Neuropsychologia 51 (2013) 2130–2141

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Aberrant cortico–subcortical functional connectivity among women with poor motor control: Toward uncovering the substrate of hyperkinetic perseveration ☆

Yana Suchy [a,*], James N. Lee [b], William R. Marchand [c]

[a] Department of Psychology, University of Utah, USA
[b] Department of Radiology, University of Utah, USA
[c] George E. Wahlen Veterans Affairs Medical Center and Department of Psychiatry, University of Utah, USA

ARTICLE INFO

Article history:
Received 22 February 2013
Received in revised form
12 June 2013
Accepted 4 July 2013
Available online 13 July 2013

Keywords:
Perseveration
Motor perseveration
Functional MRI
Aging
Motor cortex
Premotor cortex
Cognitive decline

ABSTRACT

Objective: Hyperkinetic perseveration (HKP) refers to perseverative repetition of rudimentary motor output. Although HKP is known to be associated with brain injuries and certain neurodegenerative disorders (primarily those involving the frontal lobes and the basal ganglia), an increased tendency to exhibit HKP is also commonly associated with apparently normal aging (i.e., in the absence of known neuropathology). The purpose of the present study was to examine anomalies in brain functioning associated with HKP tendencies in a non-injured brain.

Method: The present study examined functional MRI connectivity patterns associated with HKP in a sample of 24 "young" (ages 25–35 years) and 20 "old" (ages 65–75 years) healthy community dwelling women. Participants performed a motor learning task (the Push-Turn-Taptap task: PTT) known to elicit HKP. On a separate day, participants were scanned on a Siemens 3T Trio MR scanner with a 12-channel head coil, while performing a block-design motor sequence learning task that was designed to be a scanner analog for the PTT task. Cortico–subcortical connectivity patterns involving two subcortical regions of interest (putamen and thalamus) and three cortical regions (sensory-motor cortex, Brodmann Area 6, inferior frontal gyrus) were examined.

Results: Older participants exhibited a higher rate of HKP compared to younger participants. Age-related HKP was associated with hemispheric asymmetry marked by a relatively stronger right-hemisphere cortico–subcortical connectivity involving the sensory-motor cortex and, to a lesser extent, Brodmann Area 6. These patterns were distinct from connectivity patterns associated with aging alone.

Conclusions: HKP is related to anomalies involving frontal–subcortical circuits. Future research should examine specific components of the basal-ganglia circuitry.

1. Introduction

Hyperkinetic perseveration (HKP) refers to perseverative repetition of rudimentary motor output (Goldberg, 1986). Examples of severe HKP include repetitive drawing of multiple copies of a figure (such as a circle) after a person has been asked to draw that figure once; persistent drawing *over* a figure or a letter that one has drawn; or engaging in excessive unintended tapping motions after being required to tap only once or twice (Goldberg, 1986; Lamar et al., 1997). Interestingly, there appears to be an association between HKP and general cognition (Mauerberg-deCastro et al., 2009; Ruchinskas & Giuliano, 2003), likely due to the fact that even simple motor output can interfere with cognitive functioning and vice versa. For example, simple finger tapping can have deleterious effect on speech output (Kemper, Herman, & Lian, 2003), and increases in working memory demands can deleteriously affect motor performance (Fraser, Li, & Penhune, 2010). Additionally, HKP is associated with poor ability to learn novel motor sequences (Grigsby & Kaye, 1996; Grigsby, Kaye, & Robbins, 1992; Suchy, Derbidge, & Cope, 2005), as well as with decreased functional independence among older adults (Grigsby, Kaye, Kowalsky, & Kramer, 2002a, 2002b; Kraybill & Suchy, 2011; Suchy, Blint, & Osmon, 1997).

Although all forms of perseveration are often seen among individuals with lesions to the frontal lobes or related circuitry (Annoni, Pegna, Michel, Estade, & Landis, 1998; Barceló & Knight, 2002; Godbout, Cloutier, Bouchard, Braun, & Gagnon, 2004; Goldstein, Obrzut, John, Ledakis, & Armstrong, 2004; Lombardi

☆This research was supported by the University of Utah Incentive Seed Grant.
* Correspondence to: Department of Psychology, University of Utah, 380 S. 1530 E., Rm. 502, Salt Lake City, UT 84112, USA. Tel.: +1 801 585 0796; fax: +1 801 581 5841.
E-mail address: yana.suchy@psych.utah.edu (Y. Suchy).

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http://dx.doi.org/10.1016/j.neuropsychologia.2013.07.004

et al., 1999; Na et al., 1999; Nagahama, Okina, Suzuki, Nabatame, & Matsuda, 2005), HKP in particular has also been shown to be an early sign of certain neurodegenerative conditions, such as Parkinson's disease (Stoffers, Berendse, Deijen, & Wolters, 2001) or Progressive Supranuclear Palsy (Nitrini, 1987), and is commonly present among patients with vascular dementia (Lamar et al., 1997). Lastly, HKP can be seen in older adults who have experienced decreases in general cognitive status (Ruchinskas & Giuliano, 2003), as well as in children with intellectual disabilities (Mauerberg-deCastro et al., 2009).

In addition to being seen among individuals with known neurologic or cognitive dysfunction, milder forms of HKP are also common among apparently healthy community-dwelling older adults (Grigsby, Kaye, Baxter, Shetterly, & Hamman, 1998; Grigsby, Kaye, & Robbins, 1995). One typical situation in which HKP emerges is the requirement to engage in manual tapping. Specifically, when asked to produce a particular tapping rhythm or sequence, older adults tend to perform less smoothly than younger adults, and their performance is often marked by either longer or irregular latencies between taps, or occasional excessive rapid releases of greater number of taps than intended (Fraser et al., 2010; Grigsby & Kaye, 1996; Grigsby et al., 1992, 1995, 1998). Although such milder form of HKP is common and often considered "normal" in old age, it is nevertheless associated with self-reported problems in executive functioning (Bangert, Reuter-Lorenz, Walsh, Schachter, & Seidler, 2010). Additionally, with older adults increasingly relying on computers and hand-held electronic devices (which typically interface with humans via a series of well-timed taps), limitations in motor control are likely to have deleterious effects on communication and daily functioning with increasing age (Hourcade & Berkel, 2008).

In sum, among apparently healthy older adults, even mild HKP may represent an early sign of functional decline or an incipient neurodegenerative disorder, may signal beginning limitations in executive functions or other aspects of cognition, and may represent an impediment for using certain digital technologies. For these reasons, better understanding of HKP is warranted. However, despite several decades of formal recognition of HKP as a sign or either focal or diffuse cerebral dysfunction, virtually nothing is known about the specific substrates that place one at risk for engaging in HKP with increasing age.

The purpose of the present study is to examine the relationship between increased tendency to engage in HKP and fMRI functional connectivity within the frontal–basal ganglia motor circuits among healthy adults. To that end, we examined connectivity strengths of input and output frontal–basal ganglia pathways (i.e., frontal cortex to the putamen, and thalamus back to the frontal cortex), involving the sensory-motor cortex, premotor cortex and supplementary motor area, and the inferior frontal gyrus. These regions of interest were selected due to their well-documented role in motor output, response selection, and inhibition of inappropriate responses (Brendel et al., 2010; Chen, Hyland, Maier, Palmeri, & Wiesendanger, 1991; Chevrier, Noseworthy, & Schachar, 2007; Coxon, Stinear, & Byblow, 2009; Lamar et al., 1997; Park et al., 2010). We chose to focus on connectivity patterns, rather than cortical activation patterns, because it is well recognized that frontal lobe processing relies heavily on the integrity of the entire frontal–subcortical circuitry, as well as the documented HKP among populations characterized by striatal dysfunction (Nitrini, 1987; Stoffers et al., 2001). We compared the connectivity patterns within this network for individuals with vs. without HKP errors committed during a performance of a complex motor learning task that was previously shown to elicit HKP in older adults (Suchy & Kraybill, 2007). To allow generating a wide range of responses, as well as to allow determination of what level of perseveration is abnormal, we examined behavioral responses and connectivity patterns in both older and younger adults.

Table 1
Participant characteristics.

	Young ($n=24$)	Old ($n=20$)
Age (years)	28.38 (2.95) 25–35	67.50 (3.00) 65–74
Education (years)	14.95 (1.33) 12–16	13.38 (1.29) 12–16
WTAR IQ estimate	108.46 (10.89) 89–125	110.00 (11.63) 81–123
DRS-total (raw score)	139.50 (2.78) 133–144	139.40 (3.78) 132–144

Note: Standard deviations are presented in parentheses. Ranges (minimum–maximum) are presented below the means.

2. Method

2.1. Participants

Participants were 44 females recruited from two age groups: "young," ages 25–35 years ($n=24$), and "old," ages 65–75 ($n=20$). The age range of the *young* group was based on prior research showing that the brain, in particular frontal–subcortical circuitry, usually does not fully mature until early in the 3rd decade of life, with most maturation typically completed by the age of 25 years and followed by a period of relative stability (Bava et al., 2010; Lebel et al., 2008). Age range for the *old* group was selected so as to examine activation at an age that is well known to be associated with measurable declines in motor and cognitive processes (Gunstad et al., 2006). All participants were strongly right-handed as evidenced by a score of≥80 on the Edinburgh Handedness Inventory (Oldfield, 1971) and all female to avoid any possible confound secondary to gender-specific fMRI activation patterns (Bell, Willson, Wilman, Dave, & Silverstone, 2006).

Potential participants were excluded if they were not native English speakers to avoid possible impact on communicating with study staff. Additionally, string or keyboard musicians were excluded due to a documented difference in brain activation during complex motor task execution (Meister et al., 2005). Additional exclusionary criteria were any contraindications to fMRI, any history of Axis I psychiatric illness or substance abuse (assessed via Structured Clinical Interview for DSM-IV-TR Axis I Disorders-Research Version), traumatic brain injury (defined as any trauma to the head that resulted in a loss of consciousness, per self-report), neurological or medical disorder (self-report), or dementia (assessed via Mattis Dementia Rating Scale, 2nd edition) (Mattis, Jurica, & Leitten, 1988). Those with any current use of medications that could impact the central nervous system (including psychiatric medications) or any first-degree relative with any psychiatric Axis I disorder were also excluded.

See Table 1 for a summary of participant characteristics. As can be seen from the table, the *old* group was slightly less educated than the *young* group [$t=3.98$, $df=42$, $p<0.001$), although this difference is likely of little practical significance. Otherwise, groups were comparable on IQ estimate and a screening of general cognitive functioning (both p values >0.70).

2.2. Materials and procedure

2.2.1. General overview

After a complete description of the study was given to the participants, written informed consent was obtained, as approved by both the Institutional Review Board at the University of Utah and the Research Review Committee of the George E. Whalen Veterans Administration Medical Center. Participation consisted of two sessions. In Session 1, eligibility assessment and neurocognitive testing took place. In Session 2 (which always occurred on a separate day and subsequent to Session 1), fMRI scanning took place. The cognitive and fMRI tasks used in the present study were administered as part of a longer battery (as part of a larger study on lifespan changes in the frontal–basal ganglia circuitry)[1]. The entire cognitive battery took approximately 45 min and was conducted by a trained technician in a quiet testing room. The entire scanning session lasted approximately 1.5 h and included a total of 4 different activation tasks (two motor tasks and two cognitive tasks).

[1] The present manuscript represents the only instance of reporting on HKP with the present dataset. No other manuscripts have, or will, examine activation or connectivity associated with HKP in this sample.