Brain function and Tuberous Sclerosis

Many people with TSC will be aware that they or their children have some difficulties with how their brain works. Some will have very significant learning difficulties and may need special education; others may be intellectually very able, but have specific difficulties with paying attention, learning or remembering specific things. Sometimes, even if you are very able, you may find that your specific problem with concentration or organising your life, may lead to lots of difficulties.

So, we know that the brain's *function* can be affected by TSC. One of the challenges for researchers has been to identify which brain *structures* may be specifically involved in TSC.

People with TSC can have tubers in almost any part of the brain. Some have lots of tubers and others only one or two tubers. It can be very difficult to predict how tubers can affect people's learning abilities. Research studies in the 1980's and 1990's tried to see if the number of tubers, or where the tubers are in the brain, could predict whether people will have learning difficulties. Unfortunately the brain is much more complicated than that. Some people with many tubers have a high overall intelligence, while others with only a few tubers can have very significant learning difficulties. Similarly, tubers in one lobe or another does not directly explain the presence or absense of learning difficulties. There are no clear research answers to these questions yet.

Apart from tubers, most people with TSC have some subependymal nodules (SEN). They tend to be in the basal ganglia and can affect structures like the thalamus and limbic system. Very little is known about the affect of SEN on our ability to learn, remember or pay attention.

Using special brain scans, researchers have shown that tubers and nodules may not be the only sort of structural problems in the brain of people with TSC. Even in adults who have normal intelligence and lead normal lives, structural abnormalities can be seen throughout the grey matter (the neurons) and the white matter (the connections between brain regions) in the brains of people with TSC. It is possible that these fine-grain abnormalities may tell us more about *why* some people struggle with concentration or learning and *where* in the brain these difficulties come from.

ADHD, autism and othe behavioural difficulties

Researchers are trying to understand whether specific behavioural difficulties can be caused by tubers. We can't really say whether the tubers 'cause' the difficulties, but we can ask whether tubers in specific parts of the brain can be 'associated' with problems. For example, Patrick Bolton and Paul Griffiths found that children who had tubers in their temporal lobes are more likely to have autism than those who don't have tubers in their temporal lobes. Other researchers found that tubers in the cerebellum rather than in the temporal lobes were associated with autism.

ADHD is seen in many children with TSC, but research so far does not show any relationship between the location or number of tubers and the diagnosis.

No research has been done to examine the relationship between other psychiatric disorders such as depression, anxiety or psychosis and tubers. It is however important that we consider the possibility that TSC may have effects at many different levels. One of the levels may be affecting the visible structure of the brain. It is just as likely that TSC will affect that functioning of individual brain cells such as the neurons and that the changes at that microscopic and molecular level may explain why people with TSC have difficulties with learning and behaviour. The main aim of trying to understand brain function and structure in TSC, is to be able to find specific treatments such as new medications, that may improve some of these difficulties.

Conclusion

We hope that you have found this leaflet a useful guide to the brain function and to the effects of TSC on the brain. Please do remember that brain research in TSC is very much ‘work in progress’ and that researchers clearly have a long way to go towards understanding the fascinating bur complicated way the brain really works.

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Tuberous Sclerosis Association

A User's Guide to the Brain

To begin with, a few facts about the brain that are generally believed to be true. First, it seems likely that everything that is 'you' is stored in your brain. For example, your memories and your personality are all in there, perhaps much as a computer stores information about facts and programs. In addition to details about you, brains also store programs for doing things, allow you to make sense of information coming in from other parts of your body, send instructions to your body parts and carry out other tasks that we would normally describe as thinking. It can be helpful to think about the brain as a centre into which sensory information comes, is processed and then acted upon. For instance, incoming information might be telling you about things that are relatively far away, for example information coming in through your eyes or ears. It could also be information about things happening within your body, telling you that it is time to eat (or stop eating!) or that its time to go to sleep.

As well as receiving information, the brain also sends information back to other parts of the body – instructions about how to reach for your knife and fork to eat dinner, or how to get up and walk to the cupboard to get more salt. We tend to rather take these things for granted, so much so that we often don't realise that apparently straightforward things like reaching for cutlery are actually quite complex skills. As another example, walking up or down the stairs is something we usually do without consciously thinking about it.

We are so good at doing this that we don't feel as though we are thinking about it – it has become, to some degree, automatic. Consciously thinking about ascending the stairs can actually make the task more difficult. Often it is only when things go wrong that we are made to realise how effortlessly we normally do what are in fact quite complex tasks.

In the rest of this leaflet I'll try to give a brief explanation of how the brain functions and describe some of the difficulties that can be encountered when things go wrong.

How different parts of the brain communicate.

The brain sends information in two ways. The first is electrical information that gets sent down 'nerves' (**neurons**) and the second is chemical information that carries information across the gap between nerves (**synapses**) so that the next neuron can receive the message. If these processes are interrupted things can go wrong and it's worth thinking about the consequences of different types of disruption.

First, if a neuron is cut through, the information can no longer travel on to the end of the nerve and therefore cannot reach the next neuron. So, for example, if the nerve cells carrying visual information from the eye are cut then that information can no longer reach the brain, leading to blindness. Equally, if information about a limb is prevented from reaching the brain it won't 'know' what is happening to the limb. If neuron's carrying information to the rest of the body are cut, the brain's instructions can no longer be carried out.

If information from a limb is blocked then the person will have anaesthesia (from the Greek and literally meaning 'no sensation') and if information to a limb is blocked the person will have paralysis.

Things can also go wrong when chemical substances get into the gap between cells. When electrical information reaches the end of a nerve cell, chemicals are released across the gap to the next cell to continue the message. Because these chemicals carry information between neurons we call them 'neuro-transmitters'. If other chemicals get into the gap between cells then communication can be blocked, or assisted, depending on the nature of chemical. Many poisons work by blocking the neurotransmitter. Some of these interfering chemicals, like caffeine for example, are similar to neurotransmitters and work by increasing the amount of information crossing the gap between cells (the synapse).

Finally, if neurons are overstimulated, or if electrical activity spreads to the wrong cells, then disordered messages are sent out, sometimes causing the body to move uncontrollably. This is what happens in epilepsy.

A lesson from the past.

In the early 19th century a craze swept the well-to-do sections of society which involved having your intellectual and personal skills determined according to the bumps on your head. The theory behind this 'phrenology' was that the brain could be divided into a number of compartments and that each compartment was responsible for one, and only one, job. The theory also supposed that if a part of the brain was large then the skull would have to increase in size to accommodate this brain region. Thus it followed that the bigger the region, the more of the designated skill you were supposed to have. Whilst it is true to say that some brain regions seem more involved in certain tasks than others, the kind of one-to-one relationship of 'bump' and 'skill' supposed by phrenologists is unlikely to be true.

It is also worth remembering that parts of the brain could well be involved in a number of apparently different tasks.

Special jobs for different parts of the brain.

One way in which to better understand what the brain does and how it does it, is to divide it up according to what jobs different parts of the brain are responsible for. The most obvious thing about the brain is its division into two parts, or 'hemispheres'. For many purposes the right half or hemisphere controls what the left half of the body does, and the left hemisphere the right side. This means that brain damage to the the left hemisphere can cause people to be paralysed on their right side, and vice versa.

Figure 1 is a picture of the brain shown as though we were looking at a person's head from the right-hand side. We have divided this view of the right hemisphere into four different lobes, (plus the cerebellum, the 'little brain' that sits under the main part of the brain, or 'cerebrum)'. In *Figure 2* we are again viewing the brain from the right hand side, but this time it is as though we have cut away the whole of the right half of the brain, leaving only the left hemisphere. We will come back to looking at the job done by the parts shown in *Figure 2* later.

For convenience sake in *Figure 1* we have divided this view of the brain into five areas. This is not entirely arbitrary as there is some evidence for believing that these different bits do different jobs.

Frontal lobes – Not so long ago it was believed that in spite of comprising such a large portion of the brain, the frontal lobes had no special role to play. This was believed because damage to these lobes seemed to have no effect on the person's ability to do everyday activities. However, more sophisticated testing has shown that these structures are needed for thinking that includes planning ahead and solving problems. It also seems clear that our social behaviour may be dependent on intact frontal lobes. This has been known for some time, mostly because of medical descriptions of people who have shown strange changes in behaviour after brain damage. Such a case was Phineas Gage, an American railway worker who was unlucky enough to have an iron bar blown through the front of his head. Whilst Phineas retained his intellectual abilities, a number of friends noticed changes in his personality. For example, before the accident Phineas was a polite, well-spoken man, whereas afterwards he often behaved badly in public and frequently used bad language.

Figure 1 also shows a strip with a strange shaped individual with a large head and features. This is the sensorimotor strip which contains the brain's representation of the sensory information coming from different areas of the body. A pioneer in mapping these areas was the Canadian neurosurgeon Wilder Penfield. He conducted operations on patients coming in for surgery and found that if the patient was kept awake during the operation, stimulation of the various areas of the

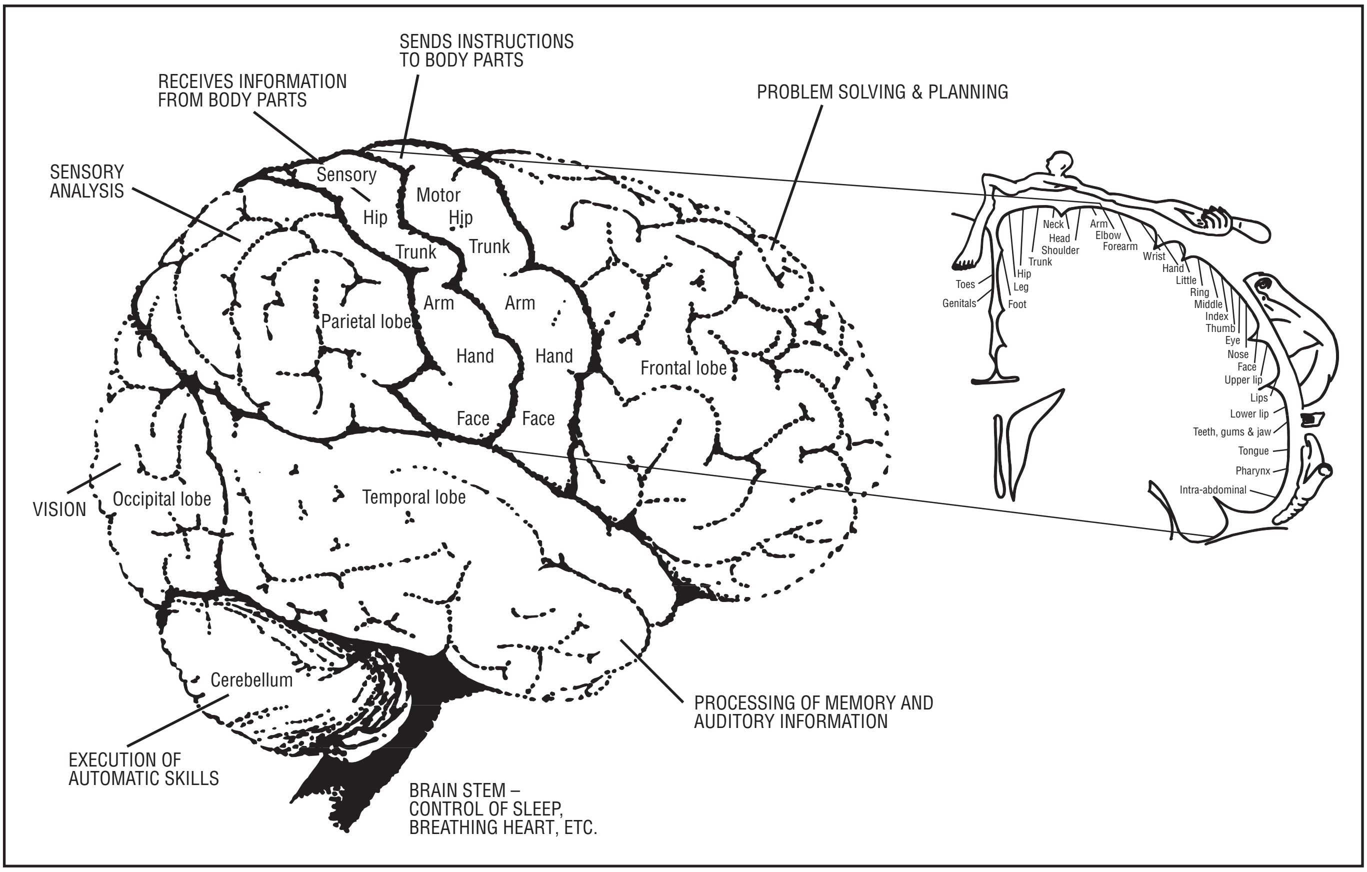

Figure 1

sensorimotor strip would cause the patient to report feeling sensations in the body part represented in that region. A similar strip exists in the frontal lobes and deals with sending information to body parts.

Temporal lobes – As with all of the lobes, the temporal lobes are involved in a number of tasks, but it would seem that they make a special contribution to memory and language skills. With respect to memory the temporal lobes contain the hippocampus, a structure that seems important in the formation of new memories. The rear part of the temporal lobes seems to be particularly interested in understanding what people are saying to you, whereas the parts near the frontal lobe (as well as parts of the frontal lobes themselves) seem particularly involved in our ability to speak. The temporal lobes are where information about sound is stored and interpreted.

Occipital lobes – This part of the brain seems to be most interested in visual information. There seem to be a number of subdivisions, one area processes colour, another processes movement, etc. We know about this subdivision because in some people specific areas get damaged and when this happens they lose only part of their visual skills. So, for example, in the medical literature there are cases of people who have become unable to see colour, as well as others who seem to have lost the ability to see movement.

Parietal lobes – Once the occipital lobes have analysed the information coming in through the eyes, this data is then sent to the parietal lobe which seems to be involved in the interpretation of what has been seen. The parietal lobes also seem to be involved when we need to pay attention to specific regions of our visual world.

One consequence of damage to the right parietal lobe is that patients will ‘neglect’ the left half of space. The patient will act as though nothing on the left exists, although information about this half of space is being received and processed by the occipital lobes. Such patients will only shave one-half of their face, or eat only the right half of their pizza and will not notice that anything is wrong.

As mentioned in our discussion of the frontal lobes, there is a strip of brain that contains areas which represent body parts. In the frontal lobe these areas control movement. This strip marks the edge at which the frontal lobes stop and the parietal lobes begins. In the parietal lobe, just across the gap (or ‘**sulcus**’) that separates these two lobes, lies a sensory area that has a brain map of the body similar to the motor map found in the frontal lobes. This strip is the brain region where information about sensations detected in body parts is represented.

Cerebellum – Until recently it was believed that we pretty much knew that the role of the cerebellum was in carrying out well-known, automatic tasks, such as the previous example of walking up or down the stairs. However, recent research has suggested that ‘the little brain’ may have roles to play in other areas of cognition, such as in memory and in making sense of our visual world.

Limbic system – This is the brain structure believed by many to be the home of our emotions and that part of the brain which places value on learning. For example, the memory of a very scary experience might make us anxious and make us try to avoid that experience in the future. The establishment of this response seems likely to involve structures in the limbic system

Brainstem – This is the junction at which the spinal cord meets the brain and appears to control important life-supporting functions such as sleep and breathing.

Thalamus – This is usually described as the ‘telephone exchange’ of the brain, as it seems to act as a centre through which information passes to and from the cortex

Corpus callosum – As previously pointed out, the brain is divided into two halves (hemispheres). However, these hemispheres are connected by a number of nerve cell bundles so that information can pass between them. The corpus callosum is the largest of these bundles.

Basal ganglia – These structures are the ones that become damaged in disorders such as Parkinson’s disease and Huntingdon’s disease. This suggests that the basal ganglia are needed in carrying out movements, as Parkinson’s and Huntingdon’s patients have difficulty in moving.

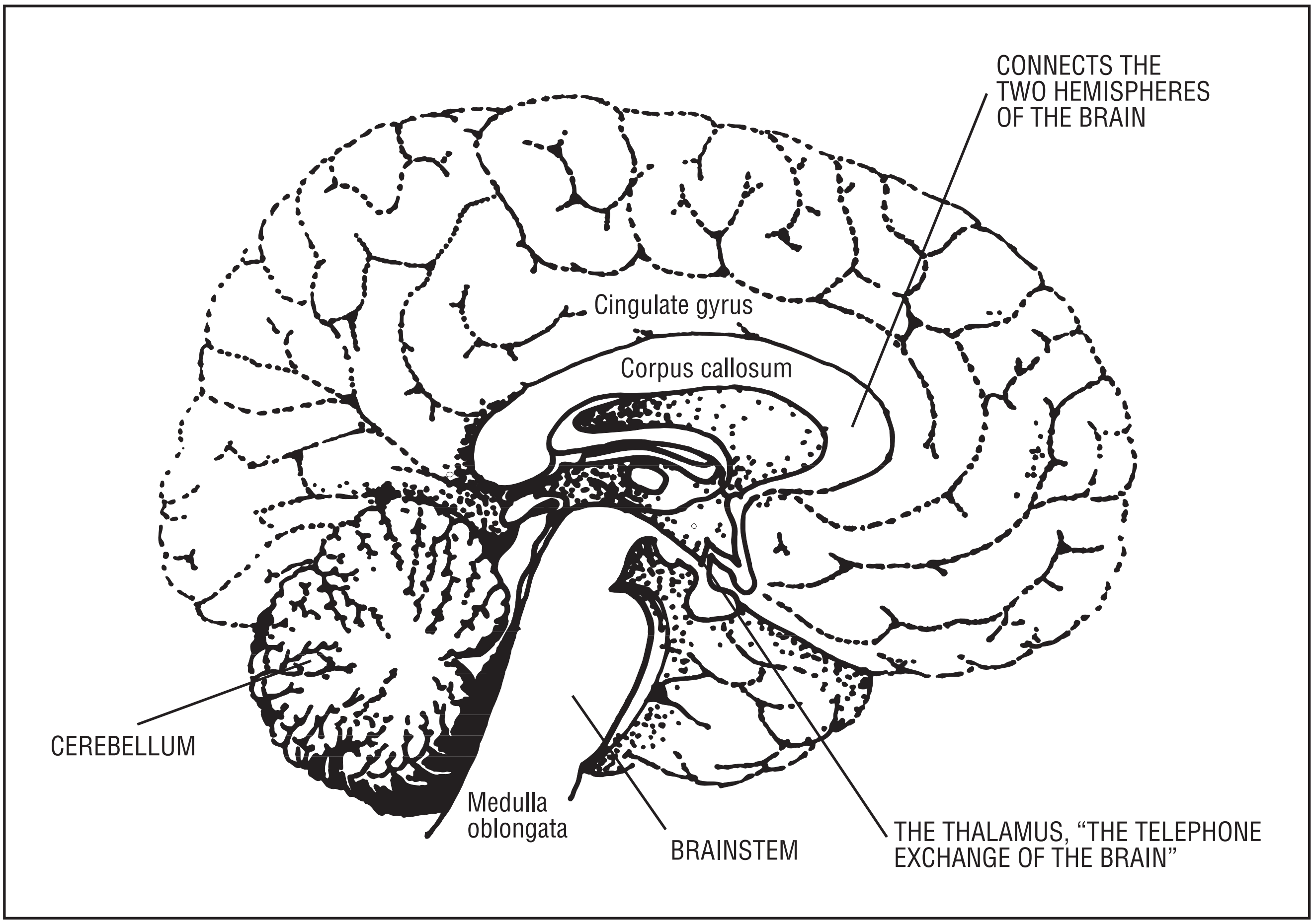

Figure 2