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Brain Lesion and fMRI Studies and the Myth of Cognitive Function Localization (Revised)

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The implications of brain lesion studies

There have been two basic assumptions long held in the traditional view of cognitive processing in the human brain: firstly, cognitive processes are exclusively functions of the cerebral cortex, and secondly, the cerebral cortex is divided into discrete areas of cognitive function. However, many observations and studies have incontrovertibly demonstrated that 1) so-called "cognitive processes" are not limited to specific areas of the brain nor reside exclusively within the cerebral cortex, but that many different areas of the brain contribute to cognitive functions, and that 2) cognitive functions in themselves are diffuse phenomena. To illustrate both points, a most obvious fact that contradicts the notion that specific "centers" of the brain, or specific regions of the brain are (either wholly or principally) responsible for specific so-called "cognitive functions," is that acquired cognitive deficits attributed to an insult [i.e., a lesion resulting from a cerebrovascular accident (CVA), a tumor, a neurodegenerative process or an impact injury] to a particular area of the brain does not necessarily correspond to the area proposed as the "center" for the cognitive function affected.

Taking acalculia as an example, it has been considered that acalculia (an acquired fundamental deficiency in the execution of tasks of elementary numeration and/or arithmetic calculation) is caused by an insult to the parietal lobe, particularly to the intraparietal sulcus as the intraparietal sulcus has been proposed to be the brain's center for numeracy and quantification (Cipolotti, Butterworth and Denes 1991; Takayama, Sugishita, Akiguchi and Kimura 1994; Dehaene and Cohen 1995; Delazar and Benke 1997; Cappelletti, Barth, Fregni, et al. 2007; Ashkenazi, Henik, Ifergane and Shelef 2008); although it has also been suggested that the angular gyrus of the inferior parietal lobule is a functional area vital for arithmetic calculation and numerical processing (Henschen 1919; Gerstmann 1940; Dahaene, Spelke and Pinel, et al. 1999; Cattaneo, Silvanto, Pascual-Leone and Battelli 2009; Grabner, Ansari, Koschutnig, et al. 2013; Roux, Boetto, Sacko, Chollet and Trémoulet 2003; Grabner, Ansari, Koschutnig, Reishofer, et al. 2009; Göbel, Walsh and Rushworth 2001; to cite a few of the relevant studies) and consequently, acalculia would be expected to result from insult to the angular gyrus (predominantly that of the left hemisphere – the left hemisphere being the dominant hemisphere in 95% of right-handed people and 60-70% of left-handed people).

However, a significant number of cases of acalculia have been documented in which, instead of insult to either the intraparietal sulcus or to the inferior parietal lobule, the cause has been traced to a lesion or lesions in other areas of the brain, for example, the left subcortical area (Corbett, McCusker and Davidson 1986; Hittmair-Delazer, Semenza and Denes 1994; Whitaker, Habiger and Ivers 1985), the left medial frontal area (Lucchelli and De Renzi 1993), the left and right frontal areas (Fasotti, Eling and Bremer 1992; Luria 1966), the right posterior area of the brain (Hécaen, Angelergues and Houiller 1961), and the left ventral temporo-occipital area of the brain (Cohen and Dehaene 1995).

Other reports have traced the cause of impaired elementary numeracy and arithmetical calculation to damage of either the left or right hemisphere in various sites in the brain, ranging from the frontal, temporal and temporoparietal areas, to the parietal area (for example: McCloskey, Aliminosa and Sokol 1991; McCloskey, Caramazza and Basili 1985; McCloskey, Sokol and Goodman 1986; Sokol and McCloskey 1988). It has even been demonstrated in a patient undergoing a therapeutic stereotaxic thalamotomy that direct stimulation of the ventrolateral thalamus has an immediate effect on numeracy and arithmetic calculation, whereby stimulation of the left ventrolateral thalamus resulted in an acceleration in counting with a corresponding increase in calculation errors while stimulation of the right ventrolateral thalamus resulted in a deceleration in counting with a constant and significant degree of calculation errors (Ojemann 1974), indicating that disturbances in the subcortical area of the brain can directly affect numerical processing. In the case of acalculia resulting from a subcortical insult reported by Whitaker, Habiger and Ivers (1985), the patient suffered a left subcortical infarct implicating much of the dorsal striatum of the basal ganglia, including the caudate nucleus, the putamen and the anterior limb of the internal capsule, in addition to implicating the periventricular white matter.

The essential problem when attempting to localize any cognitive function to a specific area of the brain is the significant and overwhelming complication presented by two major issues. The first issue is that, for example, in tracing the cause of acalculia to an insult in a general region of the brain, such as the left parietal lobe, and extrapolating from that that the identified area implicates the intraparietal sulcus or the angular gyrus as a "center" of numeracy and arithmetic calculation actually begs far more questions than it answers, especially when it is clearly, irrefutably demonstrated that insults to entirely different areas of the brain have been traced as the cause of presentations of acalculia. It could of course be argued that such insults to these other parts of the brain that do not implicate the "center" of the cognitive function of numeracy/arithmetic calculation, as proposed as either the intraparietal sulcus or the angular gyrus, but instead result in disruptions of the pathways to and from such a proposed functional "center," and that in disrupting the flow of information to and from the "center," impede the cognitive process.

However, it could just as plausibly be argued that even though the majority of presentations of acalculia for example, are traced to insults of the left parietal lobe (the left hemisphere simply an indication that it is an insult to the presumably dominant hemisphere that is most likely to result in the presentation of the disorder), the fact that insults to other parts of the brain have resulted in presentations of the disorder indicate that *those areas* are integral to numeracy and arithmetic calculation rather than the intraparietal sulcus or the angular gyrus, the latter areas simply serving as points of interconnections where critical neuronal circuits intersect, whereby an insult to those areas could result in the interruption of the transmission of signals to and from many different parts of the brain, including those areas other than the left parietal lobe, such as the frontal lobe or the subcortical area, where insults have resulted in presentations of acalculia. Without further consideration, the latter argument is no less valid than the argument for the intraparietal sulcus or the angular gyrus as the "center" for numeracy and arithmetic calculation, and, in fact, because *both* the intraparietal sulcus and the angular gyrus have been proposed as vital functional areas for numeracy and arithmetic calculation, the notion of any single discrete "center" for elementary mathematical processing is a non sequitur.

In perhaps the most comprehensive study of acalculia and dyscalculia (the latter a disorder in the *development* (as opposed to acute onset) of the fundamental cognitive facility for numeracy and arithmetic calculation), Ardila and Rosselli (2002) concluded that while damage to the left angular gyrus has been noted to cause disturbance of elementary computational ability such as that presented in primary acalculia or anarithmetia (*anarithmetia* defined as a specific *acquired* deficit in elementary numeracy and arithmetic calculation as opposed to a presented disability as a manifestation of secondary causes such as agraphia, aphasia, alexia, visuospatial disturbance, etc.), various cognitive functions are involved in numerical processing, and arithmetic calculation is, in itself, composed of a number of different, integrated cognitive processes, therefore, we must expect damage to various areas of the brain as the cause of a number of cases of acalculia with different types and severity of deficits in elementary numeracy and arithmetic calculation.

It is clear that a number of different conditions are contributory factors in the presentation of acalculia, for example the size of the area of tissue damage, the severity of damage and the linkage between the observed presentation of acalculia and the potential for deficits in the interconnection of various cognitive subprocesses. Even in anarithmetia (also known as primary acalculia), it is exceedingly rare not to find deficits in contributing areas of cognitive functioning. In terms of localization, though Ardila and Rosselli (2002) acknowledge that anarithmetia is observed in cases of left angular gyrus damage, and that this localization for primary acalculia has been widely accepted, they nevertheless argue that "it is uncommon to find cases of pure anarithmetia caused by focal lesions in the brain" (Ardila and Rosselli 2002, p. 201). They further state that, "It is not easy to find cases of primary acalculia without additional aphasic, alexic, and agraphic defects. As a matter of fact, few cases of pure anarithmetia have been described to date. Some authors have even challenged the existence of a primary acalculia not associated with other cognitive deficits (e.g., Collington et al., 1977; Goldstein, 1948)" (Ardila and Rosselli 2002, p. 201).

The preponderance of acalculia associated with other principal cognitive deficits has been to such extent that acalculia is classified into a number of different types in accordance with the principal cognitive deficit with which it is attributed to or associated. The classification of aphasic acalculia considers that the presented deficits in the execution of tasks of elementary arithmetic calculation may well originate with the general linguistic and verbal processing deficits that occur in aphasia (Grafman, Passafiume, Faglione and Boller 1982; Delazer, Girelli, Semenza and Denes 1999; and Benson and Ardila 1996). The association of aphasia (an *acquired* disturbance of the comprehension and formulation of language presenting deficits in any or all forms of language usage, including reading, writing, speaking and listening) with acalculia has been so extensive that aphasic acalculia has been further divided into the subcategories of 1) acalculia in *Broca's aphasia* (Broca's aphasia also known as agrammatic aphasia, expressive aphasia or nonfluent aphasia), 2) acalculia in *Wernicke's aphasia* (Wernicke's aphasia also known as receptive aphasia, fluent aphasia, jargon aphasia, sensory aphasia or semantic aphasia) and 3) acalculia in *conduction aphasia* [conduction aphasia also known as associative aphasia and afferent (apraxic) motor aphasia].

Broca's area (Brodmann areas 44, and 45, the pars opercularis, and the pars triangularis, respectively), located in the inferior frontal gyrus, has been proposed to be a primary center for language production, more recently been proposed to play a major role in language comprehension as well, and has been suggested as involved in various cognitive and perceptual tasks, the pars opercularis in particular suggested as playing a role in motor-related processes. Because Broca's aphasia presents as difficulty in producing coherent, syntactical

spoken or written language even though word comprehension remains intact, the condition is assumed to be linked to tissue damage in the Broca's area region of the brain, though Broca's aphasia has been observed in patients with a lesion in other regions of the brain with no damage to Broca's area.

In a study by Dahmen, Hartje, Bussing and Sturm (1982), an analysis of milder calculation defects found in Broca's aphasia revealed that linguistic alterations impaired the syntax of calculation, corresponding to the research by Delazer, Girelli, Semenza and Denes (1999) that determined that the "use of morphology and syntax represents one of the central impairments in patients with Broca's aphasia" (Ardila and Rosselli 2002, p. 203) and that Broca's aphasia, at least partially, could be interpreted as, "a disorder in language sequencing" (Ardila and Rosselli 2002, p. 203) by which numerical sequencing is altered in calculation tasks, thus, in acalculia in Broca's aphasia, mental and written calculations are seen as significantly affected by deficits in linguistic processing, primarily related to syntax and sequencing.

Wernicke's area has been traditionally located by some researchers in the posterior section of the superior temporal gyrus (STG) corresponding to the posterior part of Brodmann area 22. However, in the literature, there is considerable disagreement as to the precise location that represents Wernicke's area, as other than the posterior part of Brodmann area 22, it is often located in the anterior portion of Brodmann area 22 in the unimodal auditory association cortex in the STG anterior to the primary auditory cortex, and it is also considered by others to include Brodmann areas 39 and 40 in the parietal lobe, area 39 corresponding to the angular gyrus, and area 40 containing the supramarginal gyrus (the inferior portion of Brodmann area 40). The unimodal auditory association cortex has been considered as implicated in auditory word recognition.

Though damage to the angular gyrus has been considered to play a role in Wernicke's aphasia, the supramarginal gyrus has been considered involved in the cognitive processes in the representation of meaning and phonetics in the function of reading. Since the late 19th century, Wernicke's area along with Broca's area have been considered interlinked centers for the understanding of spoken and written language, while modern thinking considers that the functions that have been attributed to Wernicke's area seem more broadly diffused in the temporal lobe and may also be controlled by Broca's area:

> There are some suggestions that middle and inferior temporal gyri and basal temporal cortex reflect lexical processing . . . there is consensus that the STG from rostal to caudal fields and the STS [superior temporal sulcus] constitute the neural tissue in which many of the critical computations for speech recognition are executed . . . aspects of Broca's area (Brodmann areas 44 and 45) are also regularly implicated in speech processing. . . the range of areas implicated in speech processing go well beyond the classical language areas typically mentioned for speech; the vast majority of textbooks still state that this aspect of perception and language processing occurs in Wernicke's area (the posterior third of the STG). (Poeppel, Idsardi, and van Wassenhove 2008)

In 1874 the neurologist and psychiatrist Carl Wernicke reported that, from his discovery of a lesion in a patient that presented a particular form of aphasia, the left posterior section of the STG appeared responsible for the association of the syllabic or phonetic representation of words with the corresponding semantic representation (*Der aphasische Symptomencomplex: eine psychologische Studie auf anatomischer Basis*). Based on Wernicke's findings, the condition in which speech retains a natural sounding rhythm and inflection with an imposed syntactical structure, but is constructed of unrecognizable or meaningless words or

associations of words, became known as Wernicke's aphasia. The modern clinical presentation of Wernicke's aphasia is defined by the presence of the following conditions: 1) difficulties of language comprehension (in speaking, listening and reading), 2) fluent (natural sounding rhythm and inflection with an imposed syntactical structure) and usually excessively voluble but meaningless speech (containing neologisms and paraphasias devoid of meaningful content, with the omission of key words, and the substitution of words, verb tenses, pronouns and prepositions), and 3) difficulties of repetition (deficiency in the ability to repeat what one says and what one hears).

Though Wernicke's aphasia has been traditionally associated with damage to Wernicke's area, it has more recently been proposed that the condition is a result of damage to the medial temporal lobe and underlying white matter and does not really involve Wernicke's area (Kolb and Whishaw 2003, pp. 505-6). Also, though previously thought to connect Wernicke's area and Broca's area, and therefore involved in the interconnection between Wernicke's area and Broca's area in acquired speech or language disorders, new research proposes that the arcuate fasciculus connects what is considered the posterior receptive area for analysis and identification of linguistic sensory stimuli (consisting predominantly of Wernicke's area) with the premotor and primary motor areas (consisting of the greater part of Brodmann areas 6 and 4, respectively), and not to Broca's area (Bernal and Ardila 2009). Rather, it is considered that Broca's area is connected to the anterior superior temporal regions by the uncinate fasciculus, consistent with what is regarded as the sites involved in word recognition (Saur, Kreher and Schnell et al. 2008).

Since Wernicke's aphasia is primarily presented as difficulty in language comprehension largely consisting of semantic and lexical errors, it would stand to reason that individuals with acalculia in Wernicke's aphasia would have problems in saying, reading and writing numbers as semantic and lexical representations, dramatically affecting performance in numeracy and fundamental arithmetic calculation. Luria (1973) proposed that calculation errors by individuals with acoustic amnesic aphasia (a subtype of Wernicke's aphasia according to Luria) are due to defects in verbal memory, while Benson and Denckla (1969) reported that verbal paraphasias were a central component of calculation errors in acalculia in Wernicke's aphasia, a conclusion supported by Deloche and Seron (1982) and Delazer, Girelli, Semenza and Denes (1999) who reported semantic errors in the reading and writing of numbers in individuals with Wernicke's aphasia, coinciding with the study by Rosselli and Ardila (1989) that found that in individuals with acalculia in Wernicke's aphasia impairments in the execution of mental operations, particularly successive operations in solving numerical problems, were due in large part to deficits in verbal memory and lexical and semantic difficulties.

Conduction aphasia is primarily a repetition disorder, where the individual has full comprehension of what she or he has heard, but difficulty in repeating what has been said. Individuals with conduction aphasia will often make frequent errors in their speech production, transposing and substituting sounds, and though fully aware of their errors, have considerable difficulty in correcting them. Spontaneous speech, though basically fluent, without any dysprosody and grammatically and syntactically correct, often includes paraphasias and the omission or transposition of phonemes and syllables. Conduction aphasia, which is also known as afferent (apraxic) aphasia, suggesting an etiology of damage to the primary motor or premotor cortex or to the pars opercularis, has more lately been considered

to be caused by tissue damage (for example, from cerebrovascular accident) in the posterior and inferior temporal lobe or in the parietal-temporal junction of the presupposed language-dominant hemisphere, typically the left hemisphere (Damasio and Damasio 1980; and Bartha and Benke 2003).

Rosselli and Ardila (1989) reported that individuals with conduction aphasia were frequently observed to have significant calculation errors, and that those with acalculia in conduction aphasia demonstrated failures in the execution of both mental and written arithmetic operations, with particular difficulty in problem solving and in the execution of successive operations. Errors were found in reading numbers and in numerical ordering, hierarchy and decomposition. Also reported was a typical failure in "carrying over" in the general use of calculation syntax, even in reading arithmetical signs. Although Rosselli and Ardila equated the arithmetical difficulties found in acalculia in conduction aphasia with anarithmetia and correlated both anarithmetia and conduction aphasia with left parietal brain injury, such correlation is directly contradictory to Rosselli's and Ardila's observation that primary and secondary defects may be attributed to "a diverse array of underlying deficits," whereby even similar errors were attributed to highly different neuropsychological dysfunctioning, all of which cannot be attributed to any single cognitive center of the brain, nor can acalculia in conduction aphasia credibly be correlated with anarithmetia, since, by definition, acalculia in conduction aphasia occurs in connection with the cognitive disorder of conduction aphasia, not as a "pure" primary acalculia, and, as Rosselli and Ardila themselves imply, is a result of linguistic associative and syntactical deficits rather than a primary deficiency in fundamental numeracy and arithmetic calculation ability per se.

Also, while Rosselli and Ardila in their 1989 study correlate both anarithmetia and conduction aphasia with left parietal brain injury, Damasio and Damasio (1980) and Bartha and Benke (2003) include injury to the temporoparietal junction (TPJ), consisting of the inferior parietal lobule (IPL) and the caudal portion of the superior temporal sulcus (STS) as a cause of conduction aphasia, equally implicate damage to the posterior and inferior temporal lobe (the former area perhaps including some overlap with the TPJ); whereas, Ardila and Rosselli in their 2002 study (p. 201) while acknowledging that anarithmetia has been generally perceived to be caused by left angular gyrus damage, astutely point out that in reality "it is uncommon to find cases of pure anarithmetia caused by focal lesions to the brain" and that the very existence of pure anarithmetia has been challenged.

Benson and Ardila (1996) report calculation disturbances in other types of aphasia, particularly 1) transcortical motor aphasia (TMA) — also known as adynamic aphasia and extrasylvian motor aphasia — and 2) transcortical sensory aphasia (TSA) — also known as extrasylvian sensory aphasia. TMA has generally been regarded as caused by cerebrovascular accident (CVA) resulting in damage to the anterior superior frontal lobe, and is experienced as halting and effortful speech, each effort only able to produce one or two words. Although repetition remains intact, individuals with TMA may experience delays in the initiation of speech when trying to repeat words. There is a very high incidence of TMA comorbidity with agraphia, with writing much more severely impaired than speaking.

In contrast to the traditionally regarded involvement of damage to the anterior superior frontal lobe, lesions in the cortical motor areas as well as lesions in the anterior portion of the basal ganglia have been noted in TMA. Freedman, Alexander and Naeser (1984) report that the *essential* cause of TMA is a lesion disrupting the connection between the supplementary motor area (the superior portion of Brodmann area 6 on the midline surface of the hemisphere

immediately anterior to the cortical homunculus primary motor cortex leg representation) and the frontal perisylvian speech zone (Brodmann areas 44 and 45, i.e., Broca's area). Extended dysfunction may be attributed to additional damage, such as impaired auditory comprehension resulting from mostly subcortical involvement implicating lesions in the basal ganglia or adjacent areas including lesions in the anterior head of the caudate nucleus, anterior limb of the internal capsule, anterior putamen, anterior portion of the external capsule, in the claustrum, the extreme capsule, and, in the insula cortex, the latter, which, in distinction from the preceding subcortical areas, constitutes a segment of the cerebral cortex folded deep within the sylvian fissure (lateral sulcus). The presentation of stuttering in TMA is seen as attributed to a lesion in the pars opercularis (Brodmann area 44) and the lower third of the premotor region (i.e., the lower third of Brodmann area 6). The findings in this study, based on an analysis of language profiles and computerized tomography imaging, are proposed to unify disparate anatomic and psychophysiologic observations concerning three clinical conditions: 1) "classical" TMA, 2) aphasia after left medial frontal infarction, and 3) TMA during recovery from Broca's aphasia. In acalculia in TMA Benson and Ardila (1996) report difficulties in initiating and maintaining numerical sequences and significant impairment in arithmetic problem solving with failure even in understanding what the problem is about.

Transcortical sensory aphasia (TSA) is considered to involve damage to so-called locations in the temporal lobe connected with language, and is presented as problems in language comprehension and naming. In some ways similar to Wernicke's aphasia, in that individuals with TSA have deficits in comprehension while retaining fluent (natural sounding) speech, the speech is often riddled with meaningless paraphasias; however, distinct from Wernicke's aphasia, individuals with TSA often present echolalia (a compulsive repetition of words), and unlike those with Wernicke's aphasia, individuals with TSA can correctly repeat what they have said or heard.

Benson and Ardila (1996) report that in TSA significant calculation defects are observed that are associated with difficulties in language comprehension and echolalia. Delazar, Girelli, Semenza and Denes (1999) suggest that in TSA temporal-parietal damage results in a variety of language disturbances and significant calculation defects reflected in difficulties in mental and written calculation and errors in writing number words. It must be emphasized here that though TSA is considered to result from lesions in the inferior left temporal lobe near Wernicke's area (the posterior portion of the superior temporal gyrus) causing minor hemorrhage or contusion in the temporal lobe, or infarcts of the left posterior cerebral artery (PCA), the results of fMRI studies have been difficult to interpret in localizing the source of disturbance in TSA, and, due to the relative infrequency of the condition, very few systematic studies of the etiology of TSA have been conducted. Studies in the localization of the precise area of damage causing TSA have been largely inconclusive in singling out any definitive functional area: "TSA has been studied primarily in stroke patients, although it has been difficult to conduct systematic studies. One reason is that TSA occurs relatively infrequently in this population. Moreover, lesions associated with aphasia tend to be relatively large, potentially involving multiple functionally distinct areas. Furthermore, lesion localization studies of patients with TSA have typically relied on group comparisons, which are subject to individual differences. Finally, stroke patients are usually studied during recovery, where cortical reorganization and atypical patterns of language processing may be present" (Boatman, Gordon, Hart, et al. 2000).

In addition, disturbance in lexical-semantic processing has been attributed to all types of aphasia, and in particular to TSA, especially in the disconnection model of TSA which proposes a bidirectional disconnection between phonology and lexical-semantic processing; however, impaired lexical-semantic processing in aphasia, and particularly in TSA, has been attributed to highly diverse cortical regions including the temporal lobe, the temporo-occipital junction, the parietal lobe, the fusiform gyrus, and the frontal lobe (Damasio 1981; Heilman, Rothi, McFarling and Rottmann 1981; Kertesz, Sheppard and MacKenzie 1982; Alexander, Hiltbrunner and Fischer 1989; Hart and Gordon 1990; Hart, Crone, Lesser, et al. 1998; and Otsuki, Soma, Koyama, et al. 1998).

Up to this point in this discussion we have been looking at various neurocognitive problems, such as acalculia and aphasia, as discrete problems, but, in reality, cognitive problems are seldom presented as a deficit in any discrete function, but as a more general condition of neurocognitive dysfunction. As an example, aphasia, with rare exception, is basically defined as a disorder of language involving an inability to communicate through spoken or heard speech or written language (Holland 2005; Barrett 2006; O'Toole 2003; Segen 2006), and is much less likely seen simply as a speech disorder consisting of the impairment of the ability to comprehend and/or produce speech. In the former definition, aphasia involves difficulties in understanding and/or producing spoken or *written* language, whereby aphasia is seen as inclusive of alexia (an acquired condition of impairment of the ability to read) and agraphia (an acquired condition of impairment of the ability to write), either in combination with one or the other, or both. It is well recognized that aphasia most commonly occurs with both agraphia *and* alexia (Heilman, Doty, Steward, et al. 1999; De Smet, Engelborghs, Paquier, et al. 2011; Sinanovic, Mrkonjic, Zukic, et al. 2011), and in fact, the co-occurrence of aphasia, agraphia and/or alexia are a diagnostic criteria for certain subtypes of these conditions, for example, central alexia is defined as a generalized language disorder that is a part of aphasia or consists of alexia with agraphia (Leff 2004); surface alexia is always presented with surface agraphia and nearly always presented with fluent (Wernicke's) aphasia (Friedman and Hadley 1992); global agraphia is always presented with severe alexia and aphasia (Beeson 2004); central agraphia is characterized by the co-occurrence with aphasia (Lorch 2013); in deep agraphia both alexia and aphasia are often presented (Beeson 2004); Gerstmann's syndrome is distinguished by the presentation of agraphia, acalculia, finger agnosia and left-right disorientation (Vallar 2007; Carola, Di Pietro, Ptak, et al. 2004) and is often presented with alexia and mild aphasia (Sinanovic, Mrkonjic, Zukic, et al. 2011; Rusconi, Pinel, Dehaene and Kleinschmidt 2010), etc.

It is, in fact, clearly recognized that neurocognitive language disorders and other types of cognitive disorders are seldom deficits in any single, discrete function, but are presented as disorders involving a range of functions, as for example, agraphia, alexia, aphasia, agnosia, apraxia, as well as the motor disorder dysarthria, commonly presenting together (De Smet, Engelborghs, Paquier, et al. 2011; Sinanovic, Mrkonjic, Zukic, et al. 2011). Acalculia is often presented with aphasic forms of agraphia, such as agraphia associated with Broca's aphasia; fluent agraphia for numbers in Wernicke's aphasia; significant agraphic defects in the writing of numbers and the frequent presentation of apraxic agraphia and apraxic speech in conduction aphasia; as well as in nonaphasic forms of agraphia as in motor agraphia, including apraxic agraphia (in which impaired execution of motor sequences effects the ability to properly form letters and numbers), paretic agraphia (weakness or loss of movement of the writing muscles), hyperkinetic agraphia (in which involuntary hyperkinetic movements — such as tremors, tics, dystonia and chorea — disrupt the fine motor control needed for writing) and hypokinetic agraphia (i.e., micrographia — in which letters and numbers are

written in very small size, often in progressive diminution of size, and often progressively more crowded together in Parkinsonism) [Ardila and Rosselli 2002; Ardila and Rosselli 1990; Rosselli and Ardila 1989]. Luria (1966) stresses that the cognitive process of spatial orientation is a major factor in both aphasia and acalculia, and that semantic aphasia (consisting of the inability to use verbally mediated spatial concepts) is *always* associated with acalculia.

As has been previously noted herein, and articulated with corroborative studies, agraphia is most commonly presented as comorbid with alexia (Leff 2004; Lorch 2013; Friedman and Hadley 1992; Beeson 2004; Sinanovic, Mrkonjic, Zukic, et al. 2011; Rusconi, Pinel, Dehaene and Kleinschmidt 2010), and, in fact, as also previously noted, agraphia is usually comorbid with both aphasia and alexia (Heilman, Doty, Steward, et al. 1999; De Smet, Engelborghs, Paquier, et al. 2011; Sinanovic, Mrkonjic, Zukic, et al. 2011); it would therefore be expected that in many of the nonmotor-related cases cited above with acalculia co-occurring with both aphasia and agraphia, one would also find alexia.

In addition to acalculia associated with the neurocognitive language disorders aphasia, agraphia and alexia, acalculia is also known to be associated with deficits in executive functions — the cognitive abilities that comprise higher-order thinking, such as planning, strategizing, foresight, categorizing or chunking and other relational conditions and associations that constitute problem solving. In describing acalculia in association with deficits in executive functions, Ardila and Rosselli (2002, p. 207) report that because deficits in executive functions (i.e., executive dysfunction) are so pervasive in many different types of tasks, arithmetic and calculation deficits associated with executive dysfunction are difficult to detect as a particular domain of impairment. Problems in calculation as a result of impairment in executive functions are primarily due to three areas of difficulty: 1) loss of attention (inability to maintain sufficient focus on task at hand, 2) perseveration (a preoccupation with a singular response used inappropriately over and over in different tasks as an answer or solution in unrelated problem sets), and 3) failure to grasp multistep mathematical concepts [lack of ability to recognize the conditions comprising a multistep numerical solution; i.e., the inability to form a systematic overview (or "gist") of the problem and the logical deduction of a systematic, sequential resolution as a failure to logically deduce, in step-by-step fashion, the components and interrelationships of a problem and the strategy (i.e., the sequence of individual steps) by which it may be solved]. In acalculia in executive dysfunction Ardila and Rosselli (2002, p. 207) note that mental arithmetic is significantly more impaired than written arithmetic operations, and that temporal sense is highly distorted.

From the foregoing it is clear that so-called discrete "cognitive functions" do not reside in specific "centers" of the brain, but are activations of interconnected neuronal circuits throughout the brain, and that an insult to any part of the brain can result in different presentations of cognitive dysfunction, most often presenting as deficits in a number of so-called cognitive functions; and furthermore, what is commonly referred to as discrete "cognitive functions" are simply inferred concepts of gross observable behavior (that what we think we see in another's observable behavior as defined by sociocultural "norms") arbitrarily interpreted from hypothetical constructs, such as memory, attention, semantic/symbolic and syntactical processing, sequencing, numeration and quantification, planning and strategizing, etc., that are all manifestations of cognition, a facility that is indivisible into discrete components, as *all* aspects of cognition are integrated, inextricable elements of *any* aspect of cognition. As an example of the indivisibility of cognition, using the hypothetical constructs of gross observable behavior as discrete cognitive functions for

the purpose of explanation, let's analyze the cognitive components of the so-called simple cognitive function of meaningful, purposeful attention [as opposed to fixed sensory orientation (i.e., a fixed gaze) as a result of pure physically elevated sensory excitation].

The basic cognitive abilities comprising meaningful attention are as follows:

1) A basic degree of balanced sensitivity (neither hypo- nor hypersensitivity) to external stimuli as a prerequisite for 2).

2) A basic balanced attraction to (i.e., interest in) external stimuli and inherent tendency to categorize by relevant relationships (i.e., "chunking") particular stimuli as a prerequisite for 3) and 5).

3) Sufficient social cognition to define the contextual moment and to discern and prioritize the relevance of stimuli appropriate to contextual association as a component of 4) and 7).

4) Motivation as a component of 2), 3), 5), 6) and 7).

5) Directedness toward, and engagement with, relevant stimuli as a component of 6).

6) Mental stamina to stay focused on relevant stimuli sufficient to register the details or all of the relevant information embodied in the stimuli as a component of 7).

7) Sufficient memory ability to recognize relevance of stimuli and retain and recall relevant details or information therein appropriate to the contextual association necessary for attracting and holding attention by associating discrete stimuli with relevant meaning.

From the foregoing, the cognitive function of attention may be said to be comprised of 7 basic neurocognitive processes, including the cognitive functions of memory and social cognition. It may also be said that attention must also include the cognitive functions of problem solving and decision making, as defining the context and discerning the relevance of any number of stimuli in an intertwining set of associations in complex social interaction (as social cognition is necessary to attract and hold attention in social situations) most certainly requires a well-functioning level of problem solving and decision making inherent in executive functions (i.e., planning and forethought, organizing, strategizing, managing time and space, etc.) to understand the cross-relationships of one's life goals, current situation, and opportunities of the current experience in achieving the requisite steps towards one's life goals in such interaction and determining what may or may not be relevant and to what extent. It should also be recognized that a) items 1, 2, and 5 numerated above are in themselves major components of arousal of purpose; b) that "chunking" (item 2 numerated above) in and of itself, is a higher-level cognitive function consisting of logical analysis in the extraction of the major important points or critical information of stimuli and the discrimination of logical relationships therein; and c) that motivation, number 4 numerated above, rather than a discrete affective state, is a cognitive perception borne of a concept of the prospect of reward or accomplishment of goals formed from planning and consisting of memory, of social cognition, of decision making, etc.

From the above, such so-called cognitive functions as attention, memory, problem solving, decision making, social cognition, etc., are not discrete functions but merely constructs of each other – the interpreted manifestations of the unified process of basic cognition – as, by pure deductive reasoning, an attention deficit must co-occur with a memory deficit, as memory of the individual's life history and ascertainment of why a particular experience has, or particular stimuli have, meaning or relevance to the individual to hold attention and register the experience (i.e., motivation), is a fundamental requisite of attention, so that a deficit in memory impairs attention which impairs problem solving and disturbs social interaction, both of the latter requiring attention to the immediate situation or stimuli and the memory of one's accumulative knowledge, learning and the accumulative experience of one's social interactions to logically deduce the "gist" of an experience and determine its relevance and meaning to the individual's life goals and the implications of the current experience or the problem or task at hand in achieving those goals and to solve the problem, or dismiss the situation as irrelevant; whereby the so-called process of "problem solving" must include the so-called functions of "attention" and "memory," "conceptualizing," "decision making," "categorizing," "planning" and "strategizing," etc., and the so-called process of "social cognition" must include the so-called functions of "attention," "memory," "perspective taking," "affective engagement," and "problem solving," etc., which are in turn all required aspects of "attention" itself, etc.

Although the frontal lobe has been conventionally regarded as the center for certain cognitive functions, many of these functions, especially the higher-level executive and intellectual functions, rely on symbolic logic and interpretation, paradoxically, it is Wernicke's area (located in the superior temporal gyrus) that has been considered the primary area for the development of language comprehension, which involves symbolic/syntactic and semantic processing and logical sequencing. Wernicke's area then should also have a major role in symbolic logic critical for mathematics and higher abstract thinking, both of which are essential for many of the cognitive functions conventionally associated, not with the temporal lobe where Wernicke's area is located, but rather with the frontal lobe, and especially, the prefrontal lobe. Language ability itself is a requirement for many of the cognitive processes that are regarded as centrally occurring within the frontal lobe, even though, paradoxically, language ability is conventionally regarded as a function of both Broca's area in the inferior frontal gyrus and Wernicke's area in the temporal lobe. The premise that the frontal lobe is a center for higher-level cognitive functions or executive functions such as problem solving and decision making is difficult to rationalize.

In semantics and language, though relatively recent research suggests an interaction between Wernicke's area in the temporal lobe, "Geschwind's territory" (the inferior parietal lobe consisting of the angular gyrus and supramarginal gyrus) and Broca's area in the frontal cortex (see Catani and Mesulam 2008, p. 958); in an fMRI (functional Magnetic Resonance Imaging) study examining the role of different brain structures in the semantics of mathematical logic, Friedrich and Friederici (2013) argue for a 3-way interaction, with the prefrontal cortex operating on the data fed to it by a pre-motor-parietal top-down system that updates and transforms external data into an internal format that can be "read" by the prefrontal cortex, and a hippocampal bottom-up system that either detects novel information or serves as an access device to memory for previously acquired knowledge; the prefrontal cortex embodying a system consisting of three major elements: control, arithmetic logic, and

short-term memory. It is interesting to note in this study, that Wernicke's area, though suggested as a major area for symbolic and syntactical/semantic processing essential for mathematics, is not indicated as involved in the semantic or arithmetic-logical processes that were examined. But what exactly can fMRI studies tell us about functional localization?

fMRI cognitive function localization studies: Forging new understanding or misrepresentation?

In our analysis above of the so-called cognitive abilities that are inherent in all so-called cognitive functions, pure deductive reasoning as well as the brain lesion studies that we have reviewed unequivocally indicate that such so-called cognitive functions as "attention," "memory," "organization," "chunking and categorization," "conceptualization," forethought," "planning," "strategizing," "problem solving," "decision making," "social cognition," "language," "numeracy and arithmetic logic," "semantic and syntactical processing," "symbolic sequencing," "quantitative computation," etc., are rather than discrete functions, merely constructs of each other – the interpreted manifestations of the unified process of basic cognition, a process of highly integrated interconnectivity of neuronal networks that span the entire brain and react to all stimuli (external and internal; i.e., apperception, including the new information derived from the internal reconfiguration of conceptual frameworks) by the modification of synaptic connections. But then, if that is true, how does one explain fMRI studies that have purportedly isolated specific centers of the brain responsible for designated "cognitive functions?"

In answering that question, I must first interject two caveats: 1) a number of studies have recently been published that question the validity of fMRI studies purporting to localize specific centers of cognition in the brain by pointing out and explaining the various technical flaws of such studies; I am currently working on a paper synthesizing those studies and consequently do not include those studies in the discussion that follows in this paper, instead, I will present below some very general, basic problems with fMRI localization of cognitive functionality in the human brain; and 2) in this paper my discussion is primarily confined to fMRI studies, since fMRI, in distinction from other brain imaging technology, has been the predominant technology used to localize cognitive functions in specific regions of the brain.

The first concern is the design and premise of the study itself. If one presupposes a specific area of the brain is in fact the center for a particular so-called "cognitive function" and the study is concentrated precisely on that area, which is highlighted as active by the fMRI scan, what exactly does that actually show?

In the first place, as discussed above, so-called observable gross "cognitive functions" are not discrete functions, but consist of interconnected neuronal networks, so, in reality whenever any observable gross cognitive function is studied, what we are observing is the interaction of interconnected neuronal networks, so what is really being measured here, and what is the meaning of any particular area highlighted as active in an fMRI scan when many neural circuits in different locations in the brain are at work in any given task? "Any fMRI experiment is only as good as its hypothesis, design and interpretation. Silly fMRI experiments, for instance one showing men's amygdalas (which play a key role in generating emotion) light up when viewing Ferraris, are not difficult to find. But such work doesn't prove any fatal flaw in fMRI, merely poor use of a good tool. Most fMRI investigators seek not to localize brain function but to map the parts of the system that *act in different combinations for different tasks*" (emphasis mine; Nuffield Department of Clinical Neurosciences 2013).

In the second place, fMRI technology is based on blood-oxygen-level dependent (BOLD) contrast, which images change in blood flow (the hemodynamic response) as detected in the change of magnetization between oxygen-rich and oxygen-deficient blood related to energy use by brain cells. The problem with the BOLD contrast response is that the temporal resolution of the fMRI BOLD signal (the HDR or hemodynamic response) significantly lags behind the neuronal events triggering it by 1 to 2 seconds since it takes that long for the vascular system to respond to the brain's need for glucose. "Relative to other brain imaging techniques, fMRI has unequalled spatial resolution — at 7T activity can be mapped down to 1 mm. However the temporal resolution of fMRI is inherently limited by the slow blood flow response [upon which] it depends. [Studies using] fMRI cannot uncover the dynamics of mental activity on the sub-millisecond timescale on which neurons operate" (Nuffield Department of Clinical Neurosciences 2013). So, what is it exactly that the fMRI scan actually captures, and how is it related to particular "cognitive functions" associated with particular regions of the brain? Whatever the task that is presented to the subject in an fMRI study of cognitive function, it is not just the proposed "pure" mental or cognitive activity under investigation that is activated in response to the execution of the task, but also numerous sensory and motor actions that occur in reaction to the immediate and ongoing sensations of the environment, such as visual perceptions and auditory processing, the response to tactile stimulation and affective reaction (i.e., anxiety and discomfort) to confinement in the MRI machine, and involuntary responses such as eye blinking and head turning, etc., all products of neuronal activation in the brain. The question is, how much of this is registering as the fMRI image pertaining to the specific object of the study? Though there are a number of statistical averaging techniques that are supposed to filter out the noise of superfluous neuronal activity, how much of the signal reflecting response to the task under study is affected by the averaging, and what is the rationale and evidence that all that is being filtered out is not relevant?

To compensate for the lag in the fMRI BOLD signal, a number of studies have combined EEG (electroencephalography) with fMRI. In noninvasive EEG a number of electrodes are fixed to the scalp [implanted EEG may include subdural or depth electrode placement; i.e., electrocorticography (ECoG), subdural EEG (sdEEG), or intercranial EEG (icEEG)], each electrode picking up the synchronous sum of the electrical potentials of cortical neuronal dendrites [actually the sum of the electrical (ionic) charges in the extracellular space of dendrites of connected pyramidal neurons in series] near the brain's surface underlying the electrode. Each electrode registers the synchronous sum of the electrical potentials of many thousands of underlying pyramidal neurons. This synchronous sum of graded potentials ("graded potential" referring to the changes in charge in the extracellular space around the dendrites of connecting neurons having the same relative orientation and polarity in series) may be recorded as voltage potentials between any two electrodes.

Although sensitive to fractions of millisecond changes to the synchronous sum of graded potentials of the underlying neurons and thereby exhibiting very high temporal resolution, EEG is a composite reading of relative positions on the scalp or subdural surface, and considering that the total length of an axon of a single pyramidal neuron is typically measured in tens of centimeters, that can reach from one side of the brain to the other, while each electrode represents the synchronous sum of graded potentials of a limited area no larger than 6 square centimeters of overwhelmingly gyral surface as the cortical dipoles generated in the sulci mostly cancel each other out, EEG is ineffective at differentiating the activity of specific underlying regional processes or particular neurocircuits in the brain and does not

give a clear picture of what neural processes are actually at work. EEG readings are also affected by the conductivity of the skull and/or scalp or subdural surface, although averaging techniques are applied to filter out the superfluous noise, but, again, one would have to be cautious about the rationale for the averaging techniques used. It would seem to me difficult to justify EEG readings in clarifying or reinforcing fMRI imaging results in the localization of cognitive functions.

With regard to fMRI studies purporting to isolate the centers of different cognitive functions in the brain, one critical position noted by the Nuffield Department of Clinical Neurosciences, Medical Sciences Division, University of Oxford, should give one pause as follows:

> *Critics of the technique complain that fMRI overlooks the networked or distributed nature of the brain's workings, emphasizing localized activity when* it is the communication among regions that is most critical to mental function *(emphasis mine). This, along with fMRI being an indirect measure of brain activity has led to the charge that fMRI is no more than modern day phrenology - a 19th century pseudoscience which purported to character-type by examining the shape of a person's skull*. (Nuffield Department of Clinical Neurosciences 2013).

Other brain imaging technology, such as single-photon-emission computed tomography (SPECT), positron-emission tomography (PET), functional near-infrared spectrometry (fNIR or fNIRS) and diffuse optical imaging (DOI), (the latter two measuring optical absorption of hemoglobin) have the same problem with temporal resolution as fMRI because they all record the hemodynamic response such as regional cerebral blood flow (rCBF) as well as cell metabolism in PET, delayed and indirect measures of the neuronal activity in the brain. A newer and much-lauded technique of diffusion functional MRI (DfMRI) provides a much faster response to brain activation, both at onset and offset, which more clearly points out structural changes in neuronal tissues in the brain, such as the swelling of neuronal cells that occurs during tissue activation. Not an imaging technique but one recording neuronal activity in the brain, magnetoencephalography (MEG) measures the absolute magnitude of the magnetic fields produced by the electrical currents generated from the neuronal activity in the brain, recording physiological signals in fractions of milliseconds, tracking the rapid neuronal changes in the brain. Like EEG, MEG is a totally noninvasive technique, and like EEG, MEG, though offering very high temporal resolution, has similar difficulties in localizing brain activity. MEG measures the magnetic field of underlying neurocortical activity from sensors on the scalp, so that localizing brain activity from the recorded magnetic fields requires extrapolation about the sources of current based on measurements from the scalp, which, unfortunately, cannot be confirmed with any assurance, and, adding to the difficulties in defining the locations of particular neural activity, like EEG, MEG readings are also affected by the conductivity of the scalp (invasive intracranial EEG would be affected by the conductivity of the extracortical surface).

Though such imaging technology as DfMRI, nuclear magnetic resonance (NMR) spectroscopy (NMR, which, along with tissue and cell metabolism including the hemodynamic response, can also record the chemical analysis and fine details of cellular structure), and event-related optical signal (EROS) imaging, offer very exciting promise for more revealing studies of brain neuronal behavior, the essential problem of experimental design and interpretation (i.e., the premise and design of a study) remains. The premise of a specific neurological counterpart of any observable gross cognitive function, such as "memory," "attention," "problem solving," etc., is untenable, because clearly these are not discrete cognitive processes, but rather the interconnection of many neuronal circuits from

different regions of the brain. The use of the term “cognitive functions,” and defining specific cognitive functions, such as “decision making,” “quantification,” “perspective taking,” etc., are useful and necessary for understanding different abilities that may be observed in individuals and in addressing cognitive deficits that may be presented within any one or more of those behavioral domains, but they must equally be understood to be hypothetical constructs that have no real correspondence to any physically distinct process in the brain, and cannot be isolated in any particular region of the brain by any study, since, by definition, they are neurologically interconnections of neural circuits spanning the brain rather than a specific functional entity or center, and many of the neural circuits activated in any particular observable gross behavior are activated in many observable gross behaviors because of 1) the huge overlap in so-called observable functions that are simply interpreted manifestations of each other, and 2) the processing of sensory and motor action and cognition that is constant in the interaction with oneself and with the external world of one’s environment — one is always thinking, evaluating, and emotively reacting to every stimulation encountered, internal or external, including all thoughts, physical sensations, urges, desires, discomforts, etc.; i.e., amatory images of one’s date last night and reflection on how the boss will react tomorrow after evaluating one’s performance in a critical project, such thoughts creeping into whatever task in which the individual is currently engaged. How can these be isolated in the performance of a task in a study examining a particular, hypothetical, implied, observable gross cognitive function?

> fMRI only measures the secondary physiological correlates of neural activity, it is not a direct measure. This means it is not a truly quantitative measure of mental activity – when comparing the fMRI response between individuals it is impossible to say whether the differences are neural or physiological in origin. (Nuffield Department of Clinical Neurosciences 2013).

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