The Role of the Cerebellum in Schizophrenia

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Abstract

For many years the cerebellum has been considered to serve as a coordinator of motor function. Likewise, for many years schizophrenia has been considered to be a disease that primarily affects the cerebrum. This review summarizes recent evidence that both these views must be revised in the light of emerging evidence about cerebellar function and the mechanisms of schizophrenia. Evidence indicating that the cerebellum plays a role in higher cortical functions is summarized. Evidence indicating that cerebellar abnormalities occur in schizophrenia is also reviewed. These suggest interesting directions for future research.

Recent Evidence for the Role of the Cerebellum in Cognition

The tentorium was once the Maginot Line of the brain. Supratentorial regions governed “higher cortical functions,” while the humble subtentorial cerebellum performed “lower” functions unrelated to cognition. Recent evidence has illustrated the possible falsity of this dichotomy and has led to a growing group of neuroscientists to reconceptualize the cerebellum as a key player in higher cognitive functions (2; 3; 7–15).

One line of evidence for the importance of the cerebellum in cognition arises from evolutionary and developmental neurobiology. Two regions in the human brain are massively larger (by approximately 1/3) than in other higher primates who lack human capacities for complex language, high-level abstract concept formation, the creation of art in its many various forms, and social constructs such as government structure and economic principles. One region is obvious: the prefrontal cortex. The other would not be predicted by most: the cerebellum (16). Why did this convergent expansion occur? One likely explanation is that these two regions work together to perform the variety of “higher cognitive” tasks executed by the ingenious human brain.

Anatomical support for the “cerebellar cognitive theory” has been provided by a group of careful tract-tracing studies (17–23). In particular, Strick’s group has been applying retrograde and anterograde tract-mapping with herpes and rabies viruses for more than a
decade. In an elegant series of studies, they have now demonstrated point-to-point connectivity between multiple cortical regions (areas 46, 12, 9, and 40—i.e., including both frontal and parietal cortex) and the cerebellum, linked through the pons and thalamus. These studies provide very strong evidence that the cerebellum participates in neural circuits that perform higher cognitive functions of the sort mediated by heteromodal association cortices. We now know that the cerebellum is connected to many regions of the cerebral cortex by a cortico-cerebellar-thalamic-cortical circuit (CCTCC), and that the cerebellum may play a crucial role in this distributed circuit and coordinate or modulate aspects of cortical activity (see Figure 1).

Lesion studies have been a classic method for studying regional and focal neural functions. Many studies have suggested that the primary effect of cerebellar lesions is impairment in motor coordination or motor learning, supporting the prevailing view that these are the primary tasks of the cerebellum (24; 25). More recently this view has been modified. Lesion studies in humans have helped define a more purely cognitive role of the cerebellum by indicating that time perception and production are impaired in subjects with cerebellar injuries, suggesting that the cerebellum may facilitate cognition by monitoring mental events within the context of time. (26–28). In addition, lesion studies have also demonstrated that the cerebellum plays an important role in associative learning, as documented by studies of eyeblink conditioning (29). Other studies have demonstrated that cerebellar lesions may produce symptoms that are similar to those of psychiatric disorders, such as mutism (30). Cerebellar lesions do not, however, normally produce psychotic symptoms. This might suggest that the cerebellum could have no role in schizophrenia. Nonetheless, many experts now reaffirm the classic Bleulerian view that impairments in cognition are its primary symptoms and that psychotic symptoms are merely secondary (31). This change in perspective, along with the growing recognition that the cerebellum is engaged in basic cognitive functions such as timing and associative learning, has led to an emerging interest of the role of the cerebellum in schizophrenia.

Finally, extensive work done during the past decade using the tools of in vivo neuroimaging has also demonstrated that the cerebellum plays a significant role in cognition in the healthy human brain. It has been repeatedly shown that the cerebellum is activated in a variety of mental activities, even when motor activity is well-controlled, including facial recognition, emotion attribution, theory of mind attributions, directed attention, and many types of memory (2; 3; 5; 7; 11; 15; 32–37). Figure 2 illustrates some of the cerebellar regions activated in healthy normals in a variety of PET studies conducted at our Iowa laboratory. One 4Tesla fMR study of the cerebellum illustrates the value of high field imaging of the cerebellum (11) used a pegboard and compared a visually guided task and a cognitively challenging “insanity task” to evaluate the role of the dentate nucleus—the output nucleus from the neocerebellum to the neocortex—in cognition. Both tasks were similar, in that they involved movement of pegs on a pegboard, thereby controlling for the motor component. The insanity task differed from the visually guided task in that it was also cognitively challenging because it required strategic planning of the movement of the pegs within the context of specified rules, in a manner similar to the more familiar Tower of Hanoi or Tower of London tasks. All subjects (N=7) had large bilateral dentate activations during the insanity task.

**Searching for the Neural Basis of the Symptoms of Schizophrenia**

Explaining the diversity of symptoms at the neural level is one of the major challenges of schizophrenia research. Early attempts worked primarily by trying to relate a specific symptom to a specific cortical region that is likely to be involved in producing such a symptom. For example, auditory hallucinations, or hearing voices speaking when no one is
around, could be explained by an abnormality in the auditory cortex where primary auditory perception is processed (38). The abnormalities in cognitive fluency or volition, often referred to as “negative symptoms,” could potentially be explained by abnormalities in the “executive” portions of the brain, the frontal lobes (39).

The cerebellum, understood within the context of our current knowledge of its connections and cellular architecture, provides an interesting alternative for explaining the diverse symptoms of schizophrenia. Because the cerebellum participates in many different cortical activities, cerebellar malfunction could lead to many different types of cortical malfunction, and in turn could lead to the diversity of symptoms and cognitive dysfunctions observed in schizophrenia (40–42). The role of the cerebellum is probably not primary, in the sense that it is the sole region that is dysfunctional. Rather, schizophrenia is probably a disease involving the interaction between multiple components in distributed brain circuits. None is necessarily primary; on any given occasion, or during any given task, one may malfunction in a way that affects the whole system, or the interacting combination of multiple regions in distributed circuits (e.g., cortical areas, thalamus, cerebellum) may malfunction.

Cerebellar Anatomy: Implications for Cognition and the Symptoms of Schizophrenia

In addition to multiple types of symptoms, patients with schizophrenia have many types of cognitive impairments. One plausible explanation for these diffuse deficits is that some central cerebral regulatory component is malfunctioning. The evidence indicating that there is an impairment in excitatory/inhibitory tone in the cerebellum in schizophrenia, coupled with the evidence from multiple functional imaging studies showing abnormalities in cerebellar blood flow in many types of mental activity, implicates the cerebellum as one of the crucial sites where the “mischief” may be occurring.

Cerebellar anatomy is organized in a simple but elegant pattern that permits it to perform fine-tuned pattern perception, error detection, and rapid online modulation and coordination. The various results described above—decreased Purkinje cell size and decreased excitatory input to them from the granule cells—have major implications that explain cerebellar and CCTCC dysfunction in schizophrenia and related abnormalities in symptoms and cognition. (See Supplemental Text Box: Cerebellar Anatomy) The inhibitory Purkinje cells and the excitatory granule cells are especially important in cerebellar function. Working together, they help to modulate or coordinate the activity of the cerebral cortex by providing input to “deep nuclei” such as the dentate nucleus.

A key component of “cerebellar coordination of cognitive activity” is long term potentiation and depression (43). The interpretation of the input by the Purkinje cells is “programmed” through long-term depression at the dendritic spines. This program is created by input from the climbing fibers, arising in the inferior olive. The inferior olive receives input from many and varied origins throughout the cerebral cortex, and its activity conveys indication of error conditions to the cerebellum. The unique structure and connectivity of the Purkinje cells permits them to discriminate and recognize specific input conditions, such as variation in spatial locations or in patterns of auditory input. This gives the cerebellum tremendous power to make well-defined decisions about the vast amount of input that it receives. The output of the Purkinje cells goes to the deep nuclei and is inhibitory (GABAergic). Thus Purkinje cells have the important role of deciding what information is or is not returned to the cerebral cortex through inhibition of the output nuclei.

These pattern and error detection tasks normally performed by the cerebellum are presumed to respond in a flawed manner in patients suffering from schizophrenia. Instead of
modulating and coordinating, they instead misconnect the billions of pieces of information arriving from the cerebral cortex. The output is then in turn flawed. For example, the location of an auditory signal arising from the auditory cortex without an external stimulus is misinterpreted as “outside” rather than internal, leading to the experience of auditory hallucinations. A perception (e.g., a red traffic light) is connected with an erroneous matrix of associations, leading to a misinterpretation of its significance and the experience of delusions. The solution of the multiple problems examined by cognitive and neuropsychological tests is slowed, inefficient, and sometimes wrong, because the cerebellum fails to perform its error detection functions and relay the updated information to the cerebral cortex efficiently. We refer to this impairment in mental coordination as “cognitive dysmetria” (40–42).

Models of Cerebellar Function

As interest in the cerebellum has increased during recent years, several different models of cerebellar function have emerged that are relevant to understanding the possible role of the cerebellum in schizophrenia. These can be divided into three broad groups.

Model 1: The role of the cerebellum is motor or associative learning

The narrowest model emphasizes the role of the cerebellum in very limited processes. The cerebellum has been recognized to have a role in motor learning for many years. Based on the Marr – Albus model of cerebellar motor learning and control, (44; 45) the climbing fibers provide an error correction mechanism to signal the need to modify an executed motor movement or facilitate procedural learning. This is then transmitted to the deep nuclei, which in turn communicate with the cerebral cortex via a thalamic relay. Associative learning is another example of a “narrow” conceptualization of the role of the cerebellum. The classic test used to examine this is eyeblink conditioning (29).

Model 2: The role of the cerebellum includes modulation of cognitive processes, but this role is based on a very specific but basic cognitive process such as timing

Several models of cerebellar cognitive learning have been proposed. The most intensively explored example of this type of model argues that the cerebellum functions as a timekeeper, based primarily on lesion studies that indicate cerebellar injury leads to an impairment in the ability to estimate time intervals or imitate timed rhythm sequences (28; 46).

Model 3: The role of the cerebellum includes modulation of cognitive processes, and this role involves all processes performed by the cerebral cortex; the cerebellum is a “general purpose modulator” that detects patterns, pattern changes, and errors in both movement and thought and provides adaptive feedback to the cerebral cortex

Variations of this model have been proposed by Bower (47), Leiner (12), and Ito(48). This model emphasizes the fact that the cerebral cortex is comprised of a variety of specialized modules that perform specific functions such as motor performance, sensory perception, or the generation of speech. The cortical regions comprising these modules differ in cytoarchitectonics because of their specialization. The cerebellum, however, has no such cortical specialization; its three-layered cytoarchitectonics are omnipresent. Ito therefore argues from cerebellar anatomy and suggests that the cerebellum is composed of large numbers of units that he refers to as microcomplexes. These provide an adaptive control mechanism. Microcomplexes are functional subunits within the cerebellum that facilitate its function. They receive dual inputs from mossy and climbing fibers; the climbing fibers detect errors or pattern changes and act to reorganize internal connections, while the mossy fibers “drive” the complex. The microcomplexes function like microprocessors—they can be used to perform a vast array of different functions to supplement cortical cerebral
processing. They are connected to diverse brain regions (e.g., multiple different cortical areas) and therefore can play many diverse roles in brain function, including all types of cognitive processing. This model would predict \textit{in vivo} imaging studies would detect cerebellar activations in nearly all tasks performed by cerebral cortical modules.

The existing evidence does not as yet lend more credence to one of these models rather than the other. However, in view of the emerging recognition of a cognitive role for the cerebellum, the narrower role postulated in model 1 may be supplanted as more empirical data are collected to explore models 2 and 3.

\section*{Evidence for Cerebellar Abnormalities in Schizophrenia}

Work suggesting that cerebellar abnormalities occur in schizophrenia has been slowly accumulating for several decades. Heath (49) was the first to call attention to the possible role of the cerebellum. His work was followed by multiple additional studies using anatomical imaging tools such as CT and later morphometric Magnetic Resonance (mMR) that have reported abnormalities in cerebellar size in schizophrenia (50–57). Picard et al (58) recently conducted a review of the evidence for cerebellar abnormalities in schizophrenia from multiple perspectives: symptoms, neurological signs, eye movements, nondeclarative learning, and cognition. They conclude that evidence for cerebellar abnormalities is strong from some perspectives (e.g., neurological soft signs, posture, equilibrium) but that the evidence for other domains such as cognition is more heterogeneous. As they discuss, methodological issues (e.g., subjects sampled, variability in designs used to assess cognition) may explain this heterogeneity.

Neuropathology studies have provided significant evidence for cerebellar abnormalities in schizophrenia (59). Investigators have reported a decreased linear density in Purkinje cells (60) or a specific decrease in their size (by 8.3\%) (61). The latter finding is particularly significant, since Purkinje cells play a key role in modulating the output from the cerebellum to the cerebral cortex, because they provide input to the “deep nuclei” such as the dentate nucleus. The deep nuclei in turn provide the sole output from the cerebellum to the cerebral cortex.

Studies of schizophrenia using the tools of functional imaging from our own group have found a relatively consistent pattern of abnormalities in distributed brain regions that include the cerebellum. These results are illustrated in Figures 1 and 2. Abnormalities are seen in these studies in both the vermis and in the cerebral hemispheres in patterns that are task-related. Patients with schizophrenia have decreased blood flow in the cerebellum in a broad range of tasks that tap into diverse functional systems of the brain, including memory, attention, social cognition, and emotion (1; 4; 62–65). Vermal abnormalities are more frequently noted in tasks that use limbic regions (e.g., studies of emotion), while more lateral neocerebellar regions are abnormal in tasks that use neocortical regions (e.g., memory encoding and retrieval). Figure 3 illustrates some of the cerebellar regions found to be abnormal in schizophrenia in studies conducted at our Iowa laboratory. Given the broad range of cognitive functions implicated in these functional imaging studies, they appear to be most supportive of model 3.

Findings of cerebellar abnormalities using functional imaging or related technologies have also been observed by other groups using explicit methods to study the cerebellum. For example Muller et al used a finger tapping task for an fMR study in which subjects had to tap in time to a specific pace (66). Volkow et al used PET to examine cerebellar metabolism in schizophrenia and observed reductions in both relative and absolute metabolic rates (67). Daskalakis et al (68) used transcranial magnetic stimulation to the motor cortex in a cerebellar inhibition protocol and found that patients with schizophrenia had significant

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cerebellar inhibition in comparison with control subjects. In addition to these more targeted studies, abnormalities in the cerebellum have also been reported in many other functional imaging studies, but have not received any explicit attention or comment [e.g., (38; 69)]. Overall the functional literature provides relatively strong support for cerebellar abnormalities in schizophrenia, suggesting that this may be an important future direction for further work.

Other recent studies of cerebellar dysfunction have focused on the cellular and synaptic level, using the tools of in situ hybridization and immunoautoradiography. These neocerebellar regions contain broadly distributed relays to the cerebral neocortex. Examination of the expression of three synaptic proteins in the cerebellum—synaptophysin, Complexin I, and Complexin II—has illuminated their regional distribution in Purkinje and granule cells in the normal brain and demonstrated that synaptic pathology is present in these regions in schizophrenia (70). Specifically, synaptophysin is decreased by 31% in granule cells, and Complexin II is decreased by 36%, while Complexin I is normal. These results suggest that the excitatory input to the Purkinje cells is diminished in schizophrenia, creating an imbalance in the Purkinje cell inhibitory input to the deep nuclei. A change in Purkinje cell tone would lead in turn to an impaired ability of the cerebellum to integrate information and send appropriate “cognitive coordination” signals to the cerebral cortex. The decreased excitatory tone in the granule cells is also consistent with the reports of decreased Purkinje cell size, since decreased input is likely to lead to a decrease in activity and ultimately size of the dendritic tree over time. These results add further confirmation to the hypothesis that schizophrenia is a disease affecting distributed neural circuits, and that the cerebellum and the CCTCC are functionally and anatomically abnormal in schizophrenia.

Despite the growing evidence for cerebellar abnormalities in schizophrenia, it is much less extensive than that for other brain regions (e.g., frontal and temporal cortex). Until relatively recently few investigators have bothered to examine the “lowly” cerebellum. In fact, the potential role of the cerebellum was missed in many early imaging studies of either healthy normals or schizophrenic patients because it was “cut off” from the field of view, and because it is also excluded from the Talairach Atlas used to define activation coordinates in functional imaging studies. At present a role for the cerebellum in schizophrenia remains somewhat controversial, although the controversy arises in part from adherence to conservative models of cerebellar function (e.g., Model 1). However, it is also controversial because of a vast literature implicating other brain regions as well. For example, Shenton (71) conducted an exhaustive review of 193 mMR studies and found relatively consistent findings in temporal and frontal regions and a variety of subcortical regions; she considered evidence for cerebellar abnormalities to be equivocal (found in 31% of studies reviewed).

Investigators have also been actively exploring the involvement of the cerebellum in other disorders. A growing literature suggests that cerebellar abnormalities may occur in autism, a disorder that has many features in common with schizophrenia, such as impairments in cognition and social awareness. MR studies have shown that children suffering from autism have unusual growth patterns in the cerebellum early in life (72). Furthermore, functional imaging studies have indicated that autistic children have decreased cerebellar activations during a task that requires them to focus attention (73). In addition, cerebellar abnormalities observed with structural MR imaging have also been observed in children suffering from attention deficit hyperactivity disorder (ADHD) (74). Therefore, cerebellar abnormalities may not be specific to schizophrenia. The common thread among these observations is that schizophrenia, autism, and schizophrenia are usually considered to be neurodevelopmental brain disorders, and their symptoms share many common features, such as impairment in attention, social interactions, and emotional regulation.
Novel Directions for Schizophrenia Research

Studying the cerebellum and its possible modes of malfunction provides a heuristic and parsimonious approach that can be used to explore the mechanisms of schizophrenia in a variety of ways. Several novel directions are promising.

One future direction involves the use of in vivo anatomical imaging of the cerebellum in an effort to pinpoint possible abnormalities in neurodevelopmental milestones in schizophrenia. Current working hypotheses suggest that schizophrenia may be both an early and an adolescent onset neurodevelopmental disease (75; 76). Recent work demonstrates the value of in vivo anatomical MR imaging to study both normal cerebral development and abnormalities in schizophrenia (77; 78). Our knowledge of neurodevelopment in the cerebellum is more limited, but the existing evidence suggests that it is both interesting and somewhat unique. Neurogenesis continues in the cerebellum after birth and during approximately the first two years of life. In addition, based on the relatively small number of human post mortem anatomic studies of the cerebellum that are available, it appears that other neurodevelopmental processes such as myelination, dendritic proliferation, and synaptogenesis also may occur through late childhood, adolescence, and early adulthood (79). Overall, the final phases of neurodevelopment in the cerebellum are heterochronous with much of the rest of the brain—occurring relatively later. These later phases may coincide with the time of onset of schizophrenia. The relatively fine-grained gross anatomy of the cerebellum—with its small folia and even smaller deep nuclei—are likely to demand the use of higher resolution and higher field MR approaches if this strategy is pursued.

A second approach is to design functional imaging studies in a manner that explicitly targets examination of cerebellar function in the context of the three competing models. For example, a comprehensive series of experiments could be created that move through the three models using well-established protocols. For model 1, associative learning might be studied using an eyeblink conditioning protocol. For model 2 a variety of protocols are available, such as estimating the duration of time intervals, maintaining a correct rate of finger tapping that is externally paced, continuing the rate when the external stimulus is removed and the tapping must be internally paced, or judging the length of time intervals. For model 3 a variety of well-accepted protocols are available, such as the oddball paradigm or the Sternberg working memory task. If abnormalities are found using all three models, then cerebellar dysfunction in schizophrenia is supported.

A third promising approach, exemplified by the work of Eastwood (70), is to focus post mortem genomic and neurotransmitter studies on the cerebellum—a relatively uncharted territory. In addition to genes for synaptophysin and complexin, a variety of other candidate genes are obvious options for study. Some are logical choices because of their known role in modulating neural development and function, such as BDNF (brain derived neurotrophic factor), neuregulin, or dysbindin. Some are logical choices because of their role in neurotransmission, such as the gene for catechol-o-methyl-transferase (COMT). Such molecular work can be complemented by the use of in vivo spectroscopy methods to measure metabolic markers (e.g., n-acetyl aspartate) or neurotransmitters (i.e., GABA, glutamate) in the cerebellum. There is already some evidence for abnormalities in BDNF and GABA gene expression, as well as for developmental abnormalities in serotonin receptors (80; 81).

A fourth approach is to continue the dissection of the cognitive and symptomatic abnormalities of schizophrenia at the systems level. One goal is to improve the spatial and temporal resolution of functional imaging studies through high field MR instrumentation, event-related designs, and MEG and MRS studies. (82). Such approaches may help identify more specific loci of cerebellar abnormality, which may guide the choice of regions of

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interest in molecular or metabolic studies. A second goal—perhaps more distant—is to exploit the cross-species homology of the cerebellum and to identify simple cognitive tasks (e.g., associative learning, time perception) that may model the schizophrenia endophenotype and that can be used in animal studies that will facilitate the development of animal models of schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Cerebellar Anatomy

The cerebellum has a relatively simple architecture: the three-layered cerebellar cortex (molecular, cellular and granular), the corpus medullare (white matter), and the deep nuclei (fastigial, interpositus [globose and emboliform], and dentate nuclei). It has five types of neurons. Four are inhibitory GABAergic neurons (Purkinje, Golgi, basket and stellate cells), and one is an excitatory glutamatergic neuron (granule cells).

The CCTCC comprises a complete set of feedback loops between cortex and cerebellum (see Figure 1). Input to the cerebellum from the cerebral cortex is provided by a relay through pontine nuclei. The pontocerebellar fibers (mossy fibers) are glutamatergic, feeding into the cerebellar cortex and often sending collateral fibers to the deep output nuclei. In the cerebellar cortex the mossy fibers synapse on granule cells, which distribute excitatory input across several millimeters of microfolia. Granule cell axons extend into and bifurcate at the uppermost layer of the cortex. The parallel fibers arising as axons from a single granule cell typically distribute information to over 2,000 Purkinje cells, via excitatory glutamatergic neurotransmission. Each Purkinje cell, which can have input from over 200,000 granule cells, performs a complex interpretation of the vast amount of excitatory input it receives (see Figure 4). In addition, Purkinje cells receive glutamatergic input from climbing fibers, which arise in the inferior olive. Unlike parallel fibers, which make single synapses with Purkinje cells, climbing fibers wrap around the cell body and proximal dendrites, making hundreds of synapses per fiber. The unique structure and connectivity of the Purkinje cells permits them to recognize input and regulate output. They draw on the vast amount of information that they receive and make a “decision” that regulates the flow of information from the output nuclei to the cerebral cortex.
Figure 1.
CCTCC
Figure 2.
A composite representation of cerebellar regions active in various tasks in healthy subjects, based on PET studies conducted at our research center. Surface was created from the MR image of a single subject, and is viewed from the posterior. The left side is cut away to show a coronal view of the folia and corpus medulare. Anatomical regions have been colored corresponding to group results for the functional tasks. For each task listed below the activity of a baseline task has been subtracted to isolate the task of interest. For instance, for the task activating long-term memory for a word list, the baseline task was reading words. The cutaway of the surface shows the MR image of the folia at that location and the activations below the surface. For some tasks more than one region is active, so there are multiple regions labeled for that task. In all these studies different and appropriate task-dependent cortical regions were activated in addition to the cerebellum, providing support for the importance of the CCTCC as a distributed brain circuit and Model 3 of cerebellar function described above.
1. Verbal recall of a well-learned story (2)
2. Long-term memory for a word list (3)
3. Creating an empathetic narrative - Theory of Mind task (5)
4. Verbal recall of a recently learned word list (3)
5. Recall of pictures of faces (7)
6. Externally paced finger tapping (unpublished data)
7. Acquisition of eyeblink conditioning (unpublished data)
Figure 3.
A composite representation of cerebellar regions with lower activity in patients with schizophrenia than in controls. Results for 1 - 7 are from double subtraction studies (for each group the activity of a baseline task has been subtracted before the groups were compared) analyzed with a randomization analysis. Results for 8 were for fMRI analyzed where the group-by-condition contrasts compare each group’s activations with appropriate baseline conditions.
1. Verbal recall of a well-learned story (1)
2. Long-term memory for a word list (4)
3. Creating an empathetic narrative - Theory of Mind task
4. Verbal recall of a recently learned word list (4)
5. Recall of pictures of faces (unpublished data)
6. Externally paced finger tapping (unpublished data)
7. Acquisition of eyeblink conditioning (unpublished data)
8. Working memory for manipulated sets of letters (6), outlined in red.
Figure 4.
Pontine cerebellar Circuits