

## **Is autism due to cerebral-cerebellum disconnection?**

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Summary Autism has been linked to thalidomide exposure at 20-24 days gestation. At this stage, the embryo is roughly the size of this 'C', and has yet to develop its brain (except for brainstem cranial motor nerve nuclei). The neuropathology responsible for autism is presently unknown, but whatever it is, it must logically be one that can be induced by such an early occurring brainstem cranial motor nerve nuclei defect. Many mental faculties impaired in autism (such as theory of mind) depend upon the prefrontal cortex. The maturation of cerebral-cerebellar connections, due to oddities in axon development, is vulnerable to pre-existing brainstem nuclei integrity. Many higher cognitions (including prefrontal ones) are dependent upon these links raising the possibility that abnormalities in them might produce autism. I conjecture that impaired cerebral-cerebellar connections, whether caused early, as by thalidomide, or later (including postnatally) by other factors, is the missing neuropathological cause of autism.

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### **INTRODUCTION**

Anomalies provide an important source of information for the development of new theories in science (1). Autism is, at present, an aetiological mystery. It is the only form of retardation in which people can have normal intelligence. It is the only form of retardation in which skills can hyperdevelop as shown in musical, drawing, calendar calculating savants. It has profound effects ranging from sensory and motor problems to ones concerned with higher cognition such as the ability to appreciate that other people have minds.

Aetiologically, it is also anomalous: while its clinical status is well defined, MRI and microscopic examination of neurons in autistic brains have failed to identify any specific neuropathological defect. (The only differences reported so far concern those averaged across autistic and control groups; none is specific, i.e. nonautistic individuals exist with such differences.) This is puzzling since individuals with autism suffer severe (and autism-specific) cognitive impairments such as the inability to understand mental states (theory of mind) that have been linked to higher brain areas. For instance, theory of mind has been connected to certain areas in the prefrontal cortex by the brain injury (2) and by functional imaging (3). Functional impairment is found in the prefrontal cortex of autistic individuals (4) but curiously there is no parallel neural impairment (5). In spite of this link to the prefrontal cortex, we know that autism, at least in some cases, must be caused by impairments without obvious connection with this part of the brain. Autism can be caused by thalidomide at 20-24 days gestation, a date at which there is no brain (apart from brainstem cranial motor nuclei) yet in existence to be impaired. Any aetiology of autism must explain how an injury in the early brainstem (as evidenced by thalidomide-induced autism) can cause functional impairment in the prefrontal cortex.

Fortunately, the thalidomide inducement of autism itself suggests a possibility. Due to peculiarities in how axons develop, the brainstem plays a critical role (explained below) in the axonogenesis of the cerebral cortex projection (particularly its frontal part) to the cerebellum. The cerebral-cerebellar fibre track performs key functions in higher cognition (6): thus any impairment in it could therefore be expected to underlie a major form of retardation. However, abnormalities in the cerebral- cerebellar link are undetectable, and so, at present, cannot be matched up with any resulting higher cognitive impairments. It is thus plausible (and I shall argue below parsimonious and testable) to suggest that such disruption to axons between the cerebral cortex and the cerebellum is the missing neuropathology of autism. Thalidomide could through brainstem disruption cause abnormalities in this connection

which would knock-on upon prefrontal cortex cognitions (through impairing their interactions with processes in the cerebellum).

This neuropathological speculation is refutable. Though abnormalities in the cerebro-cerebellar connection are at present invisible to autopsy and conventional MRI imaging, they have recently become detectable with the new brain imaging technique of diffusion tensor MRI (7-9). Moreover, as a hypothesis, the cerebro-cerebellar disconnection theory of autism makes the specific and intriguing prediction that cognitions dependent upon this link should be impaired in autism, and those that are not, should be spared - a prediction easily tested with functional imaging. Thus, the cerebral-cerebellar connection defect theory of autism proposed here makes strong testable claims.

## **THE THALIDOMIDE-AUTISM ANOMALY**

The teratogen thalidomide induces autism at 20-24 gestation days (10). At this date the embryo is roughly the size of this 'C', and the brain (apart from the neurons of the cranial motor nerve nuclei) does not yet exist (11). Indeed, at this stage, the neural tube, out of which the future brain will arise, is only just closing. This dating of the thalidomide-autism link is precise: thalidomide is teratogenic roughly between gestation days 20 and 35 (12) with various impairments linking to specific gestation days. Between days 20-22, for instance, the outer ear is affected, between 22 and 28, the thumb fails to develop, the upper limbs are affected between days 24 and 31, the lower ones on days 27 to 33, and between days 32 and 36, the thumb has an extra joint (10). These and other stigmata precisely date the period during which thalidomide causes autism. Many factors later in embryo or even postnatal development might cause the neuropathology responsible for autism. But whatever neuropathology they induce, it logically must be one that can also be induced by impairments at this early stage.

### **Why anomalous**

Many functions impaired in autism depend upon higher brain areas that only arise after the early gestation date of thalidomide-induced autism. For example, those of the human cerebral cortex arise at the end of the fifth week, for the hippocampus at the beginning of the seventh week, and for the amygdala and the hypothalamus, they arise at the middle of the fifth week, even the neurons for the cerebellum and its nuclei only first arise at the middle of week five (13). Effects upon stem cells generating them are unlikely since such impairment would lead to acephalia (stem cells also form the bone and other tissues that later surround the brain) (14), something which does not happen. Autistic brains, if anything, tend to be larger than normal (15). This makes it anomalous how impairments at 20-24 days could have specific neurological consequences upon functions that are impaired in autistic individuals such as theory of mind that take place in the prefrontal cortex.

## **CONJECTURE**

To resolve this anomaly, I propose two hypotheses.

### **Hypothesis: 1**

Many higher cognitions depend upon the communication between the cerebral cortex and the cerebellum, and that, due to the peculiarities of their development, these connections are vulnerable to brainstem disruption. Disruption to the cerebral-cerebellar link can arise at many developmental stages - not only at the early date proposed for thalidomide (this, though, is theoretically interesting, because it identifies this connection as the target neuropathology underlying autism).

### **Hypothesis: 2**

Autism is due to disconnection of cerebral input (including the prefrontal cortex) to the cerebellum. Skills in the prefrontal cortex depend upon an active interaction with processes in the cerebellum (6). Skills such as theory of mind, that are selectively impaired in autism, I suggest, are those that are particularly dependent upon interactions between these two areas of the brain. Other skills preserved in autism are not affected because they can function in the absence of cerebral-cerebellum interaction.

### **The anomaly explained**

Axons from the cerebral cortex go to the cerebellum via a projection to neurons in the pons. However, due to peculiarities in their development, the axons going down to the pons, initially go down further to the lower medulla and the cranial nuclei in the brainstem.

It is only after growing down into the brainstem, that axon collaterals bud off and enter the pons. (Many of the initial brainstem axons indeed survive - thus the somatomotor cortex projection to the cerebellum is bifurcate and projects both to the pons and spinal and brainstem motoneurons.) However, the initial axons from other cerebral cortex areas (such as the visual cortex) die off leaving only the pons projection (16). Interestingly, a transient link from the cerebral cortex to the cerebellum exists that goes direct to it without first going to the pons: it follows the same developmental pattern of developing as a collateral to an initial brainstem projection (17). This suggests that the collateral strategy of development for reasons unknown is a developmental rule for axons developing into the pons/cerebellar region from the cerebral cortex.

Due to this initial projection to the brainstem, impairments to the brainstem could knock-on and affect the cerebral cortex-cerebellum link: this vulnerability arises because excess cerebral-pons axons (depending upon their integrity) are eliminated through 'axon sculpturing'. This elimination (at least in the rat), for example, proceeds first in a rapid period during one week in which over a third are removed, and second, in a slower period that continues until only half the original axons remain (18). Two factors determine the integrity of axons, and hence their survival, that link to earlier brainstem events. First, axons reach targets both cells (19) and intermediate substrates (20) that provide retrograde transported trophic factors (such as NGF). Second, axon connections with neurons from an early date are active (neurons in the rat brainstem, for example, are active in 'respiratory oscillations' from gestation day E 18) (21). Such electrical activity is known to determine cerebral-brainstem and cerebellar related axon survival, for instance, lack of it is responsible for the direct cortical-cerebellum link noted above being transient (22). These factors act to make axon sculpturing potentially sensitive to any earlier compromise of the brainstem. Thus, impaired connection by axons to neurons in the brainstem caused by defects to these neuron targets could knock-on and impair the integrity of the later developing cerebral cortex-cerebellum axon links.

Axon input from the frontal areas of the cerebral cortex would be particularly affected by this knock-on effect. Collaterals from the occipital and frontal regions of the cortex arrive after those from lateral areas. As Leergaard and colleagues note: 'They grow around the central core [into which early arriving axons go], bridging [i.e. infilling] the rostral and caudal entrance zones' (23). A general process in neurological development is weeding out by competition (24). Thus competition for neuron targets in the pons in the sculpturing process will delete excess axons. This will put axons from occipital and frontal areas at risk from erroneous or excessive deletion: they arrive late, and are so likely to already be competing for pons neuron targets already taken by the earlier-arriving lateral area ones. This would act to amplify any compromise upon them created by earlier impairment to the brainstem.

#### Development of input nuclei

A further possibility exists: the neurons which form the pons and the inferior olive nuclei that provide the cerebellum with its afferent input are generated in the dorsally located rhombic neuroepithelium and migrate from this lower and early developed brainstem region up to their final upper brainstem location (25). Early effects of thalidomide might affect either the integrity of their neurogenesis or their receptor expression. Again here is an opportunity to affect the input from the cerebral cortex to the cerebellum. This is less likely since though research finds abnormalities in these neurons in regard to their size - they fail to find neuron number reduction in these nuclei in autistic brains (5). However, it is possible that subtle impairment in the brainstem might leave them apparently intact though of smaller size and compromised in their function abilities (though this is not the interpretation of the researchers).

#### Autism and the brainstem

I conjecture that thalidomide impairs the development of axons from the cerebral cortex to the cerebellum because of the sensitivity and vulnerability of this link to brainstem nuclei compromise. Later in development, other impairments (of other causes) might also impair this link, so producing autism of other origins. Thalidomide, however, by causing impairment at 20-24 days gestation points the finger of suspicion to its critical neuropathological impairment being dysfunction in the link from the cerebral cortex to the cerebellum.

Though, as noted above, this connection could be impaired at times after 20-24 days, many autistic individuals interestingly seem to suffer a development compromise at this very early embryo stage. Stigma such as ear deformities known to link to this stage are common in autistic individuals (26). Moreover, autistic individuals show a high prevalence of a variant in *Hoxa1* (40% compared to 20%), a gene that is involved in the development of the lower brainstem (27). However, such brainstem impairment, cannot itself be the cause of autism. Not all autistic individuals show such stigma, and the higher functions impaired in autism are selective: for example, it affects the ability to perceive the processes underlying intentional but not mechanical events (it would be difficult to see how a brainstem impairment could produce this). Moreover, many (though only a minority) of individuals with autism show normal levels of IQ, and even relatively normal lives (for example, one is a noted animal behaviourist and autobiographer, Prof. Temple Grandin (28). This argues that the explanation must be some impairment that does not hinder brainstem function (which would have clinically obvious and important effects) but affects a component needed for certain higher cognitions processed elsewhere in the brain (for example, those dependent upon the cerebral-cerebellar link).

### **Autism and cerebral-cerebellar connections**

This theory is not without precedence: present theories of autism link it to dysfunction in the cerebellum (29), prefrontal cortex (30) or even both (31). What is novel about this theory is that it argues its neuropathology links not to these areas but the uninvestigated connections between them. This is a more probable possibility than neuron-related theories - since impairments in these have been already been examined and not found.

Cerebral cortex-cerebellum disconnection is plausible on the further grounds that it is the only major remaining defect that could impair the higher brain function that has yet to be investigated. The reason is technical: researchers at present see axon fibres connecting the cerebral cortex and the pons in detail only with the use of axon-carried biotracers. The result of this is that research upon them has been limited so far to experimental animals. Any abnormalities in this tract in human brains have thus, with the use of present techniques, been terra incognita. Therefore, if autism arose, as suggested from abnormalities in the cerebral-cerebellar link, we would expect its neuropathology to have remained, as it presently is, undiscovered.

### **TESTABLE PREDICTIONS**

This argument is a hypothesis, not a statement of fact. Fortunately, as a hypothesis, it provides strong opportunities for its refutation.

First, knock-on effects on cerebro-cerebellar axonogenesis should exist in rats treated with teratogens at E11 (the equivalent of human 20-24 gestation days) such disconnection should be found with tracers in such animals. Moreover, these animals might be expected to show autistic-like behaviours.

Second, cerebro-cerebellar axon fibre links should be grossly impaired in autistic brains. A recent development in brain imaging, diffusion tensor MRI (7-9) now provides a direct means of seeing whether such links are impaired as here required. Moreover, it predicts that higher cognitive skills that are selectively impaired in autism such as theory of mind should rely upon cerebral cortex and cerebellum co-operation but not ones unimpaired in autism such as mechanical reasoning. This should be easily confirmed, or not, by functional imaging.

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