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Part I

The nature and neurology of cluttering
1 Cluttering: a neurological perspective

Per A. Alm

Introduction

Background

The term cluttering designates a conglomerate of symptoms and characteristics displayed in varying degrees by affected individuals. No single aspect is sufficient to determine the diagnosis; it is the clustering of certain traits that constitute this syndrome¹ (see St. Louis & Schulte, chapter 14 this volume). Cluttering is a speech-language disorder, but many authors, such as Weiss (1964), have argued that the symptoms also may include non-verbal motor behaviour, temperament, and attention deficits.²

Research on cluttering is important in order to provide improved means of treatment, but cluttering may also turn out to be a condition that leads to valuable insights regarding the normal processes underlying speech, language, and attention. Furthermore, understanding of cluttering is essential for the understanding of stuttering, as they are overlapping and yet contrasting disorders. Research on stuttering is complicated by difficulties in determining primary versus secondary aspects. This problem is less apparent in cluttering.

The discussion in this chapter is intended to outline a hypothetical framework of how cluttering may be understood. It should be emphasized that cluttering is a heterogeneous disorder, possibly with different causal mechanisms in different subgroups—partly because of unclear criteria for the diagnosis. Hopefully better understanding of the mechanisms involved will result in a more strict definition of cluttering. It is a conscious decision to make the hypotheses quite detailed, which sometimes means being speculative, in order to allow empirical testing.

A brief overview of this chapter and the conclusions

While the core of cluttering may be seen in the verbal expression of fast and dysrhythmic speech, the understanding of the disorder is likely to involve a very wide range of functions and anatomical structures in the brain related to

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language, motor control, attention, and intention. There is a lot of information available from current brain research, but there is a need to integrate this, and to relate it to the symptomatology of cluttering. In order to help the reader, the tentative conclusions and suggestions will be summarized here.

It will be proposed that the core of the problems in cluttering is located in the medial wall of the left frontal lobe, i.e., the cortex on the wall between the cerebral hemispheres (see Figures 1.1 and 1.2). In brief, the model implies that the medial frontal cortex plays a central role in production of spontaneous speech, in parallel with the more traditional speech and language areas in the lateral part of the left hemisphere, such as the Wernicke’s and Broca’s areas. The medial cortex is proposed to have a coordinating role in spontaneous speech, related to the motivation to talk; planning of the phrase; retrieval of words, syntactic elements, and phonological code from the lateral cortex regions; execution of the motor sequence, and monitoring of the speech output. The key regions in cluttering appear to be the anterior cingulate cortex (ACC), the preSMA, and the SMA proper, together with the input from the basal ganglia circuits. The ACC is proposed to have the functions of a ‘central executive’, at the core of the initiation of volitional movements and speech, as well as being the centre for willful attention and high-level error monitoring. The ACC is closely related to the preSMA, which seem to be critical for the ‘assembly’ of the phrase, from the sequencing to the selection of words and word forms. The model that emerges from current brain imaging data is that the ACC, the preSMA, and the SMA proper constitute a hub or an ‘assembly centre’ in spontaneous speech, retrieving all the linguistic components from the left lateral cortex regions, such as the Wernicke’s and Broca’s areas and adjacent zones. The selection of one single word from many competing alternatives is facilitated by the basal ganglia circuits, through a ‘winner-take-all’ function. The timing of the articulation, and thereby the speech rate, is controlled by the SMA proper with support from the basal ganglia and the cerebellum. The production of speech is monitored on multiple levels, primarily through auditory connections to the ACC and the SMA.

Cluttering may be a heterogeneous disorder, with different (neural) mechanisms in different subgroups. A main mechanism proposed in this chapter is hyperactivation and dysregulation of the medial frontal cortex, which may be secondary to disinhibition of the basal ganglia circuits, for example as a result of a hyperactive dopamine system.

This review and analysis will be divided into main topics that all are intimately interrelated, making the structure somewhat loose. First, the functional anatomy of the medial frontal wall will be briefly presented, in order to provide an anatomical framework. Then the symptoms and characteristics of cluttering will be discussed. Physiological clues from the effect of dopaminergic drugs and abnormalities of EEG lead to a discussion of the possible role of an overactive dopamine system. Thereafter, the review will focus on three main aspects of speech production: (1) initiation and
sequencing of action; (2) selection of linguistic items, such as words and syntactic elements; and (3) monitoring of speech errors. The intention is to propose a comprehensive model of speech production, based on current research findings, and relate the symptoms of cluttering to this model.

**Functional anatomy of the medial frontal cortex**

*Functions of the ACC*

The connections of the ACC are characterized by convergence—it is a region where drive, cognition, and motor control interface, putting the ACC in a unique position to translate intention to action (Paus, 2001). This key role in volitional behaviour is shown by the fact that bilateral damage to the ACC results in *akinetic mutism*, a state without voluntary motor activity or speech (Paus, 2001).

*Attention* is a function that may be separated into two different aspects: (1) *spontaneous attention*, elicited by salient stimuli of interest (also known as ‘bottom-up’, where the stimuli is sufficient to catch the attention) and (2) *effortful attention*, volitionally applied based on motivation to accomplish a certain outcome (or ‘top-down’, for example when looking for a certain
The ability to maintain effortful attention seems to be dependent on the ACC, especially in case of divided attention (Loose, Kaufmann, Auer, & Lange, 2003). In fact, it seems likely that the ACC plays a central role in all tasks involving aspects of volitional control and attention, such as suppression of automatic responses, decisions under uncertainty, monitoring of behavioural errors, etc. (see reviews of studies in Botvinick, Cohen, & Carter, 2004; Posner, Rothbart, Sheese, & Tang, 2007; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Sarter, Gehring, & Kozak, 2006). It has been reported that persons with attention deficit hyperactivity disorder (ADHD) tend to have difficulties activating the ACC in demanding situations (Bush et al., 1999). Furthermore, studies have shown that the ACC also is crucially involved in working memory, in a network with the cortex in, and adjacent to, Broca’s area, and maybe other regions (Kaneda & Osaka, 2008; Kondo, Morishita, Osaka, Osaka, Fukuyama, & Shibasaki, 2004; Osaka, Osaka, Kondo, Morishita, Fukuyama, & Shibasaki, 2004).

The ACC receives input related to motivation and drive via multiple pathways, from the limbic system and cortex regions in the lower frontal lobe. Several neuromodulators, like dopamine, influence the ACC, both directly and through projections from the limbic region of the basal ganglia. Strong connections with the prefrontal cortex reflect cognitive functioning. Complex motor behaviours are initiated through the SMA, but the ACC also has more direct motor projections, to the spinal cord and to brain stem nuclei. The more direct motor output from the ACC seems to be responsible for emotional expression, such as laughing and crying (Ackermann, 2008).

### Functional divisions of the ACC and the SMA

The ACC may be divided into three functional regions: the affective, cognitive, and motor ACC (abbreviated affACC, cogACC, motACC; Yücel, Wood, Fornito, Riffkin, Velakoulis, & Pantelis, 2003), from the lower frontal end to the upper posterior end (see Figure 1.1). The core region for the ACC functions discussed above is the cogACC.

The SMA is located at the upper border of the cogACC and motACC. Interestingly, also the SMA follows this division, with an anterior cognitive part, the preSMA, connected with the prefrontal cortex, and a posterior motor part, the SMA proper, with motor functions and direct connections both to the primary motor cortex and to the spinal cord (Johansen-Berg et al., 2004; Picard & Strick, 1996). The activation in cogACC has been shown to extend into the preSMA, for example, in studies of response conflict and error monitoring (Botvinick et al., 2004; Ridderinkhof et al., 2004). It has also been shown that this region (SMA and ACC) responds to speech errors and may detect ‘spoonerisms’ (reversal of sounds) even before they are articulated (Möller, Jansma, Rodriguez-Fornells, & Münte, 2007).
Symptoms and characteristics of cluttering

Trying to understand the symptoms of cluttering from a neurological point of view is not a new endeavour. Miloslav Seeman (1970), phoniatrician of Prague, compared the symptoms of cluttering with other neurological disorders, and proposed that cluttering is the result of a disturbance of the basal ganglia system (see Figure 1.2). Similarly, the neurolinguist Yvan Lebrun of Brussels (1996) argued that traits of cluttering after brain damage or disease typically occur after damage to the basal ganglia system, as in Parkinson’s disease.

Behavioural symptoms and characteristics

Detailed discussion of the symptoms of cluttering can be found in Weiss (1964) and Luchsinger and Arnold (1965), and more recently in Daly (1993), Myers and St. Louis (1996), Preus (1996), Ward (2006), and St. Louis and Schulte (chapter 14 this volume). Though different authors have a somewhat different focus, the overall picture seems quite consistent. Ward (2006) analyzed the speech errors in cluttering based on Levelt’s model of speech and language processing, and found that cluttering affects all levels of this processing: conceptualization, formulation, and articulation. All elements of speech can potentially be affected, from the drive to talk, the sequencing of the message, the selection of words and syntactic elements, the motor output, and the monitoring of speech errors.

Figure 1.2 Basal ganglia loops, in a cross-section of a single hemisphere. The schematic figure shows a motor loop starting and ending in the supplementary motor area (SMA), passing through the putamen (part of the striatum) and the thalamus. The figure also shows the tail of the caudate nucleus (part of the striatum) in cross-section. ACC: anterior cingulate cortex.
Speech motor aspects

The speech motor symptoms are typically characterized by high speech rate, poor articulation with exaggerated blending of adjacent sounds, phoneme sequencing errors (such as *gleen glass* for *green grass*, or *bo gack* for *go back*; Ward, 2006), and reduced prosody (both timing and pitch range). However, in many cases these symptoms are strongly affected by attention, for example so that speech may sound normal, temporarily, when a tape-recorder is turned on (Daly & St. Louis, 1998). Seeman (1970) mentioned a test he used for diagnosis of cluttering: The patient is asked to repeat the syllable ‘tah’ as fast and for as long as possible. According to Seeman, many people with cluttering (PWC) are able to do this well at the beginning of the task, but after a while acceleration begins and the articulation loses precision. Some PWC also show motor deficits that are not limited to speech, such as in handwriting and general motor behaviour. For example, Seeman (1970) reported a tendency among PWC for rushed and unexpected movements, and general motor restlessness, also during sleep, of choreiform type (i.e., similar to movements seen in chorea, a type of motor disorder linked to disinhibition of the basal ganglia). Another aspect is that PWC often tend to have difficulties in recognizing and repeating rhythmic patterns (Weiss, 1964). (On motor speech activity in PWC, see Ward, chapter 3 this volume.)

Linguistic aspects

Most descriptions of cluttering include problems with linguistic processing as one aspect (e.g., Myers, 1992; van Zaalen, Ward, Nederveen, Grolman, Wijnen, & DeJonckere, 2009; Ward, 2006; Weiss, 1964), although this does not fall within St. Louis and Schulte’s current working definition (St. Louis & Schulte, chapter 14 this volume). From a linguistic point of view cluttering tends to be characterized by difficulties with: (1) word finding; (2) planning of sentences and phrases; and (3) syntactic elements. PWC often speak in short phrases of a few words, or ‘bursts’. According to Weiss (1964), this is a reflection of the thought process—that the verbal thoughts of PWC tend to proceed by clusters of two or three words at a time, instead of complete phrases. Repetitions of syllables, words, or phrases are common, as well as fillers like ‘eh’ and ‘um’. These repetitions do not seem to occur because of any motor block, but rather as a result of the difficulties to find words and to create a complete phrase. The word order may be incorrect, and sentences may be left unfinished or continue in a ‘maze-like’ fashion, leaving the listener behind. Retrieval of words, including names, prepositions, and pronouns, may be inexact, so that an incorrect word is chosen based on similarities in sound or semantic content, such as *plant* for *point*, or *fork* for *knife*. Function words may be omitted and the verb conjugation may be incorrect (Ward, 2006).
Attention, temperament, and social interaction

A typical trait observed amongst PWC seems to be reduced attention to sensory input, displayed as poor monitoring of one’s own speech production with limited awareness of cluttered speech, as well as insufficient attention to the listener. The observation that attention to speech often results in temporary normalization indicates that the necessary linguistic and motor functions may be available, but require focused attention.

Regarding personality, Weiss (1964) claimed that PWC are generally of pleasant temperament. Other traits that have been proposed to be frequent among PWC are impulsiveness, impatience, excessive talking, and being short-tempered (Daly, 1993; Weiss, 1964). One way to analyze temperament and motor functions is in terms of inhibition versus disinhibition. From this viewpoint, the traits mentioned above seem to be associated with disinhibition. However, it is important to avoid generalizing a ‘cluttering stereotype’, because PWC do differ in these respects (see also Reichel & Draguns, chapter 16 this volume).

Cluttering is defined as a speech-language disorder, but it seems likely that people who primarily have a mood disorder, such as mania, sometimes have been (mis)diagnosed as cluttering because rapid speech is a frequent symptom of the manic state (Geller et al., 2002). It is therefore possible that the descriptions of temperamental traits associated with cluttering have been biased by inclusion of cases with mania, which often is associated with irritability and being short-tempered (Geller et al., 2002). It is important to distinguish between cluttering, as a speech-language disorder, and rapid and pressured speech resulting from a mood disorder. Yet, it may be possible that cluttering and mood disorders co-occur to some extent. Familial co-occurrence of stuttering and bipolar disorder has been reported by Hays and Field (1989). There is a need for further research to clarify these issues, also regarding differences and overlap between cluttering and ADHD (Geller et al., 2002).

Physiology of cluttering

The tendency towards disinhibition as a temperamental trait also seems to be reflected in neurophysiological findings based on electroencephalography (EEG) research and response to drugs. Research on the neurophysiology of cluttering emerged in Central Europe in the 1950s and 1960s, and though the results of these studies were quite striking, this line of inquiry has not been continued.

EEG

A high percentage of PWC tend to show abnormalities in their EEG recordings. Langova and Moravek (1970) studied the EEGs of 57 PWC, and
classified 50 percent of them as abnormal and 11 percent as atypical. In addition, they noticed relatively low occurrence of alpha waves, suggesting high cortical activation in PWC. The high frequency of abnormalities is in line with other studies, as summarized by Seeman (1970), reporting abnormal EEGs in between 50 and 90 percent of the cases. There is a need for replication with modern techniques, to analyze the anomalies in more detail.

Effect of drugs

Langova and Moravek (1964) also tested the effects of two drugs, one inhibitor and one stimulant. In a group of 13 cases, improvement of speech was reported in 11 cases after treatment with chlorpromazine, a drug that blocks the dopamine receptor type D2 and thereby inhibits the activity of cortex (for a more detailed discussion see Alm, 2004). The stimulant drug (phenmetrazine, which has effects similar to amphetamine, stimulating dopamine) resulted in a worsening effect on speech (details not specified) in all of eight cases. In addition, the subjects complained of internal uneasiness and tension after the stimulant drug. These pharmacological responses are consistent with an elevated level of dopamine in cluttering, as discussed below.

Hyperdopaminergic state in cluttering?

General effects of dopamine

Dopamine is a neurotransmitter with a wide range of complex effects. It is the main factor controlling the flow of signals through the basal ganglia, which in turn modulates the excitatory state of the cortex in the frontal lobe. In short, a high level of dopamine release in the basal ganglia tends to result in a high level of activation of the cortex, with disinhibition of motor behaviour and impulses. Blockade of the dopamine D2 receptors tend to have the opposite effect, with suppression of behavioural impulses and motor activity, as shown in untreated Parkinson’s disease.

Below it will be discussed whether elevated effects of dopamine (a hyperdopaminergic state) might result in the symptoms shown in some cases of cluttering. The discussion will include effects on timing and speed, motivation and attention, and the physical growth of children. EEG anomalies were discussed above, a symptom that may be compatible with the proposal of a hyperdopaminergic state: Because elevated dopaminergic activity would tend to result in disinhibition of cortical regions, one would expect an increased rate of EEG anomalies.

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Dopamine and the control of time and speed

It has been shown that the circuits through the basal ganglia to the frontal cortex have an important role for the perception of time, as well as the timing and speed of motor behaviour (Giros, Jaber, Jones, Wightman, & Caron, 1996; Meck, Penney, & Pouthas, 2008). The effects of these circuits are consistent with the effects of dopaminergic drugs on cluttering, resulting in increased speed with increased dopamine release, and reduced speed with blocking of the D2 receptors (Meck et al., 2008). Two main factors that influence the effect of dopamine in the brain are the amount of dopamine available in the synaptic cleft and the number of receptors for dopamine on the post-synaptic neuron. A high number of receptors can partly compensate for low levels of dopamine. It has been shown, in mice, that overexpression of D2 receptors, or excess release of dopamine (after administration of amphetamine), impairs the ability to estimate time (Drew et al., 2007; Meck et al., 2008). Furthermore, mice in a hyperdopaminergic state show hyperactivity, which is reversed by block of the D2 receptors (Giros et al., 1996).

The hypothesis that the output of the basal ganglia affects the speech rate is supported by earlier work by Guiot, Hertzog, Rondot, and Molina (1961), in which electric stimulation of the ventrolateral (VL) nucleus of the thalamus (see Figure 1.2) resulted in uncontrollable acceleration of speech. The VL nucleus is the link for the output of the basal ganglia motor circuit to the supplementary motor area (SMA). This is in agreement with recent brain imaging results, reporting high activity in the VL nucleus of the thalamus in PWC (van Zaalen et al., 2009). High VL activation can be expected to be associated with disinhibition of the SMA.

The articulation rate is the result of the duration of speech sounds. The exact control of the duration of sounds is essential in order to achieve a normal prosody, with longer duration of vowels with stress and emphasis. In order to produce a long sound, the initiation of the next sound has to be delayed. If this delay is insufficient, the result will be excessive speech rate with lack of temporal prosody.

What determines the timing of the next sound, on a neuronal level? Experiments on manual movements in monkeys have shown that delayed movements are initiated when the firing rate in the cortex and the basal ganglia circuits reach a threshold. Before the initiation, the firing gradually increases in a ramp-like fashion, indicating a timing mechanism (Lebedev, O’Doherty, & Nicolelis, 2008; Lee & Assad, 2003). The threshold mechanism is involved also in externally cued movements, but then the firing increases instantaneously after the cue (Lee & Assad, 2003). This mechanism has been shown for delays of about 2 seconds (Lebedev et al., 2008; Lee & Assad, 2003), but it seems possible that the principle applies also to the shorter delays needed when producing long sounds in speech (in the range of tenths of seconds). If the basal ganglia and the cortex are hyperactivated, it seems
likely that the firing of the relevant circuits may reach the threshold prematurely, so that the delay is shortened or completely abolished. It has been reported that PWC often show a general hastiness of their movements. It is likely that the hastiness of speech and of general movements have the same neural substrate: impaired ability of the SMA proper to maintain a delay before the initiation of the next motor gesture.

What is the source of normal timing—is there ‘a clock’? It has been shown that the basal ganglia circuits play a role in the timing of longer intervals, in the second to minute range, and that the cerebellum is involved in millisecond timing (Ivry & Spencer, 2004). However, Ivry and Spencer concluded that the evidence does not rule out millisecond control also in other parts of the brain, such as the basal ganglia or local cortex regions. Both the basal ganglia and the cerebellum innervate the SMA (Akkal, Dum, & Strick, 2007), but dysfunction of the cerebellum tends to result in symptoms opposite to cluttering, with reduced speech rate and prolongation of short sounds (Ackermann, 2008).

Dopamine and motivation and attention

The exact functions of the dopamine system are still a matter of debate, but there are strong arguments that it has a key role in signalling salient events and rewards (e.g., McClure, Daw, & Montague, 2003; Schultz, 2007). An overactive dopamine system might result in reduced effects of rewards, because of a ceiling effect. For example, hyperdopaminergic mice have been shown to be indifferent to amphetamine and cocaine (Giros et al., 1996), and to have reduced preference for alcohol (Savelieva, Caudle, Findlay, Caron, & Miller, 2002).

It has also been reported that mice with an overactive dopamine system show reduced motivation in operational conditioning tasks (Drew et al., 2007). Weiss (1964) depicted PWC as carefree, careless, lacking in persistence and sense of responsibility, generally with a pleasant temperament, not taking life’s problems very seriously (including cluttering treatment), and showing a short attention span. It seems possible that this constellation of traits could be an effect of a hyperactive dopamine system, so that the motivational effect of rewards, or loss of rewards, is reduced. However, it should be emphasized that this is still speculative, and clinical reports indicate that at least in some cases the speech problems in cluttering are unrelated to motivation (D. Ward, personal communication, September 10, 2009).

Children with ADHD are often treated with low doses of stimulants in order to improve attention, though the exact mechanism of action is not known (Solanto, 2002). The results from the pharmacological trials of Langova and Moravek (1964) suggest that PWC show the opposite response to dopaminergic drugs compared with typical cases of ADHD. It is possible that the attention deficits in cluttering and typical ADHD are related to
different types of dysregulation, though affecting the same attention system. It may be argued that PWC with attention problems constitute a subgroup of ADHD.

**Dopamine in relation to weight and appetite**

It has been reported that many children with cluttering tend to be small for their age, and physically immature (Daly, 1993; Weiss, 1964). This may appear to be an odd observation, but could actually make sense within the framework of a hyperdopaminergic state. Reduced growth is a side effect of treatment with dopamine stimulants for childhood ADHD, though final adult stature may not be affected (Faraone, Biederman, Morley, & Spencer, 2008). Dopamine stimulants have been used for weight reduction, by reducing appetite; conversely, weight gain is a frequent side effect of treatment with D2-blockers. It has been shown that peripheral injections of dopamine in human newborns have a strong acute effect in reducing growth hormone secretion (De Zegher, Van Den Berghe, Devlieger, Eggermont, & Velduis, 1993). However, it is not clear whether growth hormone is affected during long-term treatment with stimulants. Another potential mechanism might be elevated metabolism, involving a slight elevation of body temperature, because hyperthermia can be an effect of stimulants (Meredith, Jaffe, Ang-Lee, & Saxon, 2005). In summary, based on observed pharmacological effects, it seems possible that also endogenous hyperdopaminergic states may result in delayed growth.

**Summary: hyperdopaminergic state**

The hypothesis of a hyperdopaminergic state in PWC may account for a large part of the reported characteristics associated with PWC: (1) the effects of drugs; (2) EEG anomalies; (3) delayed growth; (4) excessive speech rate; (5) short attention span; (6) poor awareness of speech errors; (7) temperamental traits characterized by disinhibition, impulsivity, and a relatively carefree attitude.

A functional hyperdopaminergic state might be caused by several different mechanisms, for example: (1) excessive synaptic release of dopamine; (2) deficient dopamine reuptake from the synaptic cleft; or (3) overexpression of D2 receptors. It is also possible that dysregulation of the dopamine system can be secondary to anomalies in other transmitter systems (Koprich, Johnston, Huot, Fox, & Brotchie, 2009). The indications for hereditary factors in some cases of cluttering calls for genetic investigations, especially focusing genes known to be linked to the dopamine system. A recent finding that may be relevant was published by Lan et al. (2009). They reported that different versions (alleles) of the gene for the D2 receptor increased or reduced the risk for stuttering in a Chinese population. Because of the high reported co-occurrence of stuttering and cluttering (Daly, 1996), it may be
possible that this gene is related to traits of cluttering. There seems to be no recent pharmacological trials of treatment of cluttering. However, trials investigating the effects of D2-blockers (including more novel drugs in this family, such as Abilify), as well as low-dose stimulants, would be valuable. Nevertheless, it is important to emphasize that the hypothesis of a hyperdopaminergic state is unlikely to represent a general explanation of cluttering.

**Initiation and sequencing of action: The medial frontal cortex**

**Initiation of action (and speech)**

Research consistently indicates a central role of the medial frontal cortex in the initiation of volitional action. As mentioned above, bilateral lesions of the ACC result in akinetic mutism, in which voluntary initiatives to speech or motor activity are absent (Paus, 2001). Also, persons with unilateral lesions often show lack of ideas and initiative (Ferstl & von Cramon, 2002). In fact, based on research data, it has been proposed that non-automatic cognitive processes are initiated and maintained by the medial frontal cortex (Ferstl & von Cramon, 2002).

**The dual premotor hypothesis**

In the 1980s, Goldberg (1985) and Passingham (1987) proposed that the frontal lobe has two parallel premotor networks, involved in speech and other movements. The medial network, with the ACC/SMA, was suggested to be specialized on volitional execution of well-learnt sequences, without sensory input. The lateral network, with the lateral premotor cortex, was assumed to control actions based on external information. MacNeilage (1998) included this hypothesis in his theory of the evolution of speech, and Snyder (2004), Snyder, Hough, Blanchet, Ivy, and Waddell (2009) and Alm (2005) have discussed this model in relation to stuttering. In 2007, Alm also suggested that the dual premotor model may account for some of the symptoms of cluttering (Alm, 2010).

The proposal by Goldberg and Passingham has been the focus of some empirical studies, with mixed support. The overall pattern emerging from brain imaging studies seems to be that both lateral and medial regions contribute in both externally and internally controlled tasks, with complex interaction (Crosson et al., 2001; Longe, Senior, & Rippon, 2009; Paus, Petrides, Evans, & Meyer, 1993; Tremblay & Gracco, 2006). The recent study by Longe et al. indicated that the cogACC has a direct top-down influence on the lateral prefrontal cortex. Furthermore, it has been shown in monkeys that the medial frontal cortex, including the ACC, have bidirectional
connections with temporal auditory areas (Barbas, Ghashghaei, Dombrowski, & Rempel-Clower, 1999), indicating that the medial system actually has direct access to auditory information during speech.

In summary, Goldberg’s hypothesis outlined the medial and lateral cortex as two relatively parallel systems, while the current data seem to implicate a more hierarchic relation, with a functionally subordinate lateral system. This will be discussed in more detail later in this chapter.

**Sequencing and articulation**

In the production of speech the brain has to solve several problems. One main problem is sequencing. An idea can be nonsequential, like an image. In contrast, speech always consists of a linear sequence, on many levels—a sequence of phrases, words, syllables, and sounds. In a very brief and rough summary, based on Levelt’s (1999) model, the sequencing of an idea may proceed in the following way: The semantic representation of the idea results in a grammatical frame, providing a sequential overall structure for the utterance. The intended words and the correct grammatical elements are selected and inserted in the grammatical frame. The phonological code, ‘the sound’, is activated and is structured into syllables (which may pass word boundaries), and the appropriate prosodic pattern is applied. Syllables may be described as ‘chunks’ of sounds, constituting one opening-and-closing-cycle for the mouth. The role of the syllable in the planning of speech is shown by the observation that when sounds are exchanged between syllables, like *mell wade* for *well made*, the sound almost always move to the same position within the syllable (MacNeilage, 1998).

From this brief outline, it seems clear that the sequencing process must occur simultaneously on many levels, and that the planned sequence has to be temporarily stored in some way, while the segments are articulated in serial order. An example of how the SMA plans movements in advance may be seen in a study by Gerloff, Corwell, Chen, Hallet, and Cohen (1997), in which transcranial magnetic stimulation (TMS) was used to interrupt a well-learnt sequence of complex finger movements in healthy adults. It was found that disturbing the SMA using TMS interrupted the sequence with about 1 second delay.

The preparatory planning of action is also shown by the readiness potential (RP, ‘Bereitschaftspotential’, Shibasaki & Hallet, 2006). The RP is an electric potential preceding volitional movements, and the timing of the potential in various regions shows the order of regional involvement. The early phase of the RP originates bilaterally in the preSMA and the SMA proper, up to 2 seconds before the movement. Shortly thereafter, it spreads to the lateral premotor cortex, also bilaterally. About 0.4 seconds before the movement, the late phase begins, with activation of the contralateral primary motor and premotor cortices (Shibasaki & Hallet, 2006). The same sequence seems to
apply for self-initiated speech (Deecke, Kornhuber, Lang, Lang, & Schreiber, 1985).

In a brain imaging study of word production, Alario, Chainay, Lehericy, and Cohen (2006) found that long and unfamiliar utterances activated the posterior part of the preSMA, bilaterally, indicating sequential encoding in this zone, possibly phonological sequence encoding. Articulation activated the SMA proper, but extended into the posterior preSMA (together with bilateral mouth area of the primary cortices).

In summary, the studies with different methods indicate that there is an anterior–posterior gradient within the SMA, bilaterally, with higher level planning and sequencing in the anterior preSMA, sequencing of sounds and syllables in the posterior preSMA, and sequencing of articulation in the SMA proper and the border of preSMA.

Selection of linguistic items: The preSMA

Selection of words

Neurolinguistic theories, for example Levelt (1999), typically describe the linguistic cortex regions as networks of associations, based on semantics, phonology, and so forth. A semantic concept will activate a part of the ‘mental lexicon’, with many competing words becoming more or less active. When speaking it is essential that one and only one word is selected—this is the problem of word selection. In cluttering, there is an increased risk that a competing but erroneous word is selected.

Brain imaging studies of word selection repeatedly indicate involvement of the left preSMA. This has been shown in word selection based on semantic category as well as initial sounds and rhyming (Crosson et al., 2003; De Carli et al., 2007), and both for nouns and verbs (Warburton et al., 1996). Alario et al. (2006) reported that activation from word selection was limited to the anterior half of the preSMA. Tremblay and Gracco (2010) recently proposed that the preSMA is at the core of a network for volitional selection. Activation extending into the ACC has been reported by Warburton et al. (1996) and by Carreiras, Mechelli, and Price (2006) for low frequency words. It seems possible that accessing such lesser known words would require a higher level of attention, thereby also recruiting the ACC.

Selection of grammatical forms

A role for the preSMA in selection has also been shown for grammatical aspects. In a brain imaging study, Sahin, Pinker, and Halgren (2006) investigated processing related to silent inflection of nouns and verbs, with both regular and irregular forms. In the lateral cortex, the main region was Broca’s area, but in the medial cortex, the preSMA and the cogACC also showed
involvement. The published images showed higher activation of the cogACC and the preSMA for silent inflection compared with silent reading, and higher activation for irregular verbs compared with regular verbs.

Selection by the basal ganglia?

It is of interest that this type of processing, in which ‘the winner takes all’, has been described as one of the main functions of the basal ganglia circuits. This principle is presented in Mink (1996), and more recent theoretical accounts and summaries can be found in Gazzaniga, Ivry, and Mangun (2009, pp. 301–302), Leblois et al. (2006), and Houk (2005).

As outlined in Figure 1.2, the basal ganglia can be seen as the main component in a multitude of parallel loops starting and ending in the cerebral cortex. The main cortical input to the loops comes from the same area in which they end, forming closed loops that modify the activity in the target cortical regions. Even though the closed loop seems to be the main principle of these circuits, there also appear to be some integration of inputs from other regions. It is primarily the frontal lobe cortex that is modulated by the basal ganglia, but basal ganglia output has also been found in the temporal lobe (Middleton & Strick, 1996).

It is assumed that the basal ganglia loop highlights the most coherent and consistent activity pattern of the cortex, while rival impulses are inhibited. This is accomplished by the intricate anatomy of the basal ganglia circuits, in which the output activates two competing and intermingled pathways. The direct pathway provides focused activation of the strongest pattern in the target cortical region (e.g., the word that is the most strongly activated, and which is in coherence with the activity of other relevant cortex regions). In contrast, the parallel pathways provide a more diffuse and widespread inhibition of the cortex, thereby suppressing the competing impulses. This can be described as a noise filter or a contrast mechanism, allowing the organism to focus on the most important impulse.

Traditionally, the basal ganglia were assumed to only serve motor functions, but it has now become apparent that these structures also are involved in cognitive functions and the processing of language (Booth, Wood, Lu, Houk, & Bitan, 2007; Grahn, Parkinson, & Owen, 2008; Middleton & Strick, 2000; Teichmann et al., 2008). In short, the different regions of the basal ganglia serve the same functions as their cortical targets, with cognitive functions primarily related to the caudate nucleus, sensorimotor functions to the putamen, and affective/motivational functions related to the ventral striatum. In line with this model, Crosson et al. (2003) found that selection of words activated a loop consisting of the left preSMA and the left caudate nucleus of the basal ganglia.

Houk (2005) presented a comprehensive model of how the basal ganglia and the cerebellum may interact with the cerebral cortex, to select and shape cortical activity. According to this view, the same basic principles are involved.
in the selection and shaping of motor actions as in the selection and shaping of thoughts.

In summary, the basal ganglia circuits are proposed to have the ability to highlight and select cortical activation that is congruent with activation in other parts of the cortex, and to suppress competing activity. This mechanism appears to be ideally suited to support the cortex in making the most appropriate word choice based on a network of semantic associations, or to select the correct preposition or pronoun in a certain context. Dysregulation of the basal ganglia circuits might compromise this function, making the selection less precise. If the cortex in the preSMA is hyperactive, an increased number of words may be passed on to the SMA proper for articulation, including an increased number of selection errors.

An ‘executive hub’ for speech production

In 1974 Baddeley proposed his classical model of the working memory, with a ‘central executive’ and ‘slave systems’ (or subordinate systems) such as the phonological loop and the visuo-spatial sketchpad (Baddeley, 2003). Kaneda and Osaka (2008) argued that the ACC is the main component of the central executive, and that semantic coding in the verbal working memory depends on the ACC.4

The studies reviewed above repeatedly point towards a central role of the cogACC, together with the preSMA, for: attention, verbal working memory, initiation of action, control of response conflicts, error monitoring, sequencing of speech, and selection of linguistic items. The model that emerges is that the cogACC and the preSMA constitute an ‘executive hub’ for cognitive processes and planning of actions. In spontaneous speech, this hub may be viewed as an ‘assembly centre’, in which all the components of the utterance (retrieved from the lateral cortex regions) are put together in a sequence.

The construction of an utterance requires: (1) the selection of an overall grammatical frame for the utterance, indicating the order of the semantic components; (2) selection of words; (3) selection of grammatical word forms. In all of these processes it is essential that only one alternative is selected, from many competing possibilities. If the cogACC/preSMA region is specialized in selection among competing alternatives, it seems reasonable that this zone actually constitutes a hub for the complete process of spontaneous speech (see schematic outline in Figure 1.3). Within this region there is a gradient from higher to lower level of control—from overall control in the cogACC, to sequential assembly of the utterance in the preSMA, and control of the motor execution in the SMA proper.5
Lesions resulting in release of subordinate systems

This model of an ‘executive hub’ in the cogACC/SMA region is supported by symptoms observed after unilateral lesions in the ACC/SMA region (Goldberg, 1992; Jonas, 1981; Suzuki, Itoh, Hayashi, Kouno, & Takeda, 2009). The symptoms are characterized by impaired ability to volitionally initiate an activity, but this function may be involuntarily triggered by external cues. There are reports of this phenomenon in speech (echolalia), reading (hyperlexia), and hand movements (‘the alien hand sign’—when one hand is grasping objects and makes purposeful movements that are not volitionally controlled). The common mechanism is that a subordinate system becomes disinhibited after the lesion of the ACC/SMA. It can also be described in terms of rivalry between top-down and bottom-up processes, here resulting in release of the latter (Suzuki et al., 2009).

Suzuki et al. (2009) described a woman who had suffered infarction of the left ACC. Involuntary speech was triggered by written words and by words emanating from unrelated conversations, resulting in repetition. Her right hand showed compulsive manipulation of tools. The woman tried to prevent this by holding the right arm with the left arm.
Monitoring of speech errors

One aspect of cluttering, discussed above, is a tendency to not notice and not correct errors in word selection, speech sounds, or speech rate. Several studies have shown that the cogACC exerts high-level control of errors in the intended outcome of actions (Botvinick et al., 2004; Ridderinkhof et al., 2004). Furthermore, as noted earlier, a study of event-related brain potentials in a task that elicited reversal of sounds ('spoonerisms') showed that the ACC/SMA region responded to these errors even before they were articulated.

Production of speech can be characterized by a series of conversions from higher to lower levels: semantics → words → phonological sequence → motor commands → sound. In principle, higher levels have the information to detect errors in the conversion to a lower level. The level of semantics can detect if an incorrect word has been selected. Likewise, the level that is planning the phonological sequence can detect if a sound is misarticulated. The detection of errors may occur before the sound is produced, called covert repair (Postma & Kolk, 1993), based on internal feedback within the brain. Alternatively, errors can be detected from the auditory feedback of the speech sounds.

It is here suggested that the centre of this monitoring is the cogACC/SMA. The functions and connections of this region are ideally suited for this task. If this region constitutes an ‘executive hub’, all plans for the intended outcome are available here. It has been shown in monkeys that the auditory areas have bidirectional connections with the medial frontal cortex, including the ACC (Barbas et al., 1999). There is little information about these connections in humans, but considering the primary role of spoken language in human evolution, it seems probable that the auditory connections to the frontal lobe have been strengthened rather than weakened. This suggests that auditory feedback is available to the cogACC/SMA.

Weiss (1964, p. 44) wrote that the attention of PWC often is so brief that they may give the impression that hearing is impaired, or that they have a basic disorder in perception. It is important to investigate the underlying mechanisms in more detail, in particular, to determine whether the issue is with attention, or possibly with impaired auditory connections to the medial frontal cortex in some cases. Another hypothetical mechanism is that PWC may have a general problem withholding the next segment (such as sounds, syllables, and words) in a sequence, releasing it prematurely. As discussed above, there are experimental findings indicating that segments in a sequence are initiated when the firing of relevant circuits reach a threshold (Lee & Assad, 2003; Lebedev et al., 2008). If the ACC/SMA region is hyperactivated, the ability to withhold the next segment may be reduced, because the baseline firing rate is close to the threshold for release. In other words, the execution of speech may be ‘running away’, with impaired volitional control and poor brakes.
It is very important to emphasize that the proposed models are hypotheses, and that their validity must be tested empirically. Hopefully detailed hypotheses will facilitate experimental research.

**Summary**

*A hypothesis of cluttering*

When reviewing research on the ACC and the SMA, it is striking how well the functions associated with these regions correspond to the various aspects of ‘the cluttering syndrome’. The following is a summary of functions associated with the ACC/SMA:

1. Drive, motivation, and initiation of action.
2. Inhibition of impulses.
3. Attention; monitoring and correction of behaviour.
4. Planning of sequential behaviour.
5. Selection of words and word-forms.
6. Execution and timing of sequential behaviour.

This indicates that dysregulation of the ACC/SMA may account for the full range of symptoms of cluttering. In cases with more limited symptoms, the affected area may be smaller. For example, if the symptoms are limited to speech rate and articulation, without language errors or problems of attention, this would suggest involvement of the SMA proper.

Dysregulation of these cortical regions may be a secondary effect of dysregulation of the basal ganglia circuits, possibly resulting from genetic factors. The indication of genetic heritage in many cases of cluttering implies that cluttering is not typically associated with lesions. The symptoms, the pharmacological effects, and the EEG anomalies may be consistent with hyperactivation of the dopamine system, but this does certainly not exclude other possibilities.

A hypothetical mechanism that may account for the high speech rate is that segments in the speech sequence are initiated when the firing rate of relevant circuits reach a threshold. If the SMA is disinhibited and hyperactive, this threshold may be reached prematurely, resulting in ‘runaway speech’.

**Implications for treatment?**

*Medical treatment*

Today there is no medical treatment that can be recommended. There is a need for continued research, including trials of dopaminergic drugs, genetic studies, and studies of EEG.
Behavioural and cognitive treatment

This subject is discussed in detail in other chapters of this book. From a neurological point of view, the importance of detailed assessment can be emphasized. Because PWC differ in their profile of impairments and strengths, it may be essential to prepare an individual plan for treatment. Central aspects include awareness, motivation, attention, and the ability to control speech volitionally.

Another possibility for behavioural treatment may be technical aids, similar to hearing aids. The results from studies using delayed auditory feedback (DAF) in cluttering appear to be mixed (Langova & Moravek, 1964; Ward, 2006), with a need for further studies. Another possibility is to amplify the normal auditory feedback, in order to raise attention to the speech outcome. The sound level may be a crucial factor in experiments with auditory feedback in cluttering. With future signal-processing capabilities, it may be possible to design a hearing-aid-type of device that measures the syllable rate and provide reminders to slow down (similar to an analogue device called the Hector Speech Aid in the 1970s; D. Ward, personal communication, September 10, 2009).

Difficulties in achieving a stable improvement may lead to the question of acceptance. Some neurological problems are very resistant to change. Therefore an important clinical task is to individually balance efforts to change versus acceptance.

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Notes

1 A syndrome can be defined as a group of symptoms that collectively indicate or characterize a disease, psychological disorder, or other abnormal condition. From Greek, syn-drom, ‘running together’.

2 Based on this description of traits linked to cluttering, one might assume that cluttering also affects general intelligence, but this does not seem to be the case. On the contrary, in the literature individuals with cluttering surprisingly often are described as showing very high intelligence, with an aptitude for mathematics and science. For example, Daly (1993) wrote that based on observations, people with cluttering (PWC) are usually average or above average in intelligence, and many PWCs he worked with were exceptionally bright. It is possible these reports are influenced by selection from a university environment, but in any case, it seems that intelligence typically is not an issue in cluttering.

3 The indirect pathway in the basal ganglia has been assumed to provide the main inhibition of the frontal cortex. However, it has been suggested that a hyperdirect
pathway is more important in this role (Leblois, Boraud, Meissner, Bergman, & Hansel, 2006).

4 The verbal working memory may be viewed as a buffer for planned speech, in which the idea for an utterance is stored in preliminary form. Weiss (1964) claimed that the verbal thoughts of PWC tend to proceed by clusters of two or three words. If this is correct, it seems possible that limitation of the verbal working memory is a main underlying factor.

5 An important source of information has been overlooked in this review, but should be mentioned: the classic book Speech and brain-mechanisms by the neurosurgeons Wilder Penfield and Lamar Roberts, from 1959. They summarized systematic observations of the effects of electric stimulation of the brain in awake subjects during brain surgery, and the effects on speech of surgical removal of parts of the brain. They describe the existence of a third cortical speech centre (‘the superior speech cortex’), located in the SMA and extending into the adjacent primary sensorimotor cortex. Removal of this region in the dominant hemisphere resulted in transient aphasia which, however, cleared up completely within a few weeks (Penfield & Roberts, 1959). This observation indicates that the medial cortex is necessary for speech production, but also that no essential linguistic information is stored here—the functions of the left SMA is soon compensated by the right SMA. This is consistent with the model proposed in this chapter: The primary linguistic networks are located in the lateral cortex, while the SMA has a main role in the sequencing of information retrieved from the lateral regions.

6 In Swedish, cluttering is called ‘skenande tal’, which might be translated as ‘runaway speech’.

7 Magnetoencephalography (MEG) may be an especially interesting method for the study of the medial wall cortex, because MEG is sensitive to the cortex perpendicular to the skull.

8 If a throat microphone is used, the sounds from surrounding voices and noise are attenuated, which is important if using high amplification. For telephone calls it may be easy to amplify the signal from the telephone microphone to the earpiece.

References


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