6.A Pilot Study

Arnold J. Mandell, Karen A. Selz, Tom Holroyd, Linsay Rutter and Richard Coppola NIMH Core MEG Laboratory and Cielo Institute Supported in part by the Fetzer-Franklin Trust, DARPA (Microelectronics) and the Space and Naval Warfare Center The Eyes Closed, Resting Record The time dynamics of global brain electromagnetic field activity, recorded in humans as continuous, eyes closed resting MEG (and EEG) records, are regarded by some as reflections of physiologically and psychologically relevant, emergent macroscopic behavior of nonlinearly coupled, cooperative brain systems (Basar et al., 1983; Bucolo et al., 2003; Chen et al., 2003; Friedrich et al., 1989; Haken, 2 1996; Mandell, 1983a). Others, more involved in neuronal current source localization studies of task or state-related magneto-encephalographic records (Cornwell et al., 2008; Fife et al., 2002; Garolera et al., 2007; Nolte et al., 2004) have treated the globally distributed, spontaneous neuronal current generated, brain magnetic field activity as "…high-ranked (leading eigenvalued) background activity… interfering magnetic fields generated from (not relevant) spontaneous brain activities…intrinsic brain noise…" (Sekihara et al., 1996; Sekihara et al., 2008; Sekihara et al., 2006). Covariance matrix-derived beamformers from several minutes of the eyes-closed resting record have been used in "prewhitening techniques", adding noise in order to get around linear dependency in the matrix if it is too low dimensional and to minimize interfering low dimensional intrinsic brain magnetic field noise (Sekihara et al., 2008; Zumer et al., 2007; Zumer et al., 2008). Another view of spontaneous magnetic field fluctuations have been influenced by studies of spatial (neuroanatomical) brain localization using concomitant fMRI techniques. They have suggested the existence of spontaneous, regional, above baseline activity in the normal eyes closed, resting state. This activity is particularly pronounced in medial prefrontal, parietal and both posterior and anterior cingulate, and is suppressed during goal-directed behavior (Damoiseaus et al., 2006; Griecius et al., 2003; Gusnard & Raichle, 3 2001). Activity in this "network" has been labeled "default activation" by Raichle (Raichle ME et al., 2001). The many second time scale of fMRI imaging demonstrated density variations that were characteristic for the normal eyes closed, resting condition (Biswal et al., 1995). Importantly, the spontaneous activity in the resting state also appears to involve neural network activity across several time scales (Honey et al., 2007). 14 In two state, task-no task, experimental designs, the resting activity, "default activation, " has been speculated to reflect spontaneous, task unrelated, images and thoughts (Greicius & Menon, 2004; Greicius et al., 2004; Raichle ME et al., 2001; Vincent et al., 2007). These transient mental events in the eyes closed, resting condition have also been called "daydreaming" (Singer, 1966), "task-unrelated-thoughts," TUTs(Giambra, 1989), "unrest at rest"(Buckner & Vincent, 2007), "wandering minds," and "stimulus independent thought", SITs (Gilbert et al., 2007). Psychologists that have studied inner life subjectively, William James (James, 1902) and Sigmund Freud (Freud, 1914/1955 among many others, have focused on these autonomously arising transient streams of free associations and imagery. James analogized them to the turbulent eddies of the hydrodynamic flow of consciousness which he believed these transients to be among the universal properties of the conscious human brain. Examinations of a subject's spontaneous 4 internal activity as exteriorized by the psychoanalytic instruction, "…say everything that comes to your mind…" has been central to the practice of psychoanalysis for over a Century {Fenichel, 1945 #8190). It appears that the ostensibly resting "default brain activity" in the "default network" persists in monkeys through anesthesia-induced changes in states of consciousness (Vincent et al., 2007). This result is consistent with a several decade history of research using priming, evoked potentials and task recovery paradigms to demonstrate implicit, working memorial events that occur during even surgical anesthesia (Jordon et al., 2000). The implied relationship between 2-5 second epochs of MEG activation such as that seen below in Fig. 5 as intermittent helical vortices (we call them strudels) and TUT or SIT-like subjective phenomena must remain entirely speculative. General Premise and Hypothesis It is the underlying premise of this pilot study of intrinsic brain magnetic field fluctuations that they manifest signatory patterns in transformations and measures which can discriminate among global brain states. We examine this premise by partially isolating and qualitatively and quantitatively characterizing 12.5, 54, 180 or 240 seconds of eyes closed, resting spontaneous magnetic field activity in ten resting controls and ten medicated schizophrenic probands. From our previous 5 work in brain-related physiological systems (Mandell, 1979; Mandell, 1983b; Mandell, 1987; Mandell et al., 1982; Mandell & Selz, 1993), a more specific hypothesis is suggested: Compared with controls, magnetic field fluctuations in schizophrenic patients will demonstrate relatively higher values for indices of emergent dynamical structure and relatively lower values for a variety of measures reflecting the dynamical entropy "used up" in their formation (Mandell & Selz, 1997c; Selz & Mandell, 1991; Selz et al., 1995; Smotherman et al., 1996). A MEG Derived Data Series: Symmetric Sensor Difference Sequences, ssds(i) Ten normal controls and ten age- and sex-matched schizophrenic proband subjects (see Subjects below) were studied in the National Institutes of Mental Health's Core MEG Laboratory in Bethesda, MD. A 275 channel, superconducting quantum interference device (SQUID radial gradiometer system from CTF Systems Inc. Port Coquitlam, BC, Canada (Anninos et al., 1986; Cohen, 1972; Rutter et al., 2009; Weinberg et al., 1984) was used in data collection (see Magnetoencephalographic Data Collection below). 15 6 Our approach to MEG-derived signals abrogates source orientation, localization and inverse problem tools such as leadfield matrices (Dale & Sereno, 1993; Hamalainen et al., 1993), adaptive synthetic aperture magnetometer, SAM, beamformer techniques, or projection onto Talairached MRI image reconstructed volumes (Dalal et al., 2008; Dalal et al., 2004). For these approaches to this data set, see Rutter et al (Rutter et al., 2009). In their study of spontaneous activity in the eyes closed, resting state, they found a statistically significant decrement in the amplitudes of MEG recorded posterior regional gamma (30-70Hz+) activity in schizophrenic patients compared with normal controls (Rutter et al., 2009). In that study as well as these, a high pass, 0.6 Hz, as well as 60, 120, 180 and 240 Hz notch filters were routinely applied to the individual sensor records before the computation of the sensor pair ssds(i), (the difference between the two sensor). It is our presupposition that the "…spontaneous activity… all over the brain…" (Sekihara et al., 2008) reflects global and neurophysiologically meaningful patterns of complex neuronal activity-generated magnetic field fluctuations in interaction with MEG SQUID sensors (Barone A & G., 1982; Braiman & Wiesenfeld, 1994). A magnetic flux applied to the SQUID magnetometer, gives rise to a circulating current, which in turn modulates the inductance of the autonomously oscillatory Josephson junctions (Landberg et al., 1966; Levi et al., 1977). The great sensitivity of the SQUID devices permits measuring changes in magnetic field associated with even a single flux quantum. 7 If a constant biasing current is maintained in the SQUID device, it is the voltage which is modulated by changes in phase at junctions. Phase at Josephson junctions is sensitive to the quanta of magnetic flux. We dismiss a common generalization of many MEG practitioners that most or all local polarities of the intrinsic magnetic field noise "cancel out." In the context of the somewhat analogous magnetic dynamo problem: "…given a flow in a conducting fluid, will a small seed magnetic field amplify exponentially with time…" (Finn & Ott, 1988)–we show below that ssds(i)s do– it was argued that the magnetic flux loops nonuniformly stretch and fold into themselves manifesting only partial cancellation and diffuse fine scale oscillations, in a process which can be quantified by a fractional cancellation exponent (Ott et al., 1992) and measures made on temporal-spatial intermittency. In addition, if some currents run parallel to magnetic fields, which is expected to be the case with poorly localized, multiple neocortical neuronal sources, the magnetic field lines may follow a variety of dynamical shapes in which the magnetic pressure gradient is balanced by the magnetic tension. For example, there may not be any Lorentz force, $J \times B = 0$, leading to a measurable field configuration without any net electrical current at all. We thus don't infer a particular neuronal current source (or event) for the data series. Characterizing the fluctuations allows the elucidation of patterns in the brain's global magnetic field flux dynamics without reference to anatomical location (Clarke, 1994). 16 8 example, we find a common dynamical pattern often involves intermittently appearing, multiple time scale helical vortices. We call them unwindable strudels lest they lead to the brain being called a critically loaded sand pile that spawns avalanches (Beggs & Plenz, 2005; Levina et al., 2007)). In comparison with the several second time resolution of fMRI, the MEG's superior temporal resolution, ~ 1 ms, combined with its "underdetermined" weaknesses with respect to specific brain localization when used alone (Hamalainen et al., 1993; Im et al., 2005; Lee et al., 2007; Sarvas, 1987; Uutela et al., 1998), suited our goal of characterizing magnetic field (rather than inferred neuronal) properties of what has been called intrinsic physiological brain noise (Nagarajan et al., 2006; Sekihara et al., 1997; Sekihara et al., 2005). The use of ssds(i) exploits the hemispheric symmetry of the human brain (Geschwind, 1970) and serves several purposes: (1) It imposes a natural gauge (distance serves as a traveling, local normalization procedure; (3) The ssdi(i) reduces the penetrance of electromagnetic field correlates of blink, cough, and movement as well as the cardiac and respiratory artifacts that both symmetric sensors generally share; (4) Using ssds(i) instead of the raw MEG time series tends to cancel the symmetrically shared generic MEG (and EEG) Δ, Θ, α, β, and γ modes, as well as other patterns of bihemispheric covariance; (5) Advantageous from the magnetic field point of view is the fact that using ssds(i) makes issues of 9 neuronal current source location moot; ; the spatial sensitivity profile of the ssds(i) considered as a virtual sensor typically covers a large volume of the brain. The techniques similar to that used here of paired sensor difference series, ssds(i), have been used to reduce or remove the mean and double or more the higher moments in analyses of nonstationary neural membrane conductance noise (Conti et al., 1980; DeFelice, 1977; Sigworth, 1981). NAVAL - research laboratory experiments (NRL) Florida DARPA FUTURE - HISTORICAL Behavior PROTECTING HUMAN ASSETS Bio--Silico Interface Brain technology ENHANCED HUMAN PERFORMANCE Energy transduction Cell & Tissue ENHANCED SYSTEM PERFORMAMCE Geonomisc & Engieneering Proteomics 17