preparations: the Nauta-Gygax, Fink-Heimer methods (Forbes 1974) and the modified Fink-Heimer method (Turner et al. 1980).

The insular lobe in primates including humans has connections with (1) cerebral cortex, (2) basal ganglia, (3) amygdaloid body, (4) other limbic areas, (5) the dorsal thalamus and (6) striato-pallidal basal forebrain macrosystems (Heimer et al. 1991; DeOlmos and Heimer 1999; Alheid and Heimer 1988). The extensive functional connections include (1) somatosensory connections, (2) auditory connections, (3) gustatory connections, (4) motor connections, (5) higher order association connections (6) olfactory and (7) paralimbic connections. Figures 3 and 4 summarise the circuitry of the insular lobe. Figure 5 illustrates

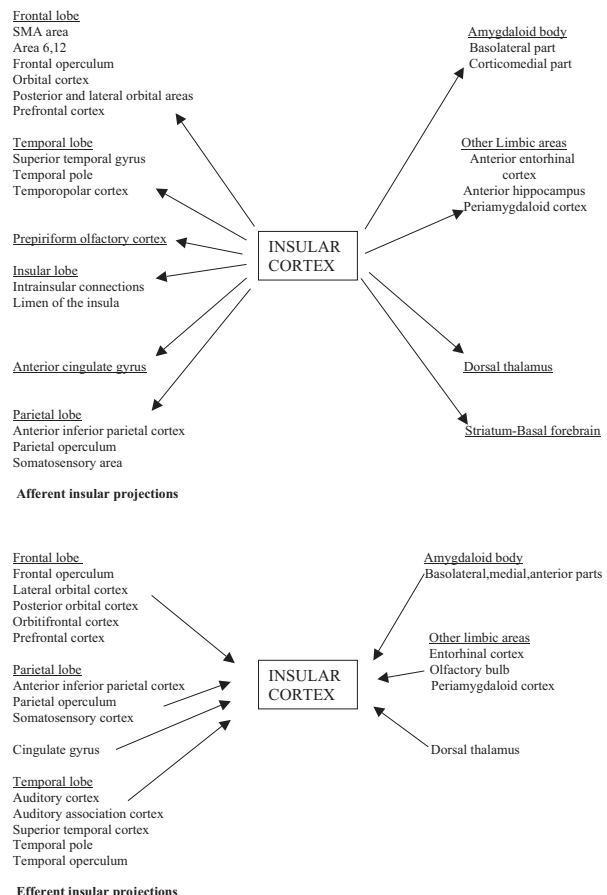


Figure 3
Afferent and efferent insular projections

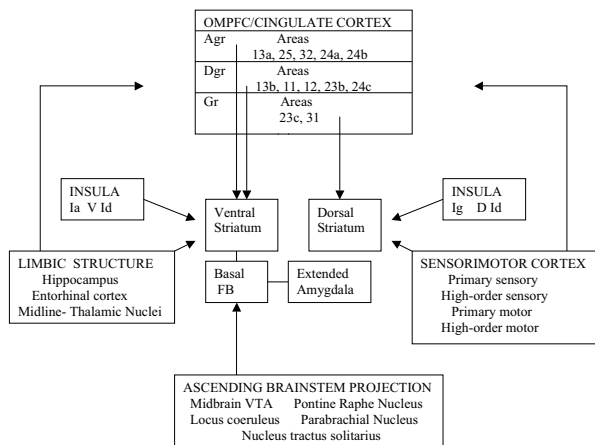


Figure 4
Summary diagram demonstrating the Basal forebrain-insulo-limbic-ventral striatum-prefrontal-cortical neuronal continuum.

Key: Agr- agranular, Dgr-dysgranular, Gr-granular, Ia- agranular insula, V Id-ventral dysgranular insula, Ig-granular insula, D Id-dorsal dysgranular insula, FB-forebrain, VTA-ventral tegmental grey, OMPFC-orbitomedial prefrontal cortex

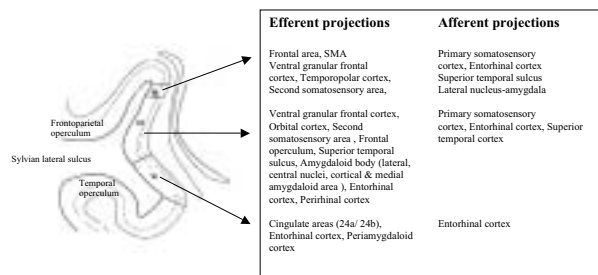


Figure 5
Schematic diagram showing the efferent and afferent projections of the insular cortex with respect to specific cytoarchitectural areas

the more detailed spectrum of cortical connections to and from specific cytoarchitectural areas of the insular cortex.

The insula has wide connections with the entire cortex, especially frontal (opercular, premotor and medial areas), temporal (auditory cortex, polar and superior temporal sulcus), and parietal (primary and secondary sensory areas). The insular cortex is also linked to the basal ganglia (via claustrum and striatum), thalamus, limbic structures (amygdala, periamygdaloid areas, extended amygdala, and entorhinal cortex), and olfactory cortex. The insula serves as an intergration cortex for multimodal convergence of distributed neural networks (limbic, insulo- limbic, insulo-orbito-temporal, prefrontal-striato-pallidal-basal forebrain and subcortical regions) and is thus a major component of the limbic lobe. In addition, the insula may provide a neural relay for conveying sensory information into the limbic system. Connections between sensory areas and limbic structures are important because they provide a means for interrelating events in the external world with relevant motivational states.

Functional correlates of the insular lobe

The function of the island of Reil and the surrounding hidden walls of the opercula has long been a subject for speculation. Our understanding has evolved and is evolving from animal experiments coupled with observations in humans with various insular lesions (tumours, vascular, epileptic) that seem related to behaviour disorders. Neurophysiological studies, including electrical stimulation of the insular cortex has contributed a great deal, and recently more has been revealed by functional neuroimaging studies.

Earlier reviews have described the insular circuitry and its functional aspects in both primates and humans (Augustine 1985, 1996). In this paper we have updated the current literature on knowledge of insular function, and the behavioural and neuropsychiatric consequences of insular lesions, with special reference to imaging neuroscience.

• Visceral sensory functions

Aura of partial epilepsy

Prior studies with experimental neurophysiological recordings from the insula of the cynomolgus macaque monkey, *Macaca fascicularis*, have shown that the anterior part of the dysgranular insula is a part of the primary gustatory cortex (Yaxley et al. 1990). From the studies of insular stimulation and electrocorticography during surgery for focal temporal lobe epilepsy, numerous visceral sensory and visceral motor functions of the insula have been elucidated. These included gustatory and olfactory sensations, epigastric gurgling, burning, rising and rolling sensations with salivation, nausea and feelings of vomiting (Penfield and Faulk 1955). The insular cortex thus represents an anatomical symptomatogenic zone or substrate for the genesis of epileptic aura in mesial temporal lobe epilepsy.

Gastroesophageal nociceptive sensation

Limbic structures became engaged when the visceral sensations were unpleasant or painful. The insula has also been linked to oesophageal distension by oesophageal stimulation studies. This has been studied by topographic mapping of cortical potentials evoked by distension of the human proximal and distal oesophagus (Aziz et al. 1995). Oesophageal stimulation was performed using a pump, which rapidly inflated a 2 cm silicone balloon positioned either 3 cm distal to the upper oesophageal sphincter or 5 cm proximal to the lower oesophageal sphincter, at a frequency of 0.2Hz, using inflation volumes which produced a definite but not painful sensation. The oesophageal distension evoked cortical potentials including an initial negative component (N1). The morphology and scalp topography of the N1 component suggested activation of the primary

somatosensory cortex, the insular cortex, or both.

Functional magnetic resonance imaging has been used to study cerebral representations of somatic and limbic activation during oesophageal distension (Binkofski et al. 1998). These data demonstrated that the secondary somatosensory-insular cortex is the primary cortical target of visceral afferents originating in the oesophagus.

Gustatory area

Taste perception in patients with unilateral insular cortex lesions has been studied where subjects were required to identify the quality and intensity of the gustatory stimuli applied separately to either side of the tongue (Pritchard et al. 1999). Damage to the right insula produced ipsilateral taste recognition and intensity deficits. Damage to the left insula caused an ipsilateral deficit in taste intensity but a bilateral deficit in taste recognition, suggesting that taste information from both sides of the tongue passes through the left insula.

The higher order projections in the human brain were studied by using positron emission tomography, which showed increased cerebral blood flow in the left insular lobe during a taste discrimination task in five normal volunteers (Fukuda et al. 1991). Increased blood flow patterns were also noted in the left thalamus and right parietal cortex in four cases. This study confirmed that the insula is involved with a higher order gustatory circuit. Another functional imaging study demonstrated activation of the anterior insula in humans while tasting salt (Kinomura et al. 1994).

• Visceral motor functions

Visceral epilepsy

The insula stimulation studies in temporal lobe epilepsy have revealed numerous visceral motor phenomena during seizures including audible rumbling (borborgymi) or gurgling noises in the gastrointestinal tract, alteration of gastric motility, belching, vomiting and the urge to defaecate (Penfield and Faulk 1955). Vomiting as a manifestation of seizures (visceral epilepsy) has been described in the literature (Mulder et al. 1954). The role of the insula in triggering vomiting as in 'ictus emeticus' was studied using video EEG and corticography (Fiol et al. 1988). It was concluded that the insula might act as a trigger to the medullary vomiting centre, probably by a pathway involving the anterior-mesial temporal structures.

The role of insular cortex in dysphagia

The insula as a cortical substrate in the mediation of dysphagia was investigated in four unilateral stroke patients with discrete lesions of the insular cortex (Daniels and Foundas 1997). CT scan localisation studies, neurological

examination, bedside swallowing evaluation, videofluoroscopy and clinical oropharyngeal examination were done in these patients. The results indicated that dysphagia was associated with lesions of the anterior insula. They postulated that the anterior insula might be important in oropharyngeal deglutition because of its connectivity to crucial cortical, subcortical and brainstem sites known to be important in swallowing. This was based on the connections of the anterior insula with the primary and supplementary motor cortices, the ventroposterior medial nucleus of the thalamus, and the nucleus of the tractus solitarius, all of which are important in the act of oropharyngeal swallowing. The connections the anterior insula has with the primary and supplementary motor cortices thus facilitate coordinated interaction of tongue, face and jaw in swallowing (Figure 6). Lesions in the anterior insula may also produce dysphagia by disrupting the processing of gustatory input by disconnecting sensorimotor information between the NTS and the anterior insular cortex. This results in a delayed elicitation of the pharyngeal swallow, which contributes to dysphagia.

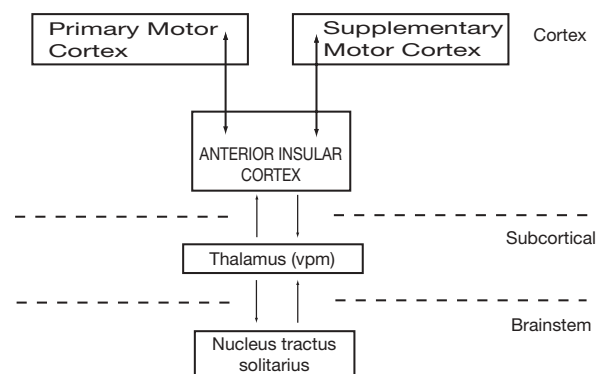


Figure 6 Diagram showing the afferent and efferent connectivity of the insular cortex to critical swallowing regions of the brain (vpm = ventroposterior medial nucleus)

A [¹⁵O] labelled H₂O PET study was conducted to identify the cerebral loci processing human volitional swallowing in healthy volunteers (Hamdy et al. 1999). Submental electromyography as well as transcranial magnetic stimulation was used to map the cortical motor representation of the pharynx. The transcranial magnetic stimulation results indicated activation of the insula in addition to sensorimotor cortex, temporopolar cortex, cerebellum and brainstem.

Prolonged dysphagia following acute stroke is associated with stroke severity, dysphasia and lesions of the frontal and insular cortex on brain imaging.

The role of the insular cortex in neurocardiology

Another important visceral motor autonomic function ascribed to the insula relates to the concept of neurocardiology, which is based upon the anatomy and physiology of cortical mechanisms of cardiac control. Literature on this concept comes from the observations of electrocardiographic changes and arrhythmogenicity accompanying acute strokes and subarachnoid haemorrhages and sudden unexpected deaths in epilepsy (SUDEP). The role of the insular cortex in cardiovascular function was experimentally studied in the anaesthetised, paralysed and artificially ventilated Sprague-Dawley rats (Ruggiero et al. 1987). This study analysed the responses to electrical and chemical stimulation of the rat insular cortex with respect to the regulation of arterial blood pressure. It was concluded that neurones within an area of the insular cortex projecting to multiple brainstem autonomic nuclei, including the cardiopulmonary segments of the nucleus of the tractus solitarius and nucleus reticularis parvocellularis innervated by baroreceptor afferents, increase blood pressure and heart rate.

The differential left/right hemisphere heart rate responses following unilateral hemispheric inactivation by the intracarotid amobarbital (ISA) test was studied in 25 patients undergoing preoperative evaluation for epilepsy surgery (Zamrini et al. 1990). Heart rate increased after left hemisphere inactivation, but decreased following right hemisphere inactivation. It seems that the right insula is involved in cardiovascular sympathetic, and the left insula in parasympathetic control. A recent study in 73 subjects using the ISA test re-investigated the differential cerebral involvement on cardiac dromotropic and heart-rate variability changes (Ahern et al. 2001). Contrary to the results of the previous study, it concluded that the right hemisphere exerted a greater parasympathetic control. The study summarised that there were more cardiac consequences of arrhythmogenicity and sudden cardiac death in patients with right hemispheric infarcts, and SUDEP for patients with right hemispheric epileptic foci.

Experimental studies in rats showed that the posterior insular cortex possesses cardiac chronotropic organisation and stimulation resulted in increasing degrees of heart block leading to escape rhythms, ventricular ectopics and ultimately death in asystole (Oppenheimer et al. 1991). These data suggest that the pathophysiological activation of the insular cortex by stroke or an epileptic seizure could lead to ECG changes, cardiac arrhythmias and sudden death.

Two studies described the association of cerebral strokes of all subtypes with specific pathological

changes in the ventricular myocardium (myocytolysis) that were not attributable to concomitant cardiac ischemic disease (Oppenheimer et al. 1991; Oppenheimer 1992). The studies noted the cardiovascular effects of human insular cortex stimulation and its lateralisation in five epileptic patients prior to temporal lobectomy for seizure control. Right middle cerebral artery infarction disinhibits insular function and causes an increase in sympathetic cardiovascular tone and the potential for cardiac consequences of stroke. Studies on ECG alterations reported that the frequency-corrected QT interval dispersion was significantly prolonged in patients with strokes involving the insular cortex (Eckardt et al. 1999). This result led to the hypothesis that the insular cortex might be involved in the regulation of myocardial repolarisation. This hypothesis has been supported by results of animal studies in which stimulation of the insular cortex was shown to lead to ventricular ectopy and death in asystole in rats (Oppenheimer and Norris 1995). Neurogenic ST depression in the ECG has been reported in a 48-year-old female patient that was related to left insular infarction and who developed sudden expressive aphasia (Chua et al. 1999).

The differential effects of stroke localisation on autonomic function parameters using heart rate variability were studied in 62 patients with age- and sex-matched controls (Tokgozoglu et al. 1999). It was concluded that stroke in the right insula leads to decreased heart rate variability, which is an important predictor for arrhythmias, and sudden cardiac death. Experimental and clinical studies indicated that certain structures such as the insula, amygdala and the lateral hypothalamus exert an influence in the autonomic control of the heart (Oppenheimer et al. 1992). Of these, the insular cortex, within the middle cerebral artery territory, is the most important cortical area that controls both parasympathetic- and sympathetic-mediated cardiovascular regulation which led to its description as 'the insula of sudden death' (Hachinski 1999).

• **Somatosensory functions**

The granular insula has a somatosensory function with somatotopic organisation and is a site of multimodal convergence among inputs from olfactory, gustatory and auditory modalities. It also plays a pivotal role for relaying somatosensory impulses into other limbic areas, having the function of a somatosensory-limbic integration cortex. This function of the granular insula has been well studied in rhesus monkeys (Schneider et al. 1993).

Positron emission tomographic brain imaging studies in humans have shown activational cerebral blood flow patterns during

somatosensory tactile-vibration stimulation of the hands and feet to be topographically localised to primary and secondary somatosensory areas and the insular cortex (Burton et al. 1993).

Cortical activation patterns during the processing of painful stimuli have been studied by intracortical recordings of early pain-related CO₂ laser evoked potentials in the human second somatosensory area during stereotactic EEG presurgical assessment of patients with drug-resistant temporal lobe epilepsy (Frot et al. 1999). This study revealed that activation of the contralateral secondary somatosensory-insular cortex represents the first step in the cortical processing of peripheral A-delta fibre pain inputs.

A review and meta-analysis of PET and fMRI studies on brain responses to pain has been performed (Peyron et al. 2000). This study reported functional activation of the secondary somatosensory area and insular regions, and the anterior cingulate cortex. Figure 7 depicts some of the main anatomical components involved in human nociceptive processing in the brain.

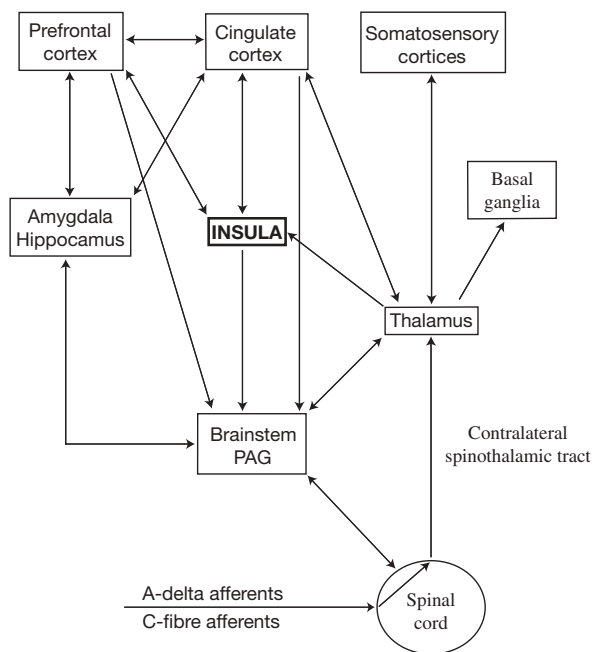


Figure 7
Schematic diagram showing some of the main anatomical components of human nociceptive processing in the brain and their possible functional connectivity (PAG= periaqueductal grey matter)

In a recent study, multimodality tests using PET, fMRI, dipole modelling and operculoinsular evoked potentials further confirmed the insula as a major site for cortical pain encoding in the human brain (Peyron et al. 2002). Another study used fMRI combined with a thalium: yttrium-aluminium-garnate infrared laser to

investigate pain and stimulus intensity in nine healthy human volunteers and showed activation of the secondary sensory cortex and insula cortex for painful trials (Bornhovd et al. 2002).

The central processing of innocuous and noxious cold stimuli was studied in human healthy subjects using magnetoencephalography (Maihofner et al. 2002). This study revealed an exclusive activation of the contra- and ipsilateral posterior insular cortex mediated by A-delta fibres. In addition, noxious cold stimuli produced activation in the contra- and ipsilateral secondary (SII) areas and cingulate cortex. This study confirmed the participation of the posterior insular cortex as the primary somatosensory area for the cortical processing of cold sensation.

Intracortical S-EEG recordings of early pain in the human second somatosensory area using CO₂ laser stimulation of A-delta fibre endings in the skin of the dorsum of the hand in humans have been studied (Frot and Mauguiere 1999). Responses were seen on the contralateral region of the upper bank of the Sylvian fissure, that is the upper part of the insular cortex (S II-insular cortex). The contralateral S II-insular cortex activation occurred through direct thalamocortical projections, while the ipsilateral side gets stimulated via transcallosal fibres coming from the opposite S II area.

The somatosensory-limbic path, relaying somatosensory information by means of the insula, also subserves tactile recognition and recall. This was studied using PET in humans, and revealed that the ipsilateral anterior insula and orbitofrontal cortices were activated during thermosensory stimulation, regarded as a submodality of touch (Craig et al. 2000). Another study employed event-related somatosensory stimulation paradigms in fMRI studies using electrical finger stimulation (Deuchert et al. 2002). Results from this study revealed cortical activation patterns to be localised to the contralateral primary, and bilaterally in secondary somatosensory cortex as well as in posterior parietal cortex and insula.

In another study, painful and non-painful somesthetic sensations were evoked by direct electrical stimulations of the insular cortex in patients with drug refractory temporal lobe epilepsy using stereotactically implanted depth electrodes (Ostrowsky et al. 2002). Both types of stimuli elicited were evoked from the posterior part of the insula. However, painful sensations evoked were lateralised to the right hemisphere.

• **Vestibular function**

The designation of the insula as a vestibular area (Augustine 1985) is based on its connections with the vestibular relay nucleus and the ventral

posterior inferior nucleus of the thalamus (Deecke et al. 1974). Vestibular information may be blended in the thalamus with somatic proprioceptive information (Deecke et al. 1977). In vertigo of cortical origin, the associated nausea and vomiting can be explained by the involvement of the insular cortex where viscerosensory impulses are combined with vestibulo-proprioceptive information. A study involving 71 patients with unilateral middle cerebral artery infarctions reported that the perception of verticality was affected in 20 of 52 patients with topographic infarctions localised to the posterior granular insula (Brandt et al. 1994). The vestibular function of the insula was studied using PET and fMRI, revealing that caloric stimulation of the ears activates the multisensory parieto-insular cortex in humans and is involved in the perception of verticality and self-motion (Brandt and Dieterich 1994; Brandt et al. 2002). The parieto-insular cortex is the human homologue of the parieto-insular vestibular cortex in monkeys.

• Auditory processing function

The insula receives afferent connections from the temporal pole, primary auditory cortex, auditory association cortex, superior temporal cortex and the temporal operculum. Auditory function has been studied by mapping cerebral glucose consumption following verbal auditory stimulation that revealed activation in the left insular cortex, the temporoparietal junction, the inferior parietal region and the corpus callosum (Kushner et al. 1987). Deficits in unilateral auditory processing disorder in a patient with stroke involving the right insula and the adjacent white matter have been described (Fifer 1993). With these reports it has been proposed that the insula is an auditory association area involved in the preprocessing of auditory stimuli and in receptive auditory aspects of language comprehension.

A more recent study using fMRI tasks of passive listening and semantic categorisation provided further insights into the role of the human insula in verbal-auditory processing (Noesselt et al. 2003). The study found insular activations in the context of different verbal or auditory-verbal tasks. Since the insula is strongly interconnected with the temporal and frontal structures, they speculated that the posterior insula might play a role in linking together the different neural networks involved in auditory processing.

• Summary - insular function

The section above summarises the various studies and investigations that lend evidence to the multifunctional activity of the insula (Figure 8). The insula is thus an important somatosensory area, as part of the human secondary somatosensory area (S II) and a pain processing area. The insula is also involved in

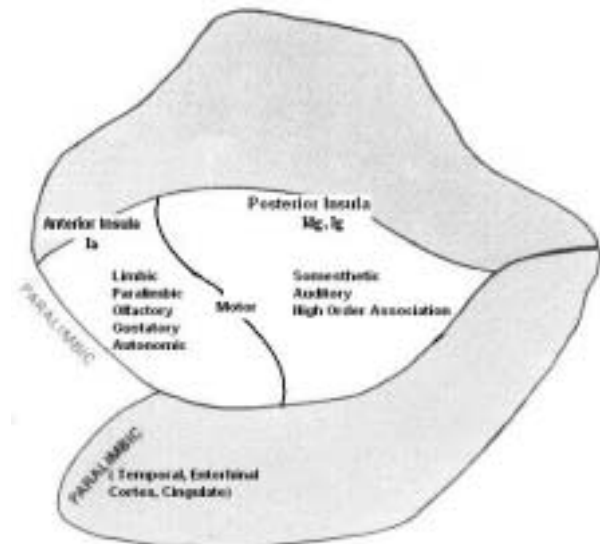


Figure 8

Schematic representation of the behavioural specialisation in the insula and adjacent regions

volitional swallowing, visceral motor sensory processing and is a cortical gustatory area. It plays an important role in cardiovascular function and cerebrogenic sudden death. The posterior portion of the insula is probably a component of the human vestibular cortex. There is evidence to suggest that the insula is involved with aspects of speech and language and auditory processing.

Since the insula forms a waystation on the pathway of the limbic-paralimbic system and is a major limbic intergration cortex, the behavioural and neuropsychiatric attributes are discussed below.

Behavioural correlates of the insular lobe

• Insula and aphasia

Historically, language disorders were the first disorders of higher cortical function to be correlated with focal brain lesions. In the literature, there is considerable controversy between various investigators about any language functions of the insula.

Some investigators had made fundamental observations that a lesion of the left insula and overlying operculum deprived a person of speech (Broca 1861). A theoretical framework of the organisation of language functions in the brain for conduction aphasia was postulated by the model of 'Leitungsaphasie' (Wernicke 1874). This postulated that conduction aphasia resulted from an anatomical disconnection of an intact Wernicke's area from an intact Broca's area by a deep white matter lesion interrupting the arcuate fasciculus. This 'disconnection' hypothesis was reformulated for the modern era by proposing that conduction aphasia is not purely due to white matter lesions, but involves

at least some of the cortex of the insula, superior temporal gyrus, and the supramarginal gyrus (Geschwind 1965). It has been concluded that the decisive lesion must be a destructive interruption of the arcuate fasciculus fibres that travel in the extreme capsule underneath the insular cortex, rather than the lesions of the insular cortex per se (Damasio and Damasio 1980).

Impaired speech initiation and poor verbal fluency as the result of MRI detected left anterior insular infarct has been reported in a 59-year-old woman (Shuren 1993). It was hypothesised that the deficits in speech initiation were related to the role of the insula in the limbic-reticular-cortical network for motivation and arousal-activation of behavioural responses in speech initiation. This is based on the reciprocal connections the anterior insula has with the limbic (cingulate and amygdala) and the reticular (thalamic centromedian-parafascicular and reticular nuclei) systems, as well as the frontal opercular regions.

A study, using PET brain imaging, of memory mechanisms in the processing of single words and word-like symbols, learning and repetition of words all revealed bilateral insular cortex activation (Raichle 1991). A study, using high-speed echo-planar magnetic resonance imaging, in humans has documented activation of the anterior insula during word generation (McCarthy et al. 1993). Another study has identified activation of mid-dorsal insula bilaterally in auditory-vocal integration in singing and in speech, using PET with MRI (Perry et al. 1993).

The role of the insula in the auditory processing underlying speech has been clearly exemplified by stroke involving the right insula. PET studies have shown deactivation of bilateral temporal/insular areas during a graded auditory-verbal memory task (Grasby et al. 1994). Phonological agraphia, a highly selective disturbance of the spelling system, has been described following a focal left anterior insulo-opercular infarction (Marien et al. 2001). The neuroanatomical and neurolinguistic characteristics of these phonologically mediated aphasic manifestations suggest a further delineation of the role of the insula in language functions in humans. To delineate the neuroanatomical basis, four case reports of 'the opercular-subopercular syndrome' have been reviewed (Bakar et al. 1998). This syndrome, also known as Foix-Chavany-Marie syndrome, is a cortical type of pseudobulbar paralysis involving the facio-labio-pharyngo-glossolaryngo-brachial regions. They stress that the neuroanatomical basis involves bilateral lesions of the cortical and subcortical frontal opercular cortex disrupting the corticobulbar tracts, rather

than the insula per se. However, in another study of brain lesions in 25 stroke patients with a disorder in the motor planning of articulatory movements, discrete lesions in the region of the left precentral gyrus of the insula were shown (Dronkers 1996). The left insula thus represents a region related to complex planning and coordination of human speech articulation.

A recent study investigated 10 patients with progressive non-fluent aphasia in an attempt to identify a consistent neural site for the language disorder (Nestor et al. 2003). Seven patients had an isolated progressive non-fluent aphasia syndrome, while the remaining three had progressive dysfluency as part of a dementia process. Compared with controls, the patients with non-fluent aphasia showed significant hypometabolism in the left anterior insula and frontal opercular region. The study concluded the left anterior insula as the anatomical site for dysfluency resulting in a deficit in motor articulatory planning (speech apraxia) combined with agrammatism.

• Insula and stroke

A study of four patients with their first acute ischaemic stroke restricted to the insular cortex revealed five characteristic clinical syndromes (Cereda et al. 2002). The five main groups of clinical presentations described were: (1) contralateral pseudothalamic sensory stroke; (2) gustatory disorder with a left posterior insular infarct; (3) acute pseudovestibular syndrome

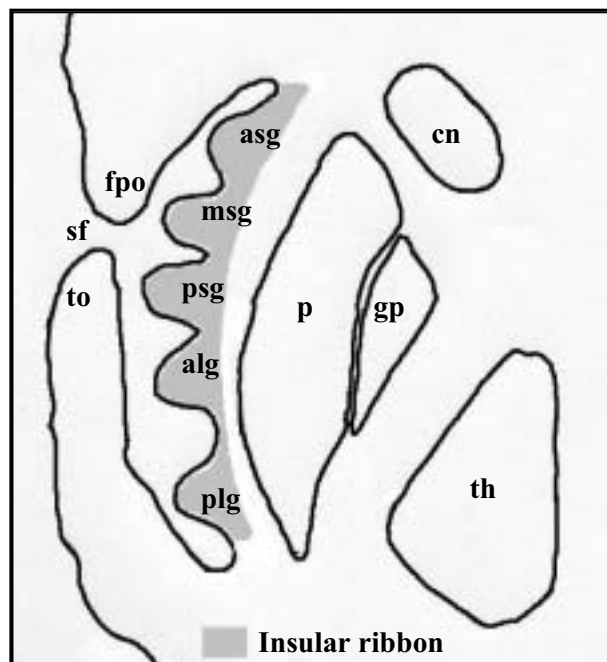


Figure 9 Schematic diagram showing an axial section of the right cerebral hemisphere through the insula depicting the 'insular ribbon' (asg = anterior short insular gyrus; msg = middle short insular gyrus; psg = posterior short insular gyrus; alg = anterior long insular gyrus; plg = posterior long insular gyrus; sf = Sylvian fissure; fpo = frontoparietal operculum; to = temporal operculum; p = putamen; gp = globus pallidus; th = thalamus; cn = caudate nucleus)

with posterior insular infarct; (4) cardiovascular disturbances with a right posterior insular infarct and; (5) neuropsychological disorders, including aphasia (left posterior insula), dysarthria, and a transient neuropsychiatric disorder of somatoparaphrenia in right sided infarcts.

The insula region has been described in the neuroradiology of acute ischaemic stroke with 'loss of insular ribbon' sign (LIR) (Koga et al. 2003). The CT scan does not usually show much in the first 24 hours of a middle cerebral artery infarction; however the 'loss of insular ribbon' represents an abnormal early reliable CT finding (Truwit et al. 1990). There is loss of definition of the grey-white interface in the lateral margins of the insula (insular ribbon) (Figure 9). The insular ribbon lies in an arterial watershed zone, and loss of the radiological appearance of insular ribbon in CT is a reflection of acute oedema due to infarction.

• Insula and pain perception

Based on connectional and functional data, several investigators have defined the role of the granular insula as a modality-specific cortical area for the processing of somatosensory information. In this context, asymbolia for pain secondary to interruption of insular somatosensory and limbic connections has been reported (Berthier et al. 1988). Unpleasant spontaneous pain generation was described in six patients with CT detected white matter lesions deep to the caudal insula and the posterior parietal operculum (Schmahmann and Leifer 1992). This pseudo-thalamic pain syndrome was attributable to a loss of cortical inhibition of the dorsal thalamus due to the disconnection of these cortical secondary somatosensory areas and the dorsal thalamus.

• Insula and neglect syndrome

A severe multimodal neglect syndrome in a right handed male has been reported following an ischaemic stroke with neuropathological evidence of infarction involving the whole right insula, adjacent white matter, and the inner cortical surface of the right fronto-temporo-parietal operculum (Berthier et al. 1987). This lesion probably disrupted the posterior insula-amygdala limbic connection, which resulted in neglect and lack of appropriate response to painful stimulation presenting as asymbolia for pain. Another study also reported that neglect was associated with right insula lesions (Manes et al. 1999a). Neglect has been commonly described with lesions in the right inferior parietal lobe (Heilman et al. 1993), the dorsolateral frontal cortex (Heilman and Valenstein 1972), the thalamus and the mesencephalic reticular formation (Watson and Heilman 1979). However, because of its connections with the limbic and sensory motor cortices, the insular cortex is believed to play a

role in affective and attentional aspects of human behaviour. The right insula infarction described by Manes led to neglect in multisensory modalities including (a) tactile inattention, (b) auditory and, (c) visual. It was therefore suggested that neglect, anergia and apathy might all be related to insula dysfunction (Manes et al. 1999b; Roaslo et al. 1997). PET activation of blood flow in the insular cortex has been demonstrated during selective-attention tasks related to visual discrimination of shape, colour, and speed of a visual stimulus has been studied (Corbetta et al. 1991).

• Insula and memory

PET studies have shown an association between changes in blood flow in the insular cortex and verbal memory. The verbal component of working or short-term memory in humans and controls has been studied using PET by employing two tasks, the covert rehearsal of visually presented letters and rhyming judgement for letters (Paulesu et al. 1993). Significant increases in blood flow patterns occurred bilaterally in area 44, in areas 22 and 24 of the superior temporal gyri, the supramarginal gyri and in the insular cortex bilaterally.

The laterality of verbal memory deficits was studied by using PET which compared verbal memory profiles by employing the CERAD (the consortium to establish a registry for Alzheimer's disease) word list memory and story A of the WMS-R (Wechsler memory scale) logical memory subtests, between a group of four right-handed patients with right insular infarction and a group of six right-handed patients with left insular infarction (Manes et al. 1999c). The results indicated that patients with left insular damage had significantly poorer performance on verbal memory tasks than patients with right insular lesions. These are consistent with PET studies in normal subjects, suggesting a role for the insular cortex in language and verbal memory tasks (Paulesu et al. 1993).

Although the functional neuroanatomy of recall has not been determined, studies have shown verbal memory impairment in patients with left temporal lobe dysfunction (Cabezo et al. 1997). The insula sends efferents to the temporal cortex including the temporal pole and the supratemporal plane. Afferent fibres to the insula arise from the temporal lobe (including the temporal pole, primary auditory, auditory association, postauditory cortex, superior temporal cortex and the temporal operculum). It is thus suggested that insular connections provide a fundamental anatomical substrate for learning and memory functions. Left insular lesions disrupt connections with brain areas that are necessary for executing memory tasks

and, therefore, lead to verbal memory deficits.

In another study, left temporal lobe hypoperfusion on SPECT was described in a patient who developed aphasia after left insular infarction (Marshall et al. 1996). These authors suggested that hypoperfusion in the left temporal lobe may have reflected a functional disconnection between the posterior insula and language areas in the temporal lobe. The sudden removal of areas of functioning brain, as occurs with stroke, may produce distant effects in functionally connected neural structures, a phenomenon termed diaschisis. Thus, the verbal memory impairment in left insular patients could be the result of diaschisis. The study hypothesised that the insular cortex forms a component of a functional neuroanatomical circuit that mediates verbal memory.

The componential role of the right insula in the functional anatomy and neural networks involved in autobiographical memory was demonstrated in another study using H₂¹⁵O PET (Fink et al. 1996). This study revealed functional neuronal activity in a network of primarily right hemispheric regions including temporomedial and temporolateral cortex, and the surrounding right hemispheric 'satellite' regions of the expanded limbic system network (Nauta 1979) such as amygdala, hippocampus-parahippocampus, insula, posterior cingulate cortex, temporoparietal cortex and prefrontal cortex.

• Insula and motoric function/ neuroplasticity

Several investigators and reports have collectively demonstrated that the anterior insula has a prominent role as a motor association area (Chollet et al. 1991; Weiller et al. 1992, 1993). An epileptic aura consisting of circling or rotational movements has been described with an insula tumour (Fiol et al. 1988) and with an aneurysm of the middle cerebral artery resting on the insula (Schneider et al. 1971). A study using PET explored the cortical/subcortical mechanisms underlying the execution of human voluntary horizontal saccadic eye movements in total darkness, and showed activation of the right insula in addition to structures in the basal ganglia-thalamocortical motor loop during the execution of voluntary saccades (Petit et al. 1993). To investigate the motoric functional aspects of the insula, regional blood flow was measured in amyotrophic lateral sclerosis patients and age-matched controls (Kew et al. 1993). It was observed that the anterior insula and premotor cortices showed significantly greater activation in amyotrophic lateral sclerosis patients than the controls during upper limb movements. It was concluded that the recruitment of the anterior insula and premotor cortices in amyotrophic lateral sclerosis patients

reflected the brain's adaptation to the injury to the corticospinal tract and suggested that the anterior insula may act as a motor association area.

This was further corroborated using PET to study organisational changes in the functional anatomy of the brain in 10 patients following motoric recovery of upper limb function from striatocapsular motor strokes (Weiller et al. 1992). The study revealed that during the performance of a motor task by the recovered hand there was greater activation than in normal subjects in both anterior insulae, the inferior parietal cortex, the prefrontal/anterior cingulate, the ipsilateral premotor/basal ganglia and in the contralateral cerebellum.

• Insula and human eating behaviour

The hypothalamus has a major role in the control of food intake. The neuroanatomical correlates of hunger and satiation in both lean and obese subjects have been studied by PET generated functional brain maps (Del-Parigi et al. 2002). The results in lean individuals indicated that the networks involved in hunger included the hypothalamus, thalamus and several limbic structures including the insula, the hippocampal formation and the orbitofrontal cortex. Satiation was associated with preferentially increased neuronal activity in the prefrontal cortex.

• Insula and sexual behaviour

Human emotions may be classified under two distinctive systems (a) the appetitive motivational system associated with positive or pleasant emotions and (b) the aversive motivational system associated with negative or unpleasant emotions. Despite the brain's central role in human appetitive sexual function, little is known about the functional neuroanatomy and patterns of brain activation associated with sexual arousal. Visually evoked sexual arousal was studied using [¹⁵O] H₂O PET in healthy male subjects to identify the activated brain areas that were time locked to sexual arousal (Stoleru et al. 1999). The brain areas activated while experiencing sexual arousal from seeing sexually explicit film clips were (a) bilateral inferior temporal cortex, a visual association area; (b) right insula and right inferior frontal cortex, paralimbic areas related to processing of sensory information with motivational states; and (c) left anterior cingulate cortex, a paralimbic area related to autonomic and neuroendocrine functions.

Another study using blood-oxygenation-level-dependent (BOLD) functional MRI demonstrated the cerebral centres controlling penile erection while visualising erotic and non-erotic film in sexually potent male volunteers and hypogonadal impotent patients (Park et al. 2001a). The sites of brain activation in response

to the erotic film were areas of inferior frontal lobe, cingulate gyrus, insula and inferior temporal lobe. The neuroanatomical correlates of female sexual arousal evoked by visual stimulation were studied in healthy female volunteers using BOLD functional magnetic resonance imaging (fMRI) (Park et al. 2001b). The activated sites associated with sexual response were the inferior frontal lobe, cingulate gyrus, insula and inferior temporal lobe in addition to thalamus, caudate nucleus and globus pallidus. These studies reveal insular activation amongst other cerebral centres in the neurobiological processes that underlie human sexual arousal.

• Insula and temporal lobe epilepsy

The landmark paper entitled 'The insula: further observations on its function' (Penfield and Faulk 1955) underlined the similarity between the symptoms observed during temporal lobe seizures and those evoked by insular cortex stimulation. Their electrocorticographic and intracortical electrical stimulation studies of the insula during presurgical evaluation of temporal lobe epilepsy patients made observations on visceral sensory, visceral motor, somatic sensory, gustatory, motor, pain and speech, and auditory/vestibular sensory phenomena. These observations were predictable when considering the dense connectivity between the insular lobe and the temporo-limbic structures.

The findings of this seminal study were confirmed from Penfield's recordings in 106 patients, which demonstrated that 50% showed spontaneous spikes or spike waves in the insular lobe in temporal lobe epilepsy (Silfvenius et al. 1964). This was further illustrated by a report of a partial seizure originating during the surgical removal of an insula tumour (Roper et al. 1993). A specific epileptic insular network, with seizure discharge propagation pathways based on the connections of the insula, the temporal pole and the amygdalo-hippocampal structures, has been postulated by Wieser (1983).

The role of the insular cortex in the genesis of temporal lobe epileptic seizures has been further explored (Isnard et al. 2000) by using 3-D reconstructed cerebral MRI-assisted stereotactic implantation of transopercular depth electrodes (Talairach and Bancaud 1973) in 21 patients with drug refractory TLE. In addition, video-EEG recordings of the ictal symptoms of 81 spontaneous electroclinical seizures were captured. All of the recorded seizures were found to invade the insula, and two patients had seizures that originated in the insular cortex itself. It was shown that scalp video-electroencephalographic monitoring did not permit differentiation between the ictal symptoms of temporo-mesial and insular discharges. The authors concluded from the study that seizures secondarily propagating to

the insular cortex were fully controlled by surgery, whereas those originating in the insular cortex were not influenced by temporal lobectomy, and persist and may be mistaken for temporo-limbic or opercular seizures. A high rate of pharmaco-resistant epilepsy from insular low-grade gliomas has been reported which stressed the relative epileptogenicity of the insular cortex and improvement after an extended lesionectomy (Daffau et al. 2002).

The involvement of the insular cortex in patients with mesial temporal lobe epilepsy with respect to the emotional symptoms were studied using ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography and ¹¹C-flumazenil receptor binding (Bouilleret et al. 2002). Unilateral mesial temporal lobe epilepsy is associated with insular hypometabolism and benzodiazepine receptor loss. This study showed that emotional symptoms correlated with hypometabolism in the anterior part of ipsilateral insular cortex, whereas somesthetic symptoms correlated with hypometabolism in the posterior insular cortex.

Through the 'looking glass' of epileptic auras, as evoked by neurostimulation of epileptic insular cortices, it may be possible to understand the functions of the insula and its topographical localisation in more detail. The functional mapping of the insula cortex in temporal lobe epilepsy (Ostrowsky et al. 2000), suggested a clear topographic specificity inside the insular cortex with respect to two different cortical networks. A visceral network for viscerosensitive and visceromotor induced responses was mapped to the anterior insula, whereas a somesthetic network was localised to the posterior insula. In this study the symptoms evoked were (a) viscerosensory sensations including nausea, epigastric pressure and an unpleasant throat sensation; (b) visceromotor responses including chewing movements, lip smacking, gustatory sensations described as a 'bad', salted or an acid taste; (c) an auditory illusion; (d) olfactory pleasant sensations; (e) a visual sensation; (f) nociceptive sensations; and (g) speech disturbances. These two networks have dense connections between more 'upstream' and more 'downstream' levels of at least five anatomically distinct networks, which help to create a highly edited subjective version of the world (Mesulam 1998).

Neuropsychiatric correlates of the insular lobe

• Insula and emotional behaviour

Insula and anxiety/phobia

Since the insula plays a pivotal role in limbic integration, complex behaviours such as simple phobia with their distinct autonomic and visceral components may recruit the insular cortex in the functional neuroanatomic

distributed networks of emotion. This was studied using PET and oxygen 15 which measured normalised regional cerebral blood flow in seven subjects with simple phobia during control and provoked states (Rauch et al. 1995). Stereotactic transformation and statistical parametric mapping were used to determine the locations of significant activation. Significant increases in normalised regional blood flow for the symptomatic states compared with the control state were seen in the right anterior cingulate cortex, the left insular cortex, the right anterior temporal cortex, the left somatosensory cortex, the left posterior medial orbitofrontal cortex and in the left thalamus. This study suggested that the neuronal circuitry that underlies anxiety associated with simple phobic symptomatic states is mediated by paralimbic structures, including the insula.

Further studies of the neural substrates of specific neuropsychiatric disorders such as obsessive-compulsive disorder, simple phobia and post-traumatic stress disorder were done to determine the shared mediating neuroanatomy of anxiety symptoms across these three anxiety disorders (Rauch et al. 1997). Relative regional cerebral blood flow was measured using PET in the context of provocation paradigms. The analysis of pooled imaging data indicated activation in the right inferior frontal cortex, the right posterior medial orbitofrontal cortex, bilateral insular cortex, bilateral lenticulate nuclei and bilateral brain stem foci during the symptomatic versus control conditions. These findings confirm the hypothesis that elements of the paralimbic belt, together with right inferior frontal cortex and subcortical nuclei, mediate symptoms across different anxiety disorders.

A study using [¹⁵O] PET investigated the brain regions that participated in externally and internally generated human emotion (Reiman et al. 1997). Emotional responses to complex visual (film generated exteroceptive emotion) and cognitive (recall generated interoceptive emotion) stimuli were compared with areas of increased regional brain activity. Recall generated sadness was found to be associated with greater increases in activity in the anterior insular cortex. This suggested that the anterior insular cortex participates in the generation of human emotional response to potentially distressing cognitive or interoceptive sensory stimuli.

The neural correlates of affective disorders have been investigated by using more advanced neuroimaging techniques such as PET and functional magnetic resonance imaging (Kucharska-Pietura et al. 2001). This work demonstrated an important role of the posterior temporal cortex, orbitofrontal cortex,

amygdaloid nucleus and the insula in the neuroanatomy of affect control.

The functional aspects of brain segregation and connectivity for emotional operations were studied by meta-analysis of 55 PET and fMRI activation studies in healthy subjects (Phan et al. 2002). The purpose of the study was to determine whether there were common or segregated patterns of activation that existed across the various emotional tasks. They divided the brain into 20 non-overlapping regions, and characterised each region by its responsiveness across individual emotions (positive, negative, happiness, fear, anger, sadness, disgust), to different induction methods (visual, auditory, recall/imagery), and in emotional tasks with and without cognitive demand. The separate brain regions that were involved in different aspects of emotion were observed to be: (a) induction by emotional recall or imagery recruited the anterior cingulate and insula, (b) emotional tasks with cognitive demand also involved the anterior cingulate and insula, (c) fear specifically engaged the amygdala, (d) the medial prefrontal cortex played a general role in emotional processing, (e) sadness was associated with activity in the subcallosal cingulate and (f) the occipital cortex and amygdala was recruited in emotion induction by visual stimuli.

Insula and recognition of facial emotional expression

The human brain is expert in analysing rapidly and precisely facial features, especially emotional expressions, a powerful communication vector. Recognition of facial expressions is critical to our appreciation of the social and physical environment, with separate emotions having distinct facial expressions.

A study which used fMRI examined the neural substrate for perceiving facial expressions of disgust, in which normal volunteers were presented with faces showing mild or strong disgust or fear (Phillips et al. 1997). The cerebral activation in response to these stimuli was contrasted with neutral faces. The right anterior insular cortex, not the amygdala, was seen to be activated by both strong and mild facial expressions of disgust, whereas the left amygdala was activated for perception of fearful facial expression. This study confirmed the crucial role of the anterior insula in the recognition of disgust facial expressions, which is critical to our appreciation of the social and physical environment. Strong disgust also activated structures linked to a limbic cortico-striatal-thalamic circuit. The anterior insula is known to be involved in responses to offensive tastes. The neural response to facial expressions of disgust in others is thus closely related to appraisal of distasteful stimuli.

This was further corroborated by a recent study

using depth electrodes implanted in patients with drug-refractory temporal lobe epilepsy (Krolak-Salmon et al. 2003). Intracerebral event related potentials to human facial emotional expression were recorded. Specific anterior insular evoked responses were elicited to disgust facial expression.

Facial (visual) self-perception was studied by using blood oxygen level dependent-functional MRI (BOLD fMRI) to measure brain activation while subjects viewed computerised morphed versions of either their own or their partner's face (Kircher et al. 2001). The results revealed that when subjects viewed themselves, increased blood oxygenation was detected in the right insula, right hippocampal formation and right anterior cingulate areas in addition to left prefrontal and superior temporal cortices. In the partner (versus unknown) experiment, only the right insula was activated. This study suggested a neural network involving the right limbic-paralimbic structures with the left-sided associative and executive regions that are recruited in the process of visual self-recognition and self-awareness.

• Insular stroke and anergia

The neuropsychiatric effects of insular damage in humans due to CT/MRI documented ischaemic strokes that were restricted to the insular cortex have been reported in the literature (Manes et al. 1999a). This study group included seven patients with left insular stroke, six patients with right insular stroke, six patients with left hemisphere non-insular stroke, and six patients with right non-insular stroke. The patients were administered a neuropsychiatry battery (Mini Mental State Exam, 28 item Hamilton Depression Rating scale, the Modified Present State Exam, etc) within a time frame of four and eight weeks after the acute stroke. It was noted that the patients with right insular lesions had a greater frequency of subjective anergia, underactivity and tiredness compared with patients with left insular lesions or non-insular lesions. It was postulated that these subjective symptoms after right insular damage may be the result of disconnection of the insula's reciprocal connections with the anterior cingulate, amygdala and the prefrontal cortex, which are circuits related to voluntary motor and willed behaviour. Insulo-amygdalar interaction (Mesulam and Mufson 1985; Berthier et al. 1988) is also essential for the affective-motivational content of perceptual experience.

Studies have demonstrated the participation of the insular cortex in the cognitive generation of affect using f-MRI studies (Teasdale et al. 1999) and it may be hypothesised that anergia, apathy and neglect may all be interrelated and that the right insula dysfunction may play a role in their production (Roaslo et al. 1997; Manes et al.

1999b).

• Insula and Gilles de la Tourette's syndrome

The regional changes in cerebral glucose metabolism using ^{18}F fluorodeoxyglucose and PET in 16 drug-free patients with Gilles de la Tourette's syndrome and 16 age-matched normal volunteers were studied by Braun et al. (1993). The results indicated that patients were characterised by decreased normalised metabolic rates in the paralimbic and ventral prefrontal cortices, particularly in the orbitofrontal, inferior insula and parahippocampal regions and this was greater in the left hemisphere. Similar decreases were also observed in subcortical regions including the nucleus accumbens, ventromedial caudate and in the midbrain. Bilateral increases in metabolic activity were noted in the supplementary motor, lateral premotor and Rolandic cortices.

In another study using FDG-PET data, it was concluded that the metabolic landscape of the syndrome was characterised by a non-specific pattern of increased motor cortical activity and a reduction in the activity of the limbic cortico-striato-thalamo-cortical projection systems (Eidelberg et al. 1997). The FDG-PET phase III step was done to explore the functional neuroanatomical correlates of Gilles de la Tourette's syndrome and hypothesised that an altered or abnormal limbic (paralimbic)-motor functional interregional relationship represents the underlying pathophysiological hallmark of this disorder (Jeffries et al. 2002). This study measured the changes in functional coupling of regional cerebral metabolic rates for glucose in various areas of the brain (elements of the cortico-striato-thalamo-cortical circuit and lateral orbitofrontal-insula structures) independently in 18 drug-free patients with age- and sex-matched controls. The results revealed abnormal functional coupling between the insula, the ventral striatum (called the 'limbic-motor interface') and the motor regions. The motivational tension that precedes the motor/vocal tics and the sense of relief that follows their expression, as well as the irritability, impulsivity, depression or self-injurious behaviour seen in more complex cases, all tend to suggest that brain regions associated with motivation or affect (lateral orbitofrontal, anterior insula, amygdala and anterior cingulate connectivity) are involved and characterised by an abnormality of brain systems that effect neural transmission from the limbic to the motor systems.

The potential importance of the anterior insula in Gilles de la Tourette's syndrome stems from its extensive interconnections with the orbitofrontal cortex, which forms part of the the ventral limbic circuit, and its somatomotor associations. A case report of the Gilles de la Tourette's syndrome in an 11-year-old male has

been associated with MRI documented left frontal multicystic changes predominantly in the gyrus rectus (McAbee et al. 1999). They proposed that lesions remote from the neuroanatomical regions of the basal ganglia can be influential by an effect on the interconnecting circuits involving the lateral orbitofrontal, cingulate, thalamus and the basal ganglia resulting in motor and behavioural phenomena similar to those seen in TS.

• **Insula and obsessive-compulsive disorder**

A case report has described a 12-year-old, right-handed boy with obsessive-compulsive behaviour and reactive depressive symptomatology, which developed on a two-year background history of headaches, vomiting and complex partial seizures (Shuren et al. 1995). He was diagnosed with OCD using the DSM-III-R criteria. Multiple MRI scans demonstrated an enhancing mass in the left posterior insula with slight peri-lesional oedema, which at open biopsy demonstrated a pleomorphic xanthoastrocytoma. The neurological, neuropsychological and radiological studies did not demonstrate frontal lobe or basal ganglia dysfunctions commonly seen with patients with OCD (Hymas et al. 1991).

It was postulated that the OCD was the result of the posterior insula tumour and proposed that the insula is an important structure in the generation of OCD in the context of a frontal-basal ganglia-posterior insula loop. Others have implicated the lateral orbitofrontal circuit to be important in the pathobiology of OCD, but not discussed the insula (Leckman et al. 1997).

• **Autism and insula-gut-brain aIC hypothesis**

It has been hypothesised that, in a subgroup of autistic-spectrum children, a link exists between intestinal pathology, attention and language, which may be derived from shared neuroanatomical pathways within the anterior insular cortex (aIC) (Binstock 2001). Several investigators have associated intestinal pathologies with autism and a growing amount of anecdotal data has indicated that a subgroup of autism-spectrum children experienced improvements in word production and receptive and spoken language in response to restoring intestinal health, such as using gluten-free and casein-free diets, and antifungal and antibiotic therapies (Horvath et al. 1999; Rimland 2000; Sandler et al. 2000). The anterior insular cortex (aIC), the 'visceral cortex', links gastrointestinal tract mucosal senses with limbic information in the amygdala and hypothalamus.

The aIC has been implicated in the functional neuroanatomy of social behaviour with respect to people with autistic disorder in relation to social and emotional perception of facial

expression processing (Critchley et al. 2000). In a study involving 25 stroke patients with articulatory deficits, the lesion location has been identified to be in the left aIC (Dronker 1996). They proposed that this neuroanatomical location might be an aetiologically significant substrate in autism-spectrum disorders interconnected with the gastrointestinal mucosa. The mechanisms of disruption of the aIC in the brain-gut axis may be due to (a) intraneuronal migration of a neurotrophic virus gaining initial access via the gastrointestinal tract and/or (b) chronic hyperstimulation of the neuronal pathways providing information about gastrointestinal conditions to the limbic regions and the insular cortex. The autonomic irregularity described in autism may have a gastrointestinal link via the NTS and the vagus nerve (Palkovitz and Wiesenfeld 1980). Various investigators have linked the aIC and gastrointestinal visceral pathways via the vagal sensory ganglia and the human nucleus of tractus solitarius (Ruggiero et al. 2000; Gesser et al. 1994).

• **Insula and depression**

That the insula has been implicated as a neural substrate in the genesis of apathy, anergia and neglect was highlighted earlier (Manes et al. 1999a). Converging clinical, *post mortem* and functional neuroimaging evidence suggest that depression is unlikely to be a disorder of a single brain region or neurotransmitter system. Instead, it is best viewed as a multidimensional, systems level disorder affecting discrete but integrated pathways involving select cortical, subcortical and limbic sites and their related neurotransmitter and molecular mediators. This theoretical construct led to the neural network model of depression which proposed that depression results from a failure of the coordinated interactions of a distributed network of limbic-cortical pathways (limbic-cortical dysregulation model) (Mayberg 1997). Resting state patterns of regional glucose metabolism using FDG-PET in idiopathic depressed patients, changes in metabolism with antidepressant treatment, and blood flow changes with induced sadness in healthy subjects were used to test this hypothesis. The three main compartments of this model include: (a) a dorsal compartment, that mediates the normal cognitive aspects of mood, comprising of dorsal prefrontal, inferior parietal, and dorsal and posterior cingulate, (b) a ventral compartment that mediates the vegetative and somatic aspects of mood, composed of paralimbic cortical (ventral orbitofrontal), subcortical and brainstem regions (ventral anterior insula, hippocampus, hypothalamic-pituitary axis and mid-brain/pons), (c) the rostral cingulate, that serves an important regulatory role in the overall network by facilitating the interactions between the dorsal and ventral compartments (Figure

10). It was found that sadness and depressive illness were associated with decreases in the dorsal compartment and relative increases in the ventral compartment. Recovery from depression by fluoxetine therapy was associated with decreases in metabolism patterns in the ventral compartment and increases in the dorsal compartment. Patients with high pre-treatment rostral anterior cingulate metabolism were identified as treatment responders and this could discriminate eventual responders from nonresponders.

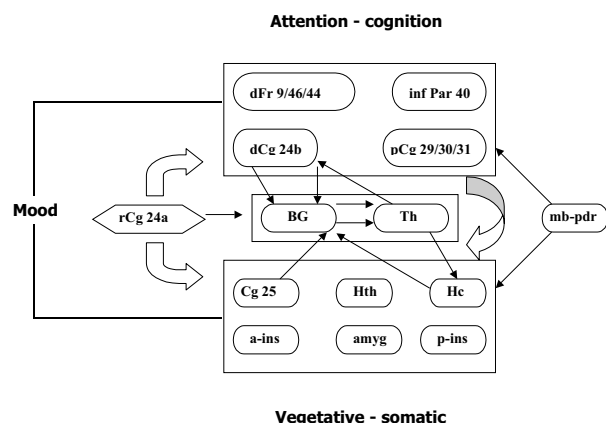


Figure 10

Neural network model of depression (Mayberg's depression model). Schematic model showing the brain regions in the dorsal limbic and neocortical compartment and ventral paralimbic compartment. Black arrows indicate segregated ventral and dorsal compartment afferents and efferents to and from the basal ganglia (striatum) and thalamus. Block arrows indicate reciprocal connections through the anterior and posterior cingulate linking the dorsal and ventral compartments. (dFr = dorsolateral prefrontal; inf Par = inferior parietal; dCg = dorsal anterior cingulate; pCg = posterior cingulate; BG = basal ganglia; Th = thalamus; Cg 25 = subgenual cingulate; Hth = hypothalamus; Hc = hippocampus; a-ins = anterior insula; amyg = amygdala; p-ins = posterior insula; rCg = rostral anterior cingulate; mb-pdr = mid brain-pons dorsal raphe)

The rostral anterior cingulate (Brodmann area 24a) has reciprocal connections with the dorsal cingulate, ventral anterior insula and ventral orbitofrontal and other structures in the ventral compartment. The bi-directional nature of this limbic-cortical reciprocity provides additional evidence of potential mechanisms mediating cognitive and pharmacological treatments of depression and the role of the insula in this circuitry.

The effects of successful paroxetine treatment in major depressive patients were studied using FDG-PET (Kennedy et al. 2001). The results were consistent with the previous study of Mayberg and provided further support for a dysregulated limbic-cortical distributed network in depression. The effect of placebo treatment was studied by measuring changes in brain glucose metabolism using PET in hospitalised men with unipolar depression (Mayberg et al. 2002). The results of clinical improvement indicated that the regions of change overlapped those seen in responders administered active fluoxetine. However, the placebo response lacked the

additional decreased metabolism in the anterior insula and other structures in the ventral compartment, which was seen in the fluoxetine responders. This pattern, seen uniquely in fluoxetine responders, was suggested to convey additional advantage in maintaining long-term clinical response and in relapse prevention.

• Insula and addictive drug behaviour

Based on the concept that the insula is a pivotal structure of the limbic lobe with a potential to serve as a limbic integration cortex, it may represent a target projection site in mediating the effects of heroin and somatic components of the anticipatory anxiety experienced by subjects when exposed to salient drug-related cues. The role of the insula was studied in human opiate addicts (Sell et al. 1999). In this study the neural response to heroin and heroin-related cues in established opiate addicts using PET functional neuroimaging was assessed. The results suggested that the ascending midbrain neuromodulatory systems were the prime targets of neurobiological processes underlying drug and drug-cue-related effects, in addition to significant activation of the insula to salient visual cues.

Structural deficiencies within limbic and prefrontal regions that may contribute to the characteristic drug-seeking and drug-taking behaviours that prevail in persons dependent on cocaine have been reported (Franklin et al. 2002). Using voxel-based morphometry in conjunction with Statistical Parametric Mapping on the structural magnetic resonance images of cocaine-dependent and cocaine-naive individuals, the study showed a decrease in grey matter concentration in ventromedial orbitofrontal, anterior cingulate, anteroventral insula and superior temporal cortices of cocaine patients in comparison to controls. Since these regions are involved in decision-making, behavioural inhibition and assignment of emotional valence to environmental stimuli, the authors proposed that structural alterations in these regions could contribute to some of the behavioural deficits characteristic of chronic cocaine users.

• Insula and neurodegenerative/infective disorders

Schizophrenia

The insular cortex is a limbic integration region that is engaged in emotional and cognitive functions. The role of the insula in the pathophysiology of schizophrenia was studied using magnetic resonance morphometry to measure insular grey matter volume (Crespo-Facorro et al. 2000). In this study insular grey matter volume and cortical surface size was measured in 25 drug-naive first episode schizophrenic patients and 25 healthy male volunteers. The study revealed morphological abnormalities of reduced cortical surface area

and grey matter volume in the left insular cortex in schizophrenic patients. These abnormalities correlated negatively with the severity of the psychotic symptom dimension.

The neuroanatomical abnormalities documented by neuroimaging include diffuse enlargement of the lateral and third ventricle by approximately 10% and diffuse reduction of cortical grey matter volume by approximately 3%-4% (Harvey et al. 1993; Lawrie and Abukemeil 1998; Zipursky et al. 1992). Considerable evidence exists in the literature to suggest that pathological change in patients with schizophrenia may be expressed at the level of spatially distributed networks that subsume multiple, densely interconnected cortical and subcortical regions (Robbins 1990; Firth et al. 1995; Wright et al. 1999). Automated dual echo MRI morphometric analysis has been done to estimate the grey and white matter deficits in a clinically homogenous group of patients who met the DSM-IV criteria for schizophrenia with negative symptoms and from healthy comparison subjects (Sigmundsson et al. 2001). The anatomical abnormalities in these schizophrenic patients with marked negative symptoms were most evident in the left neocortical and limbic regions and related white matter tracts. The significant deficits of grey matter volumes in the patient group (14%) was localised to (a) the left superior temporal gyrus and insular cortex, (b) the left medial temporal lobe, including the parahippocampal gyrus and hippocampus, and (c) the anterior cingulate and medial frontal gyri. The white matter abnormalities were found in the left temporal lobe and left frontal lobe.

Deficits in emotional expression and comprehension have been reported in patients with insular lesions (Cancelliere and Kertesz 1990). These features of insular damage are also seen in patients with schizophrenia, especially in patients with marked negative symptoms of alogia and autism. Cytoarchitectonic abnormalities in the insular cortex in schizophrenia have also been reported by other investigators (Jakob and Beckmann 1986; Wright et al. 1999).

Loss of capacity to experience pleasure (anhedonia) is a core clinical feature of schizophrenia. The neural basis of emotional processing with respect to their capacity to experience pleasure within the olfactory domain was studied in 18 schizophrenia patients matched with controls using PET and ¹⁵[O] water method (Crespo-Facorro et al. 2001). Patients with schizophrenia subjectively experienced unpleasant odours (negative hedonic affect) in a manner similar to healthy volunteers. However, in schizophrenia patients there was impairment in the experience of pleasant odours (positive hedonic affect). The

results of the regional cerebral blood flow revealed that the schizophrenia patients had decreased regional cerebral blood flow in the left anterior insula, the right nucleus accumbens, the left superior temporal gyrus and parahippocampal gyrus, the lingual gyrus and the cerebellar vermis. This failure in activation of the limbic/paralimbic regions during the experience of unpleasant odours was associated with an abnormal increase in regional cerebral blood flow in bilateral frontal cortical regions. Thus, dysfunction in distributed neural circuits affecting the complex interactions and connectivity between the limbic/paralimbic (insular cortex, nucleus accumbens, hippocampus and parahippocampal regions) and the frontal cortex may represent the neural substrates of emotional disturbances seen in patients with schizophrenia.

Frontotemporal lobar degeneration (FTLD)

Frontotemporal lobar degeneration (FTLD) is a neurodegenerative cognitive disorder characterised by progressive early distinctive behavioural symptoms associated with progressive loss of cerebral tissue in the frontal and temporal lobes. A recent study has shown significant atrophy of the insula bilaterally in both frontotemporal dementia (FTD) and semantic dementia (SemD), implicating the potential role of the insula in social behaviour (Rosen et al. 2002). They concluded that the abnormalities in the neural processing of stimulus reward contingency and autonomic feedback are important mechanisms by which damage in the orbital frontal, anterior cingulate and insular areas may produce behavioural deficits in FTLD.

Certain distinctive behavioural changes are specific and more common in frontotemporal dementia that occurs early, and has relevance for the differentiation of frontotemporal dementia from Alzheimer's disease. Recent studies have highlighted the high prevalence of alterations in food preference (craving sweet foods, food fads), appetite (increased appetite, gluttony) and eating behaviour (stereotypic eating behaviours, abnormal oral behaviours) in the frontal variant of frontotemporal dementia (Bozeat et al. 2000). The neuroanatomical implications for these specific early core behavioural features have been hypothesised to involve a network comprising the orbitobasal frontal lobe, the temporal pole, the amygdala and the anterior insular cortex (orbitofrontal-amygdala-insular network). Brain network mechanisms underlying appetite control and satiation have been studied by PET generated functional brain maps, which indicated the involvement of these structures (Del-Parigi et al. 2002).

A recent study looked into the prevalence and pattern of distinctive ritualistic and complex

stereotypic behaviours in frontotemporal dementia (Nyastanza et al. 2003). They concluded that these behaviours (foot tapping, grunting, hand rubbing, rigid adherence to routines, verbal stereotypies, repetitively eating the same food, compulsive symptoms) have a higher prevalence in FTD than in Alzheimer's disease, and suggested that these aberrant motor behaviours may have discriminatory power in the diagnosis of FTD and are a core feature of the dementing syndrome in FTD. It was concluded that these behavioural abnormalities reflected disruption of an integrated circuit involving the orbitofrontal cortex, amygdala and the insular cortex and/or the striatal circuitry.

Thus the insular cortex has been implicated in the neural processing of human eating behaviour, satiation and aberrant motor behaviour in FTD as a result of its intense interconnections with the ventromedial frontal lobe, temporal pole and amygdala. The elucidation of the pathophysiological basis for these core neurobehavioural abnormalities by future neuroimaging and behaviour studies should clarify the componential role of the insular cortex in the neural networks mediating these distinctive behavioural abnormalities in FTD.

Alzheimer's disease

A recent study implicated the insular cortex and the midfrontal gyrus in the neurodegeneration that occurs with Alzheimer's disease. In this case-control study, brain tissue samples were obtained from the insular cortex and midfrontal gyrus, which revealed DNA fragmentation in the pyramidal neurones along with dense accumulation of beta-amyloid deposition (Colurso et al. 2003). Beta-amyloid mediates neuronal injury through the process of apoptosis as evidenced by the positive assay identifying DNA fragmentation. This study identified these two distinctive neuropathologies co-occurring in the insular cortex and midfrontal gyrus, both of which are interconnected reciprocally, and with the other limbic areas.

Dementia with Lewy bodies (DLB)

This non-Alzheimer degenerative dementia is characterised neuropathologically by the presence of cortical Lewy bodies. Several studies have shown the site of cortical Lewy body density which has a consistent gradient as follows: substantia nigra > entorhinal cortex > cingulate gyrus > insular cortex > frontal cortex > hippocampus > occipital cortex (McKeith 2001). A recent study showed that Lewy pathology starts in the deeper layers of the neocortex and paralimbic regions, including the insular cortex, by using alpha-synuclein immunohistochemistry (Marui et al. 2002). In another study using the image processing

technique of voxel based morphometry, regional grey matter volume loss was shown to affect bilateral temporal and frontal lobes and insular cortex of patients with DLB compared to control subjects (Burton et al. 2002).

Neuroinfections

In an autopsy study of human herpes simplex virus encephalitis, the distribution of viral antigen within the brain was mapped (Esiri 1982). The viral antigens were mainly localised in the medial and inferior temporal lobes in addition to the insula, olfactory cortex, hippocampus, amygdaloid nuclei and cingulate gyrus. In another study using immunocytochemistry, positive viral antigen immunostaining was identified in the fronto-orbital, mediobasal temporal lobes, insula and cingulate gyrus (Charpin et al. 1985).

The insular cortex has been implicated in intracerebral Whipple's disease in addition to typical lesions involving the hypothalamus, cingulate gyrus, basal ganglia and cerebellum (Mendel et al. 1999). Whipple's disease results from a systemic infection by the bacterium *Tropheryma whippelii* and may manifest with central nervous system involvement alone, without typical gastrointestinal disease, comprising a dementia, personality change, supranuclear ophthalmoplegia and characteristic oculomasticatory-skeletal myoarrhythmia.

Insula and therapeutic neurostimulation

The neuroanatomical implication of the human insular cortex in epilepsy, treatment-resistant depression and other neuropsychiatric disorders has come to light by studying the effects of vagus nerve stimulation (VNS) in such disorders (George et al. 2000). VNS has been shown to have antiseizure and antidepressant effects. The other areas of potential research or clinical neuropsychiatric implications with VNS include anxiety disorders, obesity, addictions, sleep disorders, dementing disorders and pain syndromes.

The vagus nerve afferents synapse in the nucleus of the tractus solitarius (NTS) which then projects to the locus ceruleus, dorsal raphe, hypothalamus and the thalamus (vagus-NTS pathway). The pathway to the thalamus continues to the anterior insular cortex and limbic structures (amygdala, hippocampus, posterior cingulate gyrus, entorhinal cortex and anterior temporal cortex and orbitofrontal regions). The insular cortex also sends projections back to the nucleus of the tractus solitarius. Higher-order projections of the anterior insula are particularly dense in inferior and inferolateral frontal cortex of the limbic system.

The cerebral blood flow alterations induced during VNS revealed increased blood flow in rostral, dorsal-central medulla; bilateral hypothalami, thalami, insular cortices and inferior cerebellar hemispheres; and decreased bilaterally in hippocampus, amygdala and posterior cingulate gyri (Henry et al. 1998).

Transcranial magnetic stimulation (TMS) is another new, non-invasive technique for directly stimulating cortical neurones which has been used in treatment of mood in depression. Using ¹⁵ [O] water and PET, the changes in regional cerebral blood flow were studied after high and low frequency r-TMS over the left prefrontal cortex in ten medication-free patients with major depression (Speer et al. 2000). High frequency r-TMS was associated with significant increases in regional cerebral blood flow in the prefrontal cortex and cingulate gyrus (left > right), left amygdala and bilateral insula, basal ganglia, uncus, hippocampus, para-hippocampus, thalamus and cerebellum.

Thus functional neuroimaging tools, when used in combination with VNS and TMS, have thrown light on the role of the anterior insular cortex within the distributed neural networks that may underlie many neuropsychiatric disorders.

Conclusions

Over the course of the last two centuries, since its initial description, a great deal of work has focused on the anatomical and functional aspects of this 'hidden lobe' called 'the island of Reil'. It can be concluded that the insula is a multifaceted functional area, which has a componential role in various 'distributed neural networks' subserving human behaviour and in the causation of disorders affecting the brain and the mind. The human insular cortex is characterised by the greatest conceivable spectrum of cortical and subcortical connections, which would explain the panoply of its complex behavioural specialisations. The insula is a pivotal functional structure of the limbic lobe and plays a vital role as a limbic integration cortex. Like the extended amygdala, the insula serves as a neural relay 'satellite' station and forms an integrative anatomical, functional and behavioural unit of the telencephalon.

With the advent of state of the art neuroimaging tools for research to map brain functions it has been possible to gain further insights regarding the neural substrates and neurobiological foundations of human behaviour, and on the role of the insula. Imaging neuroscience has led to a conceptual shift in understanding of brain functional architecture from the traditional 'functional segregation approach' (segregated circuitry) to a 'dynamic network approach'

mediated by multidimensional distributed neural network connectivity (distributed circuitry). Brain functions are viewed as a working mosaic model mediated by large-scale interconnected neural networks incorporating multiple cortical regions (multimodular networks) with collaborative and overlapping functions (functional integration approach). The blueprint of complex human behaviour is now mapped at the level of multifocal neural systems rather than specific anatomical sites characterised by almost infinite richness and flexibility. It is the abnormal maladapted functional relationship between elements in a series of neural network that underlies the genesis of neuropsychiatric or behavioural disorders (network approach to behavioural neurology).

Thus the insula does not operate in isolation and functions as albeit one important element in a series of neural networks distributed throughout the central nervous system, and it is the abnormal functional relationships between the various regions that dictate the behavioural and neuropsychiatric afflictions that we relate to the insula. Further research into the inter-regional connectivity and functional aspects of the insula will be made possible by robust paradigms of computational neuroscience; the combined use of non-invasive functional neuroimaging tools (PET, f-MRI, MEG) and non-invasive cortical stimulation using TMS both in animal and human studies.

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Toward a New Prevention of Suicide in Schizophrenia

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Summary

Suicide is the primary cause of death among schizophrenic patients; follow-up studies suggested that 10-13% of schizophrenic patients die by suicide. Preventive measures based on early recognition of risk factors and the establishment of drug treatment protocols are no doubt of great help but have not resulted in a significant reduction of the number of suicides among these patients. Schizophrenia is a chronic disorder affecting all aspects of the individual's life. Prevention should therefore be addressed to various areas. This paper overviews studies dealing with major fields of interest in the prevention of suicide among patients with schizophrenia. The authors focus on the role of pharmacological treatment, psychosocial interventions and psychotherapy, the struggle against stigmatisation and the role of GPs. Prevention of suicide among inpatients with schizophrenia is also analysed. It is concluded that those integrated strategies already in use and the implementation of less known interventions should constitute a more effective prevention of self-inflicted deaths among these patients.

Key words: *suicide, schizophrenia, antipsychotics, psychosocial interventions, stigma.*

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Introduction

According to WHO estimates, approximately one million people worldwide took their lives in the year 2000, and 10 to 20 times more attempted to do so. This represents one death every 40 seconds and one attempt every three seconds, on average. No doubt, individuals affected by psychiatric illness are more represented among those who manifest suicidal behaviour. Recently, Althaus and Hegerl (2003) brilliantly investigated different approaches to prevent suicide. They thoughtfully reviewed main strategies that should be implemented in the struggle against self-inflicted death. Yet, prevention of suicide in schizophrenic patients is often a neglected issue in the literature, which somehow contrasts with the great numbers of studies devoted to the investigation of self-killing among these individuals.

Miles (1977) reviewed 34 studies of suicide among schizophrenics and estimated that 10% of schizophrenic patients kill themselves. Follow-up studies have estimated that 10-13% of individuals with schizophrenia die by suicide, which is the main cause of death among these patients (Caldwell and Gottesman 1990). Suicide attempts, which often result in completed suicide, are a burning issue among patients with schizophrenia; 20-40% of these patients do make suicide attempts (Landmark et al. 1987; Planansky and Johnston 1971; Roy et al. 1984). Compared with suicide attempts among persons without schizophrenia, attempts among those with schizophrenia are serious and typically require medical attention. Intent is generally strong, and the majority of those who attempt suicide have made multiple attempts. In addition, the methods used to attempt suicide are considered more likely to be lethal than those used by suicidal persons in the general population. Up to half the suicides among patients with schizophrenia occur during inpatient treatment. Inpatient suicides were mostly found among those of a young age group who were predominantly single, childless and socially isolated. The vast majority experienced an illness characterised by long duration and prolonged psychiatric hospitalisations or multiple admissions and discharges. Up to 50 per cent of the suicides occurred in the first few weeks and months following discharge from hospital (Roy 1986). The paranoid subtype of schizophrenia, which emphasises positive symptoms and the absence of negative symptoms, is associated with a

suicide risk that is three times greater than that associated with non-paranoid subtypes and eight times greater than the risk associated with the deficit subtypes (Fenton et al. 1997). The lifetime incidence of suicide in the general population is about 1% (Fremouv et al. 1990). It has been estimated that the life expectancy among schizophrenic persons, as a group, is shortened by 9 to 10 years, and that the excess in mortality is chiefly accounted for by suicide and accidental deaths (Tsuang et al. 1980; Tsuang and Woolson 1978).

There is evidence that those affected by schizophrenia who are more likely to commit suicide are young, male, white, unmarried, have good pre-morbid function, have post-psychotic depression, and have a history of substance abuse and suicide attempts. Hopelessness, social isolation, awareness of illness and hospitalisation are also very important risk factors in schizophrenics who commit suicide. Deteriorating health with a high level of pre-morbid functioning, recent loss or rejection, limited external support and family stress or instability are other risk factors traceable in patients with schizophrenia who commit suicide. These patients usually fear further mental deterioration and experience excessive treatment dependence or loss of faith in treatment. Suicides as a result of command hallucinations are rare, but have been reported in the literature (Zisook et al. 1995). The literature abounds with descriptions of risk factors for suicide in individuals with schizophrenia; less investigated are possible protective factors for suicide in schizophrenia (Table 1).

Despite great efforts, both on the side of drug

Table 1
Protective factors for suicide in individuals with schizophrenia

| |
|---|
| Compliance to therapy (Roy 2001) |
| Therapy with atypical antipsychotics (Meltzer 1998) |
| Family support for the illness and for the stigma that arises from it |
| Regular sessions of family therapy that is able contribute to reduce the number and the duration of hospitalizations, the number of the relapses and increases compliance to therapy (Roy 2001) |
| Suitable antidepressant therapy (Roy 2001) |
| Possibility to speak of the intention to commit suicide (Harkavy-Friedman and Nelson 1997a) |
| Family history negative for suicide (Roy 1983) |
| Support and programmes of aftercare at discharge (Farberow et al. 1971) |
| Programmes of prevention about substance abuse (Allebeck et al. 1987) |
| Possibility of working and carrying out pleasant tasks |
| Subtypes of schizophrenia as simplex and hebephrenic |
| Training in the development of social and cognitive skills |
| Limitations to the more common methods of suicide |
| Not being stigmatized |
| Live in an environment adjusted to patient's needs |
| Psychological well-being: given by the mastery of choices and by the relationships with others |

treatment and psychosocial strategies, the number of suicides among schizophrenic patients has remained unchanged (Meltzer et al. 2003).

Background analysis

In order to address, discuss and overview the problem of prevention of suicide among individuals with schizophrenia, we performed careful MedLine, Excerpta Medica and PsycLit searches to identify papers and book chapters in English during the period 1966-2004 and the Index Medicus and Excerpta Medica prior to 1966. Search terms were "suicid*", (which comprises suicide, suicidal, suicidality, and other suicide-related terms), "parasuicid*", "schizophreni*" "inpatient or in-patient", "outpatient", "psychosocial treatment or rehabilitation", "social skill training", "cognitive techniques", "social support or social adjustment", "rehabilitation counseling or social support network", "prevention". Each term was also cross-referenced with the others using the MeSH method (Medical Subjects Headings). Also, using the same databases and methods, we crossed-referenced "schizophrenia" with key words such as "atypical antipsychotics" any of "clozapine", "olanzapine", "risperidon*", "quetiapine" or "seroquel" or "ICI 204 636", "ziprasidone", "sertindol*", aripirazol* or "OPC-14597", "zotepine" as these new drugs are generally associated with some impact on suicide.

In such a way the entire literature on suicide in schizophrenia was carefully reviewed. By reviewing selected articles we identified some specific fields of interest. We also consulted a number of international experts in the field to determine whether studies selected were relevant for discussing preventive measures for suicide in schizophrenia. The authors and experts consulted performed a careful analysis of the literature data and agreed on a number of key subjects relevant to the aim of this paper. We will therefore overview studies dealing with pharmacological treatment, psychosocial intervention and psychotherapy, stigmatisation, GPs' role in preventive suicide and prevention of suicide among inpatients with schizophrenia. The aim of this study is to go over a number of suicide preventive strategies and stimulate further discussion on the field of prevention of suicidal behaviour in schizophrenic patients.

Where does prevention begin?

In normal clinical practice the doctor interacts with a subject who desires passionately the maintenance of health. On the contrary, the suicidal patient struggles to defeat the doctor and tries the self-annihilation process. Mental health professionals, or doctors as a whole, are often disorientated in relation to suicidal

patients, especially because suicide is the event most alien to the nature of medicine. Yet, many of those who decide to commit suicide contact their doctors days or weeks before the act (Blumenthal 1988; Robins et al. 1959; Andersen et al. 2000). This is also true for the schizophrenic patient (Saarinen et al. 1999). Doctors are therefore in a privileged position for delivering preventive measures. Since Bleuler (1911), suicide has been recognised as an important complication of schizophrenia. Kraepelin (1971) stated as well that "suicide, especially in the first period of the malady, is not infrequent and occurs, sometimes without recognisable cause, also in patients who for long have been weak-minded and apparently quiet."

If we consider suicide as a complication of schizophrenia we should emphasise the need to prevent complications of the illness, but taken as an event belonging to the complexity of schizophrenia, suicide may be prevented with the help of concepts referred to as primary, secondary and tertiary prevention.

• Primary prevention

Primary prevention represents the search for the prevention and elimination of risk factors. These factors include developing social isolation, substance abuse, depression, hopelessness and disappointment for lost expectations toward the future. Also, insight into the illness should be monitored very carefully, as it has become apparent that the awareness of one's illness leads to discouragement and suicide risk. Appropriate pharmacotherapy and psychotherapy should prevent the emergence of risk factors for suicide and the reduction of those factors already detected in the patient.

Patients should always be asked about their intention to commit suicide. There are no contraindications to the investigation of suicidality in schizophrenic patients. They are instead relieved by an explicit investigation, as they have the opportunity to share their inner feelings (Harkavy-Friedman and Nelson 1997b).

Care-givers should be particularly alert when something new happens, such as:

- 1) Meaningful changes: ward, therapist or therapy, family structure, relationship, residence;
- 2) Meaningful losses: family, medical staff, therapist;
- 3) Discrimination and abuse: social, emotional and/or psychological, sexual.

• Secondary prevention

Secondary prevention is identifiable as an operation that aims to check the phenomena in those subjects who have already developed risk factors for suicide. State-dependent risk factors are those that can potentially be modified (such

as depression, substance abuse, hopelessness, etc.); on the contrary, trait-dependent risk factors are unchangeable (gender, age, pre-morbid functioning, etc.). No doubt, a prompt recognition of individuals who are at risk is a key element in the prevention of suicide. Screening procedures taking into account suicidal indicators should be implemented. Patients who are depressed, substance abusers and hopeless should be monitored carefully. Also, those who have experienced multiple hospitalisations and threatened or attempted suicide should be treated according to adequate procedures, such as programmes of aftercare and psychosocial intervention.

• Tertiary prevention

Tertiary prevention is addressed to those individuals who have attempted suicide or are suicidal. Not only risk factors for suicide are identifiable in these patients, but also suicide spectrum activities are easily detected. Pharmacological interventions are no doubt of paramount importance, but psychosocial interventions also play a central role. Psychotherapy with suicidal schizophrenic patients should also be considered.

Psychopharmacology

The positive impact of atypical antipsychotics on suicidality in patients with schizophrenia has been reviewed (Keck et al. 2000). Carone et al. (1991) reported the results of treatment with typical antipsychotics and the impact on suicide in individuals with schizophrenia. These authors followed 80 young people with schizophrenia who were receiving typical antipsychotics for up to five years. After two and a half and five years there was an overall 10% suicide incidence, and as many people committed suicide as had a good outcome.

Clozapine, olanzapine, risperidone and quetiapine have shown some power in reducing suicidality among schizophrenic patients (Keck et al. 2000; Meltzer 2001). Clozapine was shown to reduce suicidality in schizophrenia, especially in treatment-resistant patients (Meltzer 1998; Meltzer and Okayli 1995; Reid et al. 1998; Walker et al. 1997; Munro et al. 1999). Meltzer and Okayli's study offers interesting elements for the analysis of the impact of clozapine on suicidal behaviour in schizophrenia. The data on suicidality during clozapine treatment were collected prospectively throughout a follow-up period. At the end of the study, in order to ensure as accurate an analysis as possible, the patients were re-interviewed and these data were compared with all available data to confirm that the authors had not missed any pertinent information (Meltzer and Okayli 1995). According to these authors the potential decrease in suicide mortality with clozapine treatment is estimated to be as high as 85%. In

terms of benefit versus risk, while 1.5 of every 10,000 patients with schizophrenia who were treated with clozapine would be expected to die from agranulocytosis (evidence suggests a percentage even lower), 1000 to 1300 would be expected to commit suicide with standard treatment (Meltzer and Fatemi, 1995). In fact, the US Food and Drug Administration recently approved clozapine for the treatment of suicidal behaviour in patients with schizophrenia or schizoaffective disorder (Meltzer et al. 2003). Yet, according to Sernyak et al. (2001) clozapine treatment was not associated with significantly fewer deaths from suicide. These authors used for the first time a matched control group to examine the effect of clozapine on the rate of suicide in patients with schizophrenia. In their sample they did not observe a significant reduction of suicides due to clozapine. According to these authors, the comparison that best reflects clinical practice and is most informative compares all patients who received clozapine with a carefully matched group of patients who were never exposed to clozapine, yielding a nonsignificant ($P=0.76$) difference in the rates of suicide. However, one third of the sample received clozapine for less than six months even though the follow-up period was five to six years. Both studies about clozapine (Meltzer and Okayli 1995; Sernyak et al. 2001) have a number of limitations that prevent a definite conclusion. Meltzer and Okayli did not match cases with a controlled group, thus each patient acted as his or her own comparison subject. This design is not as robust as a randomised, parallel-group, double-blind study (Ertugrul 2002). The study by Sernyak et al. also has several limitations: the effect of clozapine on all causes of mortality, including suicide, was compared in a study with a group chosen by the use of "propensity scaling", a potentially problematic method that has severe limitations in this context (Meltzer 2002). The authors failed to consider the variables available for subject matching and did not include the four most important characteristics necessary for matching for suicide (the number, timing and lethality of prior suicide attempts and the severity of depression at index admission). All the variables used to create a comparison group have no connection with suicidality. Despite the fact that various studies suggested that treatment with clozapine might reduce suicidality among patients with schizophrenia, future studies are needed to fill the methodological gaps mentioned above.

Atypical antipsychotics also have the advantage of improving adherence to treatment, as they are not generally associated with extrapyramidal symptoms or tardive dyskinesia. Treatment results in a better quality of life for patients and reduced risk of suicide as intolerable extrapyramidal symptoms may be likewise associated with an increased risk of suicide.

Psychosocial interventions and psychotherapy

The international literature presents various psychosocial interventions for schizophrenic patients, often requiring the integration of pharmacological, psychosocial and rehabilitative strategies in treatment. Nevertheless, the impact of these strategies on suicide has only rarely been investigated. Drake et al. (1989) pointed to the need for empathic support in reducing suicide risk. These authors suggested that clinicians should acknowledge the patient's despair, discuss losses and daily difficulties, and help to establish new and accessible goals. Social isolation and work impairment have been reported as risk factors for suicide in individuals with schizophrenia (Roy 1982; Drake et al. 1985; Nyman and Jonsson 1986). Individuals with good pre-morbid functioning are those more at risk of suicide. Interventions such as social skill training, vocational rehabilitation and supportive employment are therefore very important in the prevention of suicide of schizophrenic patients. Broadly speaking, these kinds of therapies focus on working out daily problems rather than achieving psychological insight. It has become increasingly clear that supportive, reality-orientated therapies are generally of great value in the treatment of patients with schizophrenia. In particular, supportive psychotherapy aims at offering the patient the opportunity to meet with the therapist and discuss the difficulties encountered in daily activities. Patients are therefore encouraged to discuss concerns about medications and side effects as well as social isolation, money, stigma, etc. The therapist has an active role as he gives suggestions and shares good and bad periods empathetically. The nature of these treatments and their availability vary greatly from place to place (Figures 1 and 2). Psychosocial approaches have limited value for acutely psychotic patients.

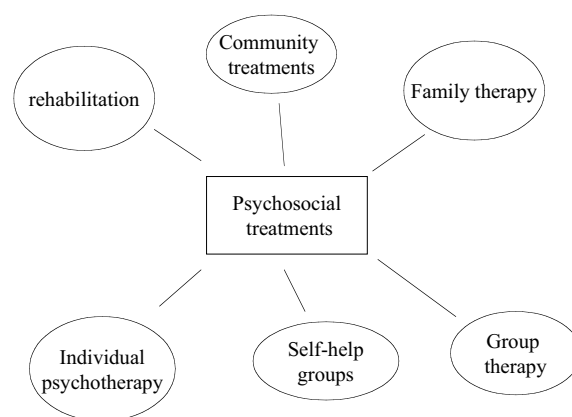


Figure 1
Psychosocial treatments for patients with schizophrenia

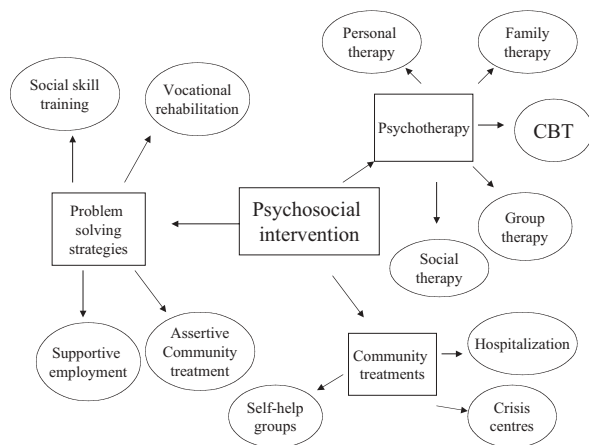


Figure 2
Psychosocial intervention that may help the prevention of suicide in schizophrenia

Investigation of psychosocial treatments for schizophrenia led to the conclusion that supportive rather than exploratory psychotherapy should be favoured (Herz 1996; Penn and Mueser 1996). Herz (1996) pointed out that many patients have cognitive deficits that impair interpersonal adjustments. These deficits include problems in thinking, poor memory, difficulty in concentrating, and distorted or inaccurate perceptions. For such reasons, an exploratory approach may be inappropriate for the vast majority of patients with schizophrenia. Mueser and Berenbaum (1990) reviewed controlled trials of psychotherapy and concluded that reality-orientated psychotherapy is superior to a dynamic, insight-orientated approach. Nevertheless, exploratory psychotherapy may have some benefits as it gives patients who have achieved a stable remission the opportunity to understand inner conflicts and discuss, within a solid therapeutic alliance, suicidal thoughts or suicidal behaviour. Patients learn to deal with the sphere of symbolism and with the thought rather than the action (suicide) (Robbins 1992; Shapiro 1991). However, any psychotherapy technique requires certain alteration and modifications of the standard approach to therapy (Weiden 1996a, b; Weiden and Havens 1994).

An approach elaborated by Hogarty et al. (1995, 1997a,b) is Personal Therapy, which includes three levels of treatment with defined criteria for progression from basic to more challenging levels. Treatment spans from early months after discharge, which aims at clinical stabilisation and therapeutic joining, to a later phase which promotes introspection and an understanding of the relationship between stressors and maladaptive response. An intermediate phase promotes skills remediation, relaxation training, role playing and psychoeducation.

There is evidence to suggest that the

combination of psychosocial and pharmacological treatments increases compliance and helps to achieve a better outcome (Marder et al. 2000).

Stigmatisation

Due to the unpredictability of schizophrenic patients' behaviour, the lay public sees their condition as potentially dangerous to others. This calls for the need to mark out these patients and, as a result, stigma towards them may ensue. Stigma may be encountered anywhere, from family to medical personnel. We recently supported the speculation that stigma may be a cause of suicide (Pompili et al. 2003a). Stigmatisation towards these patients is often unrecognised, as schizophrenic individuals are only rarely clearly rejected. In most instances, people behave ambiguously and not overtly.

Saarinen and colleagues (1999) have recognised various elements that impair the staff's ability to identify markers of suicide in patients with schizophrenia. They indicated difficulties in dealing with suicide and personal problems as major elements of the disturbance. In particular, acceptance of a patient's suicide as a solution to problems, wishes that a patient would commit suicide as a solution to his or her problem, fear of the patient and difficulties in dealing with suicidal individuals are some of the most important sources of stigma in the mental health environment. Also, following an attempt, many patients feel isolated or ignored by health professionals. Stigmatisation is crucial, as very often people who manifest suicidal behaviour are considered dangerous, weak and selfish; these considerations lead to avoidance. However, patients who attempt suicide or are at risk for suicide are the ones that most benefit from empathetic relationships with nurses and doctors (Pompili et al. 2003b). A clear example of these benefits refers to clozapine treatment. Patients need to have white blood cell counts performed weekly in order to avoid agranulocytosis. These weekly checks are said to have a beneficial effect on the social isolation and empathetic contacts that these individuals desperately need (Pompili et al. 2002a).

Unfortunately, family members are also stigmatised for their association with schizophrenia (Phelan et al. 1998). This psychiatric disorder often results in impairment of daily activities, relapses and a chronic course of illness. Family members are looked on with suspicion for dealing with their sick relative and may be subjected to lack of socialisation and reduced job opportunities. Pompili et al. (2003c) recently proposed a pattern of behaviour in a patient's relatives that might somehow communicate to the schizophrenic patient that suicide is the best solution for the overall

system. Langs' (1986) unconscious communication in everyday life might be used to support the concept that through a network of unconscious messages, people around the patient may lead him or her to conclude that suicide is the best solution for an exhausting illness. Patients may commit suicide not only when they become aware of negative expectations for the future and from a nondelusional but acutely painful awareness of the illness process, depleted self-esteem and hopelessness for the future (Fenton, 2000) but also when close to people trying to depict their situation.

GPs' role in the prevention of suicide in schizophrenia

Schizophrenic patients, who are generally prone to develop suicidal ideation, need a warm environment where they feel protected and accepted. Unfortunately, schizophrenia often evokes the idea of a treatment resistant disorder that may damage people around the patient. Strangely enough, this is true even among doctors, who may feel uncomfortable with these patients. This behaviour is even recognisable among psychiatrists and mental health professionals. Also, schizophrenic patients very often meet GPs for drug prescriptions or to request psychiatric consultation. General practitioners often do not take into consideration their role in the prevention of suicidality. According to the databases mentioned above, in the entire English scientific literature only one paper (an editorial) was published stressing plainly the need for suicide prevention in schizophrenia in general practice (Pompili et al. 2002b). Barraclough et al. (1974) found in their sample that 63% of suicides had seen their general practitioners in the month before death and 36% in the week before death. A later report found fewer patients having seen general practitioners shortly before death, which may be due to improved detection and treatment of patients at risk (Vassilas and Norgan 1993). Thus, the recognition of risk factors is an element of prevention and prediction. In fact, not only people who consider suicide often contact their doctors immediately before action, but also people who are at risk should be promptly recognised. Moreover, rejection by these figures may be the ultimate insult to very weak self-esteem. Although general practitioners may have an ancillary role in the treatment of schizophrenic patients, they may be in a strategic position to detect early risk factors or to contribute to the changing of state-dependent risk factors.

Prevention of suicide among inpatients with schizophrenia

Prevention of suicide by inpatients with schizophrenia is a daily challenge, which has to

be met with various modalities. Farberow et al. (1971) emphasise the need for careful screening of patients when they are considered for discharge or leave on pass. Such a process involves careful evaluation of the environmental factors to which the patients are returning as well as contact with their family.

Crammer (1984) highlighted the importance of taking environmental factors into account when thinking proactively about suicide among inpatients. He pointed to the potentially disruptive effects of transitions – for example, initial acclimatisation to ward life or plans for discharge or rehabilitation. He also emphasised the environmental impact of staff variables, such as low morale or the absence of key personnel, as well as the need for effective communication among relevant staff about patients judged at increased risk of suicide.

Yarden (1974) drew attention to the importance of suitable discharge plans and aftercare programmes. Supportive, supervised living arrangements are ideal. Adverse circumstances such as single-occupancy rooms or the return to a family in which the patient's presence represents a severe emotional or financial strain, most probably add to the suicide risk for a schizophrenic patient (Vaughn and Leff 1976).

With chronic, incapacitated patients, surveillance should be increased in times of personal crisis and impeding environmental change, including staff, therapist or contact person changes, hospitalisation, discharge or rehospitalisation (Caldwell and Gottesman 1990).

Some authors have suggested that variations in the ward environment because of the staffing changes might be a factor in suicidal deaths. Salmons (1984) showed that many of the deaths in one unit were associated with periods at which there were lower levels of staffing than usual. Hesso (1977) drew attention to the apparent rise in suicide rates in Scandinavian hospitals after 1955. He suggested that mentally ill patients were more likely to be admitted than previously, and thus there were more social pressures upon those who are seriously ill to conform and lead more "normal" lives. He also thought that the use of neuroleptics and open-door policies led to shorter stays for those who were ill, perhaps increasing pressure in this way. Another factor he considered was the increased personnel turnover in psychiatric hospitals, leading to less experienced staff.

An anti-suicidal ward is one with a calm routine, carried out daily by staff who are themselves unworried and confident of the immediate future. Morgan (1979) gave case histories of eight inpatient suicides who were so provocative, difficult and unreasonable that the

staff ultimately felt hostile towards them before their suicides.

Farberow et al. (1966) described the "dependent-dissatisfied" person who is able to provoke rejection and thus bring about the state they dread most: loneliness and the feeling that no one, not even the hospital nor its staff, cares.

Among long-stay patients, plans for rehabilitation or discharge may create uncertainty and disruption of a routine, leading to the death. Among the newly admitted, fear of the future may be aggravated by contact with psychiatrists or with disordered fellow patients. Where a patient is recognised to be at risk of suicide, not all the relevant staff may be properly informed. Also, low staff morale, the employment of locums, the absence on leave of consultants may all have an influence on tendency to suicide (Crammer 1984).

Bleuler (1911) attributed a detrimental effect to the then prevailing humiliating surveillance and restraint of schizophrenics, and was of the opinion that these very methods increase and maintain the suicidal drive. During recent years, modern principles of community psychiatry have been applied in the large public mental hospitals. This trend, which emphasises open doors, the abolition of involuntary restrictions, therapeutic community, early discharge and maintenance of schizophrenics within their families and communities, has brought about welcome changes in the life patterns of most mental hospital patients (Yarden 1974).

Medical staff behaviour is a potential cause of suicide when they fail to recognise suicide risk because of personal problems or difficulties with the topic of suicide. Pompili et al. (2003b, 2004) recently pointed to the role of nurses in the prevention of suicide in schizophrenia. These authors outlined the many difficulties in the care of a schizophrenic patient who is at risk of suicide and paid particular attention to staff "countertransference" reactions to these patients. We believe that having the opportunity to explore part of the psychic processes of suicidal schizophrenic patients may help mental health professionals to understand their patients better. Nursing a schizophrenic patient who is at risk of suicide involves the establishment of a very uncommon relationship. A very interesting topic is the concept of "terminal malignant alienation" (Morgan and Priest 1984, 1991). Some patients, particularly those with recurrent relapses and resistance to treatment, may be perceived by staff as manipulative, provocative, unreasonable, over-dependent and feigning disability (Schwartz et al. 1975; Morgan and Priest 1984, 1991; Kullgren 1988). Patients with fluctuating suicidal ideation are particularly likely to fall into these categories; this may lead

to under-reporting of suicidal ideation by nursing staff. This may result in criticism and a lower level of support leading to alienation. The combination of such alienation and fluctuating suicidal ideation can lead to failure in the recognition of seriousness of suicidal risk (Morgan and Priest 1984, 1991).

Various methods of suicide have been recognised among inpatients with schizophrenia. Shah and Ganesvaran (1999) found that suicide was most often performed with methods such as jumping in front of trains, trams or road traffic, jumping off buildings, hanging and drowning. These methods are consistent with previous studies (Roy 1982; Modestin et al. 1992).

Emmerson and Cantor (1993) underline the fact that almost half of the suicides in their sample occurred on a railway track close to the regional psychiatric hospital which contrasts with Symonds' (1985) suggestion that there is no relation with the proximity of suicide to psychiatric hospitals. It should be noted that the Brisbane psychiatric hospital (1993) is close to an unfenced railway line and an open access station.

Farberow et al. (1971) pointed out that while in the hospital, hanging is quite a common method of suicide, comprising 53%; jumping is the next most common method with 17%. Again, however, when the patient is out of the hospital the use of guns dominates the rest of the methods with 43%, followed by hanging 15%, poison 11% and jumping 10%. The percentages show that patients predominantly tended to use guns whereas poison, hanging and drowning were much less frequent.

Suicide precautions must be carefully adhered to by staff in order to maintain constant observation while the patient remains acutely psychotic, especially during the first week of hospitalisation. Lapses in observation should not be permitted while the patient is in the bathroom or in his/her room. As hanging is the most common method, bathroom stall bars and room and closet fixtures should be of a breakaway variety. Farberow et al. (1971) suggested the use of physical safeguards such as safety screens, or stops on the windows and the enclosure of stairwells, or installation of higher guardrails difficult to climb over, to be useful.

Shah and Ganesvaran (1999) reported that a six-lane road, a tram route and a railway station were all very close to the hospital, thus allowing for easily accessible violent methods. Reducing the accessibility of possible suicide methods can reduce suicide rates (Morgan and Priest 1984; Surtees and Duffy 1989).

Conclusions

Despite considerable research on suicide in schizophrenia, this event remains a major health problem. Antipsychotic medications certainly help to reduce suicidality, but the number of deaths due to suicide among schizophrenic patients is still much higher compared with the general population. Psychosocial interventions are of great help but lack scientific validation. Patients are rarely investigated for suicidality and different helpful treatments are often kept apart, such as reduction of stigmatisation, improved relationship with GPs and instructions given to staff to tolerate difficult patients. Families are not supported properly and prevention of suicide inside the family environment is, for the time being, missing. GPs' role is a neglected topic and it has become increasingly apparent that they may represent a key element in the implementation of preventive measures. Stigmatisation is another great problem in the prevention of suicide of schizophrenic patients, especially because stigma toward these patients can be perceived even inside closed circuits. Suicide among inpatients with schizophrenia is also a major issue and, despite the introduction of protocols in the hospital environment aimed at preventing suicide, our feeling is that we still need to work very hard to reduce suicide and to be able to handle practical tools capable of preventing suicide among these patients.

This review has a number of limitations. Firstly, no meta-analytic technique has been used to evaluate results of the various preventive strategies. Secondly, the authors chose to report those studies available in the literature that could support a broad analysis of the topic so as to offer a tutorial paper. Despite careful and systematic search, we extrapolated those studies that presented original data; however, a number of additional papers could have been added as useful sources of information.

A new prevention of suicide in schizophrenia should include the integration of strategies already in use and the implementation of less well known interventions. Proper information should be addressed to the family and, hopefully, hostility of family members toward the patient should be investigated. But information should constitute a key element for promoting changes in people's attitude toward these patients. Mass media portrayal of violent schizophrenic patients should be counterbalanced by delivering reality-based messages of their struggle for socialisation and acceptance. Last but not least, proper information should be the guide for a joint prevention between psychiatrists and GPs. The importance of GPs' role in the prevention of suicide in schizophrenia is a neglected topic with no articles published on this subject apart

from an editorial (Pompili et al. 2002b), which stressed plainly the concept mentioned above.

Suicide risk continues throughout the lifespan of the individual with schizophrenia. Mental health professionals should join forces for a better definition of guidelines specifically designed to prevent suicide among patients with schizophrenia.

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Short-Term Efficacy and Safety of Risperidone in Young Children with Autistic Disorder (AD)

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Summary

Recently, atypical antipsychotic treatments have been used in children with autistic disorder (AD). However, data on safety and efficacy of atypical antipsychotic agents in autistic children are limited. In this open, prospective trial, subjects were treated with risperidone for six weeks. Nineteen children (12 male, 7 female) aged 4 to 8 years were started on 0.5 mg daily with individual titration to a maximum of 1.5 mg daily. Behavioural assessments were completed by Conner's parent 10-item index, AD symptom checklist and CGI-Global improvement. Statistically significant improvement was observed in mean total scores of Conner's parent 10-item index from baseline to the end of study ($p < 0.001$). On the basis of the CGI-Global improvement item, 15 children were considered responders. Statistically significant improvement was also found in some aspects of social contact, impulsive-aggression and repetitive, ritualistic behaviour based on assessment with the AD-symptom checklist. Weight gain and increase in night-time sleep were the most frequent side effects.

Key words: autistic disorder, risperidone, treatment, children, adolescents.

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Introduction

Autistic disorder is a type of pervasive developmental disorder characterised by severe and pervasive impairment in several areas of development, such as reciprocal social interaction skills, communication skills or the presence of stereotyped behaviours, interests and activities (DSM IV; American Psychiatric Association 1994).

Despite the use of a wide variety of treatment methods in subjects with pervasive developmental disorders (PDD), no single treatment method has produced marked and specific effects. Nevertheless, pharmacotherapy may play an important role in the development of an individualised treatment programme (Martin et al. 1999; Herzig 1997).

Many studies report the positive effect of medication on symptoms such as hyperactivity, stereotypes and aggressive behaviours. Clinical experiences show that medication with primary effects on the dopaminergic and serotonergic systems decreases hyperactivity, aggressivity and stereotypies. Haloperidol, a dopamine (DA) receptor antagonist, has been shown to be superior to placebo in the treatment of autistic disorder, as have the serotonin reuptake inhibitors clomipramine and fluvoxamine. Unfortunately, these medications are associated with a significant risk of side effects, particularly in young children (Nicholson et al. 1998).

Risperidone is a very potent dopamine D₂ and serotonin 5HT_{2a} receptor antagonist. The therapeutic effect of this drug in people with PDD has been described in several open studies (Nicholson et al. 1998; McDougale et al. 1997; Hardan et al. 1996; Finding et al. 1997; Horrigan and Barnbill 1997). Improvements were often reported in hyperactivity, withdrawal, stereotypies and aggressive behaviour, which are often target symptoms for pharmacological intervention in PDD (Nicholson et al. 1998; McDougale et al. 1997; Hardan et al. 1996; Finding et al. 1997; Horrigan and Barnbill 1997). Recently, some case reports including young children with AD state the improvement in social relatedness after treatment with risperidone (Posey et al. 1999; Boon-Yosidhi et al. 2002). The existence of these reports motivated us to design an open-label study in young children with AD. We aimed to evaluate the effect of risperidone treatment on hyperactivity, impulsivity, stereotypical

behaviours and social relatedness.

Methods

• Subjects

Subjects were 19 children (12 boys, 7 girls), aged 4 to 8.

The subjects were all referred to the Pervasive Developmental Disorders Unit in the Child Psychiatry Department of the Istanbul Medical Faculty for evaluation and treatment. All of the participants met the criteria for autistic disorder according to DSM-IV. The diagnosis was made by consensus of two investigators for each child.

Exclusion criteria included a seizure disorder or history of seizures and history or evidence of a systemic disease. All participants were free of other psychoactive medication for at least two weeks before enrolment and for the duration of the study.

• Risperidone treatment

After two baseline visits in which behavioural ratings were obtained, subjects began to take risperidone. To ensure compliance, medication was administered by parents. Risperidone was started at 0.5 mg/day every night and was regulated individually until therapeutic effects or untoward effects were observed. The maximum dose of 1.5 mg/day was not exceeded.

• Assessments

The children were rated by:

a) Conner's Parent 10-item index, which has been shown to be sensitive to changes in behaviour in many drug studies. This questionnaire was rated twice during the study, at baseline and after six weeks (Goyette et al. 1978).

b) An autistic disorder symptom checklist, which includes 27 items, was developed by the authors according to the DSM-IV diagnostic criteria for autistic disorder. This checklist was rated by clinicians taking detailed information from parents (caregivers) and observation of the child in a semi-structured play situation during each interview. Each item on the AD-symptom checklist is scored on a 4-point scale (0 = never, 1 = rarely, 2 = frequently, 3 = almost always). The first 11 items of this questionnaire are designed to assess the severity of affective-social deficit, the next six items assess language development, and the last 10 items determine the severity of different behavioural problems that are expected in this group of children. This instrument was administered twice, at baseline and at the end of six weeks of treatment.

c) Clinical Global Impression Scale: Global improvement item was recorded at the end of six weeks of risperidone treatment.

• Statistical analysis

All subjects completed the six-week study and were thus included in the efficacy analysis. Wilcoxon signed ranks test and paired t-test were used for evaluation of efficacy of treatment.

Results

• Subject characteristics

All subjects completed the trial. Subjects were 12 males and 7 females, aged 4 to 8. Twelve of the subjects had participated in previous medication trials, but discontinued them prematurely because of intolerable side effects or lack of efficacy.

• Dosage and adverse effects of drug treatment

The optimal dose of risperidone for the 19 subjects ranged from 0.5 mg/day to 1.5 mg/day (mean 1.1 mg/day \pm 0.3). The most frequent side effects were weight gain (n=15, mean 2 kg \pm 1.8) and an increase in night-time sleep (n=7).

No clinically significant changes in blood pressure, heart rate, respiratory rate or temperature were recorded and no acute extrapyramidal side effects, seizures or cardiac events occurred. In general, risperidone was well tolerated with the most prominent adverse effect being weight gain. Other side effects disappeared after the second week of treatment.

• Behavioural assessments

Conner's parent 10-item index: Statistically significant improvement was shown in all items of this index except items number 8, 9 and 10 (Table 1). Also, a statistically significant change was observed in mean total scores of this scale from baseline to the end of the study ($p < 0.001$).

Most of the parents reported that their children seemed happier and life at home was easier for everyone after treatment.

AD-Symptoms Checklist: Assessment of treatment efficacy in all items of this scale is shown in Table 2. Statistically significant improvements were found in affective-social developmental items such as meaningful facial expression ($p=0.046$), eye contact ($p=0.005$), response to verbal stimulus ($p=0.008$), interest in peers ($p=0.025$), meaningful gesture and mimicking ($p=0.014$).

There was a statistically significant increase in the use of meaningful words ($p=0.008$). Improvement in stereotypical behavioural problems were observed in behaviours such as turning around on his axis ($p=0.008$), rocking ($p=0.02$), jumping ($p=0.01$), arm and hand flapping ($p=0.01$), odd hand movements ($p=0.025$). Also, significant reductions of aggressiveness and irritability were observed ($p=0.001$) (Table 2).

Table 1
Conner's Parent 10-Item Index

| | N=19 | Baseline | | End of study | | Z | P |
|--|--|------------|-----------|--------------|-----------|-------|--------|
| | | Mean(1)±SD | Median-1- | Mean(2)±SD | Median-2- | | |
| 1 | Restless (overactive) | 2.3±0.6 | 2.0 | 1.6±0.8 | 2.0 | 2.636 | 0.008* |
| 2 | Excitable, impulsive | 1.8±0.8 | 2.0 | 1.1±0.8 | 1.0 | 2.581 | 0.010* |
| 3 | Disturbs other children | 1.1±1.2 | 1.0 | 0.6±0.7 | 1.0 | 2.310 | 0.021* |
| 4 | Fails to finish things started (short attention span) | 2.3±0.6 | 2.0 | 1.7±0.7 | 2.0 | 2.077 | 0.038* |
| 5 | Fidgeting | 2.5±0.5 | 3.0 | 1.8±0.8 | 2.0 | 2.725 | 0.006* |
| 6 | Inattentive, distractible | 2.5±0.5 | 3.0 | 1.8±0.6 | 2.0 | 3.357 | 0.001* |
| 7 | Demand must be met immediately; gets frustrated | 2.3±0.8 | 3.0 | 1.7±0.7 | 2.0 | 2.642 | 0.008* |
| 8 | Cries easily | 1.0±0.7 | 1.0 | 0.7±0.8 | 1.0 | 1.732 | 0.083 |
| 9 | Mood changes quickly and drastically | 1.3±1.0 | 1.0 | 1.3±1.0 | 1.0 | 0.243 | 0.808 |
| 10 | Temper outbursts (explosive and unpredictable behaviour) | 1.5±1.2 | 2.0 | 1.1±0.8 | 1.0 | 1.374 | 0.169 |
| Conner's Parent 10-Item Index (Total Score) | | | | | | | |
| | Mean(1) | Mean(2) | t | df | p | | |
| | 19.6±4.7 | 12.5±4.7 | 5.763 | 18 | 0.001* | | |

Table 2
AD-Symptoms Check List

| N=19 | Baseline | | End of study | | Z | P |
|--|------------|-----------|--------------|-----------|-------|--------|
| | Mean(1)±SD | Median(1) | Mean(2)±SD | Median(2) | | |
| Meaningful facial expression | 1.2±0.5 | 1.0 | 1.4±0.5 | 1.0 | 2.000 | 0.046* |
| Eye contact (eye-to-eye gaze) | 1.2±0.5 | 1.0 | 1.6±0.4 | 2.0 | 2.828 | 0.005* |
| Response to verbal stimulus | 1.2±0.4 | 1.0 | 1.6±0.4 | 2.0 | 2.646 | 0.008* |
| Imitative play (spontaneous make-believe play) | 0.8±0.7 | 1.0 | 1.0±0.8 | 1.0 | 1.000 | 0.317 |
| Spontaneous seeking to share interests with other people | 1.7±0.8 | 1.0 | 1.5±0.6 | 1.0 | 1.134 | 0.257 |
| Involving others in activities only as tools | 1.2±0.7 | 2.0 | 1.2±0.7 | 2.0 | 0.000 | 1.000 |
| Response to smiling | 1.3±0.5 | 1.0 | 1.6±0.5 | 2.0 | 2.121 | 0.034* |
| Interest in peers | 0.8±0.7 | 1.0 | 1.1±0.8 | 1.0 | 2.236 | 0.025* |
| Interest in people | 1.0±0.8 | 1.0 | 1.3±0.6 | 1.0 | 2.449 | 0.014* |
| Meaningful gestures and mimics | 1.0±0.5 | 1.0 | 1.3±0.5 | 1.0 | 2.449 | 0.014* |
| Positive response to physical contact | 1.5±0.6 | 1.0 | 1.7±0.5 | 2.0 | 1.342 | 0.180 |
| Number of meaningful words | 18.7±47.8 | 0.0 | 25.8±59.6 | 0.0 | 2.670 | 0.008* |
| Number of meaningful sentences | 1.7±5.0 | 0.0 | 2.3±6.2 | 0.0 | 1.342 | 0.180 |
| Echolalia | 0.4±0.9 | 0.0 | 0.4±0.9 | 0.0 | 1.000 | 0.317 |
| Neologism | 0.2±0.5 | 0.0 | 0.1±0.3 | 0.0 | 1.414 | 0.157 |
| Perseveration | 0.2±0.7 | 0.0 | 0.2±0.7 | 0.0 | 1.000 | 1.317 |
| Starts to talk spontaneously | 0.3±0.8 | 0.0 | 0.3±0.8 | 0.0 | 0.000 | 1.000 |
| Walks on tiptoes | 0.3±0.8 | 0.0 | 0.3±0.6 | 0.0 | 0.000 | 1.000 |
| Interest in non-functional aspects of objects | 1.5±0.6 | 1.0 | 1.3±0.5 | 1.0 | 1.732 | 0.083 |
| Turning around on his axis | 1.0±0.9 | 1.0 | 0.7±1.0 | 0.0 | 2.646 | 0.008* |
| Rocking | 1.0±1.0 | 0.0 | 0.6±1.0 | 0.0 | 2.333 | 0.020* |
| Jumping | 1.4±1.0 | 2.0 | 1.0±1.0 | 0.0 | 2.530 | 0.011* |
| Arm and hand flapping | 1.0±1.0 | 0.0 | 0.6±0.9 | 0.0 | 2.530 | 0.011* |
| Odd hand movements | 0.8±0.9 | 0.0 | 0.5±0.8 | 0.0 | 2.236 | 0.025* |
| Head banging and other self-mutilating behaviours | 1.1±0.9 | 1.0 | 0.6±0.5 | 1.0 | 2.714 | 0.007* |
| Organising object into lines or pattern | 0.7±1.0 | 0.0 | 0.8±0.9 | 0.0 | 1.414 | 0.157 |
| Aggressivity, irritability | 1.9±0.7 | 2.0 | 1.2±0.4 | 1.0 | 3.500 | 0.000* |

CGI-Global Improvement item: On the basis of a rating of "much improved" or "very much improved" on this item, 15 of the subjects were classified as responders, three of them showed minimal improvement, one of the subjects showed minimal worsening.

Discussion

The results of this pilot study suggest that risperidone may have some effect in improving social contact, and decreasing hyperactivity-

aggressivity and stereotypical behaviours.

Aggression, irritability and hyperactivity were prominent presenting symptoms in our samples. Based on the results of the AD symptom checklist and Conner's questionnaire, it appears that risperidone may be useful in decreasing aggressivity-hyperactivity and irritability. It is comparable with results of previous studies with either traditional neuroleptics or risperidone which had shown them to be effective in reducing aggressivity in

this group of children (Nicolson et al. 1998; McDougle 1997).

In our study, as in some case reports (Posey et al. 1999; Boon Yasidhi et al. 2002), risperidone was observed to be effective in social-affective improvement. This finding is similar to the effect of risperidone in children and adolescents with schizophrenia. Risperidone had been found to improve the negative symptoms of schizophrenia including blunted affect, emotional withdrawal, passive/apathetic social withdrawal, lack of spontaneity and flow of conversation in children (Cozza and Edison 1994). It has been hypothesised that the uniquely high ratio of 5HT_{2a} to D₂ receptor antagonism of risperidone may account for its beneficial effect on negative symptoms of schizophrenia. Similar considerations may be relevant to the improvement in measures of social function observed in children and adolescents with AD. In addition, preclinical studies with risperidone have shown significant increase in social interaction behaviour between unfamiliar, but not familiar rats, when compared with conventional neuroleptics haloperidol and chlorpromazine (Nicolson et al. 1998).

One of the striking results of this study is the improvement in verbal-communicative abilities. The increase of meaningful words during treatment is considered to be a result of improvement in social responsiveness. The decrease of stereotypical behaviours has previously been reported to improve with risperidone in many studies with this group (Quintana and Keshavan 1995).

The low incidence of untoward side effects in this sample is considered to be due to the use of relatively low doses of risperidone and very slow increase over a period of several weeks. The most frequent untoward effect was weight gain. This underlines the need for nutritional counselling for children and adolescents when risperidone is prescribed. Transient adverse effects such as increase in night-time sleep, drowsiness and nocturnal enuresis disappeared after some weeks of treatment.

In summary, these preliminary data suggest the efficacy of risperidone in improving some aspects of social dysfunction and reducing impulsive aggression and repetitive, ritualistic behaviour in this sample. The relatively low incidence of untoward effects and their transient nature, other than weight gain, could result from lower dose and gradual titration. Despite these favourable results, we prefer to interpret our findings with caution due to methodological limitations.

Some of the methodological limitations of this report include the uncontrolled nature of the

study and the lack of internationally standardised measures. A critical assessment of the efficacy and safety of risperidone under double-blind, placebo-controlled conditions seems justified.

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Association Analysis of Brain-Derived Neurotrophic Factor (BDNF) Gene Val66Met Polymorphism in Schizophrenia and Bipolar Affective Disorder

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Summary

Brain-derived neurotrophic factor (BDNF) has been implicated in the pathogenesis of schizophrenia and bipolar disorder. A functional polymorphism Val66Met of BDNF gene was studied in patients with schizophrenia ($n=336$), bipolar affective disorder ($n=352$) and healthy controls ($n=375$). Consensus diagnosis by at least two psychiatrists, according to DSM-IV and ICD-10 criteria, was made for each patient using a structured clinical interview for DSM-IV Axis I disorders (SCID). No association was found between the studied polymorphism and schizophrenia or bipolar affective disorder either for genotype or allele distribution (for genotype: $p=0.210$ in schizophrenia, $p=0.400$ in bipolar disorder; for alleles: $p=0.260$ in schizophrenia, $p=0.406$ in bipolar disorder). Results were also not significant when analysed by gender. For males genotype distribution and allele frequency were (respectively): $p=0.480$ and $p=0.312$ in schizophrenia, $p=0.819$ and $p=0.673$ in bipolar affective disorder. Genotype distribution and allele frequency observed in the female group were: $p=0.258$ for genotypes, $p=0.482$ for alleles in schizophrenia; $p=0.432$ for genotypes, $p=0.464$ for alleles in bipolar affective disorder. A subgroup of schizophrenic ($n=62$) and bipolar affective patients ($n=28$) with early age at onset (18 years or younger) was analysed ($p=0.328$ for genotypes, $p=0.253$ for alleles in schizophrenia; $p=0.032$ for genotypes, $p=0.858$ for alleles in bipolar affective disorder).

Key words: schizophrenia, bipolar affective disorder, brain-derived neurotrophic factor (BDNF), genetics, association.

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Acknowledgement

This work was supported by the Polish State Committee for Scientific Research (KBN) grant No.4PO5B05320. Piotr M. Czerski is the recipient of a 2004 Annual Stipend for Young Scientists from the Foundation for Polish Science (FNP).

Introduction

The neurodevelopmental hypothesis of psychiatric disorders postulates alterations in embryonal neurogenesis and explains these changes as the result of disturbances of processes involving the trophic factors (Thome et al. 1998; Nawa et al. 2000). Disturbances of brain-derived neurotrophic factor (BDNF) have been postulated as a risk factor for psychiatric disorders and neurological diseases (Thome et al. 1998; Siegel and Chauhan 2000).

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family of growth factors (Barde et al. 1982; Leibrock et al. 1989), interacting with the trkB receptor tyrosine kinase (Squinto et al. 1991). It has trophic effects on dopaminergic (Altar et al. 1992; Shen et al. 1994; Shults et al. 1994), cholinergic (Lindsay 1995; Lindvall et al. 1994) and serotonergic (White et al. 1994; Mamounas et al. 1995, 2000) neurons. It is essential for development of sensory ganglia, cerebral cortex, hippocampus and striatum (Liu et al. 1995).

BDNF affects neuronal proliferation, survival and plasticity and is involved in hippocampal long-term potentiation (LTP), learning and memory (Lu and Gottschalk 2000; Poo 2001; Egan et al. 2003; Lu 2003; Mizuno et al. 2003).

The BDNF gene was first reported by Maisonpierre et al. (1991) to be localised on the short arm of chromosome 11 (11p13). The gene consists of four short 5' exons with separate promoters and one 3' exon encoding the mature BDNF protein (Timmusk et al. 1993; Metsis et al. 1993).

Dinucleotide repeat polymorphism (GT)_n in the promoter region 1.4 kb from the transcription start site (Proschel et al. 1992), Val66Met (196G/A) polymorphism (Cargill et al. 1999), -270C/T substitution (Kunugi et al. 2001), -374A/T and -256G/A polymorphisms (Ribases et al. 2003) have been reported in the BDNF gene and studied in psychiatric disorders. An association of the Val variant of Val66Met polymorphism and affective disorders has been reported (Neves-Pereira et al. 2002; Sklar et al. 2002), but analysis performed by Nakata et al. (2003) did not confirm such association. Met allele is associated with impairments of the hippocampal functions and episodic memory in humans (Egan et al. 2003a) and anorexia nervosa restrictive type (Ribases et al. 2003). On the other hand, Met allele has been found to be protective against depression (Sen et al. 2003) and obsessive-compulsive disorder (Hall et al. 2003). An association of the dinucleotide repeat polymorphism (GT)_n ("long" alleles 172-176 bp) with late age at onset and better response to neuroleptic treatment in schizophrenic patients have been reported by Krebs et al. (2000). An association of the A3 allele (170 bp) with schizophrenia has been described by Muglia et al. (2003). Other studies did not confirm association of this polymorphism with schizophrenia (Sasaki et al. 1997; Hawi et al. 1998; Wassink et al. 1999; Virgos et al. 2001). Polymorphism -270C/T has been investigated in bipolar disorder with negative results (Nakata et al. 2003). Two novel polymorphisms, -374A/T and -256G/A, have been reported by Ribases et al. (2003) in patients with anorexia nervosa.

In our study, we investigated allelic distribution of G196A single nucleotide polymorphism (SNP) responsible for valine to methionine substitution at amino acid position 66 in the prodomain of BDNF in the groups of patients with schizophrenia, affective disorder and controls.

Subjects and methods

• Subjects

The study was performed on 336 patients with schizophrenia (189 males with a mean age of 30.6 years, SD=11.3, 147 females with a mean

age of 33.2 years, SD=12.1), and 352 patients with bipolar affective disorder (bipolar I affective disorder: 128 males with a mean age of 45.1 years, SD=14.5; 172 females with a mean age of 47.5 years, SD=13.6; bipolar II affective disorder: 18 males with a mean age of 44.0 years, SD=12.8; 34 females with a mean age of 43.5 years, SD=14.3). Subgroups of schizophrenic (n=62) and bipolar affective (n=28) patients with early age at onset (18 years or younger) were distinguished. Patients were recruited from inpatients being treated at the Department of Psychiatry, University of Medical Sciences in Poznan, Department of Psychiatry, University School of Medicine in Bydgoszcz and Psychiatric Hospital in Koscian. All subjects were Caucasians from the Wielkopolska region. Consensus diagnosis by at least two psychiatrists, according to DSM-IV and ICD-10 criteria, was made for each patient using a structured clinical interview for DSM-IV Axis I disorders (SCID) (First et al. 1996).

The control group consisted of 375 subjects (149 males with a mean age of 41.2 years, SD=12.0; 226 females with a mean age of 40.4 years, SD=10.8). Control subjects were recruited from the group of blood donors, hospital staff and students of the University of Medical Sciences in Poznan. They were not psychiatrically screened. The local ethics committee approved the project.

• Genotyping

DNA was extracted from 10 ml of EDTA anticoagulated whole blood, using the salting out method (Miller et al. 1988). A 113-basepair fragment of the BDNF gene was amplified by PCR with primer pair described by Neves-Pereira et al. (2002) in PTC-200 (MJ Research) thermal cycler. A 20 ml amplification mixture contained 150-300 ng of genomic DNA, 0.3 mM of each primer, 0.17 mM of each dNTP, 1.5 mM MgCl₂, 75 mM Tris-HCl, 20 mM (NH₄)₂SO₄, 0.01% Tween 20 and 0.4 U of Taq DNA polymerase (MBI Fermentas). Cycling conditions were: initial denaturation at 95°C for 2 minutes followed by 35 cycles, with a profile of 94°C for 30 seconds, 60°C for 30 seconds, 72°C for 30 seconds, and final elongation at 72°C for 5 minutes. A volume of 6.5 ml of each PCR product was then digested overnight in a total volume of 10 ml at 37°C with 0.7 U of Eco72I restriction endonuclease (MBI Fermentas). Digestion products were then separated on 2.5% basic LE agarose gel (Prona, Spain) with 90V and visualised by ethidium bromide staining. Band sizes were compared with pUC19DNA/MspI DNA ladder (MBI Fermentas).

The uncut product size was 113 bp (allele A). Allele G comprised the cut bands of 78 and 35 bp.

• Statistical analyses

The Pearson's chi-square (χ^2) test and Fisher's exact test were applied to test differences in the genotypic and allelic (respectively) distribution between groups of bipolar patients, schizophrenic patients and controls. Additionally, stepwise logistic regression analyses for each diagnostic group including BDNF polymorphism, age and gender as covariates were performed. Calculations were performed using the computer program SPSS version 10. A two-tailed type I error rate of 5% was chosen for analysis. Power analysis was performed using an on-line internet service provided by the UCLA Department of Statistics (<http://calculators.stat.ucla.edu/powercalc/>).

• Results

The genotype distribution was in Hardy-Weinberg equilibrium for all studied groups, except a subgroup of bipolar affective patients with early age at onset ($p=0.021$).

The genotype distribution for the patients with schizophrenia or bipolar affective disorder did not differ significantly from controls ($p=0.210$ for schizophrenia, $p=0.400$ for bipolar affective disorder) (Table 1). When groups were separated according to gender, there was also not any significant difference in genotype distribution

(in the male group $p=0.480$ for schizophrenia, $p=0.819$ for bipolar affective disorder; in the female group $p=0.258$ for schizophrenia, $p=0.432$ for bipolar affective disorder (Table 1)). Comparing genotype distribution with regard to early age at onset (18 years or younger) there was no significant difference between schizophrenic patients and controls ($p=0.328$) (Table 2). We found an association ($p=0.032$) of Met/Met genotype with bipolar affective disorder (Table 2). Comparing genotype distribution with regard to late age at onset, we did not find any association either for schizophrenia ($p=0.154$) or for bipolar affective disorder ($p=0.537$) (Table 2).

The allele distribution in patients with schizophrenia or bipolar affective disorder did not differ significantly from controls ($p=0.260$ for schizophrenia, $p=0.406$ for bipolar affective disorder) (Table 1). When all groups were divided with regard to gender, we also did not find any significant difference in allele distribution (in the male group $p=0.312$ for schizophrenia, $p=0.673$ for bipolar affective disorder (Table 1); in the female group $p=0.482$ for schizophrenia, $p=0.464$ for bipolar affective disorder (Table 1). Comparing allele distribution with regard to early age at onset we did not find

Table 1

Genotype distribution and allele frequencies of BDNF Val66Met polymorphism for patients with schizophrenia or bipolar affective disorder, and for the control group

| | Genotype Val/Val n(%) | Genotype Val/Met n(%) | Genotype Met/Met n(%) | Total genotypes n(%) | Allele Val n(%) | Allele Met n(%) | Total alleles n(%) |
|--------------------------|-----------------------------|-----------------------------|-----------------------------|----------------------------|-----------------------|-----------------------|--------------------------|
| males and females | | | | | | | |
| Schizophrenia | 240 (71.4%) | 85 (25.3%) | 11 (3.3%) | 336 (100%) | 565 (84.1%) | 107 (15.9%) | 672 (100%) |
| Bipolar | 247 (70.2%) | 94 (26.7%) | 11 (3.1%) | 352 (100%) | 588 (83.5%) | 116 (16.5%) | 704 (100%) |
| Control | 248 (66.1%) | 117 (31.2%) | 10 (2.7%) | 375 (100%) | 613 (81.7%) | 137 (18.3%) | 750 (100%) |
| males | | | | | | | |
| Schizophrenia | 132 (69.8%) | 52 (27.5%) | 5 (2.6%) | 189 (100%) | 316 (83.6%) | 62 (16.4%) | 378 (100%) |
| Bipolar | 98 (67.1%) | 44 (30.1%) | 4 (2.7%) | 146 (100%) | 240 (82.2%) | 52 (17.8%) | 292 (100%) |
| Control | 95 (63.8%) | 50 (33.6%) | 4 (2.7%) | 149 (100%) | 240 (80.5%) | 58 (19.5%) | 298 (100%) |
| females | | | | | | | |
| Schizophrenia | 108 (73.5%) | 33 (22.4%) | 6 (4.1%) | 147 (100%) | 249 (84.7%) | 45 (15.3%) | 294 (100%) |
| Bipolar | 149 (72.3%) | 50 (24.3%) | 7 (3.4%) | 206 (100%) | 348 (84.5%) | 64 (15.5%) | 412 (100%) |
| Control | 153 (67.7%) | 67 (29.6%) | 6 (2.7%) | 226 (100%) | 373 (82.5%) | 79 (17.5%) | 452 (100%) |

Difference, schizophrenia vs. control (males and females) – $\chi^2=3.118$, $df=2$, $p=0.21$ for genotypes, $p=0.26$ for alleles.

Difference, bipolar I+II vs. control (males and females) – $\chi^2=1.831$, $df=2$, $p=0.4$ for genotypes, $p=0.406$ for alleles.

Difference, schizophrenia vs. control (males) – $\chi^2=1.468$, $df=2$, $p=0.48$ for genotypes, $p=0.312$ for alleles.

Difference, bipolar I+II vs. control (males) – $\chi^2=0.399$, $df=2$, $p=0.819$ for genotypes, $p=0.673$ for alleles.

Difference, schizophrenia vs. control (females) – $\chi^2=2.708$, $df=2$, $p=0.258$ for genotypes, $p=0.482$ for alleles.

Difference, bipolar I+II vs. control (females) – $\chi^2=1.678$, $df=2$, $p=0.432$ for genotypes, $p=0.464$ for alleles.

Table 2

Genotype distribution and allele frequencies of BDNF Val66Met polymorphism with regard to the onset of illness of subjects with schizophrenia or bipolar affective disorder and to the control group

| | Genotype Val/Val n(%) | Genotype Val/Met n(%) | Genotype Met/Met n(%) | Total genotypes n(%) | Allele Val n(%) | Allele Met n(%) | Total alleles n(%) |
|---------------------------|-----------------------------|-----------------------------|-----------------------------|----------------------------|-----------------------|-----------------------|--------------------------|
| Early age on onset | | | | | | | |
| Schizophrenia | 45 (72.6%) | 17 (27.4%) | 0 (0%) | 62 (100%) | 107 (86.3%) | 17 (13.7%) | 124 (100%) |
| Bipolar | 20 (71.4%) | 5 (17.9%) | 3 (10.7%) | 28 (100%) | 45 (80.4%) | 11 (19.6%) | 56 (100%) |
| Control | 248 (66.1%) | 117 (31.2%) | 10 (2.7%) | 375 (100%) | 613 (81.7%) | 137 (18.3%) | 750 (100%) |
| Late age at onset | | | | | | | |
| Schizophrenia | 195 (71.2%) | 68 (24.8%) | 11 (4.0%) | 274 (100%) | 458 (83.6%) | 90 (16.4%) | 548 (100%) |
| Bipolar | 227 (70.1%) | 89 (27.5%) | 8 (2.5%) | 324 (100%) | 543 (83.8%) | 105 (16.2%) | 648 (100%) |
| Control | 248 (66.1%) | 117 (31.2%) | 10 (2.7%) | 375 (100%) | 613 (81.7%) | 137 (18.3%) | 750 (100%) |

Difference, schizophrenia vs. control (early age at onset) – $\chi^2 = 2.231$, $df=2$, $p=0.328$ for genotypes, $p=0.253$ for alleles.

Difference, bipolar I+II vs. control (early age at onset) – $\chi^2 = 6.873$, $df=2$, $p=0.032$ for genotypes, $p=0.858$ for alleles.

Difference, schizophrenia vs. control (late age at onset) – $\chi^2 = 3.739$, $df=2$, $p=0.154$ for genotypes, $p=0.416$ for alleles.

Difference, bipolar I+II vs. control (late age at onset) – $\chi^2 = 1.242$, $df=2$, $p=0.537$ for genotypes, $p=0.322$ for alleles.

any significant difference between either schizophrenic patients and controls ($p=0.253$) or bipolar affective patients and controls ($p=0.858$) (Table 2). Comparing allele distribution with regard to late age at onset, we did not find any association for either schizophrenia ($p=0.416$) or bipolar affective disorder ($p=0.322$) (Table 2).

In logistic regression analyses, after controlling for age, gender and BDNF polymorphism, there was no association between BDNF polymorphism and either schizophrenia or bipolar disorder (comparing: schizophrenic patients with bipolar patients: Wald test=0.171, $df=2$, $p=0.918$; schizophrenic patients with controls: Wald test=5.416, $df=2$, $p=0.067$; bipolar patients with controls: Wald test=1.949, $df=2$, $p=0.377$).

The power to detect an association was established to be 47.2% in bipolar affective disorder and 47.1% in schizophrenia with a relative risk of 1.5, and 71.8% in bipolar affective disorder and 69.3% in schizophrenia with a relative risk of 1.75.

Discussion

In our study we did not find an association between Val66Met polymorphism of the BDNF gene and schizophrenia or bipolar affective disorder in the whole group of patients. When we divided the sample into subgroups with regard to gender we still did not find any association.

We did find an association of Met/Met genotype with bipolar affective disorder and early age at

onset ($p=0.032$). Genotype distribution in this subgroup of patients was not in Hardy-Weinberg equilibrium and association of the Met/Met genotype in this subgroup might be a false positive, however further studies on a larger group are required.

This association differs from the results of Neves-Pereira et al. (2002) and Sklar et al. (2002), where an association of bipolar affective disorder with the Val allele has been found. The Met allele has been found to be protective against depression (Sen et al. 2003) and obsessive-compulsive disorder (Hall et al. 2003). On the contrary, results obtained by Egan et al. (2003a) show an association of the Met allele with impairments in hippocampal functions and episodic memory in humans. However, the Met allele did not affect risk for schizophrenia (Egan et al. 2003b). In our own study, patients with bipolar affective disorder and Val/Val genotype had better results in the Wisconsin Card Sorting Test (WCST), the test measuring functions of prefrontal cortex, compared with Val/Met genotype patients (Rybakowski et al. In press).

The functional significance of the Val66Met substitution in the prodomain of BDNF is not clear. The Met allele is thought to be novel in evolutionary history, while Val allele is conserved among >70 species including mammals, birds and fish (Murphy et al. 2001). Egan et al. (2003b) showed that the Met allele of BDNF impairs depolarisation-dependent secretion of the protein. This might be due to the inability of Met allele to be sorted from the Golgi apparatus to appropriate secretory granules. The Met variant of BDNF protein can

be secreted in small amounts near the cell body through the constitutive pathway, but cannot be secreted at synapses.

Changes in BDNF protein level in brains or serum of schizophrenic (Takahashi et al. 2000; Durany et al. 2002; Weickert et al. 2003) and bipolar affective (Chen et al. 2001; Karege et al. 2002; Shimizu et al. 2003) patients have been reported, but there is no evidence that BDNF Val66Met polymorphism is responsible for such alterations in protein expression. Changes in BDNF expression have been reported in response to antipsychotic (Angelucci et al. 2000; Linden et al. 2000; Chlan-Fourney et al. 2002) or antidepressant (Popoli et al. 2002; Coppel et al. 2003; Ivy et al. 2003) treatment. An association of the Val/Val genotype and clozapine response in schizophrenic patients has been reported recently (Hong et al. 2003). All these data make BDNF a novel and promising target in pharmacogenetic studies.

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Child and Adolescent Electroconvulsive Therapy: A Case Report

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Summary

Electroconvulsive therapy (ECT) is a controversial treatment modality that is only rarely performed on children and adolescents. There is a marked paucity of published data relating to the indications, use, clinical outcome and complications of ECT in this age group. The ethical and moral issues surrounding the use and in particular the research of ECT in this group of patients makes controlled data very difficult to come by. The following case report and review of the literature will address some of these issues.

Key words: *electroconvulsive therapy, children, adolescents.*

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Acknowledgement

The authors wish to thank the staff of Tara Hospital for their unwavering dedication and commitment to their patients.

Introduction

Bertagnoli and Borchardt (1990) posed the question, "Is electroconvulsive therapy (ECT) a treatment option for children and adolescents?" Unfortunately this question, for the most part, remains unanswered due to the lack of controlled data. ECT remains one of the most controversial treatments in medicine, with an active and energetic campaign by various advocacy groups for it to be banned (Baker 1995; Smith 2001; Carney and Geddes 2003). Combined with this is an ever increasing range of alternative interventions, together with progressively restrictive legislation and increasing litigation risks associated with its usage. Consequently the applicability of ECT is gradually but successfully being diminished (Baldwin and Jones 1998; Taieb et al. 2001; Carney and Geddes 2003).

The situation is further complicated when the use of ECT involves children and adolescents. Due to the ongoing problem of paucity of good data, a recent review article on appropriate patient selection for ECT does not mention children and adolescents. Perhaps rather alarmingly, what is highlighted is the fact that there are no "universally agreed-upon guidelines for the ECT clinician" (Rasmussen 2003). Amongst child and adolescent psychiatrists the clinical experience with ECT in their specific patient populations is extremely limited. As recently demonstrated, only about 20% or so of these specialists have had patients treated with or have administered ECT (Parmar 1993; Rey and Walter 1997; Walter et al. 1997; Baldwin and Jones 1998). Further problems relate to the fact that many mental health professionals are never exposed to the administration of ECT in the young (Walter et al. 1999a). Also, it would seem that little attention is given to ECT in child psychiatry texts and in the training of child and adolescent mental health professionals (Rey and Walter 1997; Walter et al. 1999a). The situation reflected in the published literature for ECT use in adults is not much different. In the UK, for example, ECT is a neglected service with widespread unexplained variations in practice, with many hospitals failing to adhere to college standards, only about one third meeting the college standards, very poor consultant attendance at ECT clinics, and the ongoing use of outdated machines (Duffett and Lelliott 1998; Carney and Geddes 2003). In the USA, wide variations in the use of ECT exist and it is considered one of the

procedures in medicine with the highest variation in its application (Herman et al. 1995). Some metropolitan areas reported the use of no ECT at all. Worst of all, it seems likely that psychiatry residents in some programmes may never even have seen an ECT treatment, let alone administered one (Salzman 1998). Finally, ever increasing interprofessional contact and divergent opinions within the various multidisciplinary team members has invariably increased the probability of disagreement about optimum treatment strategies. These sources of disagreement are often entrenched in the various team members' codes of professional conduct (Baldwin and Jones 1998).

Ethical issues regarding the use of ECT, in particular in child and adolescent populations, have been the source of much debate over the decades (Baldwin and Jones 1998; Knapp 2001; Rudnick 2001). Such issues, among others, involve the problems of risk versus benefit analysis with ECT, decisional capacity and surrogate decision making, fully-informed consent and assent, and the arguments of commission versus omission of treatment. Included in this is the spreading of the burden of responsibility by enforcing case presentation to various review boards, and obtaining second or more opinions prior to commencing ECT (Baldwin and Jones 1998; Duffett and Lelliott 1998; Walter and Rey 1999a; Knapp 2001; Rudnick 2001). As has been shown, restrictive legislation does decrease ECT use (Hermann et al. 1995). Given the issues associated with ECT, psychiatrists might well be overwhelmed by ambivalence when it comes to prescribing ECT (Salzman 1998).

Against this background we now have to consider whether ECT is a treatment option for children and adolescents. With recent reviews of the available data in this regard, including the recent advances in the practice of ECT, there seems to be a common finding and answer (Frukacz and Mitchel 1995; Rey and Walter 1997; Walter and Rey 1997, 1999a; Walter et al. 1999b; Cohen et al. 2000; Bloch et al. 2001; Rabheru 2001; Taieb et al. 2001). ECT appears to be an effective and therapeutically sound and safe treatment option for adolescents. However the issue of ECT use in pre-pubertal children remains controversial.

Repetitive transcranial magnetic stimulation (rTMS) is a mode of treatment being investigated as a potentially non-invasive treatment for a number of neuropsychiatric conditions (George 1999). Some authors consider rTMS to be an experimental mode of treatment that requires much further research (Hasey 2001). More recently, other authors have recommended that rTMS should be made more available, and not only be limited to clinical research trials (Fitzgerald 2003). However, it is a

sobering thought to consider that the presence of psychosis is a poor prognostic sign for rTMS response (Kapstan et al. 2003). Also, mania induction has been reported in some depressed patients receiving rTMS (Dolberg et al. 2001; Sakkas et al. 2003). In a recent controlled study, right prefrontal TMS was found to be no more effective than sham TMS for manic patients (Kapstan et al. 2003). The role of rTMS in children and adolescents with psychiatric illness is less well studied than in adults. The data available have recently been reviewed, with the conclusion that rTMS should be considered an experimental mode of treatment, and that further studies are needed in this population group, in particular as the effects of rTMS on the developing brain are unknown (Walter et al. 2001). In support of this finding, it was recently highlighted that the safety and methodology of rTMS in children and adolescents does require further study (Lin and Pascual-Leone 2002). It is thus very difficult to make a definitive statement regarding the present efficacy and applicability of rTMS to children and adolescents. Results of further controlled trials are eagerly awaited to elucidate the role, if any, of rTMS to this population group.

The following case report aims to illustrate some of the points outlined above. Also based on the clinical observations in this case, we would like to highlight some of the common clinical challenges facing the multidisciplinary team treating children and adolescents with ECT.

Case report

• Presentation

Patient AB, a 13-year-old black female, was referred to our unit from an outlying child and adolescent unit for further management, as she was not responding adequately to the interventions being used at the time. The referring team was treating her with risperidone 4 mg nocte, and lorazepam on an as needed basis. Risperidone had been used because of her previous good response to the agent, as will be outlined in her past psychiatric history below. She had presented initially to them with a one-month history of a rapid onset of being markedly irritable, extremely restless and driven, with rapid speech, a pronounced decreased need for sleep and increased energy. These symptoms progressively worsened eventually to include the development of nonsensical speech, feelings of being poisoned by her family, bizarre and disorganised behaviour with admissions to hearing voices and seeing deceased family members talking to her.

• History

Her index episode was one year prior to the current presentation at the age of 12 years. At that point she presented with what was

eventually given as a final diagnosis, according to the Diagnostic and Statistical Manual–Text Revised (DSM IV-TR; American Psychiatric Association 2000), as a major depressive episode with mood congruent psychosis as well as co-morbid PTSD features. This diagnosis was reached after a two-month inpatient stay at the specialist child and adolescent psychiatric unit of the hospital. The apparent precipitant for this episode was reported severe sexual abuse. She responded well to citalopram 20 mg mane, risperidone 1 mg nocte and orphenadrine 50mg twice daily by mouth. On discharge she was referred to a child, adolescent and family specialist academic unit near her home, where the above biological treatment as well as intensive individual psychotherapy was continued. However, she unfortunately defaulted on both medication and all outpatient visits and was lost to follow up. This noncompliance seemed to be the precipitant for the current presentation mentioned above.

Other relevant information regarding this case includes an absence of family psychiatric history or neuro-developmental difficulties of any type. There was no evidence of substance use or abuse nor was there any evidence of organic illness of any type.

• Mental status

Upon admission to our unit, mental status examination showed her to be a fully alert, relatively unkempt, early pubescent child of very slight build. She was extremely restless and easily distractible and uncooperative. Her speech was rapid and very pressurised. She was not orientated to time and place. She was so unwell as to render the mini-mental status examination (MMSE) impossible to perform on her. Her affect was extremely labile, alternating between expansive fatuousness and fearfully distressed tearful wailing episodes. Her mood appeared dysphoric and profoundly irritable which was aggravated by extremes of psychomotor agitation. A severe formal thought disorder was noted with tangentiality and loosening of associations and at times degenerating into a near word salad. She was able to express various paranoid and persecutory delusions. Objectively she was noted to respond to both auditory and visual hallucinations. These psychotic phenomena appeared to be extremely frightening for her and resulted in disruptive behaviours and agitated screaming.

No abnormalities were found on physical examination. Her weight was 34 kg and her height 1.43 m with a BMI of 16.6 kg/m². This was not considered to be indicative of an eating disorder due to the severity of her current mood disorder and the influence this had on her neurovegetative functions. Full blood work-up also proved to be normal. Both syphilis serology

and retroviral studies were non-reactive. There was no evidence to support a co-morbid diagnosis. No formal psychiatric rating scales were used. A working diagnosis according to the DSM IV-TR (American Psychiatric Association 2000) was as follows: Axis I - Bipolar mood disorder, severe, mixed episode with mood incongruent psychotic features, together with the V-Code Noncompliance with treatment; Axis II - no diagnosis; Axis III – none; Axis IV - Problems with primary support group: in particular past history of sexual abuse; Axis V - Global Assessment of Function Scale score of 1. She was considered to be too ill for a formal neuropsychiatric evaluation.

• Treatment

She was maintained on risperidone 4 mg daily as an optimal dose as suggested in the literature (Nyberg et al. 1999). Lorazepam was continued on an as needed basis and orphenadrine 50 mg three times daily commenced. Unfortunately, her condition deteriorated further during the next two days. The risperidone was discontinued at this point. In total, she had almost six weeks of risperidone at 4 mg daily. It was considered inappropriate to increase the dose of her risperidone as she had not shown any evidence of clinical improvement at this point, and also there was already evidence of some Parkinsonian side effects. There was also the nagging possibility that the risperidone was in fact aggravating the manic-like clinical presentation (Segal et al. 2000).

In terms of adequacy of treatment duration and dose, at this point the patient was considered to be resistant, in terms of defined criteria in the literature (Marder 1996), to the treatment with risperidone, i.e. six weeks at 4 mg per day (Nyberg et al. 1999).

In an attempt to control her severe psychomotor agitation, a trial of a more sedating antipsychotic regimen was considered worthwhile. She was given intramuscular zuclopenthixole acetate (50 mg). This dose was repeated twice during the next two days (total 150 mg). At this stage she was also commenced on oral chlorpromazine at 400 mg per day, with lorazepam (up to 3 mg/24 hours) and clothiapine (up to 60 mg/24 hours) on an as needed basis. After 48 hours of observation to document response to the intramuscular neuroleptic medications it became obvious that despite all these efforts to control her symptoms she remained uncontrollable in the ward. She was not sleeping, displaying markedly disruptive behaviour and severe psychomotor agitation. She continued to respond objectively to both visual and auditory hallucinations. At this stage sodium valproate was introduced at a dose of 20 mg/kg/day. Difficulties were encountered with getting her to accept the oral medications as she would periodically refuse the

treatment. All attempts to persevere with the valproate resulted in a total of only four doses of 400 mg being successfully dispensed over the next four days. Unfortunately, 10 days after being admitted to our unit the patient refused to take any further oral medication. In an attempt to sedate her, she was given lorazepam intravenously. A total dose of 6 mg had no effect whatsoever. This was followed by clothiapine 40 mg intravenously, which did settle her partially, however she remained fully conscious and able to respond to stimuli. Two days later the situation deteriorated to a point where she refused all food and drink. It was subsequently established that this was because she believed the professional staff were trying to poison her. Intravenous fluid administration was initiated, but because the patient believed this was an attempt to kill her, she repeatedly pulled the intravenous cannula from her arm. In order to try to prevent this situation she was periodically given intramuscular lorazepam (up to 12 mg per day in divided doses) over the next three to four days. Only one dose of haloperidol 5 mg intravenously was successfully administered.

At this stage in her management it became patently obvious that the significant polypharmacy that had been initiated was having a negligible therapeutic effect. There was a significant fear of inducing an episode of neuroleptic malignant syndrome. Indeed, at one point her plasma creatine kinase levels reached 812 μ /l (2-143 μ /l laboratory reference range) but this was felt to be due to the intramuscular injections received. At no point was the patient pyrexial. Although catatonic excitement was considered a possible differential diagnosis there were insufficient criteria to warrant it at any time during the admission. The multi-disciplinary team decided at this stage to initiate ECT, as 14 days of intensive psychiatric nursing care and pharmacotherapy had clearly failed to offer any symptom control. The clinical situation dictated urgent management with effective intervention, especially since the patient was refusing to eat and drink as a direct result of her ongoing psychotic symptoms. After an intensive discussion with the patient's mother, which included education, ECT indication, procedure and protocol including possible side effects and other problems associated with the treatment, consent was given for us to proceed. Attempts at explaining the situation to the patient proved fruitless due to the extreme severity of her illness, so assent for the procedure was impossible to obtain. The first ECT treatment was finally given 17 days after admission to our unit.

• Electroconvulsive therapy

ECT is conducted twice a week in our unit, with all anaesthesia performed by a specialist anaesthetist who has many years of experience with ECT. The anaesthetist performed a detailed

physical and neurological examination prior to commencing the ECT on this patient. A paediatrician had previously assessed the patient physically before her referral to us. Electroencephalogram (EEG) and electrocardiograms (ECG) are not routinely conducted prior to ECT in our unit unless they are clinically indicated, and as such they were not performed on this patient. The patient received stimulus-dosing, bifrontal modified ECT with a Thymatron machine as described in the literature (Sackeim et al. 1987; Frukacz and Mitchell 1995; Beale 1998; Rasmussen 2003). Bilateral EEG with ECG and pulse oxymetry monitoring were initiated during the treatment. Limb isolation for motor seizure monitoring was conducted. Propofol was used as induction agent with succinylcholine as the muscle relaxant. Bifrontal ECT was chosen in this case in an effort to maximise therapeutic clinical response. This is discussed in more detail later in the text.

A relatively large dose of 200 mg of propofol (5.8 mg/kg) was required to achieve a minimally acceptable, shallow depth of anaesthetic induction. The recommended dose is 1.5-2.5 mg/kg (Fresenius Kabi 1998). Succinylcholine 20 mg was given. Due to the unfortunate necessity for the ongoing use of high doses of benzodiazepines as well as the dose of propofol required, the stimulus dosing was commenced at level 2, equating to a charge of 50.4 mC, at 1 msec pulse width at 30 Hz as the anticipation was to find an artificially elevated seizure threshold. However this resulted in a threshold seizure of 82 seconds with a bilateral tonic-clonic seizure clinically. The corresponding ictal activity on EEG showed low amplitude mixed waveforms with poor post-ictal suppression. As a result, the patient was then re-stimulated at twice seizure threshold, corresponding to a charge of 100.8 mC, 1 msec pulse width at 30 Hz. This second stimulus resulted in a 39 second bilateral tonic-clonic seizure clinically. Ongoing EEG recording, however, showed persistent ictal activity, which was pharmacologically aborted after 120 seconds for fear of inducing status epilepticus. She needed 20 mg of diazepam as well as 2 mg of clonazepam intravenously to achieve this. Her recovery thereafter was uneventful. Once she was fully awake, which occurred about one hour after her treatment, she was found to be disorientated to time and place, but not excessively sedated as would have been expected. There was no clinical evidence of ongoing ictal activity at that point. As early as the following day, therapeutic benefits of the ECT were noted. She appeared less driven and made better contact with nursing staff. To our surprise, she also agreed to take oral medication and was commenced on haloperidol 2.5 mg nocte, biperidine 2 mg thrice daily and lorazepam on an as needed basis for behavioural control. Despite the clinical improvements

indicated above, the decision to continue with ECT was made based on the fact that the patient was still significantly unwell and the team was hoping to achieve rapid symptom resolution.

For her second ECT she needed a total of 150 mg propofol (4.41 mg/kg) as the induction agent with 20 mg of succinylcholine. A bifrontal stimulus at a charge of 100.8 mC, 1 msec pulse width at 30 Hz did not induce any ictal activity at all, clinically or on EEG. Re-stimulation at a charge of 201.6 mC, 1 msec pulse width at 50 Hz resulted in a 16 second bilateral tonic-clonic seizure, with good post-ictal suppression and no evidence of ongoing ictal activity on EEG. Recovery was uneventful. Once again it was noted that she was now more settled in the ward, making good contact with nursing staff and only occasionally appeared to be responding to hallucinations, which were subjectively far less frightening to her and resulted in much less disruptive behaviour. At this time sodium valproate 400 mg and lithium 200 mg, both twice a day, were added to her treatment regimen. The addition of lithium and sodium valproate at this point could probably be considered to be controversial. Purists would insist on using ECT with as little concomitant medication as possible, and certainly this is a principle that one does try to follow whenever possible. However, in cases such as the one described, the clinical situation is one of such urgency that withdrawing medication during the course of ECT in a patient receiving only two ECT treatments a week is often not clinically feasible. In units where emergency ECT can be given more frequently or even daily, withdrawing all treatments is an ideal that can be achieved on occasion. In our unit lithium is used concomitantly with ECT from time to time, and the patients are run at plasma levels at or near 0.6 mmol per litre without any problems being encountered. As pointed out by Schou in his review (1991) the data supporting the absolute necessity for stopping lithium prior to ECT is not controlled and is mainly based on retrospective reports. He concludes that lithium can be used with ECT providing the clinician is cautious and the patient is closely monitored (Schou 1991). Indeed, current ECT Guidelines (Victorian Government 2000) do not consider lithium as an absolute contraindication with ECT. Similarly, the anticonvulsant mood stabilising agents, in this case sodium valproate, are not considered to be contraindicated with ECT even though it is recognised that these agents increase the seizure threshold (Victorian Government 2000). Once again the risk to benefit ratio of artificially elevating seizure threshold versus therapeutic behavioural and illness control between ECT treatments must be weighed up and carefully evaluated by the treating team. In our case it was considered to be a fair trade off at this time, especially as there was an episode of prolonged ictal activity with

one treatment. Given the failure to achieve adequate behavioural control with high dose neuroleptics and benzodiazepines in this case, the mood stabilisers were a very attractive option.

The third ECT treatment required only 80 mg of propofol (2.3 mg/kg) with 20 mg of succinylcholine to achieve good depth of anaesthetic induction. Due to what appeared to be a rapidly escalating seizure threshold a bifrontal stimulus at a charge of 302.5 mC, 1 msec pulse width at 60 Hz was delivered. This resulted in a bilateral tonic-clonic seizure of 14 seconds with a corresponding EEG duration. Due to the short duration of the seizure and the ongoing severity of her psychiatric illness it was decided to re-stimulate her at a charge of 403.4 mC, 1 msec pulse width at 70 Hz which resulted in a 21 second bilateral tonic-clonic seizure with corresponding EEG duration. No post-ictal complications were noted and her recovery was uneventful.

The patient continued to show clinical improvement, but was not yet euthymic or apsychotic and as such it was decided to continue with the ECT in order to achieve full symptom resolution prior to stopping. The team was also fearful that premature termination of the ECT treatment would result in a flare up of her psychotic and mood symptoms. With the fourth to the sixth treatments she required 80 mg of propofol (2.3 mg/kg) and 20 mg of succinylcholine. Her seizure threshold continued to increase. She was subsequently given 402.3 mC for the fourth treatment and two treatments at 504 mC bifrontal stimuli for the fifth and sixth treatments, which resulted in adequate therapeutic seizures lasting 13, 14 and 14 seconds respectively. All lorazepam was stopped after the fourth ECT treatment, as it was no longer needed for behavioural control.

At this stage, the patient was clinically euthymic and apsychotic. Full symptom resolution had taken 21 days since the commencement of the ECT. By the end of the course of ECT her plasma levels of lithium were 0.79 mmol/l and that of valproate 578 μ mol/l (350-700 μ mol/l). Unfortunately, however, she had gradually developed a dense retrograde and anterograde amnesia with almost no recollection at all of the events surrounding her admission to hospital, her symptoms during the course of her stay or the treatment she had received. Indeed, it appeared that she had forgotten about having the ECT as well. At this time she scored 20/30 on MMSE, losing points on registration, attention and recall.

Her medication was adjusted for maintenance treatment, to haloperidol 1 mg nocte, sodium valproate 400 mg twice a day, lithium 800 mg/day (serum level = 1.01 mmol/l) and

orphenadrine 1 mg thrice daily, as needed. She was referred to daily occupational therapy and was also enrolled to attend the hospital school to assist with her rehabilitation.

Two weeks after her last ECT, despite having been on therapeutic doses of two mood stabilising agents, she suddenly developed an elated mood and became irritable and intrusive and was diagnosed as having a relapse of mania. Haloperidol was increased to 1 mg twice a day by mouth. Her mood settled again within one week without the need for repeating the ECT.

Her mood state remained stable and her cognition gradually improved. Repeated MMSE scores never exceeded 27/30 for a follow up period of 10 weeks after the last ECT. There were persistent attention and recall deficits. She did however remain euthymic and apsychotic and was eventually discharged nine weeks after her admission. Her discharge medication was sodium valproate 400 mg twice daily, lithium 400mg twice daily, haloperidol 0.5 mg mane and 1 mg nocte and orphenadrine 1mg thrice daily as needed. There were no side effects of note. She was to attend follow-up at a community clinic near to her home. Telephonic consultation with the mother confirmed that the patient remained well and stable three months post discharge, was compliant on medication and was coping with her schoolwork.

Discussion

Some of the points we wish to highlight from the case report are as follows:

1. The initial need for significant doses of sedative hypnotic and induction agents which changed once the ECT was commenced.
2. The unequivocal and dramatic clinical response to the ECT.
3. The attention and memory deficits noted post ECT and the protracted nature of these symptoms in an attenuated form.

Point 1. The rapid dose reduction in sedative hypnotic and anaesthetic induction agents seemed to be due to the altered sensitivity the patient displayed to the therapeutic effects of these agents once the ECT was commenced. We are unaware of any literature that can explain such a clinical finding over such a brief period of time, especially regarding the anaesthetic induction agents. One could speculate that the ECT rendered the patient's central nervous system more sensitive to the drugs concerned. It has recently been demonstrated that ECT does temporarily disrupt the blood-brain-barrier (BBB), and increases cerebral blood flow and cerebrovascular permeability (Devanand et al. 1994). It may be possible to explain the decrease in dosage of these agents administered on the

basis that far more of the products were reaching the CNS receptor targets than before the commencement of the ECT. Another possibility is that the ECT influenced the receptors themselves in such a way as to render them more sensitive to the effects of the agents administered. We find this unlikely as the changes in sensitivity were noted after a single ECT. Another possibility is the influence of ECT on the primary psychotic illness itself. By attenuating this condition the patient becomes more responsive to the therapeutic pharmacological agents. Although the precise mechanism by which this clinical finding is achieved is unknown, it should be subjected to further controlled research. One possibility could including pre- and post-ECT imaging studies like SPECT to investigate receptor drug occupancy levels.

Point 2. As highlighted in the case report, this young lady can be regarded as having been severely ill, to a life-threatening degree. Significant doses of oral and parenteral medications, from numerous different classes of agent, had failed to improve or control her symptoms. Pressures to achieve symptom control were significant, yet the treating team found itself being increasingly fearful of the risks associated with vigorous polypharmacy. The decision to use ECT in this case was strongly influenced by the fact that the patient stopped eating and drinking in the unit. However, in our opinion, ECT should not be reserved for cases in such extremes. The patient had been in our unit 17 days prior to the first ECT. Some may argue that we should have waited for three to five weeks before commencing ECT to be certain of the efficacy (or lack thereof) of the prescribed medication. On the other hand, one could argue that perhaps ECT should even have been initiated sooner, prior to the patient refusing oral treatments, once it became clear the very large doses of intramuscular antipsychotic medications were not producing the desired clinical effect. Given the severity of the symptoms experienced, and our inability to commence oral mood stabilising agents, we felt that ECT was justified at such an early stage.

The consequences of denying a young patient a potentially therapeutic intervention (ECT) due to limited controlled data versus subjecting her to pharmacological regimens that do not produce desired clinical effects or which expose the patient to very real side effect problems, have to be carefully considered. This risk to benefit analysis is extremely important, especially in the light of the fact that there are no available data or accepted theoretical considerations suggesting that ECT is unsafe in this population group (Rudnick 2001). The ethical arguments as outlined in the literature (Rudnick 2001) of "playing it safe" by not giving ECT is founded on the premise that to give the

treatment (commission) would be more harmful than not to give the treatment (omission). As we have attempted to highlight in this case, it is our experience that ECT is indeed a highly effective treatment and should not be withheld from young patients unless clinically contraindicated.

One of the side effects noted with ECT in young patients is an increased incidence of prolonged seizures. As indicated in a recent review (Rey and Walter 1997) this has been a concern in adolescent ECT, and it was documented on one occasion in this case. However, it was easily brought under control and did not appear to induce any further tardive seizures or other episodes of prolonged seizures. Indeed a number of the treatments would have been considered of "short" duration, lasting only 14 seconds, and yet being clinically efficacious. This may have also been a complicating factor with the use of propofol as the induction agent. Interestingly, the prolonged seizure occurred with the first treatment when a large dose of propofol (200 mg, 5.8 mg/kg) was administered. The "short" duration seizures occurred with much more modest doses of propofol (80 mg, 2.3 mg/kg). This situation implies that the propofol was not directly influencing the seizure threshold, and that the short duration of subsequent treatments were almost certainly due to the rapidly elevating seizure threshold as outlined previously. Given the afore mentioned, we would certainly recommend that our colleagues be vigilant for prolonged seizures as a potential side effect, but it is certainly not a reason to withhold ECT in this population group.

The determination of the seizure threshold in this case is of particular interest. Despite the patient having been on large doses of intramuscular lorazepam the day prior to the initial treatment (12 mg/24 hrs), and having received 200 mg of propofol as an induction agent, her threshold was still found to be at level 2 (Sackeim et al. 1987). This rather surprising finding is hard to explain, given the concomitant treatments that she was on. The implication may be that her threshold was intrinsically very low, and elevated to this "normal" level by the anticonvulsant medications she was receiving. Clearly much further research data is needed to investigate the nature of seizure thresholds in young patients.

Point 3. Difficulty in separating out the side effects observed in patients treated with ECT while on concomitant lithium and valproate treatment is a situation often encountered by ECT practitioners. In an ideal situation, ECT should be conducted without concomitant pharmacotherapy, as highlighted in the literature (Rey and Walter 1997). In reality, this is often not possible, as outlined by the case above and acknowledged by respected

guidelines (Victorian Government 2000) and literature reviews (Rey and Walter 1997). Although the valproate and lithium were only commenced after the second ECT treatment, and would only have reached significant plasma levels well after the first three ECT treatments had been given, they may have influenced the seizure threshold in the later stages of the treatment course. These agents may well have impacted on the degree of cognitive side effects observed, but one needs to consider the profound memory and cognitive side effects that are well documented to occur with high dose benzodiazepine treatments, as was the case with this patient. As has been clearly demonstrated, however, these agents certainly could not have contributed to the dramatic initial clinical improvements observed, which must have been entirely due to the ECT.

Another factor influencing the side effect profile of ECT is the bilateral versus unilateral electrode placement. Bifrontal ECT treatment was the choice in this case, as outlined earlier, in order to maximise clinical response and hopefully minimise adverse events. Other reasons for this choice included the following. Given the potentially life-threatening severity of her illness, therapeutic efficacy of the ECT was considered crucially important. Consequently a bitemporal approach would have been considered, as this placement remains the "gold standard for efficacy" (Rasmussen 2003). However, given the paucity of data pertaining to the neurocognitive side effects of ECT in young adolescents, we attempted to attenuate this problem by opting for bifrontal electrode placements as opposed to bitemporal. As indicated in the literature (Rasmussen 2003) bifrontal ECT has comparable efficacy to, and may cause less cognitive side effects than, bitemporal ECT. Rasmussen also points out that for particularly severely ill patients bifrontal placements are appropriate (Rasmussen 2003). As such, we felt it would perhaps unfairly disadvantage the patient to commence right unilateral ECT at this point. However, given our most recent experiences with psychotically manic adolescents (unpublished data) high dose right unilateral ECT certainly is effective and is now the preferred placement in our ECT unit, even in the severely ill patient.

Another critical issue in severe manic conditions treated with ECT is at what point it is appropriate to commence treatment with maintenance mood stabilising agents. It is well documented that post-ECT relapse rates approach 90% within six months in depressive disorders (Sackeim et al. 2001). We are unaware of any controlled data for manic conditions. However it is our experience, as indicated in this case, that symptom relapse often appears shortly after discontinuing the ECT. In order to try to minimise the risk of this occurrence,

prophylactic medications are often commenced at some point during the later part of the ECT course in order to have therapeutic levels of maintenance agents at the time of treatment termination. As shown in this case, despite our efforts the patient had a manic relapse two weeks after the last ECT. Fortunately this responded to a slightly higher dose of haloperidol without the need for further ECT treatment. On the other hand one could argue that in severe conditions, as outlined in this case, perhaps one should opt for continuation ECT (C-ECT) once symptom resolution has occurred, as opposed to aggressive polypharmacy. As highlighted recently, C-ECT is underused and insufficiently studied (Petrides 1998) making the decision to utilise this modality very difficult, particularly in the adolescent population. We are unaware of any literature providing guidelines for C-ECT in adolescents. In this particular case the patient had never had a trial of mood stabilising agents for symptom prophylaxis and as such it would have made the decision to proceed with C-ECT very difficult to justify.

Clarification of the basic mechanisms of the response noted is worthy of specific research. The enduring impression is one of efficacy and treatment response to the ECT, with a reduction in required medication. While the cognitive impairment was noticeable, there was attenuation over time with ultimately a return to functionality. Regarding the ECT procedure, the case illustrates specific treatment challenges together with both therapeutic outcome and complicating side effects.

Conclusion

Given the paucity of literature in this patient population, the case described contributes specifically to the ECT knowledge base in terms of outcome, side effects and procedure. Optimisation of approach will require further study of ECT in this population group, which we hope will be judiciously applied in appropriate settings. The concern for the risks, while justified, needs to be balanced with the understanding of the benefits, so that a potentially life saving modality of treatment is not inappropriately withheld from deserving cases.

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Reversible Neutropenia during Treatment with Olanzapine: Three Case Reports

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Summary

Olanzapine is an atypical antipsychotic with a low incidence of extrapyramidal-motoric side effects. Its chemical structure is related to clozapine, which is known to induce neutropenia in up to 3% and agranulocytosis in approximately 1% of patients. It has been discussed controversially whether olanzapine also has a potential to induce neutropenia and agranulocytosis. Up to now, seven case reports of haematopoietic disturbances during olanzapine treatment have been published, including one case of olanzapine-induced agranulocytosis (Naumann et al. 1999), two cases of neutropenia (Steinwachs et al. 1999) and one leucopenia (Meissner et al. 1999). We report three subjects with reversible neutropenia under olanzapine, with rapid normalisation of neutrophil cell counts after discontinuation of olanzapine. In one case neutropenia occurred after administration of a single dose of olanzapine, in another case after 6 weeks of treatment. In both cases, patients had no clinical complications. In the third case, neutropenia appeared after 1.5 years of treatment followed by development of pneumonia. Two cases were recorded within the German drug surveillance project (AMSP); the third case was observed in a randomised, double-blind, multicentre study comparing olanzapine with clozapine.

Key words: olanzapine, neutropenia, side effects.

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Prior presentation

This paper was presented in part as a poster at the Congress of the Arbeitsgemeinschaft Neuropsychopharmakologie (AGNP), Nuremberg 2001.

Introduction

Olanzapine is a neuroleptic agent belonging to the class of thienobenzodiazepines. It is chemically and pharmacologically related to clozapine. Olanzapine was clinically introduced in Germany in 1996. In the literature, on the one hand, there are five case reports of patients who initially developed neutropenia or leucopenia under clozapine and were consequently changed to olanzapine. In three cases, the haematological abnormalities resolved after changing to olanzapine, but in two cases neutropenia persisted (Benedetti et al. 1999; Lambert et al. 1998; Swartz et al. 1999). On the other hand, a meta-analysis of different studies showed that 3500 patients treated with olanzapine did not develop agranulocytosis (Beasley 1997). Neutropenia (defined by a neutrophil cell count between 1000 and 1500 neutrophils/ μ l) was found in 4.6 % of these patients, but in no case necessitated discontinuation (Tran et al. 1997). The olanzapine summary of product characteristics (SPC) states that haematological abnormalities like leucopenia and thrombopenia were reported rarely.

The large official database of the US Food and Drug Administration (FDA), which collects spontaneous reports, does not give evidence for an increased incidence of agranulocytosis under treatment with olanzapine compared with risperidone and quetiapine (E.Lilly Germany, personal communication). However, 74 (19.3%) of 384 case reports up to July 2000 regarding olanzapine-induced side effects registered at the German federal drug administration (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) reported abnormalities of leucocyte counts. A causal relation between haematological abnormalities and olanzapine treatment could not be proved in all these cases (Bundesärztekammer 2001). Therefore, we would like to report in more detail three further patients from our clinic who developed neutropenia while on olanzapine treatment, including a discussion of the relationship between side effect and medication.

Case report 1

The female patient originating from Bucharest developed an impairment of cognitive function and disturbance of concentration when she was 16 years old. Catatonic schizophrenia was diagnosed at the age of 26 for the first time. After treatment as an inpatient, she was stable on 300 mg amisulpride for several years. During this time she began to study music, which obviously overburdened her increasingly. At the age of 30 the patient was admitted to our hospital. She was being treated with 6 mg risperidone but had been taking her medication irregularly. She had then discontinued this medication because of extrapyramidal motor side effects. She had been verbally aggressive and dismissive for some days and she had frequently refused to take food. Again she presented the clinical picture of catatonic schizophrenia, and had to be admitted involuntarily because of her aggressive behaviour, missed treatment and lack of disease insight. Because of amenorrhea, sonography was performed, revealing polycystic ovaries accompanied by increased testosterone levels. Magnetic resonance tomography demonstrated a gradual frontal atrophy of the brain.

Initially she was treated with 10 mg haloperidol and 4 mg lorazepam. The initial blood cell counts revealed 5000 leucocytes/ μl and 2800 granulocytes/ μl . After changing to monotherapy with 20 mg olanzapine because of extrapyramidal side effects, leucocyte numbers decreased to 3800/ μl and granulocytes to 1400/ μl , fulfilling the criteria for granulocytopenia. There were no clinical symptoms or other signs of infection. Despite a good therapeutic response, olanzapine was discontinued and haloperidol was re-introduced. Blood counts normalised within a few days, resulting in 5100 leucocytes/ μl and 2600 granulocytes/ μl .

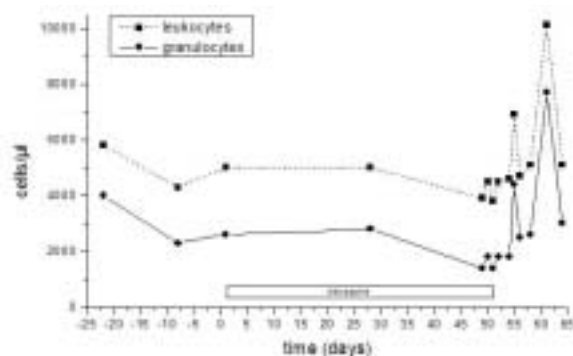


Figure 1
The development of leucocytes and granulocytes under treatment with olanzapine (Case report 1)

Case report 2

A graduate school director suffered from a schizophrenic psychosis for 16 years. He was

initially treated at the age of 50 years because he developed an acute delusion that the police were persecuting him. Frontal and parietal cortical atrophy was revealed by cranial computed tomography. Delusions were nearly therapy-resistant under neuroleptic treatment. During the following years he was repeatedly hospitalised because of re-exacerbation of psychosis. He felt as if he was being affected by external radiation, and developed pronounced negative symptoms with social retreat. At the age of 66 years, acutely exacerbated systematic delusions led to the current admission. He always felt irradiated by foreign powers and reported feelings of electrical shocks. During a period of three years he was continuously treated as an inpatient, as no sufficient recovery could be achieved.

At the age of 68, he developed leucopenia with 3600 cells/ μl and granulocytopenia with 900 cells/ μl during continuous treatment with olanzapine. Until the occurrence of neutropenia, the patient had been treated for a period of several weeks with olanzapine in daily dosages up to 40 mg. At the time when granulocyte numbers decreased, the dosage of olanzapine had been reduced to 25 mg per day. Simultaneously, the patient was co-medicated with 40 mg nifedipine for arterial hypertension and 20 mg metixen-HCl because of orofacial hyperkinesis and tremor of the right hand. The dosage of nifedipine had been raised from 20 to 40 mg two weeks before. Twelve days before, cephalexine, a transient antibiotic prophylaxis because of a fracture of the nasal bone, had been stopped.

All medication (Figure 2) was stopped after the occurrence of neutropenia, although under olanzapine treatment a gradual recovery of psychotic symptoms had been reached and a prompt discharge of the patient was planned.

Bisoprololfumarate and acetylcysteine were prescribed for bronchial infection. After a change to 5 mg haloperidol per day, the blood cell count normalised, and four days later the leucocyte count was 7900/ μl and the

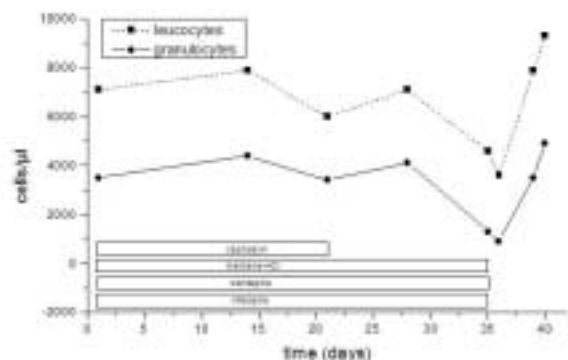


Figure 2
The development of leucocytes and granulocytes under treatment with olanzapine (Case report 2)

granulocyte count 3500/ μ l. The patient developed serious parkinsonism and pneumonia with respiratory insufficiency after four days of haloperidol treatment, which resulted in transfer to an internal medical unit.

In the medical history of this patient, a neutropenia with 400 cells/ μ l was reported when he was on a combination of haloperidol and lorazepam. However, a two-year course of treatment with 150 mg clozapine led to no change in blood count.

Case report 3

This patient, who applied for asylum in Germany because of political prosecution in Sri Lanka, was transferred to our department for the first time at the age of 29 because of catatonic schizophrenia. CCT demonstrated rounded frontal horns, which could be interpreted as a result of brain damage during early infancy, but no other abnormalities. Because neuroleptic medication was ineffective, he was treated with electroconvulsive therapy, resulting in clear clinical improvement of the catatonic symptoms. However, with delusions persisting, he travelled throughout France and the Netherlands in the ensuing years. During acute exacerbations repeated admissions therefore took place to several psychiatric hospitals.

At the age of 35, the patient was actually again referred to our department because of an acute exacerbation of schizophrenia, dyskinesia, akathisia and torticollis spasticus, probably induced by treatment with typical neuroleptics. He reported that he was the sun and the light of the world. His persecutors must have kidnapped his girlfriend, so that he was seeking her kidnappers in Europe.

Leucocyte and granulocyte counts were within the normal range. Two months earlier the patient had discontinued his bi-weekly depot medication with flupentixol 20 mg. Six years before, during a previous treatment with 250 mg zotepine and 40 mg fluphenazine, haematological side effects had not appeared. After taking 2 mg lorazepam with no other medication a granulocyte count of 1700/ μ l was observed; however, by the following day the count was again within normal range.

After inclusion in a double-blind multicentre randomised study comparing olanzapine with clozapine, the patient took one single dose of 10 mg olanzapine. Again the granulocyte count decreased to 1500/ μ l for the following two days (Figure 3). After excluding the patient from the study and discontinuation of the medication, the granulocyte count increased again and normalised spontaneously to 2000/ μ l the following day. During subsequent monotherapy with 12 mg sertindole, again low and

fluctuating granulocyte counts were observed with a minimum count of 1700/ μ l.

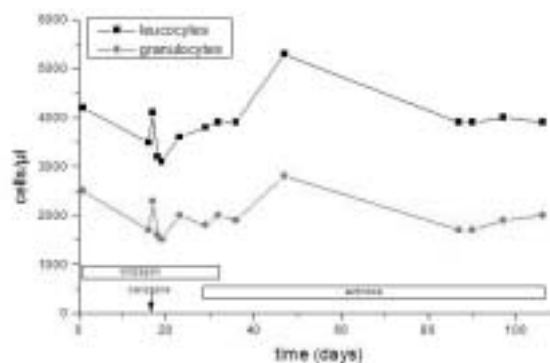


Figure 3
The development of leucocytes and granulocytes under treatment by olanzapine (Case report 3)

Discussion

In the first case, a reversible granulocytopenia occurred during olanzapine treatment, producing neither clinical symptoms nor the need for specific treatment. A relationship with olanzapine is probable, because the patient was treated in monotherapy; there were no haematological abnormalities in the history and the granulocyte count normalised within 10 days after discontinuation of olanzapine.

In the second case, the granulocyte count decreased to 900/ μ l, which demanded immediate discontinuation of olanzapine. In this case, a bronchial infection occurred followed by pneumonia with respiratory insufficiency. The high-dose treatment up to 40 mg olanzapine given for a few days might be the cause of the granulocyte decrease. Such a causal relationship with olanzapine is possible in this case, but alternatively an influence of the co-medication nifedipine (Voth and Turner 1983) or an association with a bacterial infection can not be excluded. An unfavourable additive haematotoxic effect of both drugs, olanzapine and nifedipine, is also possible. Because the bronchial infection developed four days after the beginning of neutropenia, we suppose that there was no causal relationship between infection and the development of neutropenia.

On the one hand, in the medical history of this patient neutropenia as low as 600 granulocytes/ μ l had been observed during a combined treatment with 15 mg haloperidol, 0.5 mg lorazepam and 25 mg levomepromazine six years before. On the other hand, a two-year treatment with 150 mg clozapine did not lead to a decrease of granulocyte counts.

In the third case report, an idiopathic vulnerability for the development of granulocytopenia during treatment with psychoactive drugs may have pre-existed, as

fluctuating granulocyte counts and neutropenia occurred during treatment with lorazepam, olanzapine or sertindole. However, this vulnerability was not detected in this patient during treatment with zotepine, fluphenazine and lorazepam several years before. Therefore, it cannot be excluded that in this case a cyclical granulocytopenia existed independently of the drug application (Dale and Hammond 1988).

In the case reports presented, treatment with olanzapine was discontinued after the development of granulocytopenia. In cases 1 and 3, discontinuation of treatment resulted from marginally low granulocyte counts with neutropenia at 1400/ μ l and 1500/ μ l. In the case of clozapine, the manufacturer recommends drug discontinuation at a leucocyte count below 3000/ μ l or granulocyte count of 1500/ μ l or below. Thus, if this recommendation is applied for granulocytopenia during olanzapine treatment, only the second case had a clear indication for treatment discontinuation. Because changes of medication might result in psychopathological deterioration, the immediate drug discontinuation was probably too quick, and had a questionable basis in the other two cases.

Patients who have developed blood dyscrasias on clozapine or other antipsychotic drugs may be at higher risk of developing white blood cell count disorders during olanzapine treatment (Sartorius et al. 2003). In contrast, a number of studies that specifically studied patients with clozapine-induced white blood cell abnormalities did not find any problems with white blood cell counts after switching these patients to olanzapine (Steinwachs et al. 1999; Beasley et al. 1997; Loeffler et al. 2003). Kodesh et al. (2001) suggest that leucopenia during olanzapine treatment may be a dose-dependent phenomenon, because leucopenia disappeared with a dose decrease in the three patients they described.

However, the findings in many of the reported cases are confounded by the fact that patients were not on olanzapine alone, but received additional psychotropic drugs, in many cases even other antipsychotic medications (Sartorius et al. 2003).

Regarding our own observations and based on the current literature, we conclude that neutropenia or agranulocytosis during treatment with olanzapine is a rare phenomenon, which occurs with a comparable incidence during risperidone and quetiapine treatment (data on file, E. Lilly). In patients on newer atypical neuroleptics, drug-related neutropenia was documented in only five patients during treatment with olanzapine and in one case with risperidone by the German drug safety programme in psychiatry (AMSP) in

a population of 122 562 patients between 1993 and 2000 (Stuebner et al. 2004). Our cases, as well as the vast majority of published case reports, do not support the view that the clinical manifestation of olanzapine-associated neutropenia is comparable to clozapine-induced agranulocytosis. The latter is a potentially life-threatening disorder accompanied with a total loss of neutrophil precursor cells in the bone marrow and needs 1 to 3 weeks for remission if clozapine is immediately discontinued and a treatment with granulocyte stimulating factor (G-CSF) is introduced (Loeffler et al. 2003).

In summary, our case reports suggest that regular monitoring of the differential blood count is necessary if low granulocyte counts are observed, and one must consider both medical history and the follow-up treatment in the further therapeutic procedure. Furthermore, it appears to be prudent to monitor white blood cell counts (especially neutrophil counts) of patients being treated with atypical antipsychotic drugs and patients with a history of drug-induced white blood cell count disorders, as well as patients treated with other drugs bearing a risk of white blood cell aberrations (Sartorius et al. 2003). Regarding the sensitivity for antipsychotic-induced blood dyscrasias in the scientific community, we recommend using the terms neutropenia or agranulocytosis very carefully in order to avoid premature labelling of a single abnormal neutrophil count, possibly resulting in unnecessary stigmatisation of the suspected drug. Especially the term agranulocytosis should only be used if the neutrophil count is below 500/ mm^3 combined with clinical signs of inflammation (Bankowski et al. 1999), which helps to exclude those cases where a simple laboratory failure is the cause of abnormal neutrophil counts.

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Sexual Dimorphism in Obsessive-Compulsive Disorder

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About 10 years ago we noticed a sex difference in the performance of a neuropsychological test in obsessive-compulsive disorder (OCD) patients (Gross-Isseroff et al. 1996). Subsequently, we further documented this finding (Zohar et al. 1999a) and, in 1999, we published a review on the possibility that a sexual dimorphism in OCD existed (Zohar et al. 1999b).

Since then, several publications have presented data lending further support to the sexual dimorphism hypothesis. Thus, two papers (Mundo et al. 1999, 2002) have claimed that there is a differential behavioural and biochemical response to clomipramine among OCD patients. Other studies have shown that association and/or linkage to genetic markers of OCD are different in male and female patients (Nestadt et al. 2000; Alsobrook et al. 2002; Lochner et al. 2004). Lately, a basic animal study has shown sex differences in the performance of an alternation task, supposedly an animal model of OCD (Ulloa et al. 2004).

In view of this burgeoning information, which sustains the hypothesis of sexual dimorphism in OCD, we would like to urge investigators in the field to include sex comparisons, even if these are not an inherent part of their studies.

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